BOOK OF ABSTRACTS

DOMBAY ORGANIC CONFERENCE CLUSTER DOCC-2016

International Conference
"Modern Trends in Organic Chemistry"

9th Eurasian Meeting on Heterocyclic Chemistry

Conference for young organic chemists

29th May – 04th June, 2016
Dombay, Russia

WELCOME

Dear Participants,

On behalf of the Organizing Committee, it is our pleasure to invite you to attend the Dombay Organic Conference Cluster, DOCC-2016. DOCC is organized by the Department of Chemistry of Moscow State University and Department of Chemistry of North Caucasus Federal University.

This International Forum combines several interrelated scientific events:

- International Conference "Modern Trends in Organic Chemistry",
- 9th Eurasian Meeting on Heterocyclic Chemistry,
- Conference for young organic chemists.

The international conference "Modern Trends in Organic Chemistry", formerly known as New Directions in Chemistry of Heterocyclic Compounds, held in the Northern Caucasus region in 2009, 2011, and 2013, has now become a part of the conference cluster "Dombay-2016". The past three forums were initiated and organized by Prof. A. Aksenov.

Eurasian Meetings on Heterocyclic Chemistry (EAMHC) are a series of conferences on heterocyclic chemistry that began in Russia in 2000. It attracts attendees from industry and academia, mainly from Europe and Asia, but also from the other continents. Launching the EAMHC was the idea of Prof. E. Babaev. The meetings were held in European and Asian parts of the continent: in Russia – Suzdal - 2000, Novgorod the Great - 2002, Novosibirsk - 2004, Greece (Thessaloniki – 2006), Kuwait – 2008, Spain (Alicante – 2010), Turkey (Istanbul – 2012) and Georgia (Tbilisi – 2014).

Scientists 30 different counties and from over 40 cities of Russian Federation will take part in DOCC-2016. In the frame of this meeting, we will also host our First Summer Workshop for Young Scientists, for undergraduate and graduate students and postdoctoral fellows.

The Organizing Committee created exiting scientific program including:

8 plenary lectures,
13 keynote lectures,
39 invited lectures,
34 oral communications,
21 young scientists presentations

More than 150 poster reports.

We cordially welcome you to the DOCC in the very south of Russia! We wish all of the participants an inspiring and productive conference and an enjoyable stay in Dombay!

Co-Chairmen of Organizing Committee,

Professor Valentine Nenajdenko

Professor Alexander Aksenov

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PLENARY LECTURES

Catalysis in organic synthesis

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In the report we are going to consider the results obtained in our laboratory in MSU covering the following topics:

1. Nano-catalysis by the supported Pd and Cu in cross-coupling and carbonylation reactions.

2. Catalysis in the addition reactions of S-H and P-H bonds to triple bond.

3. Asymmetric Friedel-Crafts reaction catalyzed by different Lewis acids with chiral ligands.

4. Synthesis of polyazamacrocycles and porphyrin dimers and trimers using Pd- or Cu-catalyzed C-N bond formation.

Recent Advances in Synthesis

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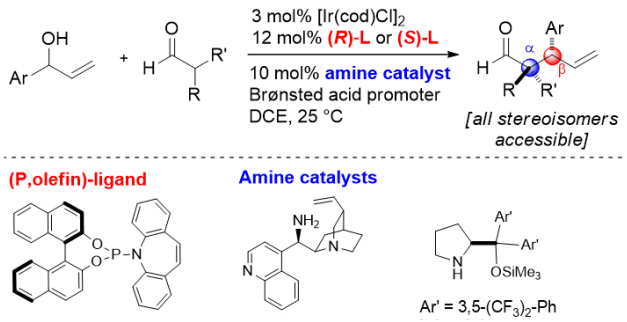
The ability to readily access small-molecule building blocks at will has important consequences for the discovery and development of novel medicines and materials. It is particularly beneficial when the chemical methods are convenient while at the same time economically and environmentally tenable and sustainable. A focus of our research program at ETH-Zurich is the identification, study, and development of novel reactions and methods for preparation of functionalized structures. We are especially interested in catalytic processes that are easily executed and utilize readily available starting materials. We will discuss several new reaction processes that provide ready access to a host of fundamentally versatile building blocks for synthesis, terpenes, halolipids, and bioactive small molecules.



Design and Applications of Metal-Catalyzed Reactions for Sustainable Chemistry

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The design of ”green” synthetic methodology and new approaches to sustainable energy are major goals of modern catalysis. Traditionally, catalysis by metal complexes has been based on the reactivity of the metal center, while the ligands bound to it influence its reactivity, but do not interact directly with the substrate. In recent years, complexes based on “cooperating” ligands were developed, in which both the metal and a ligand interact with the substrate and undergo bond making and breaking in key steps of the catalytic cycle, thus providing exciting opportunities for catalytic design.

We have developed a new mode of metal-ligand cooperation, involving ligand aromatization – dearomatization, which provides a new approach to the activation of chemical bonds. Pincer-type complexes of several transition metals exhibit such cooperation, including complexes of Ru, Fe, Co, Rh, Ir, Ni, Pd, Pt, Mn and Re, leading to facile activation of various chemical bonds. This has led to fundamentally new, environmentally benign catalytic reactions, including several reactions which either produce dihydrogen or consume it. Synthetic and energy-relaed applications based on these reactions will be described.

Porphyrin Analogues: A Personal Journey

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Expanded porphyrin is a term we introduced into the literature in 1988 to describe larger homologues of natural and synthetic tetrapyrrolic macrocycles. Expanded porphyrins, along with many other contracted, isomeric, and core-modified porphyrin analogues, are now known. Expanded porphyrins, in particular, have seen application in areas as diverse as anion recognition and transport, self-assembly, liquid-liquid ion extraction, photodynamic therapy, and anticancer drug development. In recent years expanded porphyrins have helped increase our understanding of aromaticity and antiaromaticity. One approach to extending these latter frontiers involves making systems whose size, shape, and electronic structure is rigorously controlled. Another involves replacing the pyrrolic subunits typically found in expanded porphyrins with subunits, such as pyridine, that do not normally allow for through conjugation. In this lecture, an update on recent systems that have been synthesized and studied in our laboratories will be presented. Particular emphasis will be placed on systems that show promise as drug leads. Also discussed will be macrocycles that support unexpected electronic configurations, including unusual [4n +1] π-electron semi-aromatic peripheries, and new compounds that may provide experimental support for the long-sought, but hitherto elusive concept of 3-dimensional aromaticity. Also discussed will be expanded porphyrin-based self-assembly. Several lead references are provided below.

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This work has benefited from support from the U.S. National Science Foundation, The National Institutes of Health, the Cancer Research and Prevention Institute of Texas, The U.S. Department of Energy, as well as the Robert A. Welch Foundation and the Korean World Class University program. Startup funding from Shanghai University is also acknowledged. Productive collaborations with a number of groups, including those of Profs. Dongho Kim, Shunichi Fukuzumi, T. K. Chandrashekar, Christophe Bucher, Dirk Guldi, Pradeepta Panda, Changhee Lee, Jan Jeppesen, Masatoshi Ishida, Evgeny Kataev, and Tomas Torres, are also gratefully acknowledged.

Organic Synthesis and Catalysis for Sustainable Society
Flow "Fine" Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods

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The concept of flow "fine" synthesis, that is high yielding and selective organic synthesis by flow methods, will be presented. Flow methods have several advantages over batch methods in terms of environmental compatibility, efficiency, and safety. However, synthesis by flow methods is more difficult than synthesis by batch methods. Indeed, it has been considered that synthesis by flow methods can be applicable for the production of simple gasses but that it is difficult to apply to the synthesis of complex molecules such as natural products and active pharmaceutical ingredients (APIs). Therefore, organic synthesis of such complex molecules has been conducted by batch methods. On the other hand, syntheses and reactions that attain high yields and high selectivities by flow methods are increasingly reported. Flow methods are leading candidates for the next generation of manufacturing methods that can mitigate environmental concerns toward sustainable society.

Modern organic synthesis is used for the synthesis of a wide range of useful compounds, and many synthetic reactions can be used to achieve high yields and high selectivities. Although the phrase "fine organic synthesis"[1] is used occasionally, the word "fine" is often omitted because modern organic synthesis has developed to the stage that only reactions that proceed with high levels of control and efficiency are used routinely. On the other hand, according to classifications of synthetic methods, conventional organic syntheses involve almost exclusively batch methods, and the term "modern organic synthesis" is actually an abbreviation of "organic synthesis by batch methods." Again, because "by batch methods" is self-evident, it is typically not necessary to include the clarification.

Fine synthesis by batch methods	⇨	**Conventional organic synthesis**
Fine synthesis by flow methods	⇨	***Flow "fine" synthesis***

However, syntheses and reactions that attain high yields and high selectivities by using flow methods have also been increasingly reported. These methods are properly classified as organic synthesis, however, as mentioned above, because modern organic synthesis is "organic synthesis by batch methods," it seems inappropriate to call these methods simply organic synthesis. It may be termed "organic synthesis by flow methods;" however, at this moment, the quality and quantity of organic synthesis may be different between "organic synthesis by batch methods" and "organic synthesis by flow methods." Therefore, instead of "organic synthesis by flow methods" we may use the term "flow *fine* synthesis," which is "fine organic synthesis by flow methods," wherein "fine" is the goal of flow synthesis.[2]

In this presentation, several examples of flow "fine" synthesis using heterogeneous catalysts will be introduced.[3]

References

[1] The phrase "fine organic synthesis" may not be very common as an English phrase but is often used as the corresponding Japanese; "Seimitu Yuuki Gousei," where "Yuuki Gousei" is "Organic Synthesis" and "Seimitsu" is corresponding to "Fine." The meaning is close to *Stereoselective Synthesis* or *Modern Organic Synthesis*.

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Early and (Mainly) Recent Views of the Metalated Flatlands

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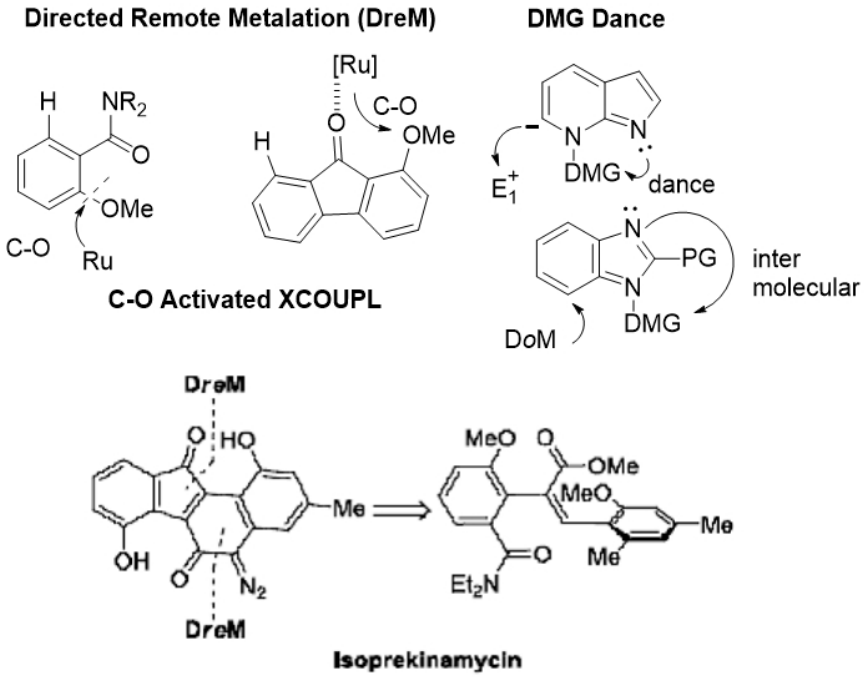
"Before the advent of DoM, the preparation of contiguously substituted (e.g. 1,2-, 1,2,3- or 1,2,3,4-) aromatic compounds, using the directing effect of the various substituents in S_EAr reactions was a major challenge and required many steps to accomplish."

Kürti, László, Czakó, Barbara
Strategic Application of Named Reactions in Organic Synthesis, Elsevier, 2005, p 420

"It is now a mainstay in aromatic functionalization as it accords both efficiency and full regiocontrol over the introduction of multiple functional groups. … represents a unique and effective replacement for electrophilic aromatic substitution … which is especially arduous for heteroaromatic compounds."

Hudlický, Tomáš, Reed, Josephine W.
The Way of Synthesis, Wiley-VCH, 2007, p 112

A selection of these themes (below) including new departures into Ir- and Ru- catalyzed DoM-enhancing connections will be described.



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Concepts and Catalysts for Ion-Controlled Reactivity in Organic Synthesis

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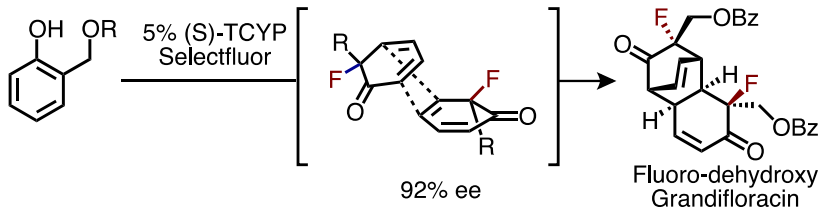
The past decade has witnessed remarkable development in the use of cationic gold(I) complexes as homogenous catalysts for the transformation of carbon-carbon π-bonds.[1] Several years ago, we demonstrated that the reactivity of these complexes could be controlled by modification of the counter anion to these cationic transition metal complexes.[2] This discovery provided a general platform for inducing enantioselectivity in reaction not only using cationic transition metal complexes, but also with reactive cationic reagents and intermediates. For example, we have applied this concept towards the development of enantioselective electrophilic fluorination under chiral anion phase transfer conditions (Figure 1).[3] More recently, we have demonstrated that the chiral anion phase transfer catalysis can be employed combination with enamine organocatalysis and transition metal catalysis.[4] The use of these ionic interactions to control selectivity of cationic species has generally relied on small molecular anions.[5] As an extension of this concept, we have been exploring the use of supramolecular assemblies (Ga_4L_6 tetrahedral) as chiral anion for catalysis or as the anionic component in reactions catalyzed by cationic transition metal complexes.[6]



Scheme 1. Enantioselective Fluorination of Phenols by Chiral Anion Phase Transfer Catalysis[3b]

References

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Direct C-H Bond Transformations Toward Construction of π-Conjugated Polycycles

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π-Conjugated polycycles have been studied intensively in the field of synthetic chemistry and materials science due to their structural variation, versatile optoelectronic properties, varied packing structures, and a wide application in electronic devices. Among the synthetic methods, the direct C-H bond transformation without pre-functionalization of aromatic C-H bonds has become a challenging methodology for the synthesis of various π-conjugated polycycles.[1] Recently, we have developed various new C-H bond transformations including C-H bond activation, cascade annulation, and one-electron oxidation for constructing diverse π-conjugated polycycles.

Pd-Catalyzed cascade crossover-annulation for synthesis of dibenzo[*a*,e]pentalenes

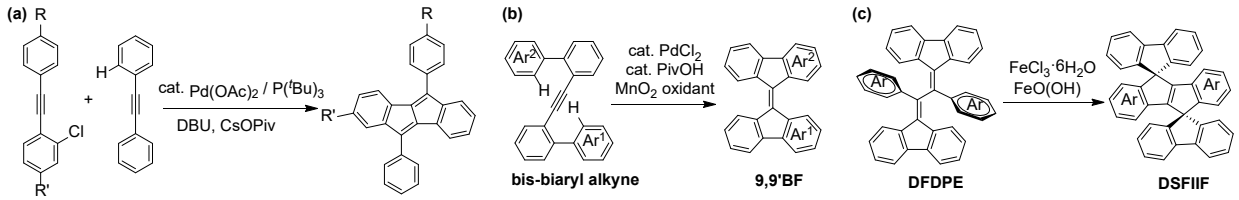
The multisubstituted dibenzopentalenes bearing functional groups at the 5- and 10-positions exhibit high stability and drastically changed electronic and structure properties compared to the parent dibenzopentalene. In this context, we have developed a novel and selective Pd-catalyzed crossover-annulation of *o*-alkynyl arylhalides with 1,2-diarylacetylenes through a C-Cl/C-H cascade cyclization for the synthesis of dibenzo[*a*,*e*]pentalenes (Scheme 1a).[2] The reaction proceeds through a Pd-catalyzed cascade carbopalladation and C-H bond activation.

Pd-Catalyzed dual C-H activation of bis-biaryl alkynes for synthesis of 9,9'-bifluorenylidenes

9,9'-Bifluorenylidenes (9,9'BF) derivatives were found to be useful nonfullerene-electron-accepting materials in bulk-heterojunction solar cells. We have developed a novel and efficient Pd-catalyzed dual C-H activation/annulation transformation of bis-biaryl alkynes for the construction of 9,9'BF derivatives (Scheme 1b).[3] The combination of the $PdCl_2$ catalyst with the MnO_2 oxidant and PivOH additive is vital for realization of the present catalytic transformation.

$FeCl_3$-Mediated oxidative spirocyclization of difluorenylidene diarylethanes

Fluorene-based spirocycles have currently attracted a great attention as important optoelectronic materials in various fields of organic electronics due to their unique structural features. We have developed a novel and highly efficient $FeCl_3$-mediated oxidative spirocyclization of 1,2-di(9*H*-fluoren-9-ylidene)-1,2-diphenylethanes (DFDPEs) toward synthesis of a new class of dispiro-linked π-system of dispiro[fluorene-9,5'-indeno[2,1-*a*]indene-10',9''-fluorenes] (DSFIIFs) (Scheme 1c).[4] The highest fluorescence quantum yield was up to 0.94 in solution.



Scheme 1. New C-H bond transformations for construction of π-conjugated polycycles.

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KEYNOTE LECTURES

Stereoelectronic control of cyclizations and fragmentations

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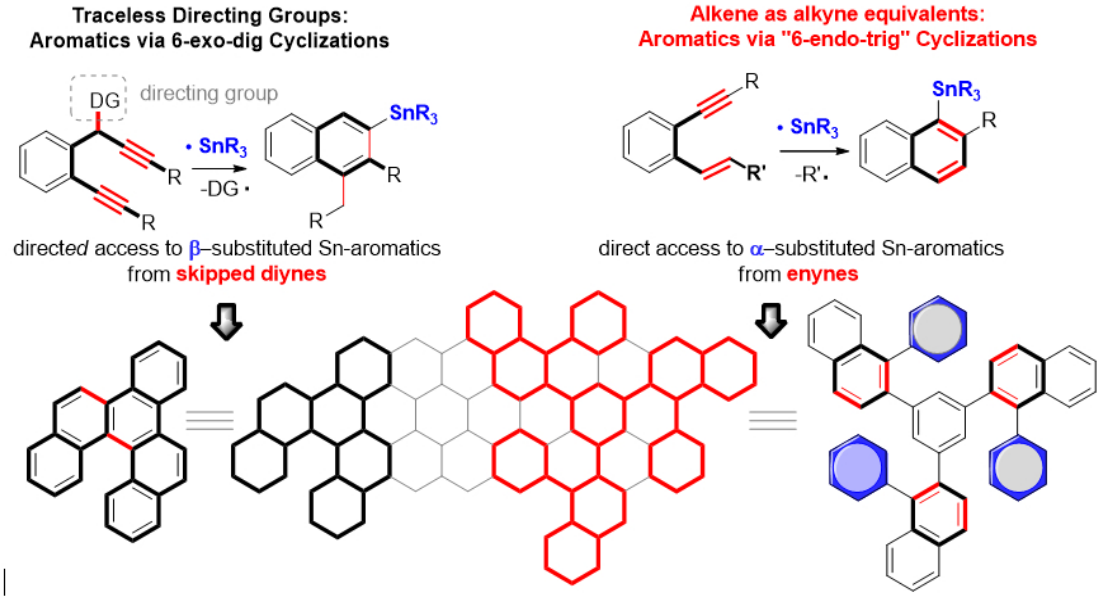
Recently, we had redefined the rules for utilizing the rich chemical potential of alkynes[1] in the formation of cyclic structures.[2] I will discuss applications of the new rules to the preparation of extended polyaromatics[3] and further synthetic opportunities arising from fusion of cyclization cascades with self-terminating fragmentations that allow the use of alkenes as synthetic equivalents of alkynes.[4]



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Video Movies of Chemical Transformations

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Mechanistic studies of chemical transformations utilize very efficient spectral methods, namely NMR, MS and IR among many other well-known tools. None of the analytic methods makes it possible to achieve direct visualization of chemical transformations. Interpretation and correlation (often empirical) between structure and spectral data is typically carried out, instead. Direct visualization of chemical reactions, "video movies" of chemical transformations, would be an outstanding opportunity to reveal real mechanisms and develop new areas of chemistry.

The problem retains high level of complexity and can not be easily solved at the molecular level. Nevertheless, a fascinating progress has been made towards direct visualization of chemical transformations in the nano-scale dimensions.

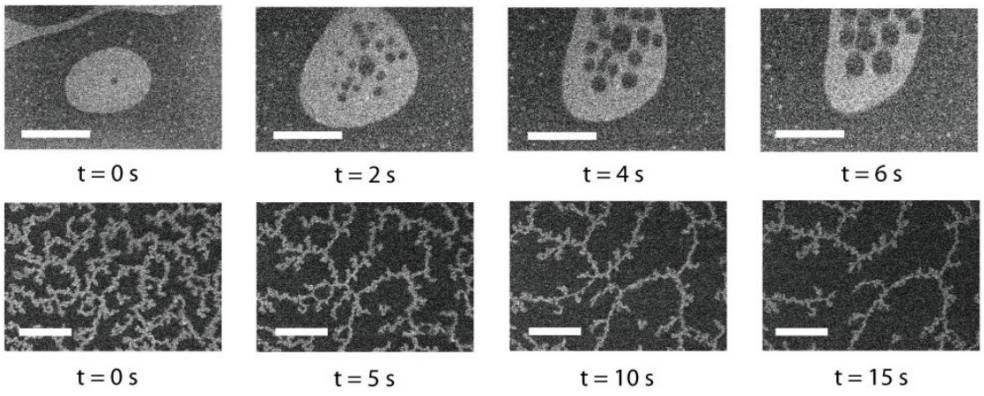

Fig. 1. Snapshots from video movies reflecting dynamic process in the electron microscopy study [1].

In this presentation, capturing dynamics of the chemical processes using electron microscopy will be presented and discussed for the reaction of biomass conversion to 5-HMF [1]. The transformation was directly visually followed and recorded as video movies (Fig. 1). Developing imaging technique to visualize reactivity was achieved in the area of catalysis [2] and connected with regular spectral studies [3,4].

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Natural Products: An Opportunity for Discovery in Chemistry and Biology

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I will present results related to a structurally novel antibiotic termed Mangrolide A, which was isolated from a marine actinomycete from the mangrove swamps in the Bahamas. Structurally, mangrolide A shares similarity to fidaxomicin (trade name = ®Dificid, Cubist Pharmaceuticals), which is a clinically approved narrow-spectrum antibiotic used for the treatment of the Gram-positive pathogen *Clostridium dificile*. However, Mangrolide A exhibits potent and selective bactericidal activity against Gram-negative pathogens, including those associated with cystic fibrosis and hospital-acquired pneumonia infections. Mechanism of action studies revealed that Mangrolide interferes with the ribosomal proofreading process, leading to an increased rate of error in protein synthesis. This is the first example of a macrolide glycoside structure displaying the mechanism of action found for aminoglycosides. The frequency of antibiotic-resistant bacteria is currently rising at an alarming rate; therefore, the need to identify new antibiotics has reached a critical level. It is estimated that greater than 1.7 million hospital-acquired bacterial infections occurred in 2008 (4.5 per 1000 patients), resulting in more than 100,000 deaths. The estimated costs on the U.S. health care budget attributed to these infections are $5 billion annually. Clinicians are increasingly concerned about the threat of Gram-negative pathogens, such as *Pseudomonas aeruginosa, Acinetobacter baumanii* and the Enterobacteriacaeae, the main causes of hospital-acquired pneumonia. In a recent CDC survey 26% of *P. aeruginosa* isolates and 37% of *A. baumanii* hospital-isolates were resistant to the most common antibiotic treatments. While there have been a few approved clinical candidates for Gram-positive pathogens, new treatments for Gram-negative pathogens have stalled in recent decades. ***Thus, the need for antibiotics that are effective against Gram-negative infections has become a medical necessity.***

New efficient metal-free methods for the regioselective synthesis of 1,2,3-triazoles

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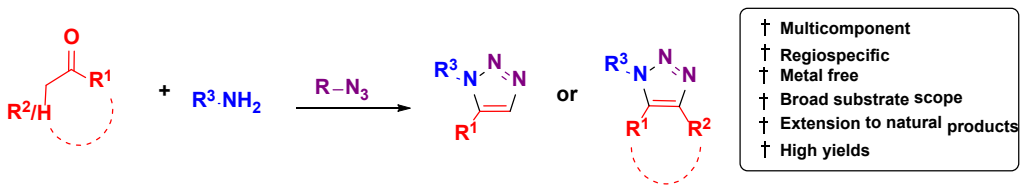
Heterocycles containing 1,2,3-triazole rings belong to a class of well studied molecules due to their diverse applications such as in pharmaceuticals, agrochemicals, material chemistry etc. Copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) has proven very valuable for the regioselective synthesis of 1,2,3-triazoles.[1] However, the toxicity of the heavy metals in living cells made this strategy not ideal for some biological applications. Several alternative methods were developed, but the major drawbacks are the formation of other regioisomers and the difficulty in making the starting materials. Therefore, the design and discovery of a new metal-free triazole synthesis is of great current interest.

Recently, our group has designed two general and powerful strategies to synthesize triazole heterocycles *via* metal-free pathways.[2] The first method involves an organocatalytic three-component reaction for synthesizing fully functionalized 1,2,3-triazoles from readily available building blocks namely aldehydes, organic azides and nitroalkanes where an intermediate Knoevenagel adduct was formed by an organocatalytic reaction.[2b] Intramolecular variants lead to fused 1,2,3-triazole derivatives.[2c]

The second approach has involved a metal-free route towards the synthesis of fully functionalized or 1,5-disubstituted 1,2,3-triazoles from easily available primary amines, ketones and 4-nitrophenyl azide as a renewable source of dinitrogen *via* an organocascade process. The applications of this methodology in medicinal and supramolecular chemistry will be also discussed.[2d]



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Artificial macrocycles by MCR and applications

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Artificial macrocycles hold great promise in drug discovery as an underutilized compound class.[1] The believe is based on their general large surface area which can be suitable to target flat featureless and large receptor surface areas, such as protein protein interactions. Artificial macrocycles typically violate Pfizer rules of oral bioavailability in several features. Since most relevant medicinal chemistry targets are intramolecular reasonable passage through membranes is key to biological activity. The rules governing membrane diffusion are poorly understood for macrocycles, however. Moreover short and efficient synthetic pathways are needed to access large numbers of divers macrocycles to discover biologically active macrocycles. The Dömling laboratory is involved in macrocycle chemistry using multicomponent reactions and applications since >15 years.[2] A summary of our recent work in the area of macrocycle synthesis, screening and computation is given and several applied examples from my laboratory will be discussed.[3, 4]

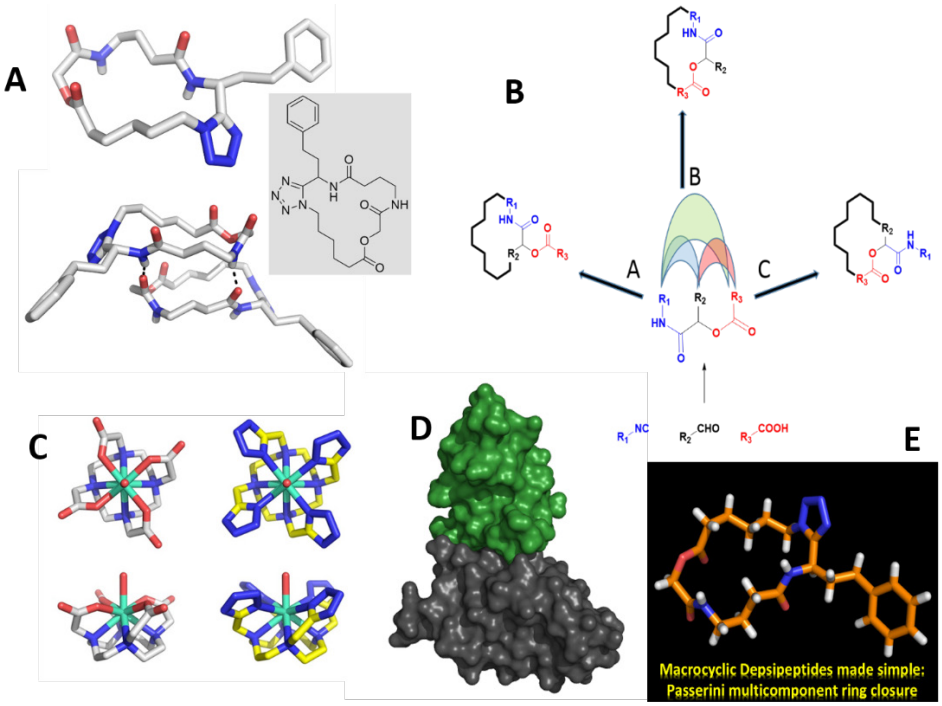

Fig. 1. A: 18-Membered artificial depsipeptide made by Ugi and Passerini reaction. B: Three topologically possible ways to close a macrocycle by the Passerini reaction. C: Gd-TEMDO complex for MRI made by Ugi MCR. D: Cocrystal structure of human PD1-PDL1 as an example of a marcocycle target. E: Macrocyclic depsipeptides made simple by MCR.

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Part of the work was financially supported by the NIH (1R01GM097082) and by Innovative Medicines Initiative (grant agreement n° 115489).

Silicon Tether Motif in C-H Functionalization Reactions

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We have developed a set of new transition metal-catalyzed C-H activation methodologies employing a silicon-tether motif. These methods feature: (a) use of silyl group as a tether between a substrate and a reagent, thus transforming intermolecular reaction into intramolecular reaction; (b) employment of a silicon-tethered directing group, which is traceless or easily convertable into valuable functionalities; (c) use of silyl-tethered reacting groups; and (d) introduction of new *N*/Si-chelation concept that allows for a remote activation of aliphatic C-H bonds.

The scope of these and some other transformations will be demonstrated and the mechanisms will be discussed.

Design and Developement of Novel Organosulfur Synthons as Versatile Intermediates for Heterocycle Synthesis

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Small molecule heterocycles' play important role in both drug discovery and material science research providing one of the richest source of diversity, besides serving as rigid scaffolds for further display of a range of functionalities. Therefore design and development of new pathways leading to efficient synthesis of novel heterocycles, displaying skeletal and functional group diversity is emerging as an important area in both synthetic organic and medicinal chemistry.

For past several years, our research group has been engaged in design and development of new efficient methodologies for a wide range of substituted and fused five and six membered heterocycles utilizing organosulfur synthons such as polarized ketene dithioacetals and the corresponding *N,S*-acetals derived from them, as versatile building blocks. We have recently developed and synthesized new class of organosulfur synthons based on 2-halo(het)arylacetonitriles, azalactones, 1,3-monothioketones and utilized them for designing new reactions for diverse class molecular entities such as benzo[*b*]thiophenes, arylacetylenes, functionalized heteroarenes, substituted oxazoles, thiazoles pyrazoles, thiophenes, indoles and other novel heterocyclic scaffolds of biological importance. Some of our recent results on these new synthetic methods based on these easily accessible organosulfur building blocks involving organometallic methods, radical cyclizations, transition metal catalyzed intramolecular C-C, C-N and C-S bond formation via cross-coupling and C-H activation reactions, and cycloaddition and domino reactions of activated methylene isocyanide anions, along with some of the serendipitous reactions will be presented in the lecture.[1]

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Total Synthesis of Alkaloids Using Transition Metals

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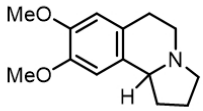
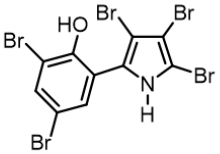
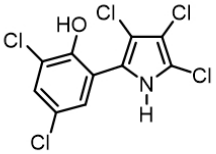
We have developed a novel route to pyrroles by silver(I)-mediated oxidative cyclization of homopropargylamines which was applied to the synthesis of the pyrrolo[2,1-*a*]isoquinoline alkaloid (±)-crispine A (*RSC Adv.* **2013**, *3*, 1089). Further improvement of our approach to pyrroles led to an efficient silver(I)-catalyzed process that was used for the synthesis of pentabromopseudilin and pentachloropseudilin (*Angew. Chem. Int. Ed.* **2009**, *48*, 8042; *Eur. J. Org. Chem.* **2014**, 4487). The pentahalogenated pseudilins represent a novel class of inhibitors for myosin ATPase. Pentachloropseudilin is specific for the inhibition of class-1 myosins (*J. Med. Chem.* **2011**, *54*, 3675; *Nature Cell Biol.* **2015**, *17*, 397). Moreover, the halogenated pseudilins are also allosteric inhibitors of the enzyme IspD, which catalyzes the non-mevalonate pathway to terpenes (*Angew. Chem. Int. Ed.* **2014**, *53*, 2235).



(±)-Crispine A

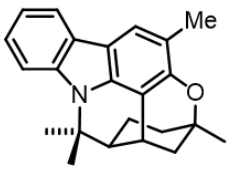


Pentabromopseudilin

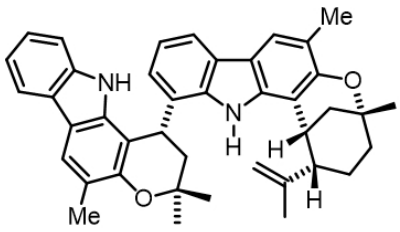


Pentachloropseudilin

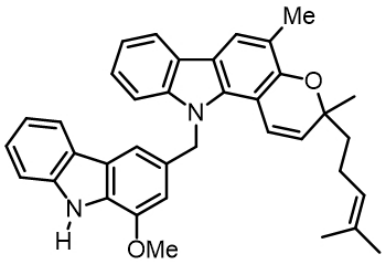
Carbazole alkaloids are attractive targets for organic synthesis because of their broad range of useful biolocical activities (*Chem. Rev.* **2012**, *112*, 3193). We have developed two highly convergent synthetic routes to the carbazole ring system using either an iron(0)-mediated or a palladium(II)-catalyzed oxidative cyclization as key-step (*Top. Curr. Chem.* **2012**, *309*, 203; *Chem. Eur. J.* **2012**, *18*, 770). Via our palladium(II)-catalyzed approach, we have developed an efficient route to 2-hydroxy-3-methylcarbazole which has served as crucial intermediate for a biomimetic synthesis of mahanimbidine (*Chem. Eur. J.* **2013**, *19*, 14098) and for a novel domino Sonogashira coupling/Claisen rearrangement/electrocyclization reaction to the biscarbazole murrafoline-A (*Angew. Chem. Int. Ed.* **2013**, *52*, 11073). Diverse pyran annulation procedures have been applied to the total syntheses of a broad range of pyranocarbazole alkaloids (*Org. Biomol. Chem.* **2014**, *12*, 3866; *Chem. Eur. J.* **2014**, *20*, 8536; *Chem. Eur. J.* **2014**, *20*, 9504; *Org. Biomol. Chem.* **2014**, *12*, 6490; *Tetrahedron* **2015**, *71*, 3485; *J. Org. Chem.* **2015**, *80*, 5666; *Synthesis* **2016**, *48*, 150) including the biscarbazole chrestifoline-C (*Org. Biomol. Chem.* **2014**, *12*, 3831; *Chem. Eur. J.* **2016**, *22*, 2487).



Mahanimbidine
(Curryangin, Murrayazoline)



Murrafoline-A



Chrestifoline-C

Transition Metal Vinylidene Medaited Catalysis for Use in Organic Synthesis

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Transition metal vinylidene complexes are organometallic species derived from alkynes that are isomeric to pi- and sigma-alkyne complexes. Our laboratory has been engaged in the development of C–C bond-forming processes that make use of terminal alkynes via mechanisms involving a transition metal vinylidene as a catalytic intermediate. A range of new reactions have been developed such as enyne cycloisomerizations, which convert simple acyclic unsaturated substrates to their cyclic isomers,[1] and other tandem processes such as hydrative, alkylative, and carboxylative cyclization reactions.[2-4] More recently, in a departure from these ring-forming processes, our explorations have been focused on the oxygen-transfer to the metal-bound carbene. This approach has led to the discovery of oxygenative coupling reactions that occur through the intermediacy of a metalloketene arising from oxidation of a metal vinylidene. [5] Presented in this talk are the design, implementation and mechanism of the oxygenative transition metal vinylidene-mediated catalytic reactions.

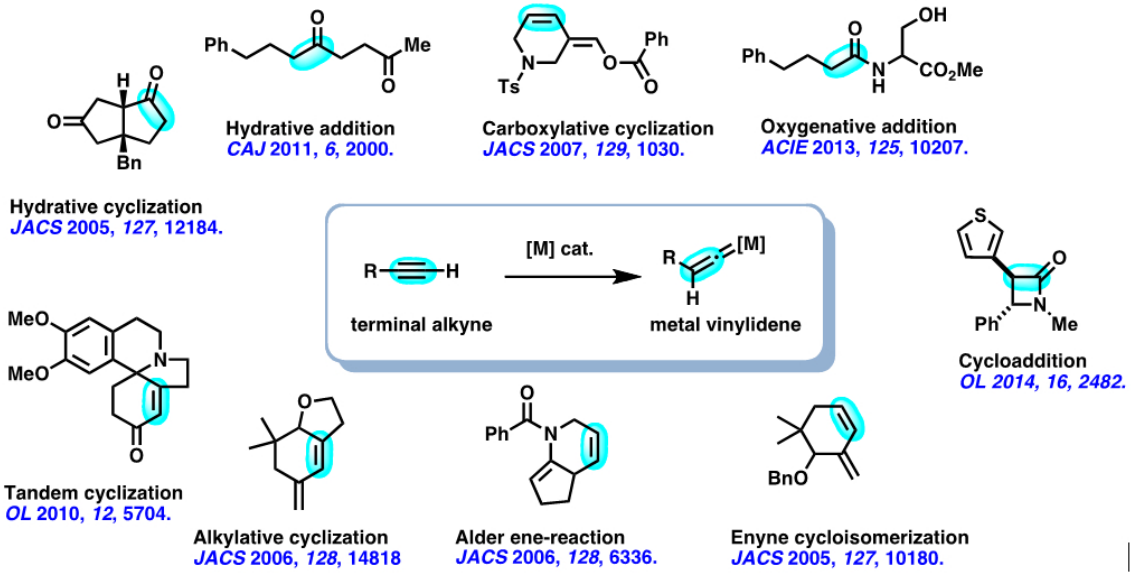

Fig. 1.

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Advances in Macrocyclic and Supramolecular Chemistry: From Heteracalixaromatics to Coronarenes

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For more than a decade, we have established and developed the macrocyclic and supramolecular chemistry of heteracalixaromatics (Figure 1A).[1,2] Owing to the self-tunability of a V-shaped cavity and electronic property originated from the interplay between the bridging heteroatoms and adjacent aromatic rings, heteracalixaromatics exhibit unique binding properties and have become powerful and versatile synthetic receptors to recognize diverse charged and electron neutral guest species.[2,3] To seek for novel and functional macrocyclic hosts that have a cylindroid cavity, we have very recently proposed corona[n](het)arenes (Figure 1B), a new type of synthetic macrocycles which are composed of heteroatoms and para-(het)arylenes in an alternative fashion.[4,5] In this talk, I will first give a brief introduction of the chemistry of heteracalixaromatics highlighting the application of the macrocycles in the study of anion-π interactions and of high valent organocopper chemistry. I will then describe the designed synthesis of various oxygen, sulfur and sulfone-linked corona[6](het)arenes. The conformational structures of the macrocycles will be discussed followed by their applications in selective binding towards organic cations in both organic and aqueous solution.[4-6]

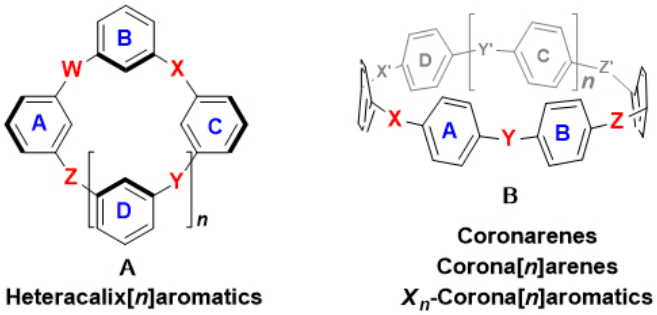

Figure 1: General structures of heteracalix[*n*]aromatics (A) and corona[*n*]arenes (B)

Keywords: heteracalixaromatics, coronarenes, host-guest interactions, molecular recognition

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[6] Q.-H. Guo, L. Zhao, M.-W. Wang, unpublished results.

Enantioselective Addition of Organomagnesium Reagents to Carbonyl Compounds

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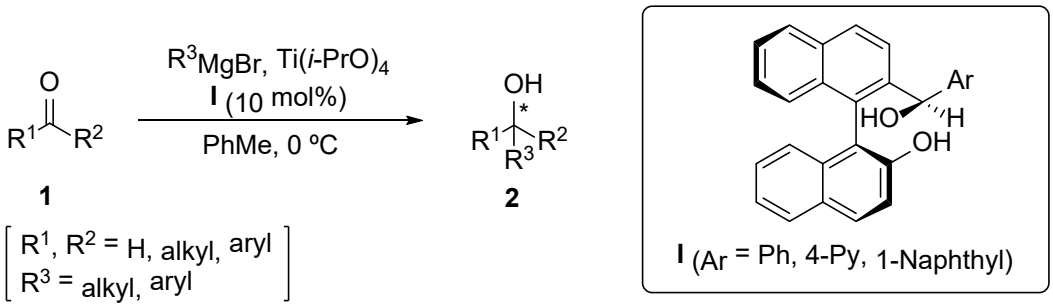
One of the most useful methodologies to create carbon-carbon bonds is the addition of organometallic reagents to carbonyl compounds. The asymmetric version of this reaction allows the generation of a sterocenter and at the same time of an alcohol functionality [1]. However, the use of Grignard reagents in this process has been explored with limited success. As chiral ligands, TADDOL [2] or BINOL [3] derivatives have been reported to be useful for the mentioned transformation, being so far only efficient for the addition to aldehydes. In the last few years we have used ligands of type **I** for the enantioselective addition of Grignard reagents to aliphatic and aromatic aldehydes and ketones (**1**) in the presence of titanium tetraisopropoxide to yield chiral alcohols (**2**) (Scheme) [4,5].



Scheme

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Synthesis and applications of enantiomerically enriched polysubstituted 4-nitroprolinates

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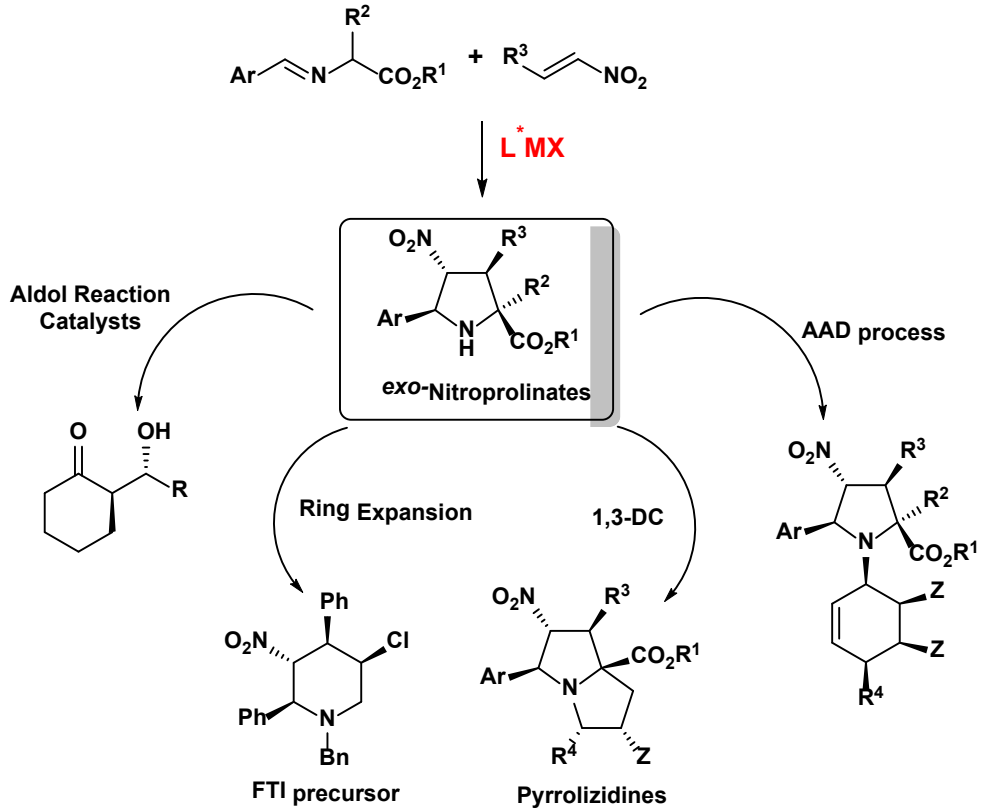
The family of 4-nitroprolinates emerged in 2005 as promising therapeutic agents, for instance as inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma, in murine model of colon carcinoma metastasis and with potent antiadhesive properties in several cancer cell lines. Here we will describe the enantioselective synthesis of *exo*-4-nitroprolinates by metal-catalyzed 1,3-dipolar cycloadditions of azomethine ylides and nitroalkenes. These compounds have been applied in organic synthesis as chiral organocatalysts in aldol reactions, as intermediates in the synthesis of potential inhibitors of farnesyl transferase (FTI), as 1,3-dipole precursors in the synthesis of polysubstituted pyrrolizidines and as starting amines in Amine-Aldehyde-Dienophiles (AAD) sequences.



Synthesis of Heterocyclic Compounds Containing Highly Polarized Exocyclic Carbon-Carbon Double Bonds

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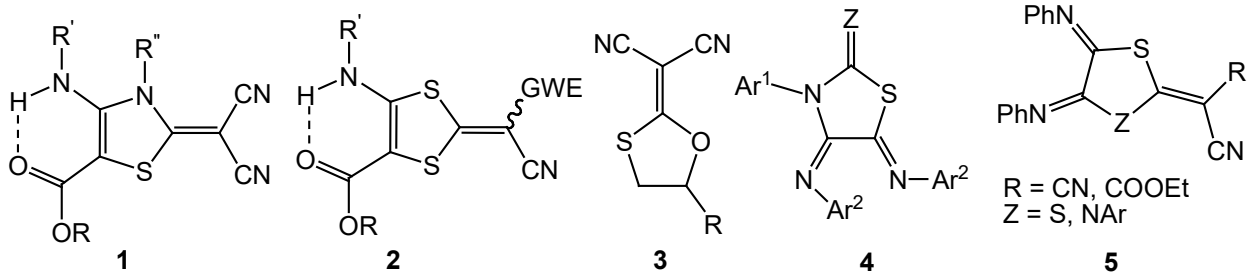
The concept of polarized (or push-pull) olefinic systems has played an important role in organic chemistry for four decades.[1, 2] A push-pull olefin is a type of olefin characterized by an electron-withdrawing substituent on one side of the double bond and an electron-donating substituent on the other side. This makes the π bond very polarized. The rotational barrier for a push-pull olefin is lower than that of an ordinary olefin.[1-3] The polarized structure of the C=C bond is discernible by ^{13}C NMR spectroscopy due to the extreme deshielded position of the alkene C-atom on the donor side and the contrastingly shielded position of the C-atom on the acceptor side of the push-pull alkene.[1-3]

As part of our current studies on the development of new routes in heterocyclic synthesis, we report the synthesis of push-pull olefinic systems shown in Scheme 1. Various features of these polarized olefins will be presented and discussed.



Scheme 1. Push-pull olefinic systems.

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Asymmetric Direct Transformations of Aromatic Compounds

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In this talk, the progress from the You laboratory on the development of catalytic asymmetric dearomatization processes and asymmetric direct C-H functionalization of aromatic compounds will be introduced.

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INVITED LECTURES

Applications of "intellegent" reaction media for functionalization of arenes

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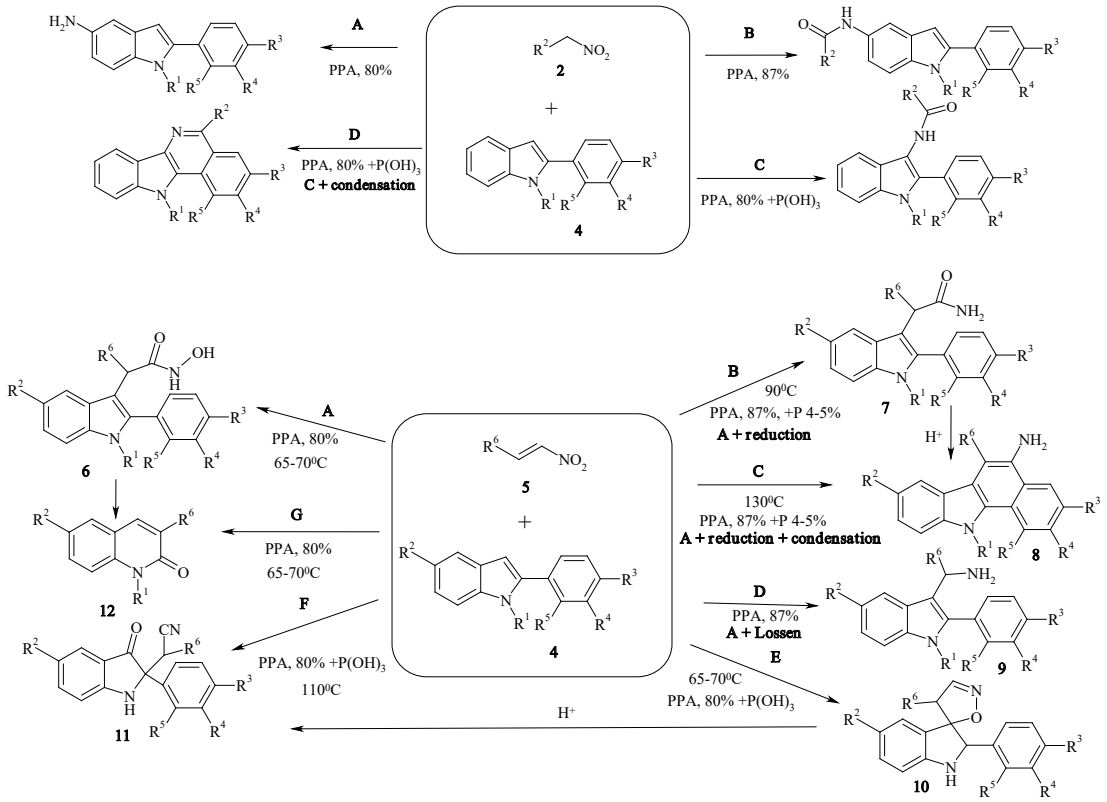
The presentation will describe new methods for direct functionalization of arenes. The emphasis is placed on the recently suggested paradigm of "intelligent reaction media", which currently is being actively developed in our laboratories. The concept of this innovative approach involves increasing of the reaction diversity due to ability to trigger only one of the many possible pathways by incorporating subtle modifications of the reaction media. This approach is illustrated by the following examples [1-3]:



Scheme 1. Graphic Abstracts.

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Design, Synthesis and Application of Calixarene Based Receptors

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One of the main topics of the investigations in Supramolecular Chemistry is the molecular design and synthesis of highly selective receptors for molecular recognition, extraction and membrane transport of ionic, neutral and zwitterionic species. Design of compounds possessing specific aggregative functions is particularly attractive. Thiacalixarene derivatives have many advantages in the construction of molecular recognition systems, i.e. the variety of spatial structures, the diversity of functioning and relative availability.

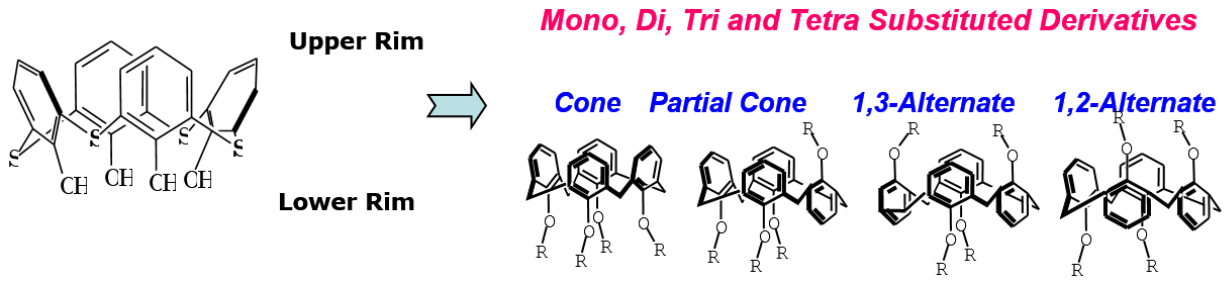

Fig. 1.

The main approaches to the stereo and chemoselective functionalization of calix[4]arene platforms that allows to change significantly hydrophilic-lipophilic properties of macrocycles and to raise efficiency and selectivity of the interaction with substrates will be presented. The strategies and methods for the synthesis of a new class of nanosized macrocyclic compounds - calixarene conjugates will be demonstrated as well. The structure of obtained macrocyclic compounds were established by 1D and 2D NMR spectroscopy, MALDI-TOF mass-spectrometry and X-ray.

There will also be examined regularities of aggregation and complexation of calixarenes with substrates of different nature: non-electrolytes, cations, anions. Particular attention will be paid to the application of calixarene derivatives for the construction of various supramolecular and nanosystems, devices and «smart» materials: nanoparticles, metal-coordinated networks, Langmuir-Blodgett nanolayers etc.

The investigation of their conformational behavior, extraction and sensors properties was carried out. The important "structure–property" regularities of guest binding by calixarene derivatives are established.

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Copper Catalyzed Cyclopropane Synthesis

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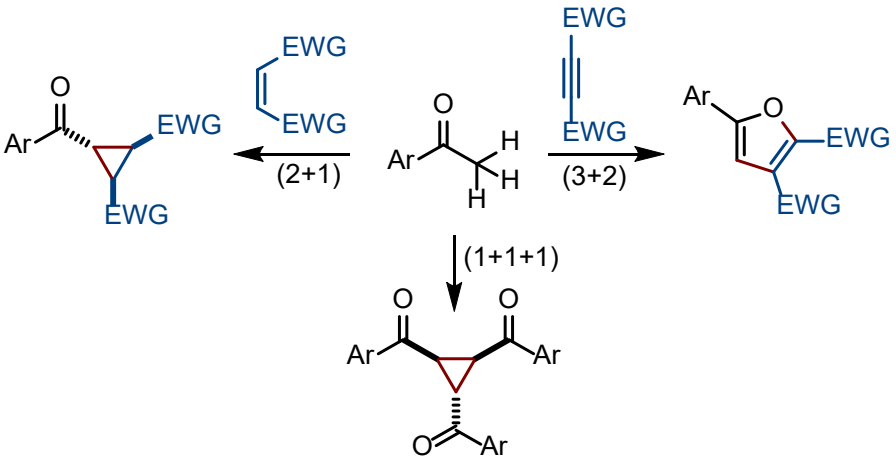
Cyclopropanes represent versatile synthons in organic synthesis with unique reactivity. Strained carbocycles are present in many natural, biologically and medicinally important products.[1] The synthesis of the cyclopropane moiety has evoked considerable interest, which resulted in the development of different synthetic strategies. These methods require the application of reactive pre-functionalized reagents. Therefore, the development of novel practical methods for the straightforward synthesis of cyclopropanes using non-functionalized materials remains a considerable challenge and their elaboration is highly desired.

We developed a copper-catalyzed cyclopropanation of maleimides with acetophenone derivatives with broad scope.[2] This reaction represents an unprecedented example of copper catalyzed stereoselective synthesis of annulated cyclopropanes. Mechanistic studies revealed a novel reactivity for copper catalyzed radical reactions. This method was applied for furan synthesis using catalytic annulation of acetophenone derivatives and alkyl acetylenedicarboxylate with a broad reaction scope.[3] The operationally simple method offers direct access to multisubstituted furan derivatives. Furthermore, we discovered an extraordinary (1+1+1) cyclotrimerization for the cyclopropane synthesis.[4] The cyclotrimerization was applied in a stereoselective synthesis of small saturated carbocycles from non-functionalized acetophenone derivatives. A broad scope of the cyclotrimerization was demonstrated and detailed studies on the reaction mechanism were performed.



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Cultivating over thirty years the passion to build heterocycles from 1,2-diaza-1,3-dienes: the force of imagination

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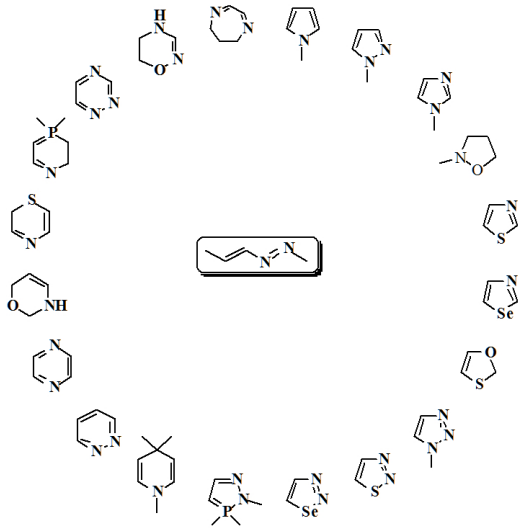
Pyrroles, pyrrolines, pyrazoles, pyrazolines, imidazoles, imidazolines, imidazolidindiones (hydantoins), 2-thioxoimidazolinones (2-thiohydantoins), isoxazolidines, thiazoles, thiazolines, thiazolidines, 2-iminothiazolidinones, selenazoles, selenazolines, 1,3-oxathioles, 1,2,3-triazoles, 1,2,3-thiadiazoles, 1,2,3-selenodiazoles, 1,2,3-diazaphospholes, pyridines, pyridazines, dihydropyridazines, tetrahydropyridazines, pyrazines, dihydropyrazines, tetrahydropyrazines, piperazines, 1,3-oxazines, 1,4-thiazines, dihydro-1,4-thiazines, tetrahydro-1,4-thiazines, dihydro-1-aza-4-phosphinine, 1,2,4-triazines, tetrahydro-1,2,4-triazines, 1,2,4-oxadiazines, tetrahydro-1,4-diazepinones, 1,4-benzodiazepines and mixed heterocyclic systems have been obtained from 1,2-diaza-1,3-dienes.[1-19]



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Reactions of sulfonylazides with thioamides

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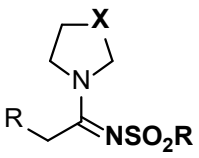
Sulfonyl azides, mostly tosyl- and mesyl azides, exhibit diverse reactivity and are widely used in organic synthesis [1, 2]. They serve as diazo transfer agents, allowing to synthesize various types of diazo compounds from C–H acidic compounds [3,4], azides from amines [5] and *N*-unsubstituted 1,2,3-triazoles from enamines [6]. In cycloaddition reactions to acetylenes leading to 1-sulfonyl-1,2,3-triazoles they are the source of the sulfonyl triaza fragment [7]. In the synthetic approach to *N*-sulfonyl derivatives of diamino alkenes by reactions with enamines they serve as the source of sulfonyl imino fragments [8]. In the last decade, two powerful synthetic methods were developed based on metal catalyzed processes for the generation of *N*-sulfonyl azavinyl carbenoids and *N*-sulfonyl ketenimines [9, 10] from acetylenes and sulfonyl azides followed by interactions with various nucleophilic reagents to form a huge variety of different types of valuable heterocyclic and organic compounds, such as amidines, sulfonamides, azadienes, α-aminoketones, cyclopentadienes, etc. Also in these reactions sulfonyl azides provide sulfonyl imine fragments to the reaction products. Reactions of sulfonyl azides with various kind of thioamides are carefully studied by Hatanaka and Bakulev groups [11, 12]. These reactions being carried out in the absence of a base are given an access to amidines **1**. Recently we have shown that cyanothioacetamides react with azides to form 1,2,3-triazoles **2** and 1,2,3-thiadiazoles **3** and **4** depending on the nature of azide and thioamide and base used.

Short review on reactivity of azides towards thioamides will be presented here.



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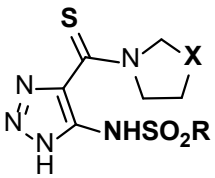

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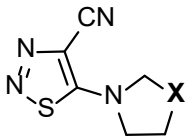

4

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Electrophilic Transformations of Some Functionally Substituted Alkynes

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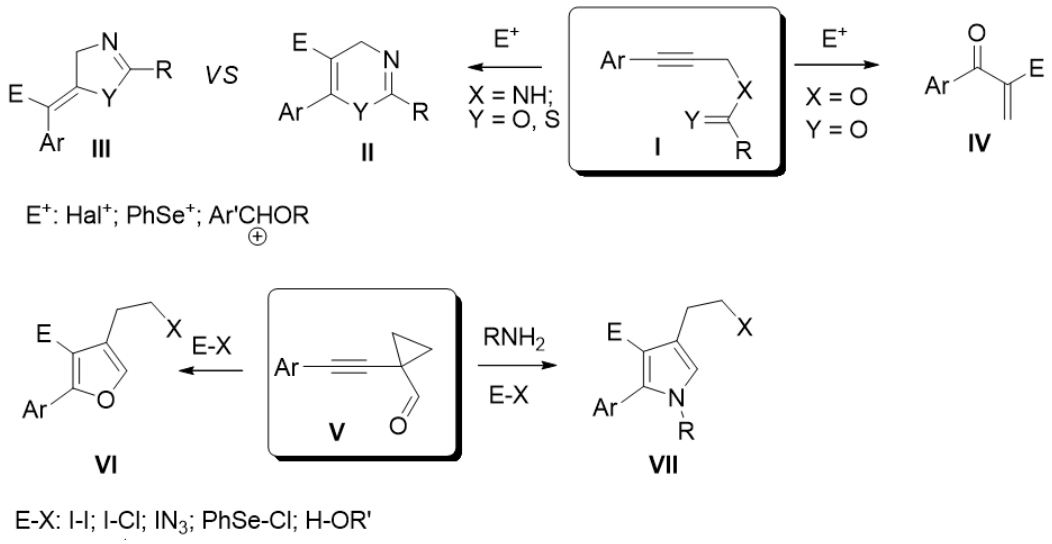
In the past decade an explosive increase of interest in electrophile-mediated cyclizations of alkynes has taken place. This methodology has become an original field of carbo- and heterocycles synthesis resulting in formation of halogen- or chalcogen substituted compounds; and thus obtained materials are suitable to undergo further synthetic transformations [1].

During this talk some recent results of our group will be presented.

We have discovered that propargylic amides, carbamates, ureas and thioureas **I** (X = NH) easily undergo metal-free halogen-, chalcogen- or oxocarbenium ion mediated yne-carbonyl or yne-thioxo ring closure processes. On the basis of our findings, very efficient synthetic protocols of functionalized *4H*-1,3-oxa(thia)zines **II** or 4,5-dihydrothiazoles **III** have been developed. Moreover, we have proved that while propargylamine derivatives undergo electrophilic cyclization reactions, propargyloxy group having materials **I** (X = O) are able to rearrange into α-functionalized enones **IV**.

Additionally, we have shown that 1-(arylethynyl)cyclopropanecarbaldehydes **V** are useful substrates for preparation of polysubstituted furanes **VI** and pyrroles **VII**.



Scheme 1.

The mechanistic aspects of the reactions together with scope and limitations will be discussed.

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4,5-Dihydro-2*H*-imidazo[2',1':2,3][1,3]thiazolo[4,5-*e*]isoindoles as potent analogues of Quizartinib

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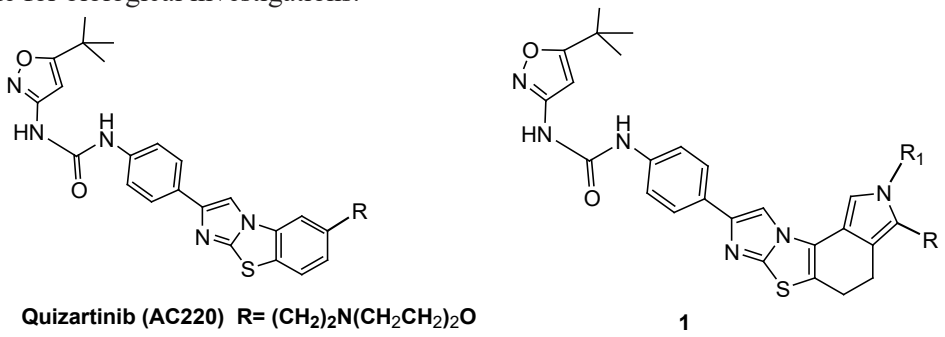
Acute myeloid leukemia (AML) is the most common and aggressive form of acute leukemia in elderly people. A number of potent small molecule FLT3 inhibitors such as Sunitinib (SU-11248), and Sorafenib (BAY- 43-9006), have been investigated as potential therapeutic agents for the treatment of AML.[1-3] However, they demonstrated not optimal for the treatment of AML because not sufficiently potent, suboptimal oral pharmacokinetic (PK) profile, lack of adequate tolerability at efficacious doses that contribute ultimately to poor inhibition of FLT3 in AML patients.[4] AB-530 is an extremely potent and highly selective FLT3 inhibitor with good PK properties, and it was found to regress tumors in mouse xenograft model using MV4-11 cells. However, the aqueous solubility and oral PK properties at higher doses were not promising for clinical development. Removal of the carboxamide group led to **Quizartinib** (**AC220**),[5] which not only retained the potency and selectivity of AB-530 but also showed improved solubility and PK profiles. In this light, we have planned the synthesis of a novel series of FLT3 inhibitors of type **1** (Figure 1), as analogues of **AC220**, in which a pyrrole unit is condensed to the imidazobenzothiazole scaffold. The so obtained tetracylic structure is a new ring system, thus, any decoration of the core structure was potentially suitable for biological investigations.



Quizartinib (AC220) R= $(CH_2)_2N(CH_2CH_2)_2O$ **1**

Fig. 1. Quizartinib, 1-(5-*tert*-butyl-1,2-oxazol-3-yl)-3-[4-(4,5-dihydro-2H-imidazo[2',1':2,3][1,3] thiazolo[4,5-*e*]isoindol-8-yl)phenyl]urea (1).

Twenty derivatives of the ring system, properly decorated, have been achieved using a multistep sequence, and tested at the Oncotest GmbH, Freiburg (Germany) against 12 hematological cell lines, 10 derived from AML and 2 CML (chronic myeloid leukemia) (K562, KCL-22) cell lines as negative controls. Dovitinib, Quizartinib (AC220) and TCS 359, which target FLT3, were used as reference drugs. Among the 20 compounds tested, five were identified with very good potency, exhibiting a geometric mean IC_{50} < 1 μM (0.348-0.960 μM). Four out of these five compounds showed, similar to the 3 reference drugs, pronounced activity towards the cell lines MV4-11 and MOLM-13 (IC_{50} 0.011-0.262 μM), indicating that they likely act through inhibition of FLT3.

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Interclass recyclizations of pyrimidinium salts under the action of amines, hydrazines and hydrazides of caboxylic acids

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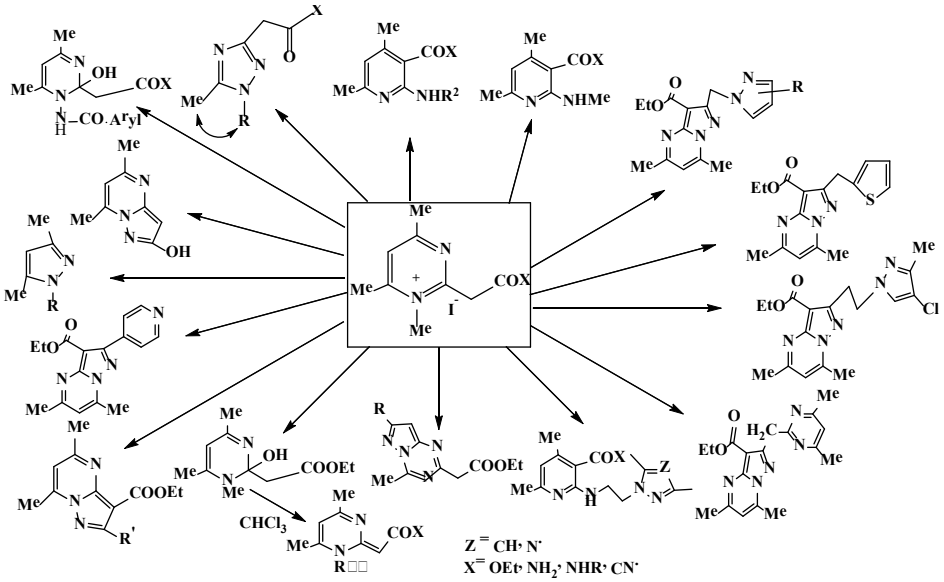
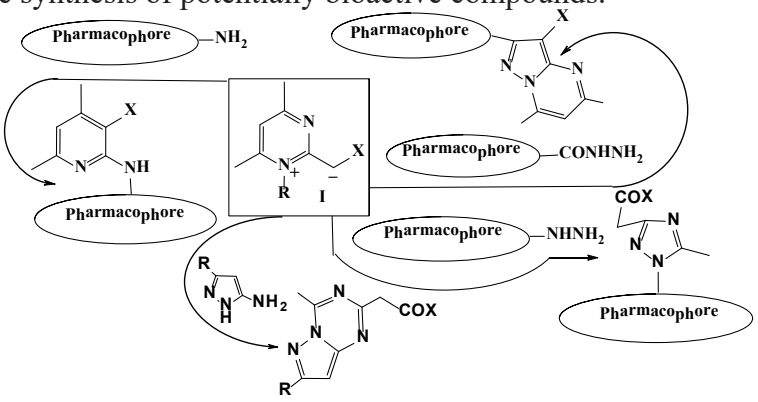
Methods for transition of 1-alkylpyrimidinyl-2-acetic acid iodides to derivatives of various heterocycles have been presented. The reactions with primary amines, substituted hydrazines and hydrazides of aliphatic and heterocyclic carboxylic acids afforded polysubstituted derivatives of pyridine, pyrazol, 1,2,4-triazole, as well as (pyrazolo[1,5-a]pyrimidine, pyrazolo[1,5-a]-1,3,5-triazine) annelated systems.



By introducing into the reactions compounds containing biogenic and pharmacophore groups, the methods are used for the synthesis of potentially bioactive compounds.



The work has been accomplished within the program of the joint Russian-Armenian grant 13RF-087 of the State Committee of Science of the Ministry of Education and Science of the RA and RFBR u 13-1D334), as well as in the framework of the “Program of the Development of Russian-Armenian University 2014-2016”.

Novel Fluorinated Organozinc Reagents

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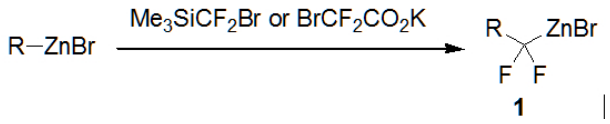
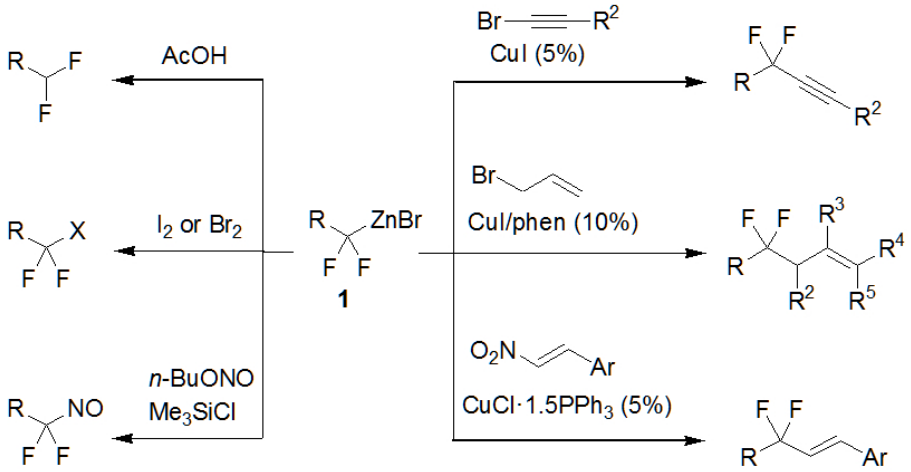
We propose a general method for the preparation of fluorinated organozinc reagents **1** by insertion of CF_2-fragment into carbon-zinc bond [1-4]. In this process, (bromodifluoromethyl)trimethylsilane or potassium bromodifluoroacetate were used as sources of difluorocarbene.



Scheme 1.

Reagents **1** may be protonated by acid or may react with halogens or a nitrosating agent. Cross couplings of **1** with various electrophiles were mediated by copper(I) catalysts.



Scheme 2.

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Novel Colchicinoids as Potential Antitumor Agents

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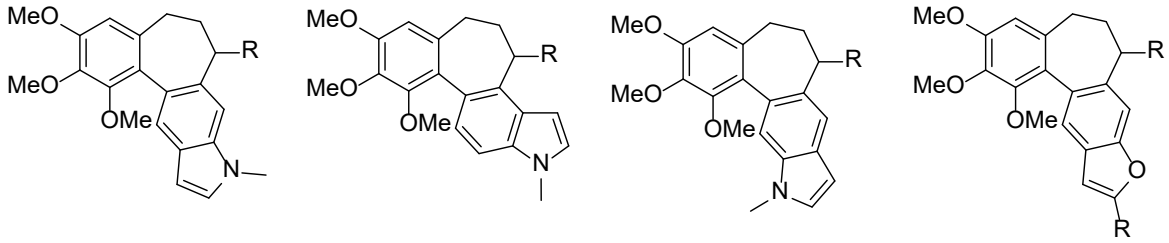
A range of indole - and furane-containing allocolchicinoids was synthesized:



R = OH, N_3, NH_2, NHAc

Several from synthesized compounds manifested high *in vitro* and *in vivo* antitumor activity.

Acknowledgments

We thank the Russian Foundation for Basic Research (project 14-03-91342), The Ministry of Education and Science of The Russian Federation (project 4.619.2014/K).

Fluorescent ‘light-up’ probes for DNA detection based on crown ether-annelated styryl dyes

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Cyanine dyes, in particular styryl dyes, exhibit remarkably high affinity towards nucleic acids along with a significant change of their photophysical properties upon DNA binding. These properties are used for DNA detection and quantification in a variety of methods and techniques such as the polymerase chain reaction, DNA fragment sizing, DNA staining, DNA damage detection, flow cytometry, and evaluation of biological activity.[1]. Although interactions of several styryl dyes with DNA have already been described, only relatively few investigations include sufficient data to deduce the binding modes. In this respect, DNA-binding properties of 15-crown-5-derived mono- and bis-styryl dyes were investigated in the presence of calf thymus DNA. To access the factors that influence the DNA association in the series of these ligands, the structure of the molecules was varied by either changing size of the heterocyclic moiety or altering the position of the styryl substituents. The major binding mode for the monostyryl dyes is intercalation, for bisstyryl dyes the interaction with DNA through the minor groove binding was found. Notably, binding of the dyes to the nucleic acids leads to a fluorescence enhancement by a factor of up to 54.

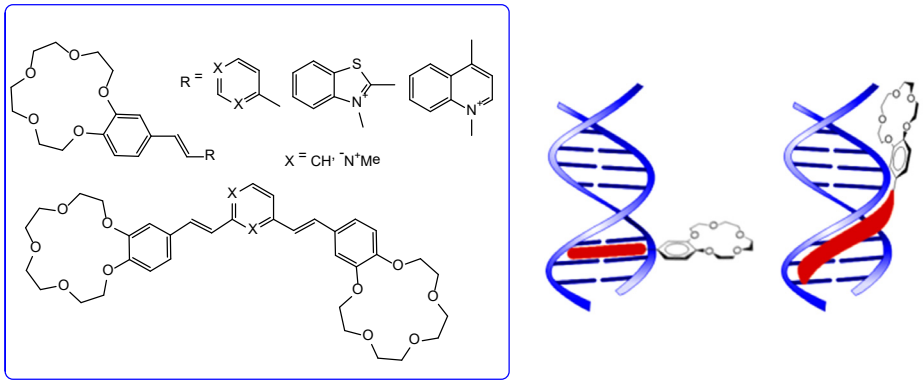

Fig. 1. Structures of the studied dyes and modeles of their interactions with DNA

Recently, we described novel oxidative photocyclization of styryl substituted azines to polycyclic heteroaromatic cations involving formation of a new C-N bond [2]. This photochemical transformation was successfully used for *in situ* generation of a DNA-intercalating photoproduct directly in the presence of nucleic acid representing a rare example of photocontrolled binding with DNA.

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This work was supported by ERA.NET-RUS program (project of Russian Ministry of Education and Sciences № 14.616.21.0037).

Synthesis of new, highly luminescent derivatives of 2,2'-bithiophen-5-yl substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole

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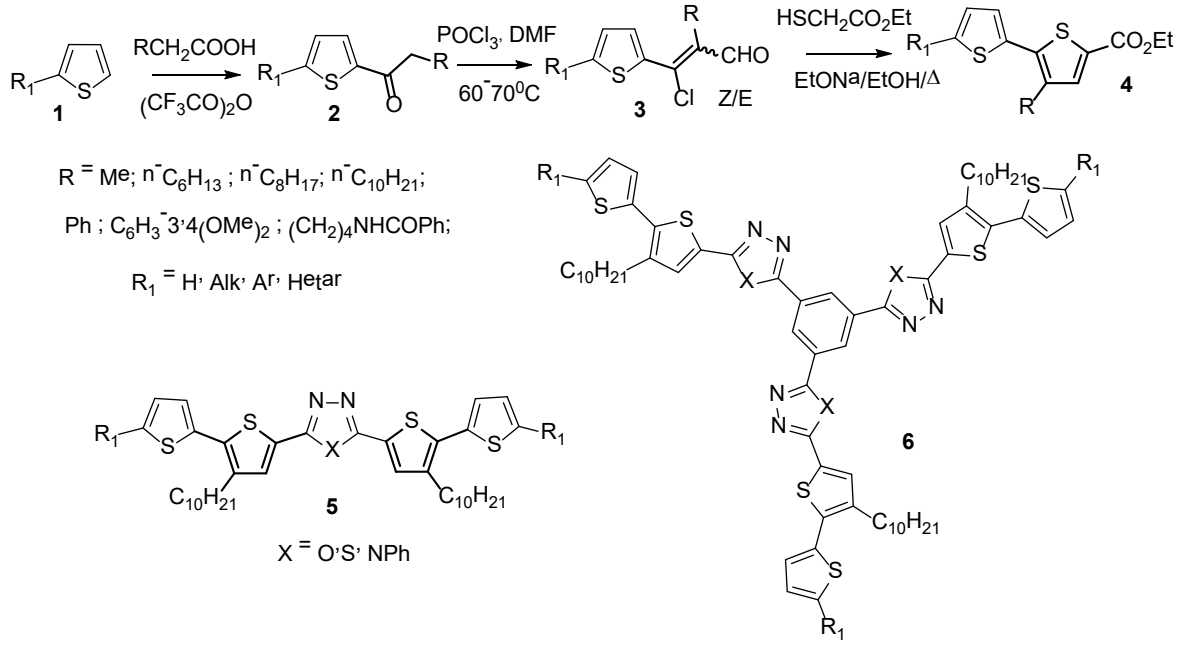
A simple and efficient approach is developed for the synthesis of substituted 2,2′-bithiophene-5-carboxylic acids and esters which is based on thiophene ring closure in the Fiesselmann reaction. Using this method, derivatives containing a long alkyl chain with or without an end functional group or an aryl substituent can be conveniently prepared [1].



These compounds were used for the synthesis of symmetrically disubstituted bithiophene derivatives of 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazolestar **5** as well as star-shaped conjugated molecules, consisting of a benzene central unit and three symmetrically attached arms of thia- or oxadiazole substituted with alkyl- or dialkylbithiophene **6** [2,3]. These molecules are promising for application in (opto)electronics and electrochromic devices. All studied compounds show blue photoluminescence in solution. They were used for fabrication of the light emitting diode guest-host configuration where they emit bluish or green light [4].

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2-Heteroarylimino-5-benzylidene substituted -4-thiazolidinones as multitarget agents

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Since the last century it has considered that medicine should be selective as much as possible and it should be act on a single molecular target. It may be expressed by the following phrase: "One medicine - one Target". Such selectivity may be explained by decrease of side and undesirable effects.

But actually patients with diseases having a complicated pathogenesis are often prescribed several medicines. Each of these medicines usually acts on a single target.Despite of each of these medicines is considered as acting on a single target, in combination they induce a complex biological response. Thus, it is currently replaced by the concept of "multitargeted drugs". No one pharmaceutical agents exhibits complete selectivity of action; no one disease could be completely cured by action on a single target. Network pharmacology, pleiotropy of pharmacological action – novel emerging scientific terms.

Prof. Camille Wermuth is one of the first researchers who suggested that balanced modulation of several targets can provide advanced therapeutic effects' and favorable side effects' profiles compared to the action of a selective ligand, particularly for complex diseases.

Taking into account that various thiazole and thiazolidinone derivatives [1,2] possess anti-antimicrobial activity as well as anti-inflammatory activity [3,4] because in many cases the inflammation is a result of microbial infection we report hear the synthesis (scheme 1) and evaluation of antimicrobial as well as anti-inflammatory activity of novel 2-heteroarylimino-5-benzylidene substituted -4-thiazolidinones of general structure (fig.1).

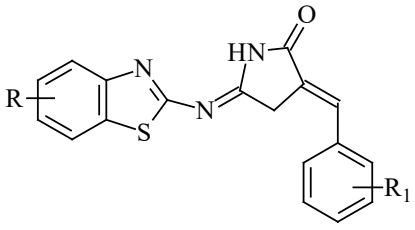

Fig. 1. General strauctur of designed and synthesized compounds

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From aliphatic nitro compounds to nitrosoacetals and back to functionalized nitro compounds

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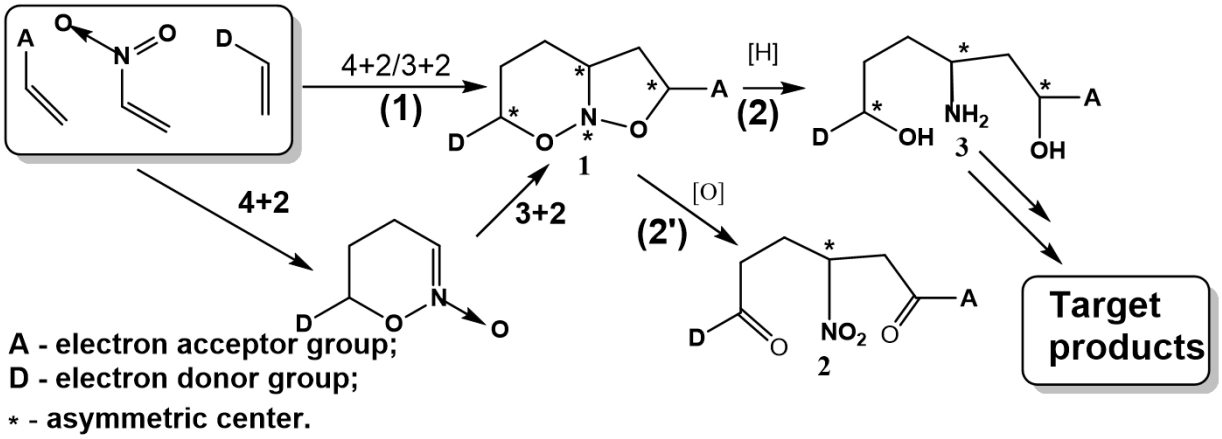
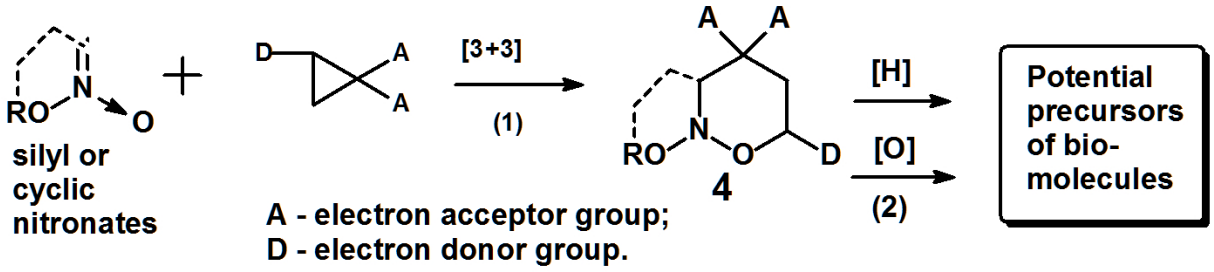
Aliphatic nitro compounds are used successfully in various strategies of organic synthesis for preparation of polyfunctional substrates[1]. The most effective example that illustrates this thesis is Profs. S. Denmark approach (see Scheme 1). With this strategy the scientific Denmark's group had realized the asymmetric synthesis near to 20 natural alkaloids.



Scheme 1. Profs. S. Denmark tandem 4+2/3+2 sequence.

Nitroso acetals **1** can be considered as key intermediates for approach that cited above. The involving of many nitronates in formal [3+3]-cycloaddition with donor-acceptor cyclopropanes[2] allowed one to extend essentially the group of these acetals (see Scheme 2, derivatives **4**).



Scheme 2. [3+3]-cycloaddition as new reaction of nitronates.

The selective reduction of O−N−O fragment for bicyclic nitroso acetals **1** or **4** was very known before. And here we will discuss a selective oxidation of this fragment with some peroxides to give respective functionalized nitro compounds.

In fact we are dealing with umpolung of standard reactivity of aliphatic nitro compounds.

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This work was supported by Russian Foundation for Basic Research (Grant # 15-03-05703).

Novel Purine Conjugates as Promising Biologically Active Compounds

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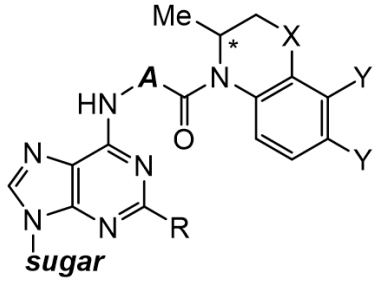
Purine and its derivatives play an important role in the metabolism of living organisms. Therefore, the chemical modification of these compounds is considered as a promising approach for designing new pharmaceutical agents. Purine derivatives, including nucleoside analogues, have been widely used for the treatment of cancer, viral and other diseases.

The purpose of this study was to design novel purine conjugates with amino acids, peptides and heterocyclic amines.



R = H, NH_2
X = O, S, CH_2
Y = H, F
A = amino acid fragment
sugar = ribose, deoxyribose, arabinose, etc.

We implemented a number of synthetic approaches to the preparation of novel purine conjugates, which is a sequence of reactions such as synthesis of enantiopure heterocyclic amines via acylative kinetic resolution [1], nucleophilic substitution of the chlorine atom in 6-chloropurines with an amine derivative [2], introduction of a linker (amino acid fragment) [3], chemical or chemoenzymatic glycosylation of the modified purine bases [4]. Due to the fact that in many cases the biological activity of chiral compounds depends on their configuration, we focused on the development of preparative methods for enantiomerically pure derivatives and analysis of their optical purity.

So, we have developed the synthetic approaches and prepared a series of novel purine derivatives. As a result of testing the biological activity of the compounds obtained the experiments *in vitro,* we identified a series of compounds possessing significant antiviral and antimycobacterial activity.

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Oxidative aminoaziridination: past, present, and future

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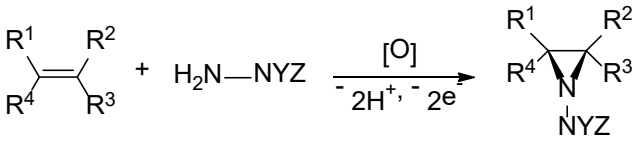
Aziridines attract close attention for at least two reasons [1,2]. Firstly, these compounds feature a broad range of biological activities. Secondly, release of the strain energy upon aziridine ring cleavage is a driving force for a vast of transformations, from whence aziridines are synthetically useful precursors to a wealth of functionalized nitrogen heterocycles and acyclic compounds. Therefore discovery of new efficient methods for the synthesis of aziridines remains an issue of current importance.

Oxidative aminoaziridination is one of the most general ways for the formation of an aziridine cycle, which allows stereospecific one-step transformation of easily available unsaturated starting compounds to *N*-aminoaziridine derivatives, and tolerates many functionalities.



Scheme 1. General scheme of oxidative aminoaziridination

The result of oxidative aminoaziridination is determined by the three main components: *N*-aminocompound, an oxidant and a substrate. Their role and properties will be considered in details. The oxidative aminoaziridination is always completely stereospecific. Its stereoselectivity usually depends on the presence of the reagent groups capable to strong intermolecular interactions in transition state such as OH or NH groups or bulky chiral substituents, and will be discussed too.

Products of oxidative aminoaziridination can undergo various subsequent transformations, with a three-membered ring opening as a rule. These processes can be divided into two types. The first one is breaking of the C-C bond to generate octet-stabilized 1,3-dipoles, so called azomethine ylides, which are able to participate in a plethora of intra- (rearrangements) and intermolecular (1,3-dipolar cycloaddition) reactions. The second type of aminoaziridines transformations includes thermal or catalytic breaking of C-N bonds, which is followed by numerous intra- and intermolecular processes resulted in functionalized nitrogen five-, six-, and seven-membered heterocycles, hydrazones, hydrazinoalcohols, hydrazinothioles *etc.* Besides this, substituents at exocyclic nitrogen atom can be regarded as protective groups giving an opportunity to get from *N*-heteroarylaziridines to *N*-aminoaziridines with a free $–NH_2$ group, and easy cleavage of a weak N-N bond allows preparing aziridines with an unsubstituted nitrogen atom. As both aminoaziridines and almost all products of their transformations are of great interest because of their potential biological activity, one can hope for promising prospects of this very useful transformation.

Authors thank the Russian Scientific Fund for financial support (grant No. 14-13-00126).

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Soft Functional Materials from Bile Salts

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Functional molecular gels are being increasingly investigated owing to their potential applications in various fields such as biomaterials, sensing, optoelectronics *etc*. Among many known gelators, bile acid derivatives are known to form self-assembled fibrillar networks (SAFINs), eventually leading to the immobilization of solvent molecules around them. We have recently developed a variety of gels from bile acid derivatives, and with metals salts derived from them. The use of these novel soft materials for the design of nanostructured materials, luminescent hydrogels and enzyme sensors will be presented in this lecture.

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This work was supported by grants from the Department of Science & Technology, New Delhi, and from the Indo-French Centre for the Promotion of Advanced Research, New Delhi.

Copper catalyzed reaction of N-substituted hydrazones with CCl_4. New C-C-bond forming reaction and efficient approach to 4,4-dichloro-1,2-diazabutadienes-1,3

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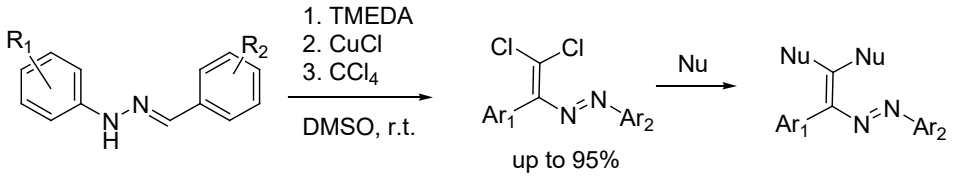
Recently we found that N-substituted hydrazones of aldehydes can react with carbon tetrachloride in the presence of copper chloride as a catalyst. As a result, we found a new catalytic reaction which allows to create carbon-carbon double bond. We found that this transformation leads to formation of 4,4-dichloro-1,3-diaryl-1,2-diazabutadienes-1,3 and developed a new general method for their preparation in up to 95% yields. The prepared dienes are very valuable building blocks due to both chlorines are activated to nucleophilic substitution with EWG azo-group. Broad range of C-, N-, O-, S-nucleophiles can be used to open access to variety of valuable molecules.



Nanostructured Films of Organic Semiconducting Polymers via Transition Metal Catalyzed Surface-Confined Polymerization

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An ability to control nanoscale morphology and molecular organization in organic semiconducting polymer thin films is an important prerequisite for enhancing efficiency of organic thin-film devices including organic light-emitting and photovoltaic devices. Current "top-down" paradigm to such devices is based on utilizing solution-based processing (e.g. spin-casting) of soluble semiconducting polymers. This approach typically provides only modest control over nanoscale molecular organization and phase separations. A promising alternative to using solutions of pre-synthesized semiconducting polymers would be a "bottom-up" approach to prepare surface-grafted semiconducting polymer thin films by surface-confined polymerization of small-molecule monomers. In this presentation, we describe development of an efficient method to prepare polythiophene thin films utilizing surface-confined Kumada catalyst transfer polymerization (Fig. 1). In our study, we provided evidence that this surface-confined polymerization happens by the controlled chain-growth mechanism which enabled reliable preparation of polythiophene thin films with thicknesses up to 100 nm. Extensive structural studies of the resulting thin films using X-ray and neutron scattering methods revealed detailed information on molecular organization and bulk morphology of the films, and enabled further optimization of the polymerization protocol. One of the remarkable findings from the structural studies was that surface-confined polymerization delivers thin films with unique morphology where the polymer film consists of 40-60 nm size crystalline domains, with the individual polymer chains densely packed in helical structures which propagate in the direction normal to the film surface. Achieving such a mesoscale organization is virtually impossible with traditional methods relying on pre-synthesized polymers, and it may deliver unique practical opportunities for thin-film devices based on these films. In addition, a special feature of the surface-confined polymerization is that it can be used for the preparation of large-area uniformly nanopatterned polymer thin films. This was demonstrated using combination of particle lithography and surface-confined polymerization.

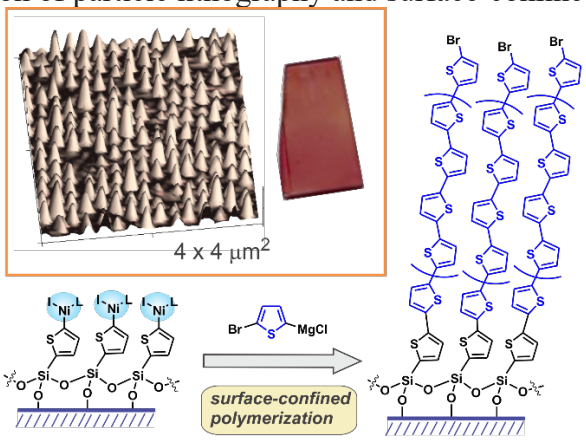

Fig. 1. General scheme of surface-confined Kumada polymerization. Insert: an AFM image of a nanostructured polythiophene thin film prepared by surface-confined polymerization (left) and a photograph of the quartz slide with the nanostructured polythiophene thin film.

This work was supported by the National Science Foundation (grant DMR-1006336) and is currently supported by the U.S. Department of Energy under EPSCoR Grant No. DE-SC0012432.

β-Formyl-β-nitroenamine: Useful Synthetic Tool for Push-Pull Systems

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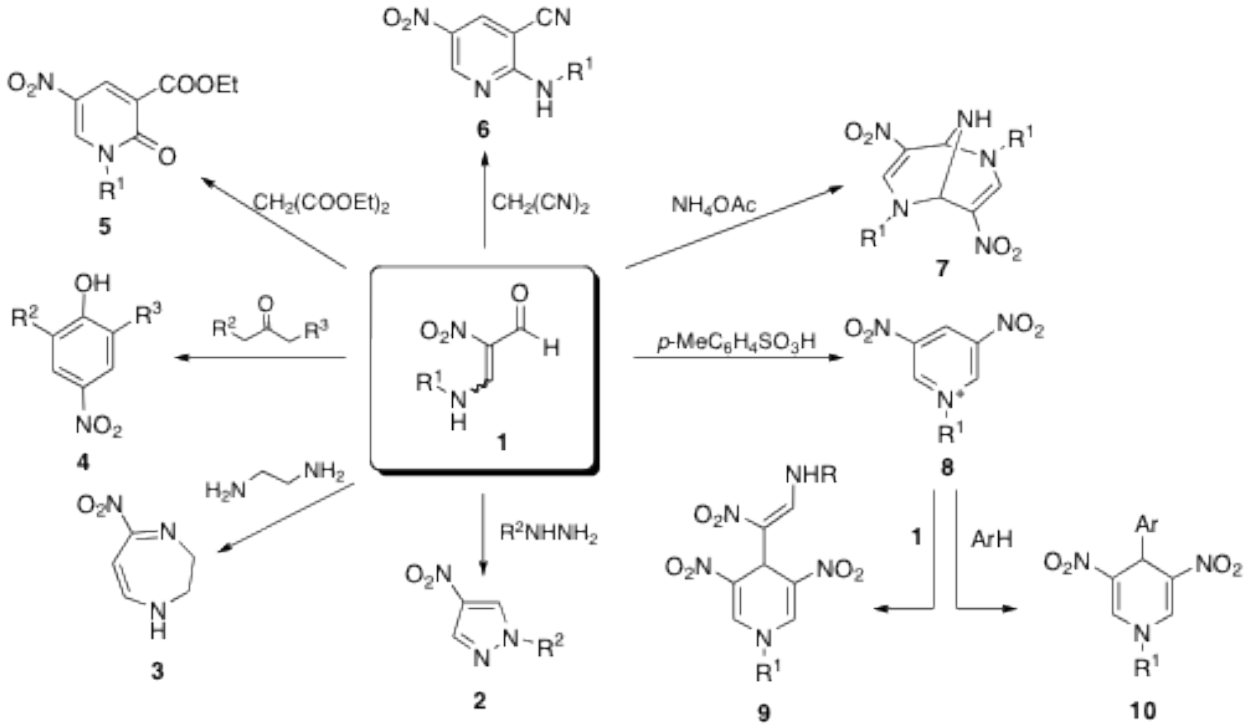
β-Formyl-β-nitroenamines **1**, one of the push-pull alkenes, have biased electron density as well as an electrophilic formyl group and a nucleophilic amino group. The multi-functionality exhibits versatile reactivity to facilitate the synthesis of polyfunctionalized compounds possessing push-pull property.



The nitroenamine **1** serves as a synthetic equivalent of unstable nitromalonaldehyde to afford nitropyrazoles **2**, nitropyrimidines, nitrodiazepines **3**, and nitrophenoles **4** upon treatment with dinucleophiles such as hydrazines, amidines, 1,2-diamines, and ketones, respectively [1,2]. When active methylene compounds are allowed to react with the nitroenamine **1**, polyfunctionalized pyridones **5** and 2-amino-5-nitropyridines **6** are obtained [3]. In addition, the nitroenamine undergoes self [4+2] condensation to afford 3,5-dinitropyridinium ion **8**, which is easily trapped by benzene derivatives leading to 4-arylated 1,4-dihydropyridines **10** [4]. In addition, nitroenamine **1** underwent the Hantzsch type réaction upon treatment with aldehydes in the présence of *p*-toluenesulfonic acid to afford 1,4-dihydropyridine **10** [5]. The obtained products have push-pull property transcribed from nitroenamine **1**, which is useful for developing new functional materials.

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Synthesis of CF_3-Containing Molecules *via* Carbenoid C-H Functionalization

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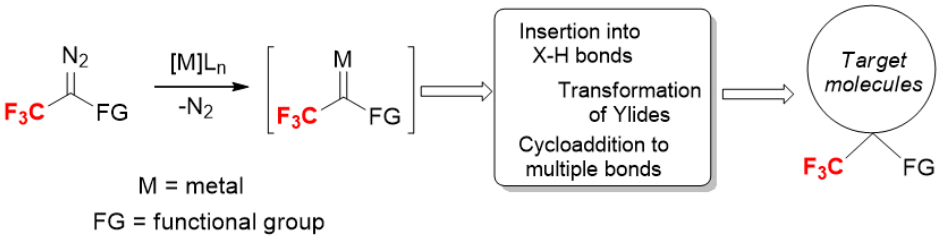
An efficient access to a variety of CF_3-containing aromatic and heteroaromatic compounds, including cyclic amino acid derivatives have been elaborated. The method includes *in situ* generation of high electrophilic CF_3-carbenoid from the corresponding functionalized α-CF_3-diazo compound under metal catalysis and its subsequent reaction with appropriate nucleophilic partner.[1-5]



Synthetic application of CF_3-diazocompounds in different types of metal-catalyzed transformations, *e.g.* insertion into X-H bonds, ylide transformation and cycloaddition to multiple bonds will be presented.

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Abnormal nucleosides and peptides containing tetrazolyl moiety

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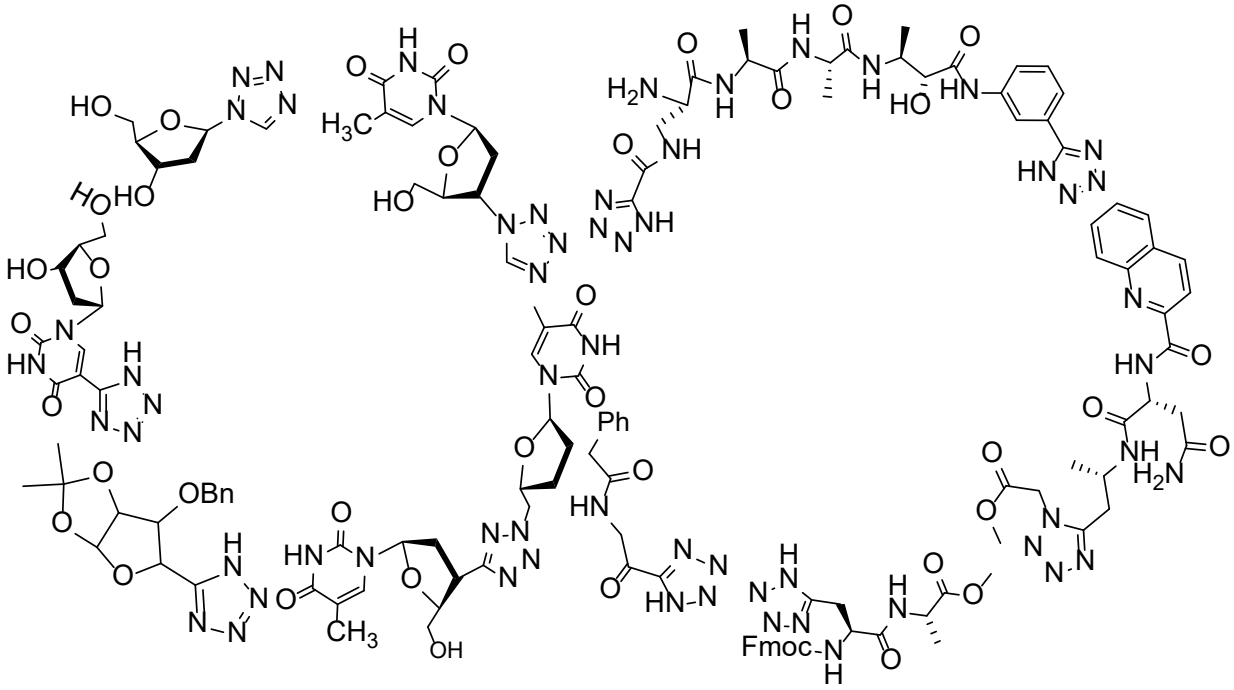
The directed synthesis and study of the biological activity of abnormal nucleosides and peptides is a promising area of modern medical chemistry. Studies of compounds which contain the tetrazole ring are of special importance within this framework. The tetrazole analogues of nucleosides and peptides with high antiviral, antimicrobial activity, and effectively acting on the immune, cardiovascular and nervous systems are known [1],[2].



The trends and prospects for the development of the chemistry of such types of abnormal nucleosides and peptides are outlined according to an analysis of the scientific bibliography, as well as the authors own researches.

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Synthesis, properties and appliction of low bandgap star-shaped oligomers

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Various star-shaped molecules based on triphenylamine (TPA), which is known as efficient electron-donating block with low cost, high electrochemical stability and hole transporting ability, are used in organic photovoltaics (OPV) [1]. In this presentation synthesis, thermal and optical properties of star-shaped low bandgap oligomers and their application as donor materials in OPV will be considered. In particular, we synthesized and investigated a series of novel star-shaped molecules with TPA or *tris(*2-methoxyphenyl)amine central units linked through (oligo)thiophene π-bridge to different terminal electron-withdrawing groups: dicyanovinyl (DCV), alkyl-DCV, phenyl DCV or ethylphodanine (Rh) (Figure 1) [2-5]. Systematic variations of the central donor and terminal acceptor units, lengths of both solubilizing alkyl chains and oligothiophene π-bridge in the molecules investigated allowed elucidating the structure-properties relationships in this series of organic semiconducting materials. Our studies revealed that oligomers with alkyl- or phenyl- substituted DCV groups (R' = alkyl or Ph) demonstrate significantly better solubility, electrochemical and oxidation stability as compared to their full analogues with common DCV groups (R' = H) and allows to achieve the energy convertion efficiency up to 4.0 – 5.4% in solution-processible bulk heterojunction organic solar cells [3-6].

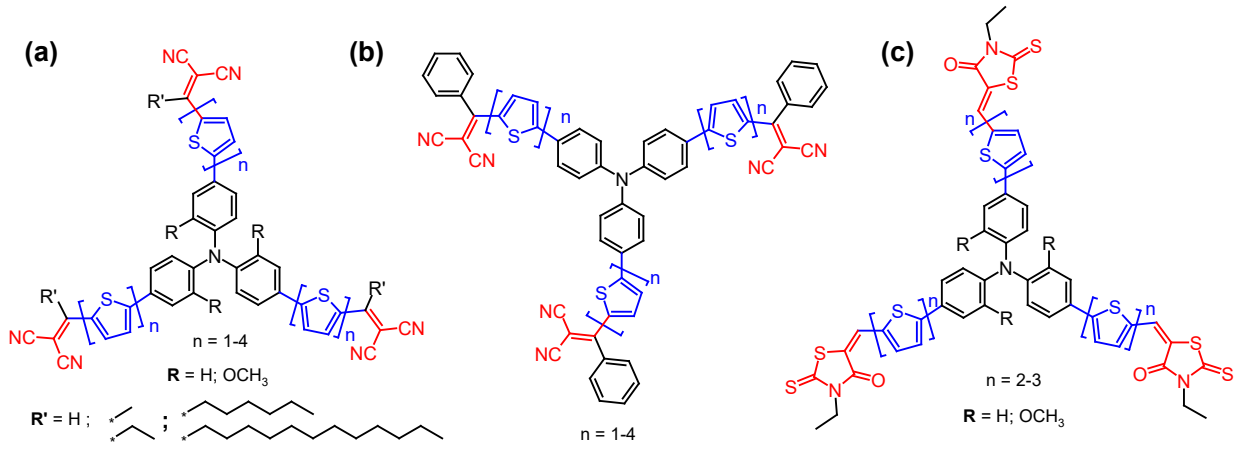

Fig. 1. Novel star-shaped oligomers with alkyldicyanovinyl N(Ph-nT-DCV-Alk)$_3$ (a) phenyldicyanovinyl N(Ph-nT-DCV-Ph)3 (b) and ethylphodanine N(Ph-nT-Rh)$_3$ (c) electron withdrawing groups.

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Fused 1,2,5-thiadiazoles: synthesis and application in material chemistry

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1,2,5-Thiadiazoles have attracted much attention because of various possibilities for use in medicine, analytical chemistry and industry [1]. 1,2,5-Thiadiazole-based materials play an important role as π-type building blocks for organic electronics and conductive charge-transfer complexes. Also they are of special interest as the precursors of stable radical anions [2]. Although methods for the preparation of fused 1,2,5-thiadiazoles are numerous and well elaborated, there is still a lack of syntheses of derivatives containing electron-deficient heterocycles.

Novel approaches to the preparation of 1,2,5-thiadiazoles as monocyclic, as well fused with heterocycles will be presented. The mechanisms of these transformations will be discussed.

In addition, the application of the compounds obtained in the synthesis of new stable radical anion salts and charge-transfer complexes will be reported.

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Stereoselective Transition Metal-Catalyzed Additions to Cyclopropenes: Hydrophosphorylation, Hydroformylation, and Hydroboration

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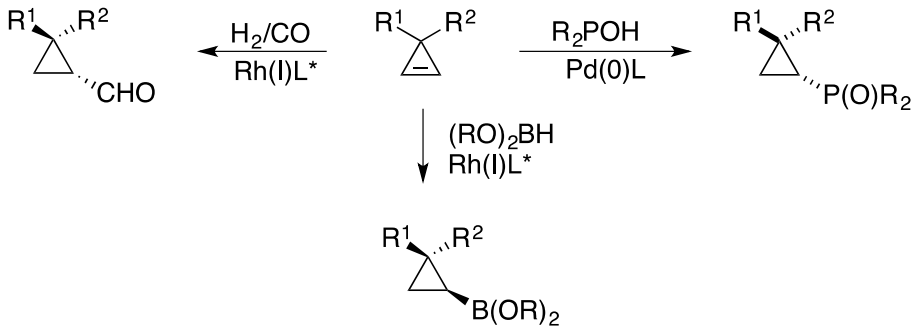
Efficient catalytic transformations enabling efficient additions of various entities across the carbon-carbon bond of pro-chiral 3,3-disubstituted cyclopropenes will be outlined. Due to high -density and possibility to release of enormous strain energy, it was possible to get cyclopropenes involved in many catalytic transformations unavailable for non-strained olefins, but more typical for alkynes or allenes [1]. Furthermore, C_S-symmetric topology and constrained geometry of these substrates permits for installation of one or several new stereogenic centers, and allows efficient control of asymmetric induction. Although such strain-released transformations in the presence of transition metals could be accompanied by facile cleavage of the fragile small cycle followed by oligo- and polymerization, an appropriate design of the catalytic system and accurate optimization of the reaction conditions allows for predominant formation of the corresponding chiral cyclopropanes. Our new developments in this area will be demonstrated, showcasing diastereoselective hydrophosphorylation and hydrophosphynylation processes [2], asymmetric hydroformylation methodology [3], as well as most recent results on asymmetric hydroboration reaction [4][5] (Scheme 1).



Scheme 1.

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Azolo[1,5-a]pyrimidimes and their derivatives in searching the agents against sepsis

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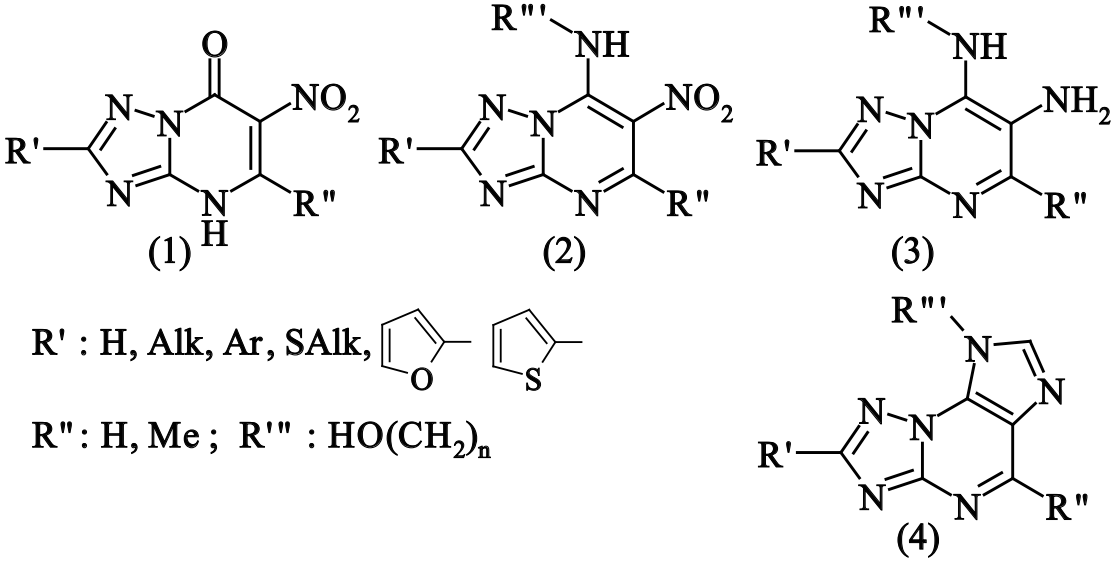
Sepsis which has microbial and viral nature is serious sequela of infectious diseases. The significant funds and intellectual resources of major scientific research collectives are expended to fight the sepsis. The picture of biochemical processes of the sepsis is very diverse, but it has been attracted the attention to the key role of the receptors action in the activation and inhibition of sepsis in recent years. One of the important objects in this direction are adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and compounds acting on them (agonists and antagonists). The molecular structure of such receptor effectors simulates purines, their azoloannelated analogues and and non-natural nucleosides in most cases.

The objects of the development and creation of agents against sepsis as assumed A_{2A} inhibitors of receptors became triazolopyrimidines (1-3) and triazolopurines (4) which is close in structure to purines.



There were analyzed the database, offered the most promising objects, were developed the methods of synthesis and were found the first active compounds in the study. As the most promising members of the group were identified representatives among water-soluble compounds such as (1) which showed an active activity against sepsis. It should be noted that the compounds do not have antimicrobial activity indicating their impact on the regulated processes by receptors.

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The heteroannulated pyrimidines based on polyfluoroalkyl-3-oxo esters derivatives

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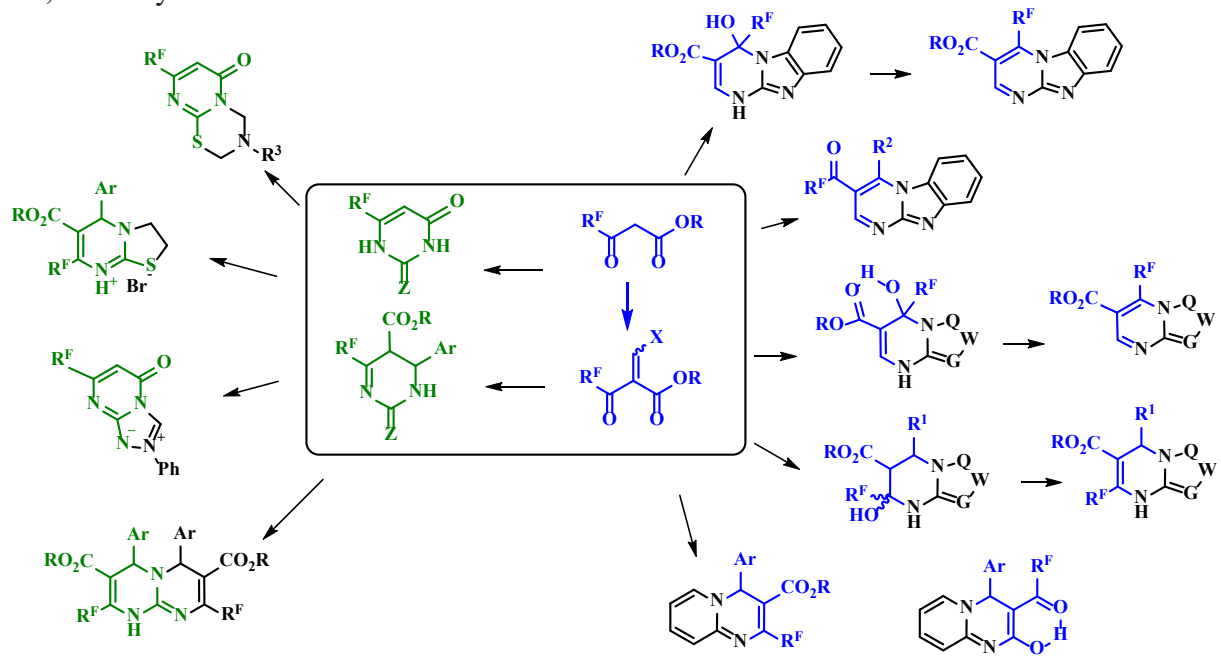
The heteroannulated pyrimidines possess a large range of biological activities as analogs of natural purine bases. The paths to heteroannulated pyrimidines synthesis based on the derivatives of polyfluoroalkyl-containing 3-oxo esters are discussed.

The suitable substrates for synthesis of functionalized heteroannulated pyrimidines are 2-methylidene-substituted polyfluoroalkylated 3-oxo esters. 2-Arylmethylidene-3-oxo-3-fluoroalkylpropionates add aminoazoles at polyfluoroacylvinyl moiety to generate tetrahydroazolo[1,5-*a*]pyrimidines. However, the interaction with 2-aminopyridine proceeds at both the polyfluoroacylvinyl and alkoxycarbonylvinyl fragments to give pyrido[1,2-*a*]pyridines as cyclocondensation products. 2-Ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates react with aminoazoles to give dihydroazolo[1,5-*a*]pyrimidines with a gem-aminoalcohol fragment at the polyfluoroalkyl substituent. The reaction of 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates with 3-amino-5-hydroxypyrazole results in ethyl-2,7-dihydroxy-7-polyfluoroalkyl-4,7-dihydro-pyrazolo[1,5-*a*]pyrimidin-6-carboxylates which depending on the reaction conditions can be either recyclized into 3-hydroxy-4-(polyfluoroalkyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-carboxylates or dehydrated to 2-hydroxy-7-(polyfluoroalkyl)pyrazolo[1,5-*a*]pyrimidin-6-carboxylates. In contrast 5-aminotetrazole reacts with 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates to form ethyl 2-azido-4-alkylpyrimidine-5-carboxylates which are capable of subsequent nucleophilic substitution.

The pyrimidines derived from polyfluoroalkyl-3-oxoesters are also the block-synthons to the synthesis of thiazolo-, triazolo- and pyrimidopyrimidines. The multi-component cyclization of 6-polyfluoroalkyl-2-thiouracils with formol and the primary amines via the sequential double Mannich reactions is a convenient method to pyrimidines with annulated thiadiazine ring. The wide range of the aliphatic, aromatic, heterocyclic amines and amino acids can be involved in these transformations.



This work was supported by UB RAS № 15-21-3-5

Advances in the Development of the Synthesis of Linear Hetareneanthracenediones

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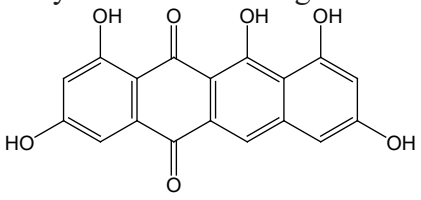
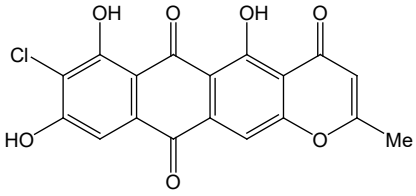
Anthraquinones and their analogues are widely used as scaffolds for the design of antitumor drug candidates. Among derivatives of anthraquinone linear hetarene-fused anthracendiones (hetareneanthracendiones) are especially promising for the antitumor drug discovery. Thus, tetracyclic antibiotics Saintopin (**1**) and related Topopyrones (e.g. **2**) with anthracenedione moieties were identified as potent dual inhibitors of Top1/2 which efficiently block tumor cell growth.

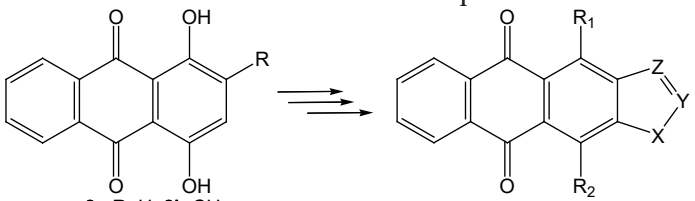


Saintopin (**1**)



Topopyrone B (**2**)

Therefore, the aim of our study was the development of a methodology for preparation of hetareneanthracendiones. Series of new derivatives hetareneanthracendiones **4** functionalized with hydroxyl or alkoxyl groups in the *peri*-position of the quinone ring were synthesized starting from a commercially available quinizarine or 2-methyl-quinizarine (**3a,b**). Developed schemes which included from three to eight steps are efficient for the synthesis of pyrrole, furan, thiophene, pyrazole, imidazole, isoxazole, isothiazole and triazole fused derivatives of anthraquinone.



3a R=H; **3b** CH_3. **4** X=NH,O, S; Y,Z=CH, N; R_1, R_2=OH, OAlk.

Obtained hetareneanthracendiones **4** are useful as scaffolds for the searching of new anticancer agents. Subsequent introduction of pharmacophoric groups into hetareneanthracendiones lead to the discovery of potent Top1/2 inhibitor which blocked the growth of pleiotropically drug resistant tumor cells *in vitro* and *in vivo* [1-4]. In addition, some G-quadruplexes ligands as potent inhibitors of telomerase and effectors of oncogenes transcription were designed and prepared based on heteroarene-fused anthracenediones [5-8].

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Difluoromethanesulfonyl Hypervalent Iodonium Ylides for Electrophilic Difluoromethylthiolation Reactions under Copper Catalysis

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Difluoromethylthio group (SCF_2H) has emerged as a next potential subject in pharmaceuticals and agrochemicals. The SCF_2H group has the potential to be a weak hydrogen-bonding donor, which results in a suitable hydrophilic/hydrophobic balance of SCF_2H-substituted molecules. Thus, incorporation of SCF_2H into biologically active molecules should permit the efficient design of novel, viable drug candidates. In 2013, we reported that trifluoromethanesulfonyl (SO_2CF_3) hypervalent iodonium ylide **1** is an efficient reagent for the electrophilic trifluoromethylthiolation reaction[1] (Figure 1). Despite its carbon-SO_2CF_3 structure, a reactive SCF_3 species is unexpectedly, but effectively released from **1** via C-S bond cleavage under copper catalysis allowing it to be transferred into a wide variety of nucleophilic substrates including enamines, indoles, β-keto esters, pyrroles, allylsilanes, silyl enol ethers, allyl alcohols and boronic acids.[1] Inspired by this powerful reactivity and wide substrate generality, and linked to the mechanistic uniqueness of iodonium ylide reagent **1**, we disclose herein an investigation of novel shelf-stable electrophilic difluoromethylthiolation reagents **2** and their reactivity towards a variety of nucleophiles. Difluoromethanesulfonyl (SO_2CF_2H) hypervalent iodonium ylides **2** were found to be useful for electrophilic difluoromethylthiolation of a variety of nucleophiles to provide corresponding SCF_2H products. The reactivity and reaction mechanism of **2** are discussed.

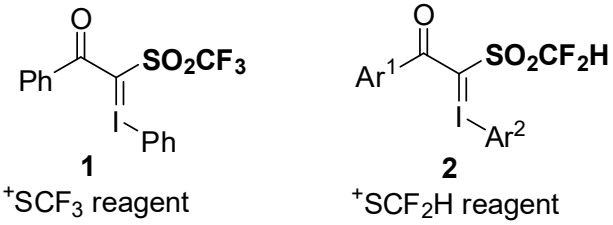

Fig. 1.

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Metals@Cyclodextrin Topological control and catalysis

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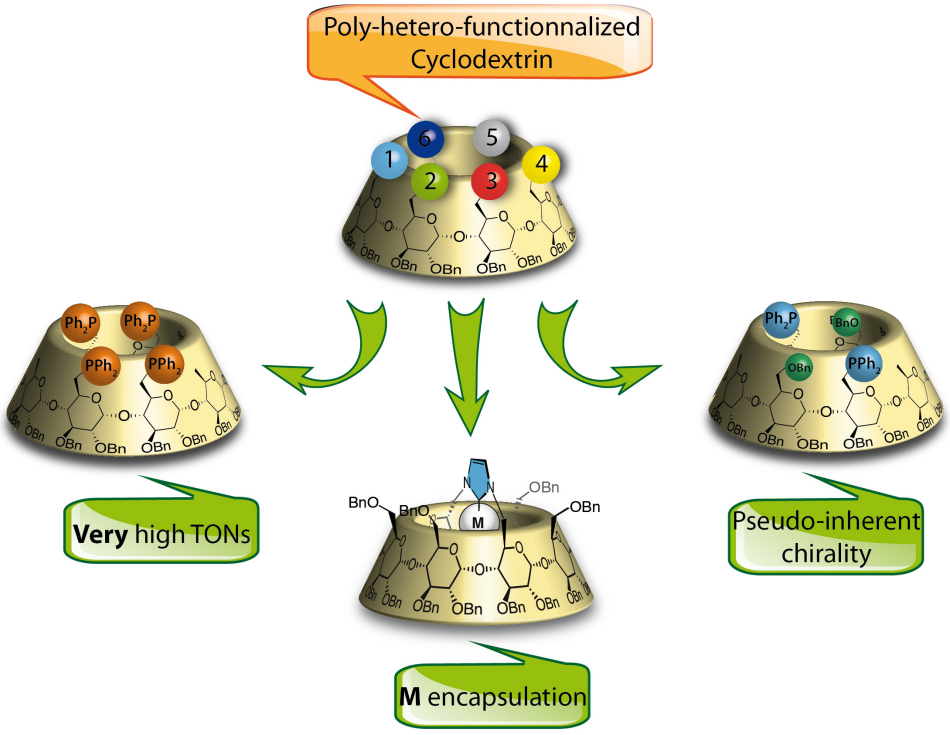
Association of a metal with a cavity is an efficient way to promote selectivity in catalytic processes. Functional molecular cavities are therefore needed, but the regioselective hetero-functionalization of a C_n symmetrical molecule is a challenge for the chemist. We have recently solved this problem for cyclodextrins, naturally occurring, readily available cavities.[1] We then used those cavities as platforms for metal liganding, and promoted opposite enantio-induction with regioisomers, [2] or very high turnover numbers.[3] We also were able to encapsulate the metal into the cavity through capping of the cyclodextrin with a NHC ligand inducing an original set of interactions and cavity-dependent regio- and enantio-selectivities.[4]



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Recent developments in oxazolidine chemistry

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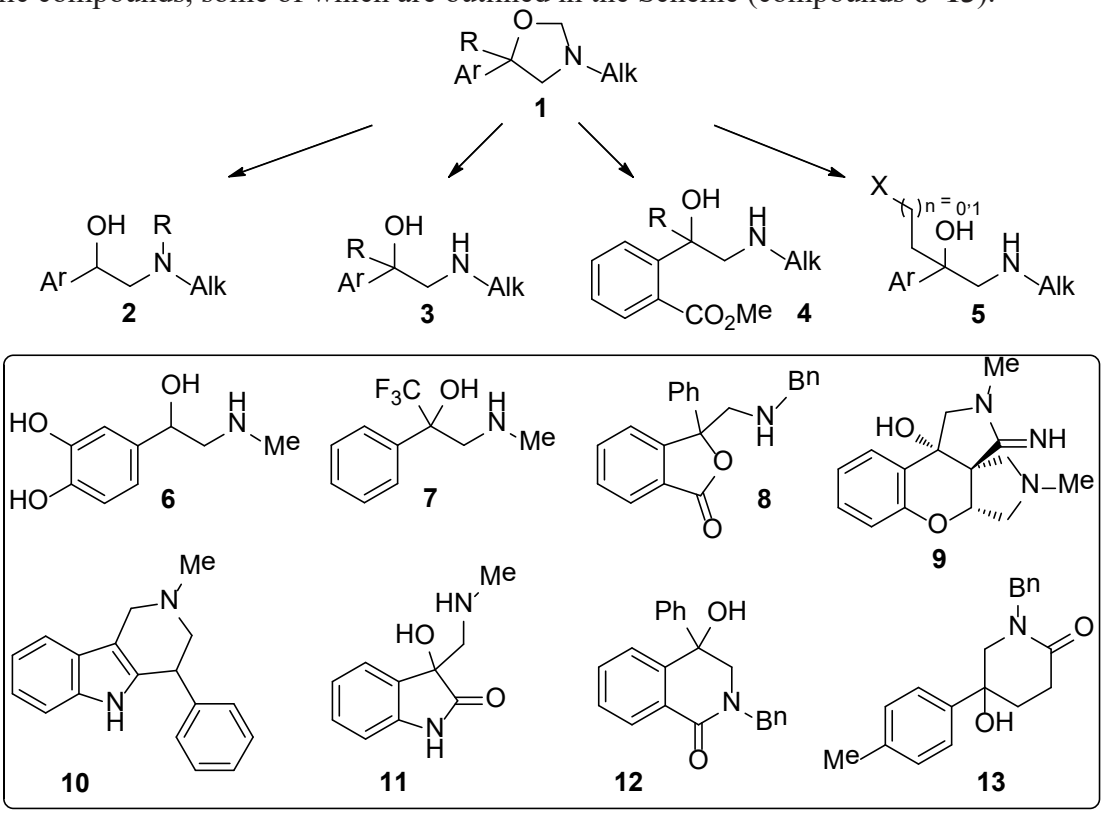
Substituted oxazolidines **1** could be prepared from carbonyl compounds and nonstabilized azomethine ylides. We have developed a practical route to 2-alkylaminoethanols **2–5** from aromatic aldehydes and ketones, including functionalized ketones, via an 1,3-oxazolidine intermediate, followed by its demethylenation [1–3]. This one-pot synthesis provides ready access to a set of diverse carbo- and heterocyclic compounds, some of which are outlined in the Scheme (compounds **6–13**).



All these products have long occupied a special place in organic chemistry because of their very widespread in Nature and valuable pharmacological properties. An easy opening of the substituted aryloxazolidine ring into 2-alkylaminoethanols allows us to consider sarcosine as a synthetic equivalent of methylaminomethyl carbanion and use this transformation to produce various heterocyclic systems [4,5]. Our results strongly suggest that we are dealing with a new oxazolidine methodology for the synthesis of a wide range of natural and unnatural compounds.

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An old/new love: nitrothiophenes and surroundings

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The study of the behaviour of nitrothiophenes with nucleophiles has been firstly centred on the examination of their "benzenoid" reactivity (reaction mechanism; comparison with other aromatics; effect of substituents; steric effects; catalysis) and then on their "non-benzenoid" reactivity (cine-substitution in 3-bromo-2-nitrobenzo[*b*]thiophene; ring-opening and cine-substitution in 3,4-dinitrothiophene; tele-substitution in 2,5-dialkyl-3,4-dinitrothiophenes; ring-opening in 2-nitrothiophene, 3-nitrothiophene and 3-nitrobenzo[*b*]thiophene).

At the same time also the ability of polynitrothiophenes to interact with naphthalene (giving π-adduct) was examined. Taking into account the behaviour of super-electrophiles with super-nucleophiles able to give rice to the formation of Wheland/Meisenheimer (WM) complexes, we have examined the reactivity of 2,3,4-trinitrothiophene and of 2-bromo-3,4,5-trinitrothiophene (superelectrophiles) with some supernucleophiles, such as some sym-triaminobenzenes.

As a function of the experimental conditions used different course of the reaction have been observed (isolation of WM complexes; nucleophilic substitution of bromine or of a nitro group, eventually followed by formation of the salt between 1-nitroso-2,4,6-triaminobenzenes and 2,4-dinitrothiophen-3-ol).

All of these reactivity aspects will be examined.

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Porphyrazines on the basis of hydrogen cyanide

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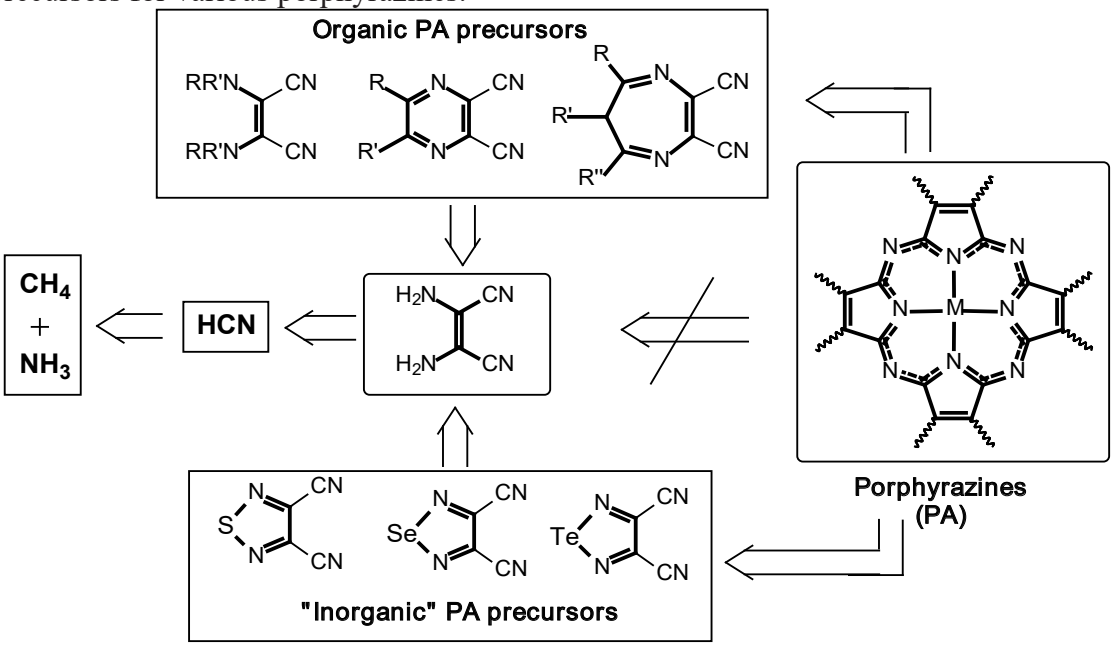
Phthalocyanines (tetrabenzoporphyrazines) are the most easily available and widely practically used synthetic tetrapyrrolic macrocycles [1]. Porphyrazines derived from diaminomaleonitrile (DAMN, tetramer of HCN) can compete with phthalocyanines both in accessibility and in diversity of useful properties. Although DAMN can't be used directly in the synthesis of porphyrazine macrocycle, its condensation with mono- and dicarbonyl compounds and with inorganic electrophiles leads to active dinitrile precursors for various porphyrazines.



DAMN was first used in the synthesis of porphyrazines by Linstead [2] and now variously substituted tetrapyrazinoporphyrazines (octaazaphthalocyanines) are easily available [3]. We have extended family of heterocyclic phthalocyanine analogues and prepared first 1,4-diazepinoporphyrazines [4] and 1,2,5-chalcogenadiazoloporphyrazines [5,6]. The latter can be considered as peculiar "inorganic" porphyrazines which due to high electron deficiency are perspective functional materials for organic electronics. Our recent achievements in the chemistry of 1,2,5-chalcogenadiazolo-, pyrazino- and 1,4-diazepinoporphyrazines will be also presented.

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1-Halopolyynes as Synthons in Organic Synthesis

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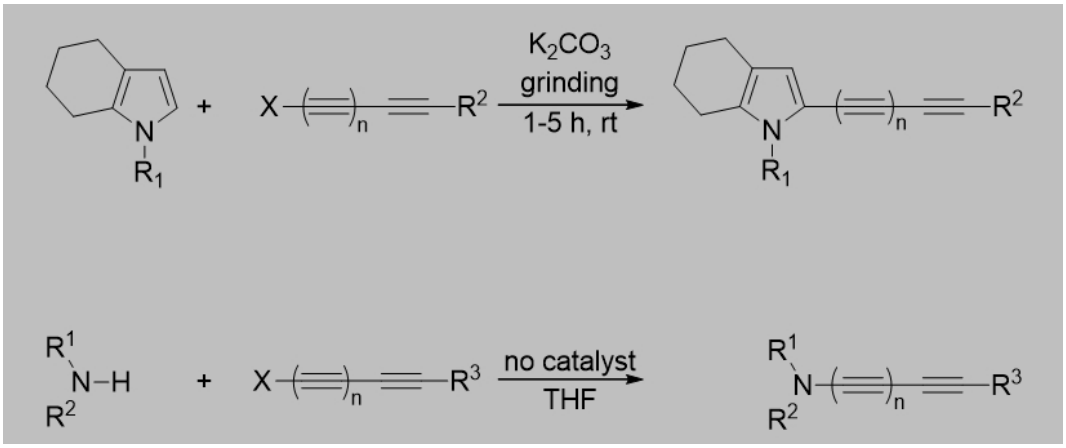
Carbon-rich compounds attract a constant interest of the scientific community and long polyynes, which are model compounds for carbyne - the hypothetical linear allotrope of carbon - take an important place among them. Although carbyne still remains elusive due to the difficulties in its preparation, polyynes have a significant application potential, for example as precursors of conducting polymers, as molecular wires and switches in nanoelectronics or as materials with nonlinear optical response.[1]

1-Halopolyynes are extremely rare and constitute a class of polyynes with interesting reactivity like for instance in topochemical crystal-to-crystal polymerization.[2] We have explored the synthesis and reactivity of these compounds in the last few years[3] and the recent advances are presented in this contribution.

First, an application of substituted pyrroles and 1-halopolyynes (with carbon chain up to octatetrayne) as useful precursors of polyynyl-substituted heterocycles will be shown (see Scheme 1). As far as we know, it is the first example of the formal inverse Sonogashira coupling for 1-halopolyynes and very convenient way to polyynyl substituted pyrroles.



Scheme 1. Use of 1-halopolyynes in the synthesis of functionalized heterocyces and amine end-capped polyynes.

Moreover, the reaction of 1-halopolyynes with secondary amines will be presented (see Scheme 1). This very convenient protocol allows to obtain novel amine-end capped polyynes under very mild and transition metal-free conditions. Novel polyynes are surprisingly far more stable than simple ynamines and undergo reaction with water less likely.

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Ligand Development for Green Synthesis of Chiral Drugs and Natural Products

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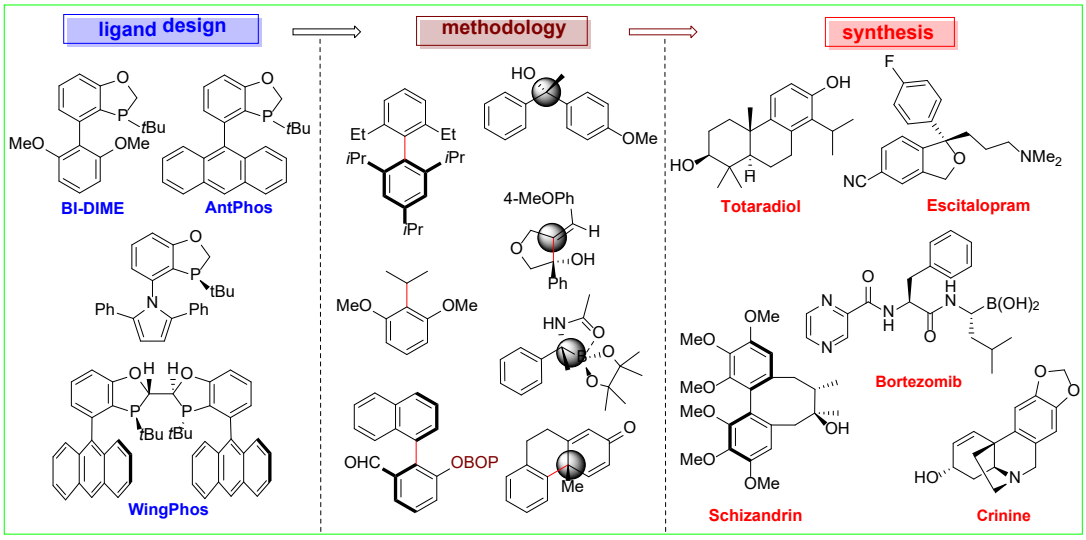
Development of efficient asymmetric catalytic methods for the synthesis of chiral natural products and drugs remains a significant challenge. Our research program is focusing on exploring practical and efficient transition-metal catalyzed asymmetric transformations and their applications in green syntheses of natural products and drugs. Using a series of genuinely designed P-chiral ligands as tools, we have developed a few highly efficient asymmetric catalytic methodologies particularly in cross-couplings[1] and constructions of chiral quaternary stereocenters,[2] which have been successfully applied in efficient syntheses of chiral drugs and natural products.



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Cyclic peroxides

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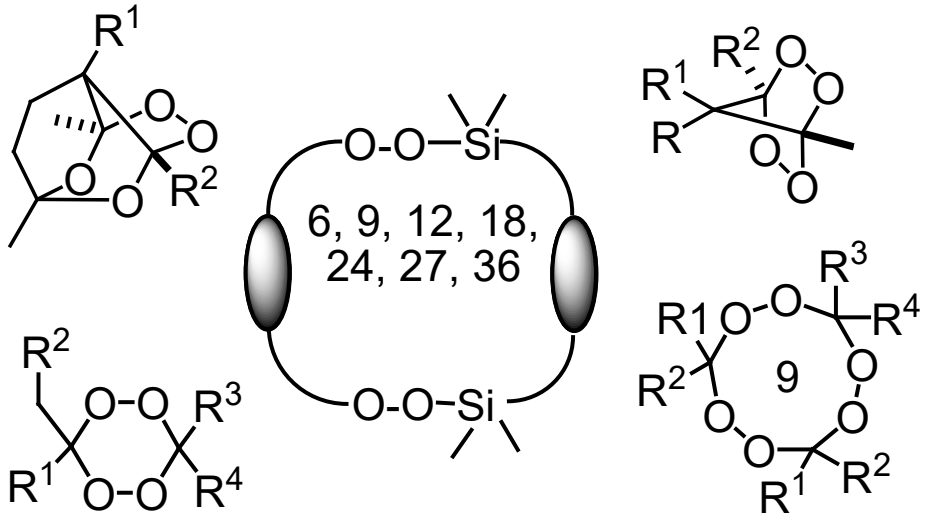
In the last decades, organic peroxides have received considerable attention from chemists and drug design experts, which is associated with a need in the search for drugs for the treatment of parasitic diseases, such as malaria and helminth infections. Considerable progress has been made in the design of effective peroxide antimalarial drugs. Some synthetic peroxides exhibit activity equal to or higher than that of artemisinin. Peroxides having antitumor or growth-regulatory activity were also documented. In our work we developed new methods for synthesis of various types of peroxides.



It was found that some of peroxides possesses pronounced antischistosomal properties and anticancer activity.

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Synthesis of Nitrogen-Containing Versatile Compounds via Organocatalyzed Multi-Step Domino Reactions

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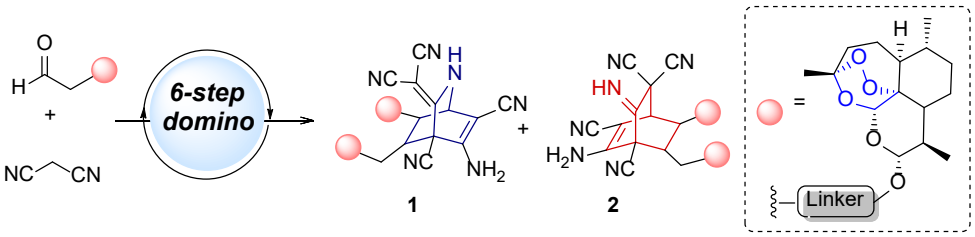
Multi-step domino reactions are among the most elegant and economically attractive methods allowing to form complex molecular scaffolds from simple components *[1]*. Whereas successful examples of organocatalyzed triple, and even quadruple domino reactions were reported in recent years to provide complex mono- and bicyclic compounds, to our knowledge, no organocatalyzed five- and/or six-step domino reaction has been reported till recently.

Based on our previous studies on the asymmetric organocatalytic Mannich-type reaction and aiming to extent the scope of this transformation *[2]*, we recently discovered a novel sustainable and atom efficient organocatalytic six-step domino processes for the facile preparation of complex molecular architectures (Scheme 1), *azabicycles* and *carbobicycles*, which otherwise are difficult to access via traditional methods *[3]*. In addition, *artemisinin-isoquinuclidine* and *artemisinin-carbobicycle* hybrids **1** and **2** with strong antiviral and antimalarial activities could easily be prepared via this six-step domino reaction.



Scheme 1. Generation of complex azabicycles and carbobicycles in a single operation from two simple compounds

Furthermore, recently we developed an unprecedented organocatalyzed four-component (ABC_2) five-step branched domino reaction, which can be combined with subsequent few reaction steps in one-pot, providing a straightforward multi-step one-pot route to new *pentachromophoric aromatic systems*/*organic dyes* and functionalized bioactive *quinazolines* with only a single work-up procedure and starting from simple and readily available compounds *[4]*.

These recent results will be discussed in this presentation.

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Organic Synthesis Involving Sulfur Dioxide as Solvent and Reagent

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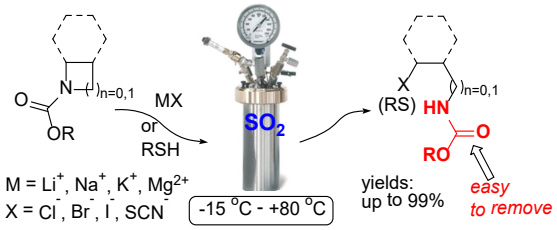
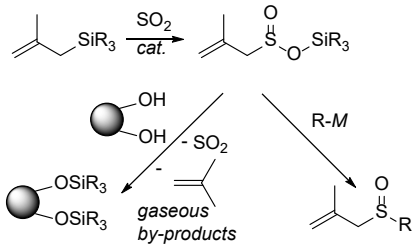
Sulfur dioxide, which is a gas at ambient conditions, reveals a rather long liquid range: it boils at -10 °C and freezes at -75.5 °C. Most importantly, SO_2 condenses easily by compression due to its high critical temperature (157.35 °C, 7.88 MPa) and its phase diagram predicts only ~10 atm pressure at 60 °C in a closed reactor. Sulfur dioxide has a high dipole moment (1.61 D), therefore it readily can dissolve both organic and inorganic salts. On the other hand, SO_2 has been reported as reaction medium for processes involving carbenium ions.



This has prompted us to search for organic reactions that would profit from their running in liquid SO_2 as a reaction medium [1]. We have discovered that carbamate-protected aziridines and azetidines undergo efficient ring-opening reactions in liquid SO_2 with I and II group metal halides, including NaCl and KBr [2]. The advantage of this approach is based on the fact that carbamate groups (Cbz, Boc) can be easier removed if required than their well-described sulfonamide counterparts.

We have also found application of liquid SO2 as an interesting solvent for the Ritter reactions [3]. The screening of suitable Lewis acid catalysts and scope and limitations of amidation reaction under these conditions will be discussed.



Additionally, we have optimized the synthesis of trialkylsilyl methallylsulfinates from sulfur dioxide and the corresponding methallylsilanes and successfully applied them in a traceless silylation of alcohols, polyols and hydroxy carboxylic acids [4]. The developed methodology is applicable for both qualitative and quantitative GC analysis of thermally unstable and nonvolatile compounds. Furthermore trialkylsilyl methallylsulfinates can be used as starting materials in sulfoxide synthesis [4c].

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Domino reactions of alkynes and arynes in the synthesis of *N*-heterocycles. Recent advances

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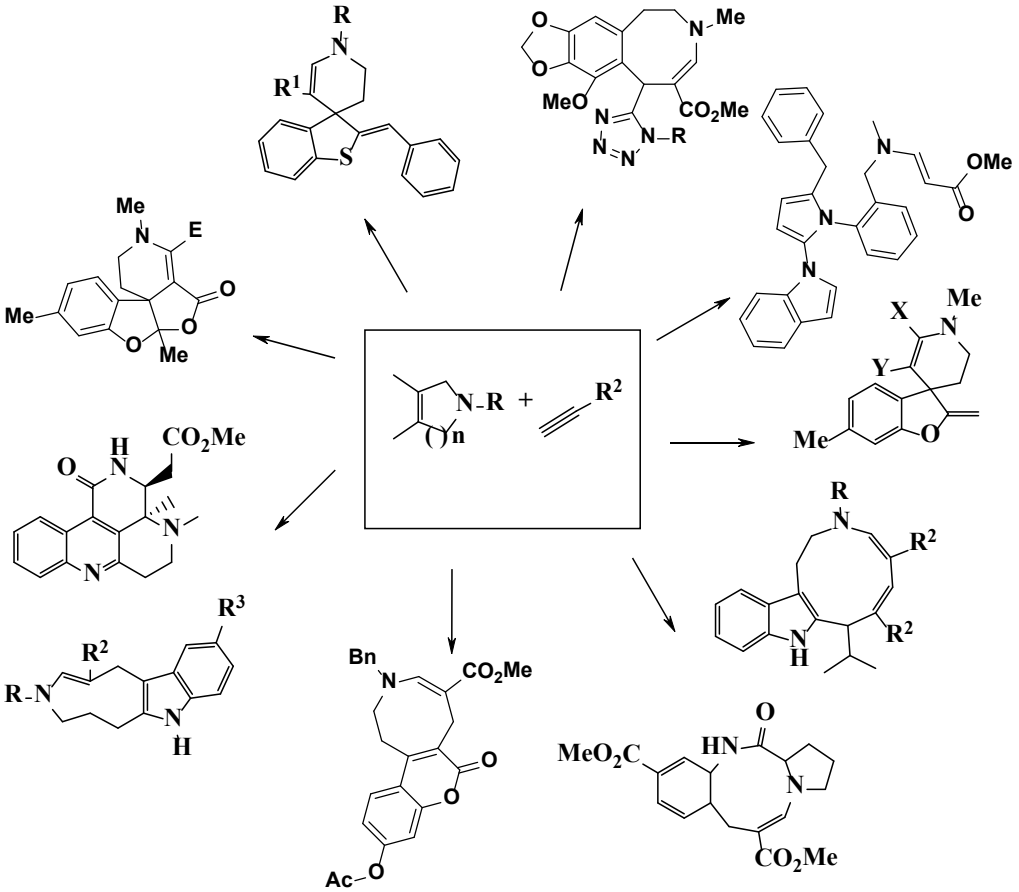
The development of new convenient and step-economical approaches to N-containing heterocyclic compounds, producing less waste and by-product, continues to be of considerable interest and important for modern organic and medicinal chemistry, particularly, for drug discovery and development. In the past several years, we and others have developed a series of Michael addition triggered domino reactions that provided easy access to multiple functionalized ring structures of chemical and pharmaceutical interest



Scheme 1

This lecture will cover recent results obtained in the synthesis of heterocyclic molecules based on reactions initiated by the Michael addition with the emphasis on *N*- heterocycles reactions with alkynes and arynes.

This work was supported by the Russian foundation for basic research (grants #14-03-00311 and 16-53-540004 viet-a)

Synthesis of Indolinones and 2-Sulfa and 2-Phosphorindolinones

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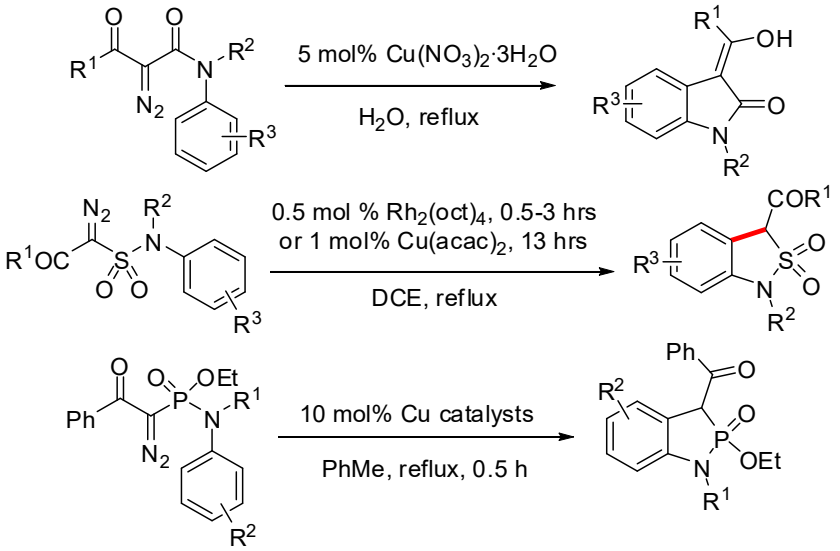
Indole and indoline derivatives are importantly biological compounds and extensively exist in natural products [1]. Sulfindolinones (1,3-dihydro-2,1-benzisothiazole-2,2-dioxides, benzo--sultams) and phosphorindolinones (2-alkyloxy-2,3-dihydro-1*H*-1,2-benzazaphosphole-2-oxides) are sulfur and phosphorus analogues of indolinones. They have been paid much attention both in synthetic and medicinal chemistry recently [2,3]. After successfully economical and green synthesis of 3-alkylideneoxindoles in moderate to excellent yields from α-diazo-β-ketoanilides under the catalysis of copper nitrate trihydrate in water [4], the synthesis of benzo-γ-sultams has been realized via the Rh/Cu-catalyzed intramolecular aromatic C-H functionalization of *N*-aryl-1-diazoalkanesulfonamides [5]. An efficient synthesis of 1-alkyl-3-benzoyl-2-ethoxy-2-oxophosphorindolines that are not accessible by previously reported methods has been successfully achieved via the copper-catalyzed intramolecular aromatic C-H insertion of ethyl *N*-aryl-1-diazo-2-oxo-2-phenylethylphosphonamidates. The current methods are featured with mild and clean conditions, inexpensive catalyst, and simple operations. The reaction mechanism was also discussed.



Scheme 1. Synthesis of indolinones and 2-sulfa and 2-phosphorindolinones

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ORAL LECTURES

Phosphorous acid as effective catalyst in spiro[indole-3,5'-isoxazoles] synthesis

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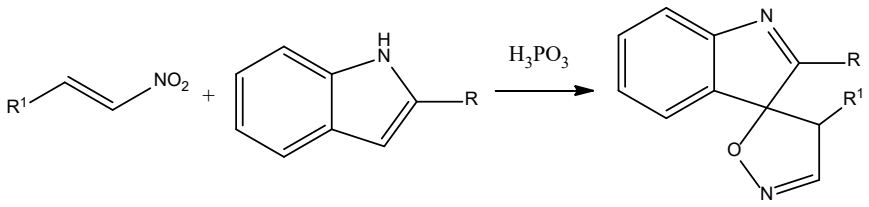
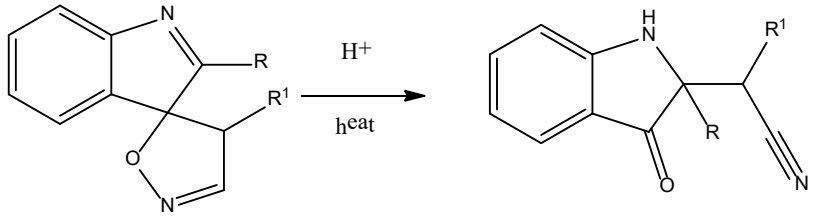
P53 plays a pivotal role in the regulation of cell cycle, apoptosis, DNA repair, senescence and angiogenesis, and consequently carcinogenesis. Approximately 50% of human cancers, the TP53 gene is mutated or deleted. Recently it was shown that spiroisoxazoline oxindoles moiety can perfectly mimic the indole side chain of Trp23 of p53. This fact made these compounds quite active against cancer cells. The GI50 = 29.1 μM. Despite the interesting activity synthesis of these compounds includes represent a large number of stages with total yields that are not very high.

In our laboratory we have discovered a brand new opportunity to relative 4'H-spiro[indole-3,5'-isoxazoles]. These compounds can be obtained in a nearly-quantative yields from available indolylnitroethenes or directly from indoles and β-nitrostyrenes. These transformations take place in a medium of really small molecule which is phosphorous acid. Thus mixing together of indole β-nitrostyrene and phosphorous acid at room temperature leads to formation of desired product.



Scheme 1. 4'H-spiro[indole-3,5'-isoxazoles] synthesis

Further heating leads to rearrengement of spiro compounds to 2-(3-oxoindolin-2-yl)acetonitriles



Scheme 1. Rearrangement

This project was supported by grants from the Russian Science Foundation (grant #14-13-01108)

Ring Transformations Leading to 2-Aminoimidazoles

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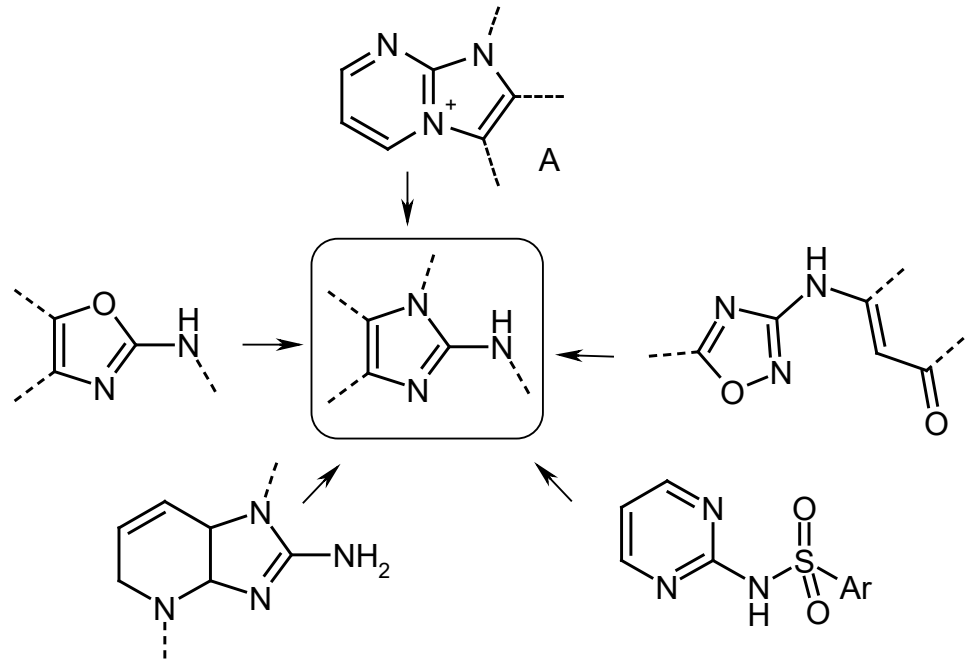
2-Aminoimidazoles have been reported to have cytotoxic, antimicrobial, or antifungal properties. They are found in marine sponges belonging to the Calcarea family. In spite of the simplicity of 2-aminoimidazole, the synthetic routes leading to this scaffold are surprisingly complicated [1]. Novel methodologies involve formation of the 2-aminoimidazoles from other heterocycles.

The present report has the goal to overview the ring transformation methodologies leading to 2-aminoimidazoles. In particular, our methodology of using imidazo[1,2-a]pyrimidines and their salts (A) will be reviewed [2]. This methodology allowed us to obtain broad series of natural alkaloids with 2-aminoimidazole moiety.



Scheme

References
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This work was supported by Russian Science Foundation (grant No. 16-13-10060).

Studying of the mechanisms of intercellular interactions of the niosomal form of the anticancer drug AX-7 with the plasma membranes of erythrocytes

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A synthesized compound N-hydroxy-2- (2- (naphthalen-2-yl) -1H-indol-3-yl) -2-phenylacetamide (Ax7) in vitro showed the high cytotoxic activity against glioblastoma cancer cells [*A.V. Aksenov, et all, 2015*]. We have developed a niosomes form anticancer drug Ax7. When encapsulating Ah7 substance in organic silicon niosomes their size was 80 - 120 nm. In the study of the physical properties niosomes it has been shown that they have a high elasticity. This will provide them the opportunity to good to pass through small capillaries and intercellular spaces The effectiveness of the inclusion of the drug Ax7 in niosomes is more than 80%. This is due to lipophilic substances and using as a solvent 1,2 - propyleneglycol. Flyuoroistsentsii defined wavelengths for antitumor solid matter, which amounted λex = 322 nm and λ em = 422 nm. We have studied the effect of the drug on the structural and physical properties of plasma membranes. It has been shown that the interaction the organosilicon niosomes with plasma membranes increases their fluidity. As a result, the plasma membrane becomes permeable to water and other small hydrophilic molecules. Growing rate of lateral diffusion of integral membrane proteins. This may accelerate the delivery of drugs and biologically active substances into the cell. Furthermore, these changes will help accelerate the transduction of external signals and to improve the regulation of cell metabolism. New form anticancer drug Ax7 has low toxicity when administered subcutaneously to rats (LD50 = 64 mg / kg).

The results will be used in pre-clinical trials of the drug. The analysis of the average particle size of 4 samples using atomic force microscopy mainly revealed the value of less than 100 nm [Fig. 1], indicating to nanodimension used for the delivery of doxorubicin niosomes of silicone nature. Thus, the application of methods for determining the content of spectrofluorophothometry of niosomal form Ax7 in blood serum determined excitation the wavelengths and fluorescence of niosomal form N-hydroxy-2- (2- (naphthalen-2-yl) -1H-indol-3-yl) -2-phenylacetamide were determined, which amounted λex = 322 nm and λ em = 422 nm. Certain changes in physical contact parameters and structural properties allow to study the kinetics of membrane concentration N-hydroxy-2- (2- (naphthalen-2-yl) -1H-indol-3-yl) -2-phenylacetamide in the blood and to find the optimal therapeutic dose, methods and modes of administration of anticancer drugs.

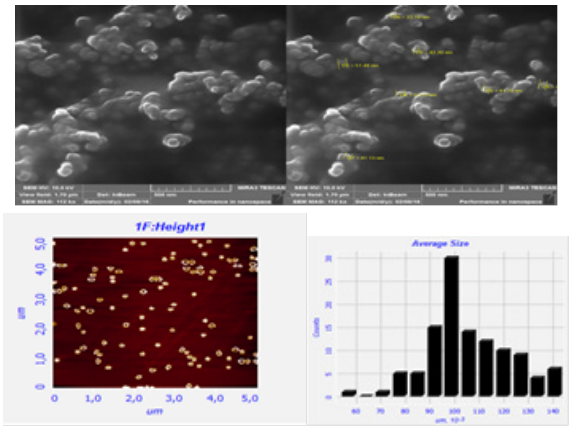

***Figure 1**: Atomic Force Microscopy of the sample 3 and the histogram of the average particle size to their number*

Development of synthesis methodology for DNA-encoded chemical libraries

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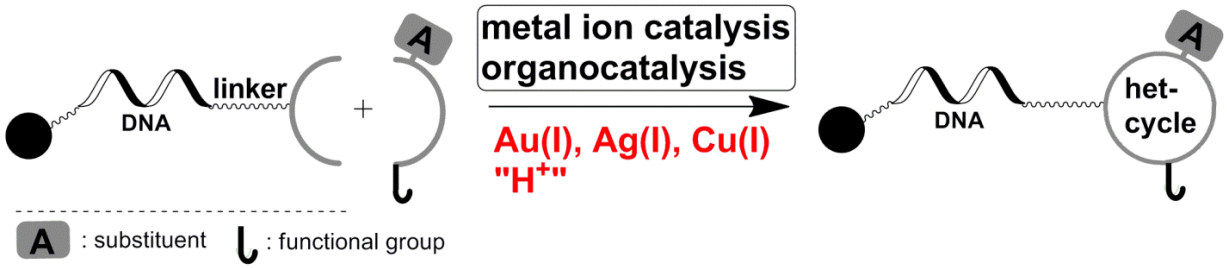
Bioactive small molecules are used as probes to elucidate biological systems or serve as starting points for drug development programs. The selection of large, pooled DNA-encoded small molecule libraries (DELs) represents an attractive technology for target-based identification of bioactive small molecules.[1] A DNA-encoded molecule is a chimeric structure consisting of a drug-like compound covalently connected to a DNA strand serving as bar code identifier. DELs are synthesized through iterative, combinatorial organic preparative chemistry and enzymatic encoding steps. As all chemical steps are performed in the presence of the DNA bar code tag, chemical methodology applied to DEL synthesis strictly needs to be DNA-compatible. Methodology usable for the synthesis of DELs is currently restricted to mostly carbonyl and Pd-catalyzed C-C cross-coupling reactions. This restriction defines a challenge for organic chemists: Development of synthesis methodology for DELs is desperately needed to expand chemical space covered by these libraries.

We developed a solid support-based synthesis strategy that broadens the range of applicable catalytic methods.[2] Among the catalytic systems that are now available for DEL synthesis are organocatalysts, and transition metal ions such as Au(I), Ag(I), and Cu(I). Our strategy opened access to substituted and functionalized heterocyclic scaffold structures as encodable DNA-conjugates from simple, readily available starting materials. For example, application of transition metal catalysts furnished DNA-heterocycle conjugates through [3+2] cycloaddition reactions. Some of the newly synthesized DNA-conjugated heterocycles display structural motifs from natural products, while others represent core structures of clinical candidates or approved drugs. All heterocyclic scaffolds were designed to enable subsequent DNA-encoded combinatorial library synthesis by well-described, robust reactions.



Scheme 1. Solid phase-based transition metal ion- and organocatalyzed synthesis of DNA-heterocycle conjugates serving as starting points for encoded library synthesis.

References

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This work was supported by the BMBF grant 131605.

New multicomponent syntheses on base of polyfluoroalkylated 3-oxo esters, methyl carbonyl compounds and amines

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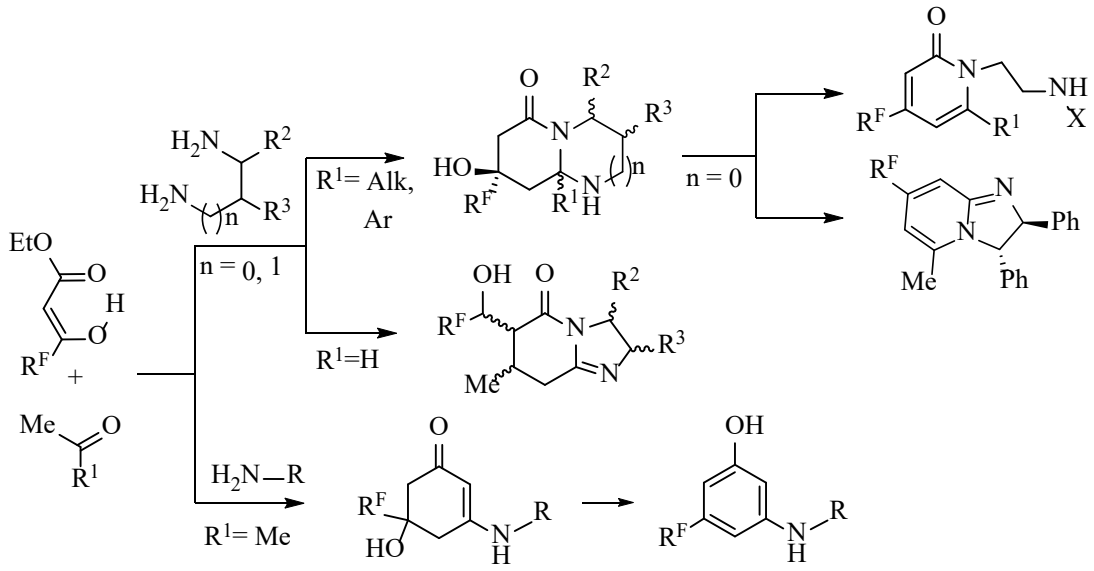
We have found novel three-component reactions based on cyclisation of polyfluoroalkylated 3-oxo esters, methyl carbonyl compounds and amines. The use of 1,2- and 1,3-diamines in these reactions leads to 7-hydroxy-7-polyfluoroalkylhexahydroimidazo[1,2-*a*]pyridin-5-ones and 8-hydroxy-8-polyfluoroalkylo ctahydropyrido[1,2-*a*]pyrimidin-6-ones, respectively. These reactions proceed efficiently in regiospecific manner with high diastereoselectivity. We have analyzed the scope of this method. The plausible mechanism of three-component reaction has been suggested. According to preliminary mechanistic studies diamine in this process acts not only as a reagent but also as a base thereby catalyzing this cyclization. Under dehydration the hexahydroimidazo[1,2-*a*]pyridinones were shown to undergo the imidazole ring opening at C^{8a}-N^{1} bond to give the *N*-substituted pyridin-2-ones or 7-polyfluoroalkyldihydroimidazo[1,2-*a*]pyridines. The use of acetaldehyde instead of methyl ketones in these reactions changes the direction of three-component reactions and resulted in 6-(1-hydroxypolyfluoroalkyl)-7-methyltetrahydroimidazo[1,2-*a*]pyridin-5-ones. The synthesis of this heterocyclic scaffold includes an aldol condensation of acetaldehyde with the formation of crotonaldehyde followed by the cyclization with diamine and 3-oxo ester. When monoamines are used in the reaction with polyfluoroalkylated 3-oxo esters and acetone another cyclization route is realized to yield 5-hydroxy-5-polyfluoroalkylcyclohex-2-enones that can be dehydrated to 3-amino-5-polyfluoroalkylphenols.



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This research was financially supported by UB RAS № 15-21-3-5.

Diversity oriented synthesis of polycyclic heterocycles through the condensation of 2-amino[1,2,4]triazolo[1,5-*a*]pyrimidines with 1,3-dicarbonyls

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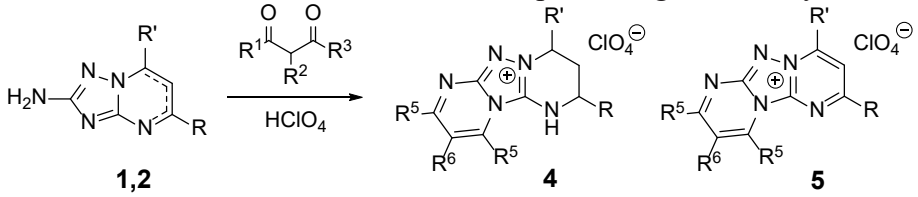
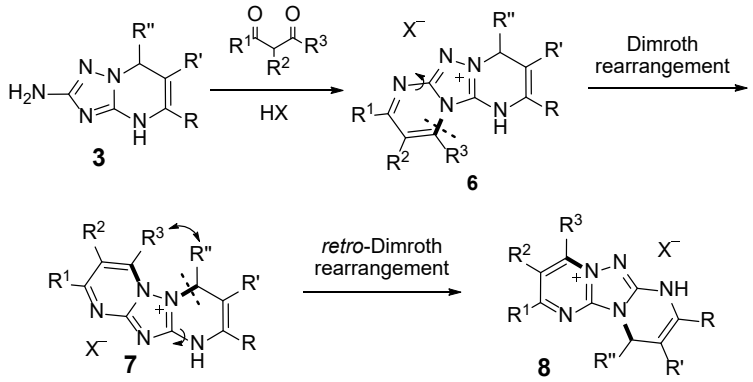
The report discusses a new methodology [1] for the preparation of diversely substituted polycyclic derivatives of triazolopyrimidine based on acid- and base-catalyzed cyclocondensation between 2-aminosubstituted [1,2,4]triazolo[1,5-*a*]pyrimidines **1-3** and 1,3-dicarbonyls (1,3-diketones, β-ketoesters, *etc*). The orientation of the pyrimidine rings in the resulting polycondensed heterocycles depends on the saturation of the pyrimidine cycle in the starting aminotriazolopyrimidines. 4,5,6,7-Tetrahydro- (**1**) and aromatic (**2**) aminotriazolopyrimidines react with dicarbonyls at the 2-NH_2 and N-3 to selectively yield the corresponding [1,2,4]triazolo[1,5-*a*:4,3-*a*']dipyrimidines **4, 5** (Scheme 1). Cyclocondensation between derivatives of 4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidines **3**, which contain a carbonyl group as a substituent in position 6 of the triazolopyrimidine system, and 1,3-dicarbonyls is accompanied by a cascade rearrangement through intermediates **6** and **7** with unusual recyclization of the dihydropyrimidine ring to afford partially hydrogenated [1,2,4]triazolo[1,5-*a*:4,3-*a*']dipyrimidines **8** with reversed annulation of the aromatic and hydrogenated pyrimidine rings (Scheme 2). The proposed methodology for the synthesis of polycyclic derivatives of triazolopyrimidine is based on the application of readily available starting compounds and demonstrates a broad substrate scope and high efficiency.



Scheme 1.



Scheme 2.

References

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N-Heterocyclic Carbenes – a Workhorses of Organic Synthesis: a Case of 1-Adamantyl-3-Arylmethylimidazoles

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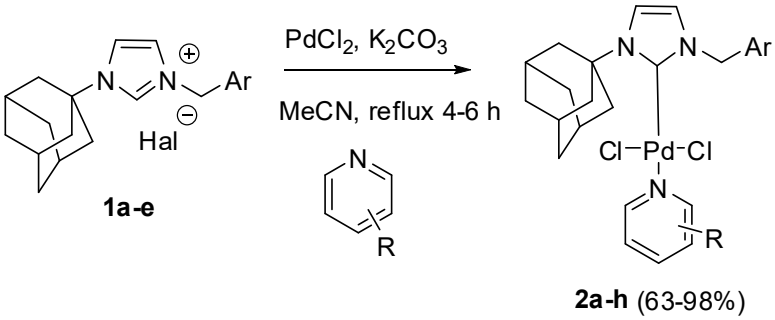
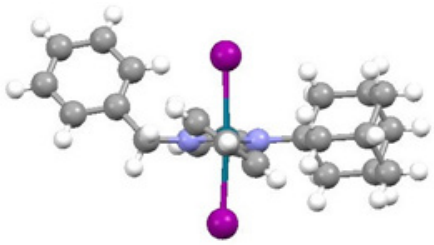
The successful isolation and characterization of an N-heterocyclic carbene in 1991 opened up a new class of organic compounds for investigation. From these beginnings as academic curiosities, N-heterocyclic carbenes today rank among the most powerful tools in organic synthesis, with numerous applications. Satisfactory reactivity and the desired molecular function of N-heterocyclic carbene emerges by combining various steric and electronic properties. In this connection unsymmetrical N-heterocyclic carbene ligands represent new trend in research.

A series of new unsymmetrical adamantyl-substituted imidazolium salts (**1a-d**, 78-95%) were synthesized and used for generation of PEPPSI-type complexes (**2a-h,** Scheme 1). Representative examples of imidazolium salts (**1a,b,c**) have been characterized by X-ray diffraction analysis, as well as corresponding diiodide complex (**3**).

Scheme 1.





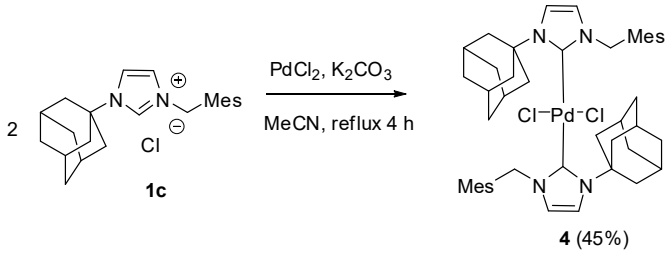
3

1: **a** Ar = Ph, Hal = Br; **b** Ar = 3,5-$Me_2C_6H_3$, Hal = Br; **c** Ar = 2,4,6-$Me_3C_6H_2$, Hal = Cl, **d** Ar = 2,3,5,6-Me_4C_6H, Hal = Cl; **e** Ar = 1-Naphthyl, Hal = Cl; R = H, 2-Me, 3-Me, 4-Me, 3-Cl.

The new complexes displayed activities as precatalysts for Suzuki-Miyaura cross-coupling reaction between phenylboronic acid and aryl bromides in propanol-2 (yields 75-98%) or phenylboronic acid and aryl chlorides in water (yields 35-37%).

Using stoichiometric amounts of NHC ligand and $PdCl_2$, in the absence of pyridine, binuclear palladium complex (**4**) was obtained (Scheme 2). The structure of complex (**4**) was supported by NMR ^1H spectrum and X-ray analysis.

Scheme 2



Another reactions of new N-heterocyclic carbenes, including organocatalysis, will be also discussed.

This work was supported by Russian Foundation of Basic Research (Grant No. 16-33-00147).

Catalysis of radical polymerization by ruthenacarboranes: from catalyst development to functional polymers

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The production of polymers with desired properties is one of the most challenging tasks in the area of modern organic synthesis. Nowadays such polymers are required as novel functional materials in different areas of industry starting from biomedical applications and water purification and ending in aerospace technologies. The development of methods of controlled radical polymerization in the end of 20th century and its dramatic evolution in the past 15 years resulted in appearance of various polymer topologies such as gradient, block-, graft and random copolymers having different properties. The mentioned progress in modern polymer chemistry is the result of achievements in the area of organic and organometallic chemistry which has given novel ligands and catalysts for polymerization processes.

This work is devoted to the development of novel catalytic systems based on ruthenium carborane complexes and its application to the synthesis of polymers with desired molecular weights and topology. We have synthesized series of ruthenium carborane complexes with diphosphine ligands and investigated their catalytic activity in Atom Transfer Radical Polymerization of various monomers. It was established that systems based on synthesized ruthenacarboranes and aliphatic amines are capable to initiate polymerization and to conduct it in a controlled manner. The structure of the catalyst has a crucial impact on its catalytic activity. So, our results are clearly demonstrate that it is possible to tune the catalyst be varying auxiliary ligands. The conducted model experiments showed that the role of amine in the polymerization mixture is consisted in reducing of ruthenium catalysts into the lower oxidation state. Other organic reducing agents such as glucose, tin 2-ethylhexanoate, etc. also can be used as catalyst regeneratos.

The polymers formed in these conditions are characterized by desired molecular weight and low polydispersity. The developed catalytic system based on ruthenacarboranes were further applied for obtaining random and block- copolymers based on methacrylic monomers: methyl methacrylate (MMA), ethyl methacrylate (EMA), isobornyl methacrylate (IBMA) and tert.-butyl methacrylate (TMBA). Using the proposed catalytic system chain extension of monofunctional PMMA macroinitiator by IBMA, EMA or TBMA was performed. A series of block-copolymers with different length of the second block were prepared by variation of a polymerization time. The linear increase of molecular weight on conversion is observed. The M_n values of the obtained samples are in a good agreement with theoretically calculated ones indicating the proceeding of the process in the controlled mode in accordance with ATRP mechanism.

The obtained PMMA-b-PIBMA and PMMA-b-PTBMA copolymers were further chain extended with TBMA and IBMA respectively to achieve triblock copolymers. The polymerization of third monomer proceeded smoothly giving copolymers with higher molecular weights. The successful polymerization of the third block indicates the high percentage of living chain ends in the polymer formed.We have investigated triple random copolymerization of above mentioned monomers using the same catalytic system. The results of the experiments performed indicate the proceeding polymerization in living mode with increasing molecular weight on conversion.

This work was done under the task of Ministry of Education and Science of Russian Federation (Proj 736) and supported by Grant of President of Russian Federation (Proj No MK-7578.2015.3).

Interplay between aromaticity of 3a,6a-diaza-1,4-diphosphapentalene and N→P bonding interaction

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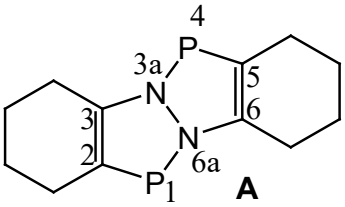
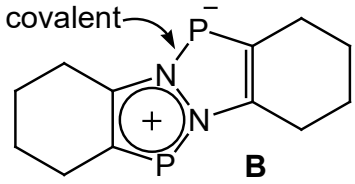


A

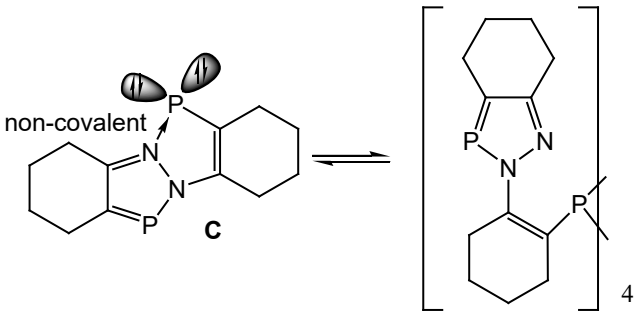
Diamagnetic 3a,6a-diaza-1,4-diphosphapentalene (DDP) [1] displays extraordinary properties compared to the usual azaphospholes, which may be explained by a peculiar bonding situation, which is governed by the interplay between 10π- and 6π-aromatic stabilization together with the N⟶P bonding interaction which may vary from covalent to non-valent. The specific chemical properties of DDP may be better understandable while using the canonical formulas depicted below:



B

The formula **A**, displaying formally divalent phosphorus, does by more clear the addition reactions of DDP with halocarbons (BnCl, Ph_3CCl, CF_2Br_2, CH_2Br_2, F-C_6H_4-R and others) which provide 1,1- or 1,4-addition products depending on the substrate. 1-P atom in 1,1-adducts becomes hypervalent (trivalent, four-coordinate) with N▪▪▪ P non-valent interaction.

DDP can have an induced high negative charge density on one of the phosphorus atoms due to the charge transfer from one phosphorus atom to another and the 6π-aromatization of one of the heterocycles (structure **B**). The 10π-electron system provides two electrons for the formation of the P⟶ M coordination bond, as we have shown by an example of Hg(II), Sn(II), Ge(II) and In(III) complexes; the lone pair at the phosphorus atom is not involved in the coordination.



C

It has been found that DDP undergoes oligomerization to $(DDP)_4$ in ether solutions slowly and reversibly, that may be rather inherent to the structure **C** displaying formally monovalent phosphorus. Some polar molecules (R_3SiCl, R_3GeCl, Cp_2TiCl_2) promotes transformation of DDP to tetramer, whereas UV irradiation of $(DDP)_4$ in toluene solution provides monomer for several minutes.

Possessing certain reducing activity, DDP easily converts Ph_2PCl to Ph_4P_2, $PhPCl_2$ to $(PhP)_5$ and PCl_3 to red phosphorus in hexane at room temperature. Interaction of DDP with its 1,4-dichloro-derivative affords dark-violet thin film showing a very broad absorption band in the range of 800−1100 nm corresponding to the formation of conjugated assosiates with intermolecular interaction combining π-stacking and N-P-hypervalent bonding between neigboring blocks.

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New developments in the Castagnoli-Cushman reaction

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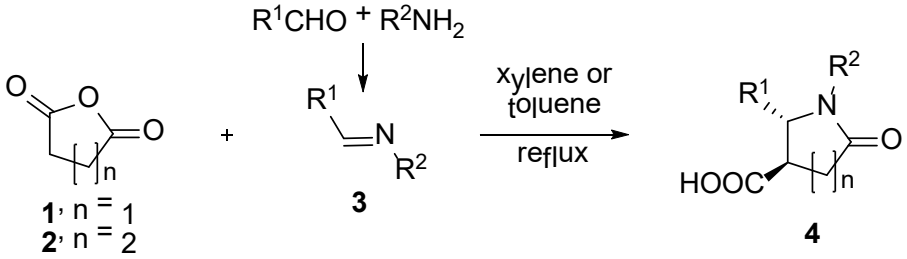
The Castagnoli-Cushman reaction (of imines **3** with dicarboxylic anhydrides among which **1** and **2** are most popular) or CCR is gaining importance in so-called Lead-Oriented Synthesis as it gives a facile access to the privileged γ- or δ-lactams **4**. The latter is an intuitively defined area of synthetic, scaffold-minded chemistry aimed at constructing new organic compounds of low lipophilicity (cLogP < 3) and molecular weight (MW < 300) which are expected to have higher value in drug discovery.



Considering our interest in multicomponent chemistry and related atom-economical approaches, we sought to contribute to the field of CCR. Synthetic strategies that are well developed for other multicomponent reactions (skeletal reagent diversity, post-condensational modifications) were seldom applied toward the CCR which made it very exciting to apply the same mentality to this useful scaffold-generating transformation. The talk will provide a condensed perspective of our efforts in this area during the period 2014-2016.

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Novel Sulfur Heterocycles and Oxathiamacrocycles on the Basis of 3,4-Dichloro-2(5*H*)-furanones and Dithiols

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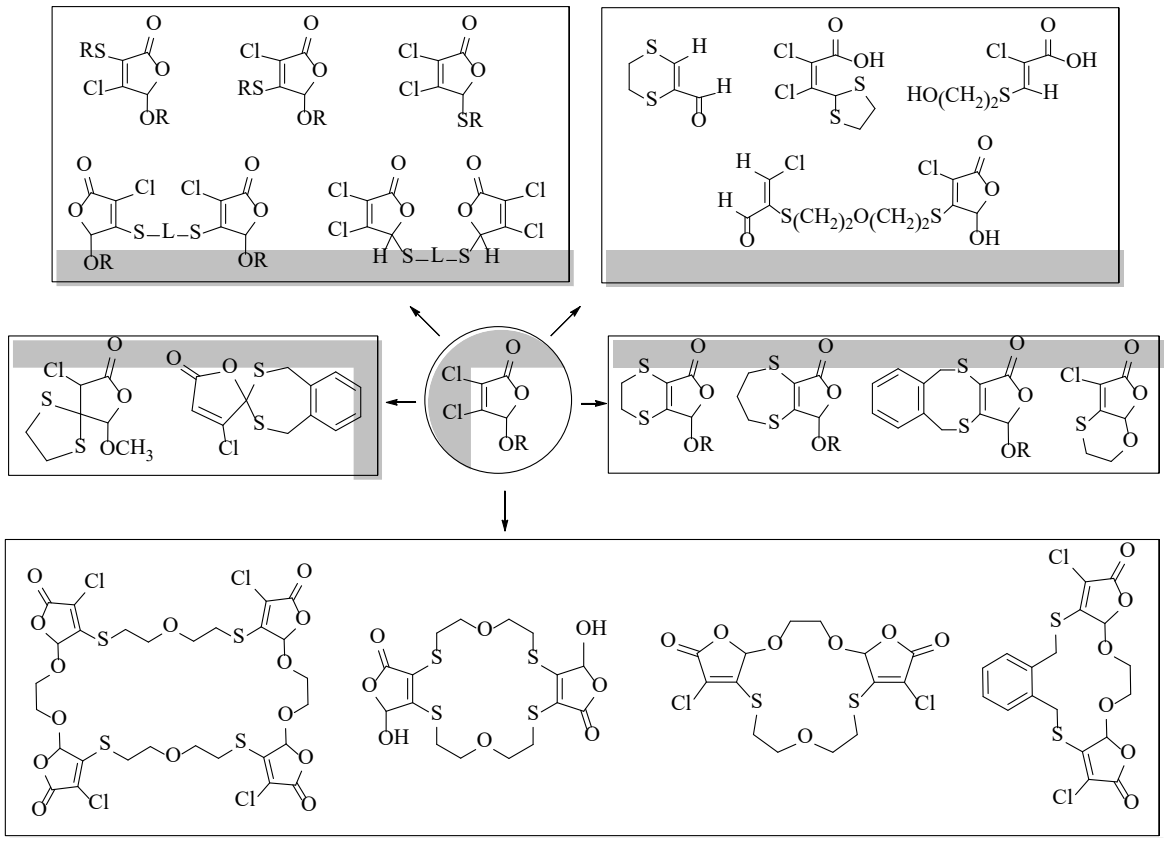
2(5*H*)-Furanone derivatives are naturally occurring and extremely useful heterocyclic compounds in various branches of medicine, agriculture, technology, and organic synthesis. In connection with our ongoing projects related to chemistry of sulfur-containing derivatives of five-membered *O*- and *N*-heterocycles and in a further effort to reveal the potential of 3,4-dichloro-2(5*H*)-furanones as a useful building blocks for the synthesis of new sulfur heterocycles, we performed a systematic study of the reactivity of furanones toward sulfur-containing binucleophilic reagents. The utilization of different dithiols in the reactions with 3,4-dichloro-2(5*H*)-furanones allowed us to obtain previously unknown sulfur heterocycles of different structural types: *bis*-thioethers that combine a dithiol moiety and two γ-lactone rings bridged through their carbon atoms C^4 or C^5, new types of the sulfur-containing fused and spiro bicyclic systems, several products of the lactone ring opening reactions. A series of novel furanone based [2+2] and [1+1] oxathiamacrocycles were designed and synthesized under different reaction conditions and using various dithiols.



Scheme 1. *S*-heterocycles and oxathiamacrocycles derived from 3,4-dichloro-2(5*H*)-furanones.

The work was supported by the Russian Science Foundation (project No 15-14-00046)

From Palladium to Copper catalyzed reactions and rediscovering the potential of microbiological transformations: new and revisited trends in Steroid Chemistry?

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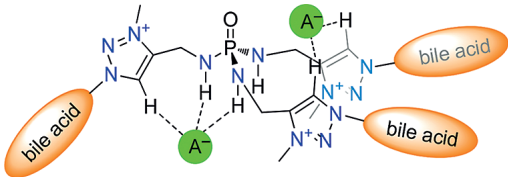
The steroids occupy a unique position among natural compounds due to high biological activity and involvement in the most important processes in living organisms. In the last two decades Pd-catalyzed cross-coupling reactions have been extensively applied to the modification of steroids [1,2]. We used this methodology for the synthesis of the potential aromatase inhibitors [3]. Taking into account a significant advance achieved during recent years in the so-called «modified Ullmann chemistry», the Cu-catalyzed reactions may become promising tools for steroid derivatization, especially for the synthesis of azolyl-substituted steroids, developed as new agents for cancer therapy [4a]. Moreover, high cost of palladium and appropriate phosphine ligands prompts to search alternative conditions for catalytic reactions aiming at their possible application for industrial scale synthesis. In particular, the conventional Pd-catalyzed Sonogashira coupling of steroids has been successfully applied for the synthesis of new biologically active compounds. We proposed a new protocol for the synthesis of steroidal enynes via Pd-free Sonogashira coupling [4b].

Another copper-catalyzed transformation (CuAAC) has been employed in the reactions of steroidal azides with various terminal alkynes. The developed synthetic protocols allowed us to attach a triazolyl moiety to both the side chain and the steroidal backbone directly and in high yields. The presence of Cu(II) in the reaction mixtures was shown to invoke D-homo rearrangement under mild conditions. A judicial choice of copper pre-catalysts permitted us to carry out the “click” reaction either coupled with tandem D-homo rearrangement or in the absence of this follow-up process [4c]

The CuAAC reaction was used for the preparation of a series of bis- and tris- 3- and 24-5β-cholanetriazolyl derivatives of phosphorus acids, including anion-binding triazolium sites and hydrophobic cholane residues. Anion binding properties of tris(triazolium) ligands were studied for a series of inorganic and organic anions and high complexation constants were observed with fluoride, hydrosulfate and benzoate anions in mol ratio 1:2 [5].



However in spite of a wide application of modern synthetic and catalytic approaches, often only microbiological transformations remain the most cost-effective way to introduce hydroxy- groups or double bonds in specific positions of steroidal skeleton to produce pharmaceuticals [6].

We are grateful to RFBR grant №16-03-0390 for financial support.

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New Supramolecular Containing Polyfunctional Substituents Spirocyclic SystemsDesigned for Light Operated Elements of Molecular Photonics

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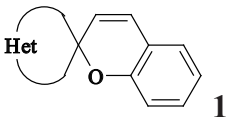
Photochromic materials like spiropyrans [1] which possess photochromic properties both in solutions and in solid matrices are often used as elements of molecular electronics and photonics. Spirocyclic compounds can be used in the optical memory devices and in light controlled molecular switches as

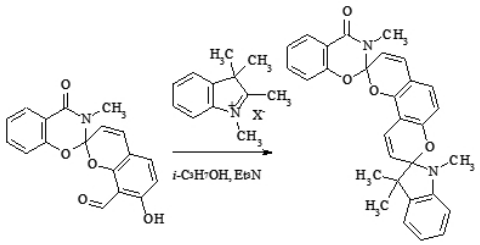


1

well as a chemical sensors for the determination of the metal content in the environment [2,3]. Search of promising materials for molecular photonics is associated with the development of new hybrid multifunctional materials based on photochromic compounds with multiple properties at the same time: optical, magnetic, luminescent as well as coordination-active etc.

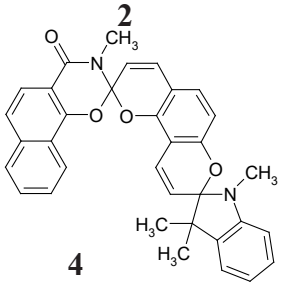
Spiropyrans like **1** contining orhto-*located* hydroxy and formyl groups were used for synthesis of asymmetrical bispiropyrans **2**. The structure of them was set by IR, NMR and X-ray spectroscopy.

A colored photoinduced form the spiropyran **2** was formed of its solution by 365 nm UV irradiation in stationary mode, but only one [2H]-chromene cycle was opened.



2 3

Complex absorption spectrum of bispiropyran 4 (Fig.1) under similar conditions of irradiation and changing of spectrum after time-resolved experiment indicate opening of both [2H]-chromene rings. This can be explained by the fact of the condensed benzene ring presence in benzoxazinone fragment of molecule.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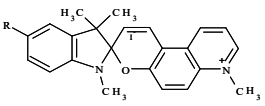
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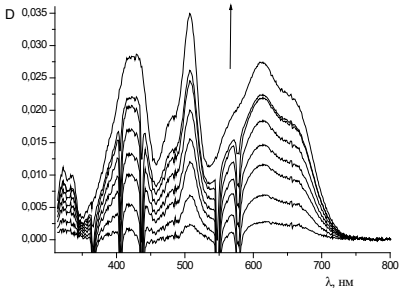

Fig.1

Spiropyrans containing [2H] benzopyran moiety condensed with heterocyclic fragments are particularly actual because many heterocycles exhibit fluorescent properties and such “hybrid” molecule will combine both the changing of color and fluorescent characteristics by action of activating radiation.

Derivatives of such systems containing a quaternary nitrogen atom, are of particular interest as a so-called photocontrolled magnetics containing complex salt magnetically active anions where the photochromic component is used positively charged spiropyran.

In this way abovementioned systems could be positioned as active elements for molecular photonics.

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Design of new hybrid heterocyclic systems incorporating furoxan ring

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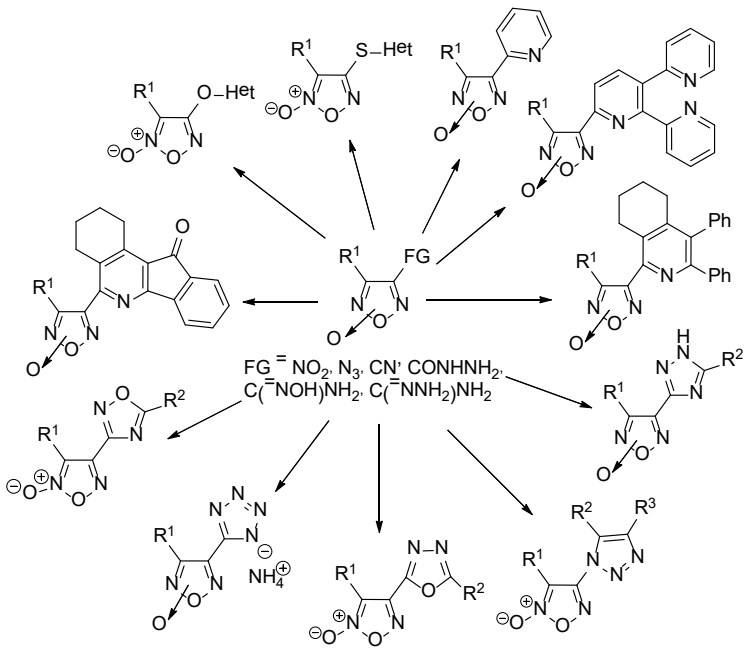
One of the main trends in the design of potential drugs with improved pharmacokinetic profile is the formation of new structures through a molecular hybridization of diverse compounds with known pharmacological activity. In particular, such approach has been widely used for the construction of hybrid molecules containing structural motifs capable of releasing nitric oxide (NO). Our ongoing scientific interests are connected with the synthesis and utilization of nitrogen and nitrogen-oxygen aromatic heterocycles, first of all, 1,2,5-oxadiazole 2-oxides (furoxans) which also belong to a class of NO-donors. Over the past decade, the design of bioactive furoxan derivatives has been focused on the development of hybrid molecules which contain, along with the furoxan ring, other pharmacophoric heterocycles. On the other hand the furoxan derivatives attract considerable attention as high energy compounds due to a positive enthalpy of formation and the presence of two active oxygen atoms in the furoxan molecule. In this work the different approaches to a design of wide series of novel heterocyclic systems containing pharmacophoric and/or energy rich poly-nitrogen (nitrogen-oxygen) heterocycles (1,2,3- and 1,2,4-triazoles, 1,2,4- and 1,3,4-oxadiazoles, tetrazole, 1,3,4-thiadiazole, pyrimidine, tetrahydroisoquinoline, indenopyridine, terpyridine etc.) attached to the furoxan ring either directly through C-C and C-N bonds or by means of heteroatom (S or O) or heterocyclic bridges are presented [1-5].



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1,3-Bis(benzo-1,2,3-triazolyl)propane isolation by selective complexation and flash column chromatography

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Cyclic organic compounds with azole cycles are able to form strong bonds with metal ions. Mechanism of the process is similar to claw grip, sometimes the grip is by claw and tail of a scorpion. For this reason these compounds were called «scorpionates». Similar substances have antioxidant activity, bind heavy-metal ions and constitute capacitious sorbents. Nowadays active search of new «scorpionate» ligands is performed.

When 1,3-bis(benzo-1,2,3-triazolyl)propane (2BTAPR) was synthesized, product consisted of three isomers (1,3-bis(benzo-1,2,3-triazol-1-yl)propane, 1,3-bis(benzo-1,2,3-triazol-2-yl)propane, 1-(benzo-1,2,3-triazol-1-yl)-3-(benzo-1,2,3-triazol-2-yl)propane). Copper(II) chloride solution in acetone was added to 2BTAPR acetone solution dropwise. Two hours later, complex was separated from supernatant on a glass filter and washed with acetone. Dried complex was decomposed by dimethylsulfoxide. During the day, 2BTAPR isomers were precipitated by a ten-fold water volume. Precipitates of the isomers were separated from water phase on a glass filter, washed with water and NH_4OH solution to remove copper traces.

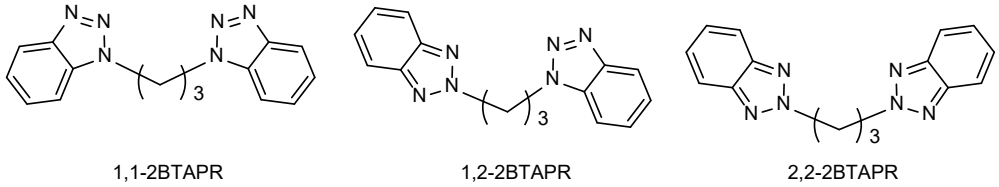

Fig. 1. Structure of 2BTAPR isomers

Overall yield of 2BTAPR isomers after isolation was about 40%. The most stable copper complex was obtained with 1,2-isomer. One the other hand, 2,2-isomer didn't form copper complex at any ratio used. Pure 1,2-isomer was obtained, 1,2- and 2,2-BTAPR was isolated successfully. Purity and containing of separated isomers were detemined by gas chromatography mass-spectrometry.

Table 1. Yield and isomers fraction composition after isolation by complexation

Molar ratio $CuCl_2$:2BTAPR	1:1		1:2		1:4		1:5	
Summary yield, %	39.7		44.1		33.3		39.7	
Fraction	Precipitate	Super-natant	Precipitate	Super-natant	Precipitate	Super-natant	Precipitate	Super-natant
Containing 1,1-2BTAPR	+	+	++	+	+	++	-	+
Containing 1,2-2BTAPR	++	-	++	-	++	-	++	-
Containing 2,2-2BTAPR	-	++	-	++	-	++	-	++

Column chromatography was carried out using Buchi Sepacore system (stationary phase – silica, eluent – ethyl acetate:hexane 1:1, flow – 10 ml/min) with fraction 10 ml collection. Efficiency of separation was monitored by thin layer chromatography, fractions with individual isomers 2BTAPR were combined. Solvent was distilled under vacuum, the isomers were dried.

Isomer melting points were determined. They were 138-141 °C, 79-80 °C and 120-122 °C for 1,1-, 1,2- and 2,2-2BTAPR respectively.

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Findings on the way to an efficient synthesis of *Amaryllidaceae* alkaloids

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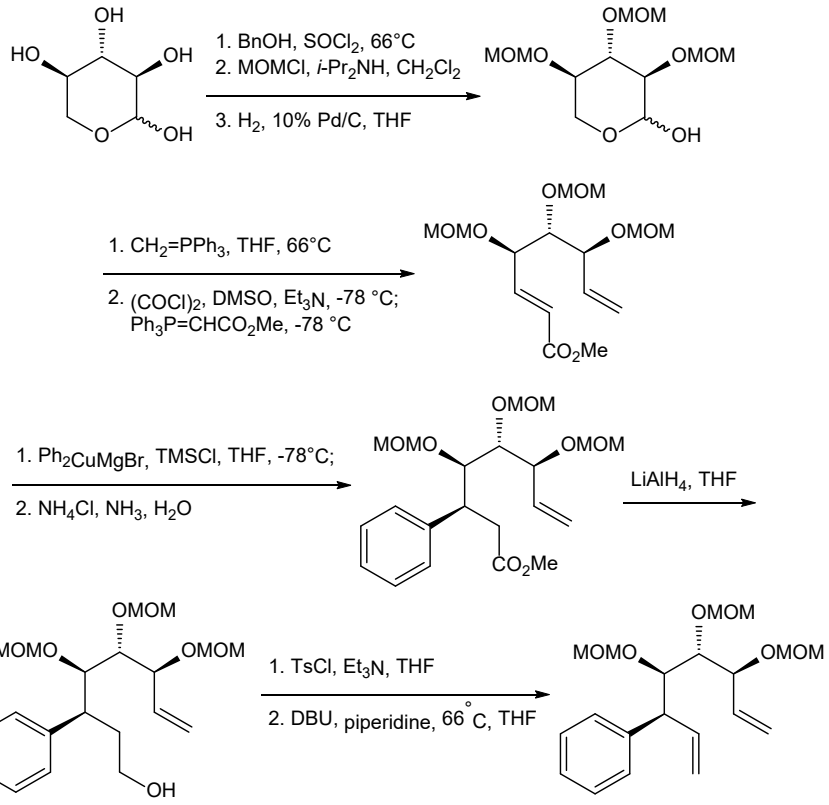
While the published approaches to cyclitols are numerous, the growing demand for these compounds fuels further synthetic work aimed at improving the preparative efficiency and achieving high levels of stereo- and regiocontrol. In this context, the naturally occurring *Amaryllidaceae* alkaloids, arylcyclitols pancratistatin and narciclasine as well as their 7-deoxy analogs have presented the synthetic community with a tremendous challenge.

Although the extensive synthetic work has led to a number of total syntheses of pancratistatin and other *Amaryllidaceae* alkaloids, the problem of supply has not been solved.



Scheme. Synthetic sequence showing a new efficient route

Structurally novel cyclitols, 1-aryl-1-deoxyconduritols F, were efficiently prepared from D-xylose utilizing RCM as a key step [1]. Various aromatic residues were incorporated in the cyclitol skeleton with a total stereochemical control utilizing a diastereoselective aryl cuprate addition to a γ-alkoxy enoate [2].

The multi-step sequence has been optimized in this research for the production of the gram-quantities of these compounds by an application of MOM-protection group and double-bond installation step by usual elimination procedures. The firm foundation is set in place for the completion of a practical synthesis of the natural pancratistatins and their aryl analogs.

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Efficient Protocol for Analysis of Chiral Carboxylic Acids by ^{19}F NMR

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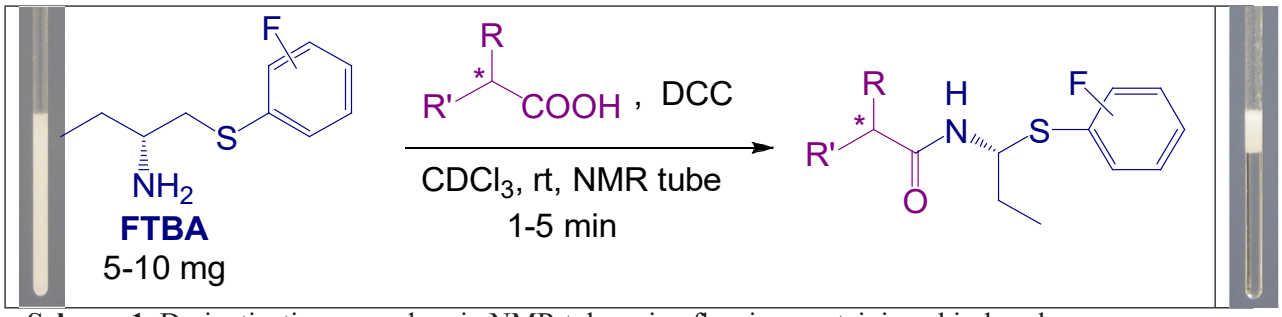
Develompent of new approaches to obtain complex chiral molecules with unprecedented selectivity is a cornerstone problem of modern organic chemistry [1]. Efficiency of every synthetic or catalytic procedure is based on the value of enantiomeric excess (ee) of the product formed which is usually determined by chiral HPLC or GC. Nevertheless, nowadays NMR spectroscopy and fluorescent methods of ee determination become an attractive and reliable alternative [2, 3].

Recently we have developed efficient «in tube» protocols for analysis of chiral alcohols and amines using ^{77}Se NMR spectroscopy [4, 5]. Use of hetronuclear NMR allows quick assignment of signals of the analyzed compounds and provide excellent enantiodiscrimination to exclude overlapping of the signals under consideration.

In continuation of these investigations we have developed a series of fluorine-containing chiral probes (FTBA) for derivatization of chiral carboxylic acids (Scheme 1). High sensitivity of ^{19}F NMR (comparable to ^{1}H NMR) provides quick and accurate analysis of chiral carboxylic acids within 1 min (Figure 1).



Scheme 1. Derivatization procedure in NMR tube using fluorine-containing chiral probes.

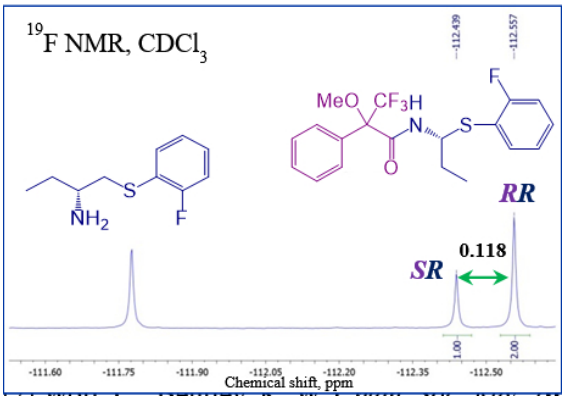


Figure 1. Representative example of ^{19}F NMR spectrum of diastereomers formed.

Though no significant substituent effect on enantiodiscrimination was observed, unique intramolecular interactions were found in some derivatives which may be highly promising for absolute configuration determination.

Synthesis of fluorine-containing chiral probes, optimization of the derivatization procedure and scope of analyzed chiral carboxylic acids as well as structural investigations will be discussed.

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This work was supported by Russian Science Foundation (Grant No. 14-50-00126).

Synthesis and properties of electron-deficient 4*H*-chromenes

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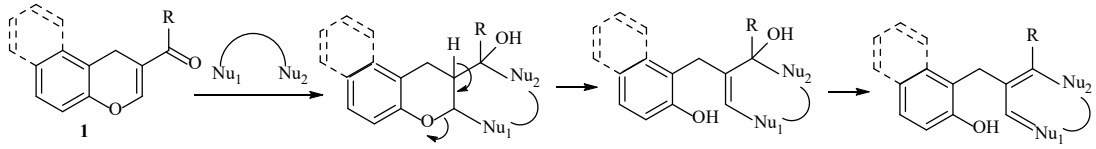
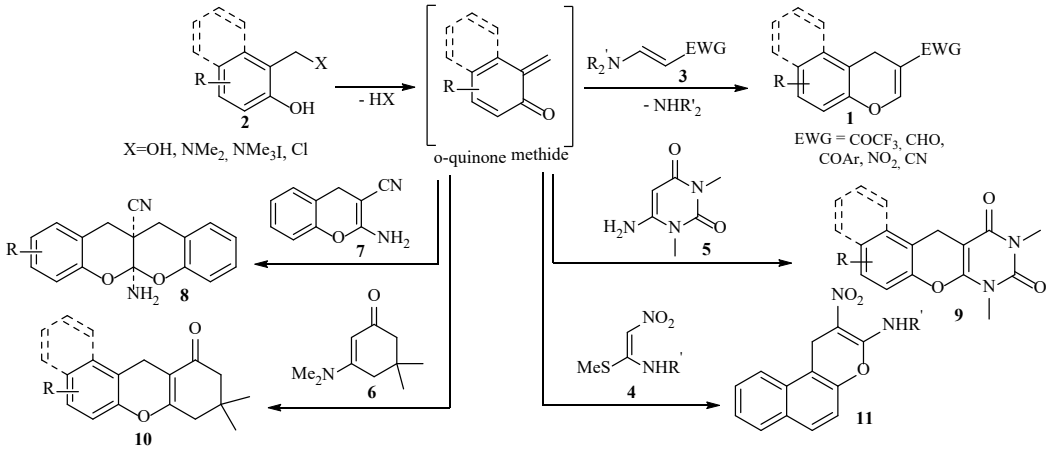
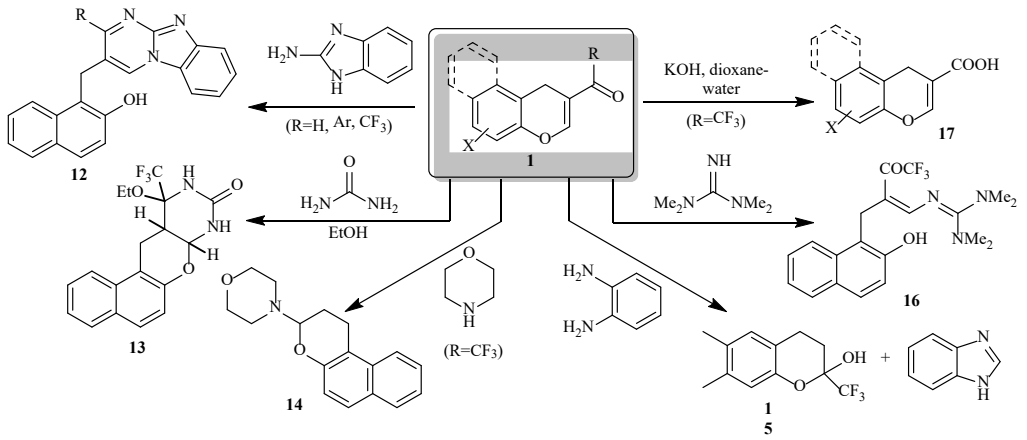
The introduction of the electron-withdrawing group (EWG) at the 3-position of the 4*H*-chromene system **1** changes the reactivity of the pyran ring with respect to nucleophiles. The diversity of properties of these compounds is because of the fact that they are highly reactive push-pull alkenes (α,β-unsaturated ketones, aldehydes, nitriles etc.) with a good leaving group at the β-carbon atom, whose role is played by the phenolate anion.



So far, however, such 4*H*-chromenes have not received much attention despite their potential interest as building blocks in organic synthesis for the construction of heterocycles. *o*-Quinone methide moiety is known to be a powerful synthon for preparation of various fused pyran derivatives. We are reporting now on the formation of this type of heterocycles from *o*-quinone methide precursors **2** and push-pull olefines **3**, **4**. This reaction with enaminones **5**, **6** and enaminonitrile **7** of heterocyclic series is useful for the synthesis of the fused chromenes **8**–**10**.



Afterwards, the recyclizations of the electron-deficient chromenes **1** with a variety of N,N-, N,O- and N,C-binucleophiles and some other reactions were investigated. Some examples are given below.



The study was carried out with the financial support of the Grant Council of the President of the Russian Federation (State Program for support of young Russian scientists, grant MD-5833.2016.3) and the Russian Foundation for Basic Research (grant 15-43-02304 r_povolzhye_a).

Recent trends in drug discovery: USA, EU and Russia

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The number and the kind of approved innovative drugs enable us to see the way the medical chemistry and pharmaceutics will develop in the next few years. It become even more clear while comparing the dynamics and/or situation in different countries.

USA FDA report on Novel New Drugs [1] presents innovative drugs which were approved in USA during the last year. The number for 2015 is 45. Compared to previous years its the most since the all-time record of 53 set in 1996. There are 21 (47%) drugs for treating of orphan diseases in the list. Looking back in 2014 and 2013 we see 41% and 30% respectively so it can be called a trend. As for more common nosologies there are some of definitely high priority (for example, multiple myeloma) while the new drugs for some diseases are not represented at all. One more trend is a relatively large number of the second-line and the next lines therapy drugs, especially in oncology.

2015 was a record year fo EU too. There are 39 novel drugs approved and the percentage of orphan drugs increased also [2]. Generally the trends in EU are similar to those in USA, but the relative amount of some nosologies differs.

Generic manufacturers switched to more complex products such as biosimilars, generic copies of molecularly complex biologic drugs. It can lead to significant changes on pharmaceutical market in the nearest future.

In Russia there are no official reports or any systematic reviews on approved new drugs, but indirectly it can be concluded that the common US and EU trends are not observed in Russia. However, we can see some local trends. Surely it's not a time to speak about domestic novel drugs or orphan drugs development but in context of import replacement there are some possibilities for new generic manufacturing and improving quality of existing ones.

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Synthesis and neurotrophic activity of functionalized derivatives of pyrano[4',3':4,5]pyrido[2,3-b]thieno[3,2-d]pyrimidines

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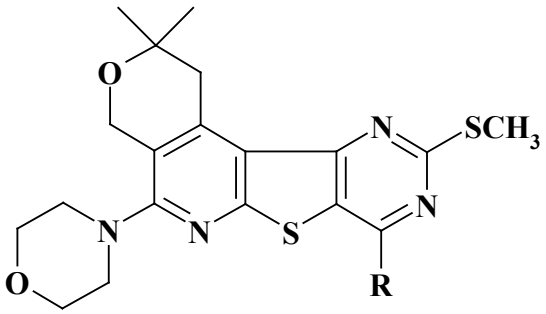
Plant derived pyrano[3,4-c]pyridines show broad ranging pharmacological effects. The derivatives of thieno[3,2-d]pyrimidines are structural analogues of purines and also are the biologically active substances. On the other hand tetracyclic fused system containing pyran, pyridin, thiophene and pyrimidine ring can be considered as analogues of heterosteroids which is known to display varied bilogical effects.

In this work we report on synthesis of functionalized of pyrano[4',3':4,5]pyrido[2,3-b]thieno[3,2-d] pyrimidines derivatives and study of their neurotrophic activity. Synthesis of 2-thiomethyl-4-chlorothieno[3,2-d]pyrimidine was carried out starting with 1-amino-2-etoxycarbonilpyrano[4,3-d] thieno[2,3-b]pyridine. Further, development of the methods for the preparation of amino, alkoxy and alkylsulfanyl derivatives by the nucleophilic substitution of the 4-chloroderivative of condensed pyrimidine.



R = OH, OR, SH, SR, NR^1R^2.

The novel copoumnd were found to have neurotropic properties. However the tester compounds couse some kind of sedation depressing the behavior unlike the tranquilizer diazepam which shows anxiolitic and activating effects.

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Problems of chemical safety in mountainous ecosystems

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Chemical Safety is when people and biota do not experience chemical stresses, i.e. the effects of organic, inorganic and organometallic toxicants are at the environmentally safe level, what does allow to preserve health of people and biodiversity of ecosystems (1). **Chemical boomerangs** are the compounds, which, being introduced by people into our life to execute special tasks (to protect plants – pesticides, to exchange heat – polychlorinated biphenyls - PCBs, to retard flame – polybrominated diphenyl ethers - PBDEs, etc.), after executing these tasks are returning to the people and affecting negatively their health (1)**. Chemical Sputniks** are the compounds, which enter atmosphere from various anthropogenic sources and perform short and long (including world round) itineraries before being deposited with rain and snow in various regions of our planet (1**). The problems of chemical safety in the mountains** have been created both by chemical sputniks and due to the mining and smelting industries and have led to acute or chronic intoxications. In particular, the removal of Pb, Cd and Hg from the earth's crust, where they can be relatively immobile, has transferred them to exposure pathways leading to humans and the environment (2). As to the **persistent organic pollutants (POPs),** it has been shown (3) the absence of local contaminant sources, annual mean air concentrations measured with XAD-resin based passive air samplers generally displayed relatively minor differences along an altitudinal transect. This indicates relatively efficient atmospheric mixing on the scale of a mountain slope. However, **even relatively minor local sources, such as vehicular traffic, can dominate concentration gradients in otherwise remote regions.** Whereas the deposition rates are generally hypothesized to increase with elevation (because temperatures drop and precipitation rates increase), **the soil organic matter content in mountains at medium and high latitudes tends to decrease with elevation and in particular will drop strongly above the tree line** (4). Accordingly, temperate mountain soils from intermediate elevations may often display the highest concentrations of organic contaminants. POPs like OCPs, PCBs and PAHs are a concern for the ecosystems of remote areas (such as alpine regions) and human health as they are bioaccumulative, resist degradation and cycle for long time in the environment. **Most POPs are considered to be ubiquitous in the global atmosphere (5), and concentrations expected to decrease with height, which, however, has hardly been addressed so far.** XAD-resin based passive air samplers were used to measure the concentrations of HCB, endosulfan-1, α-HCH, γ- HCH, p,p'- DDE and p,p'- DDT over an altitudinal transect from 2638 to 5605m a.s.l. in the Central Himalaya (27º44'-27º60'N, 86º43'-86º50'E). Whereas there is no known usage of these chemicals in this high altitude region, they are used extensively on the Indian Subcontinent. Air concentrations were similar to those found in North American mountains.

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Synthesis and coordination chemistry of bis(azolyl) derivatives with hydrocarbon linkers

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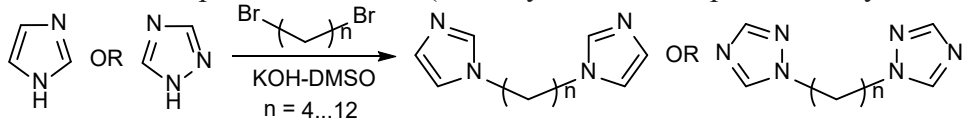
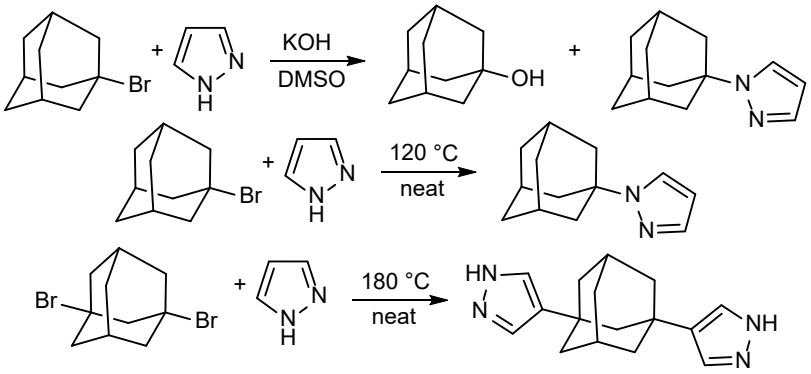
The study is aimed on design and synthesis of new heterocyclic ligands, in which two (or more) azolyl moieties are separated by a hydrocarbon linker. Ligands of this type are capable to form coordination polymers, including metal-organic frameworks (MOFs) – promising functional materials with important catalytic, electrochemical and photophysical properties [1-3].

Neutral nitrogen ligands are often used as auxiliary building blocks for MOFs, pyridine ligands are most widely studied [4]. Our efforts are concentrated on the synthesis of multidentate ligands based on azoles – pyrazoles, imidazoles, triazoles [5]. Heterocyclic moieties may be joined by flexible aliphatic spacers or rigid cage hydrocarbons. The former were prepared by substitution reaction between azoles and dibromoderivatives in a superbasic medium (dimethyl sulfoxide – potassium hydroxide, Scheme 1).



Scheme 1.

1-Bromoadamantane reacted with pyrazole in a superbasic medium to give a mixture of 1-adamantylpyrazole and 1-hydroxyadamantane. Pure azolyl and di(azolyl)adamantanes were prepared by melting of the reagents in PTFE reactor at 120 °C and 180 °C correspondingly (Scheme 2).



Scheme 1.

It is interesting to note that in case of 1,3-dibromoadamantane C-alkylation of the pyrazole ring was observed instead on N-alkylation. The structures of the products were confirmed by NMR and mass spectra.

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This work was supported by the Russian Fund for Basic Research (RFBR), project No. 16-33-60149.

One-Pot Three-Component Condensation of Arenes with Aldehydes and Aminonitriles. New Synthesis of a Variety of Fused Pyrrolo[2,3-d]Quinolines

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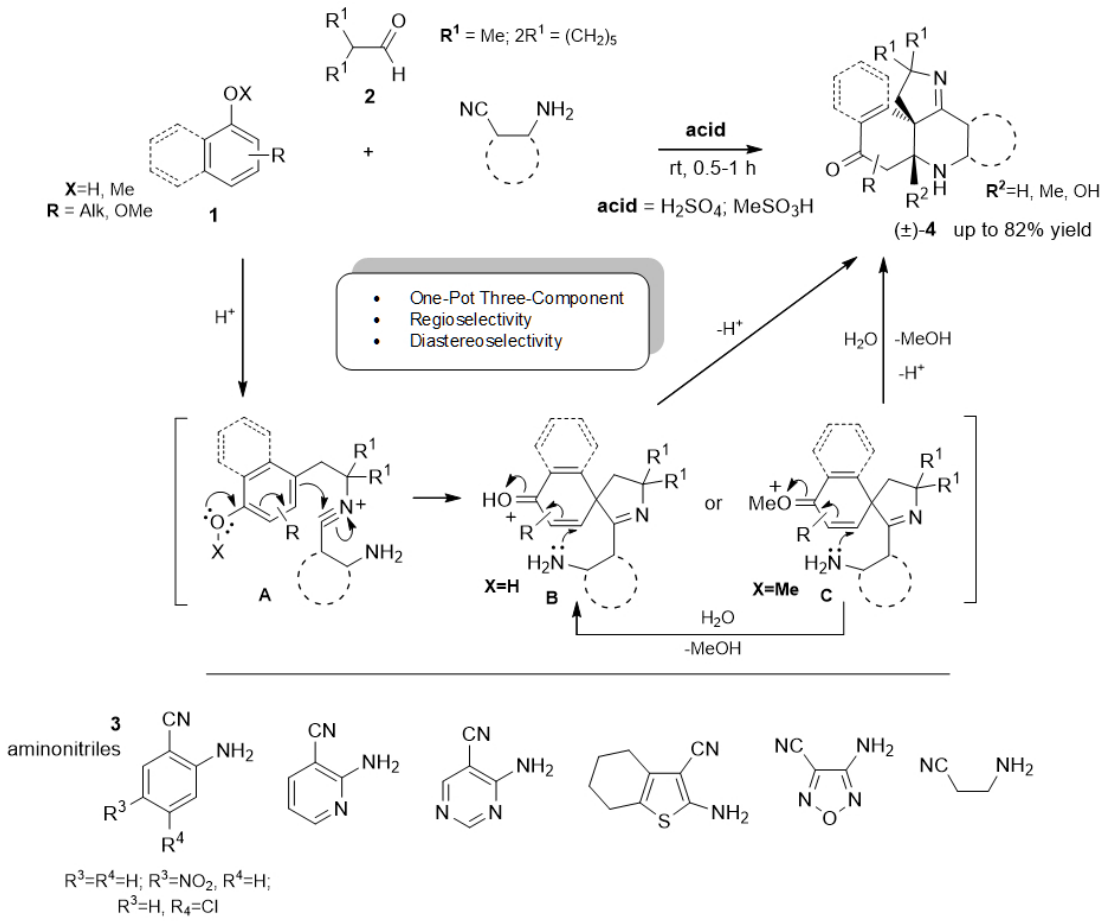
A novel and efficient approach to fused pyrrolo[2,3-d]quinolines **4** via one-pot three-component acid-catalyzed condensation of electron-rich arenes (hydroxy- and methoxybenzenes and naphthalenes) **1** with α-branched aldehydes **2** and a variety of 1,2-aminonitriles **3** has been developed (Scheme 1). The scope and limitations of this reaction have been investigated by using a range of functionalized arenes **1** and aminonitriles **3**. This domino intramolecular reaction proceeds via an electrophilic *ipso*-dearomatization/aza-Michael addition sequence and provides excellent regio- and stereoselective formation of products **4** with moderate to good yields.



Scheme 1.

This work was supported by Russian Foundation for Basic Research (grant no. 16-03-00561)

Pseudo-living OLED devices based on tetra-substituted furans and diphenanthro[9,10-b; 9,10-d]furanes

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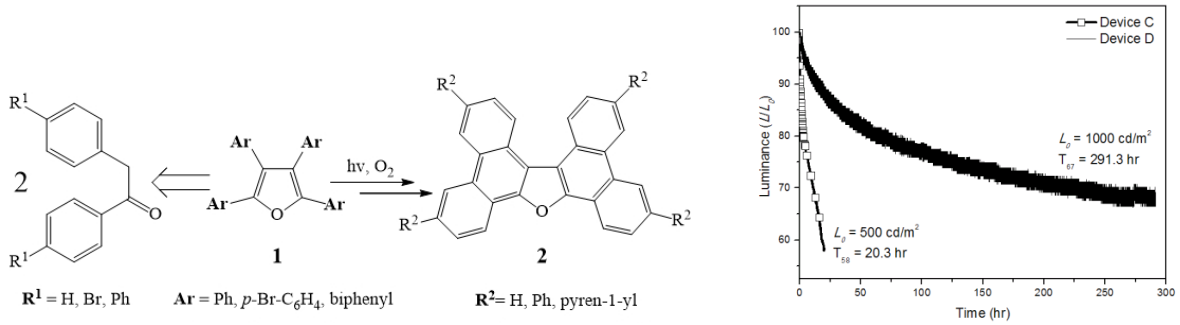
One of the most serious challenges in the organic LEDs technology is the fast degradation of blue emitting materials due to an oxidation and degradation of organic molecules by O_2 and H_2O diffusing through a protective capsule of diodes, that leads to the exponential drop in brightness of OLED devices [1] (Scheme 1, right side). At the moment there is no satisfactory solution of this problem.

We proposed a novel approach to the problem of enhance lifespan of blue diodes *via* inclusion of photochemically active diazo compounds and tetra-substituted furans and furan-3-ones (as a hole-transport layer, HTL) in the cell structure. During the cell functioning these compounds undergo an oxidative photocyclization with absorption of oxygen and formation of diphenanthro[9,10-b; 9,10-d]furanes – very stable blue emitters (λ_{em} = 400-450 nm, brightness up to $4 \cdot 10^4$ cd/m^2) [2,3]. Thus, the process of regeneration of the emitting material realizes due to the photochemical transformation of adjoining HT layers.

In the report the constructions of OLED cells and their working parameters as well as synthetic ways for emitting and supporting organic compounds will be described in details.



Scheme 1. *Left*: synthetic scheme and general structure of the organic emitter. *Right*: diagram brightness/time of the "burning up" of OLED prototypes based on phenanthrenes.

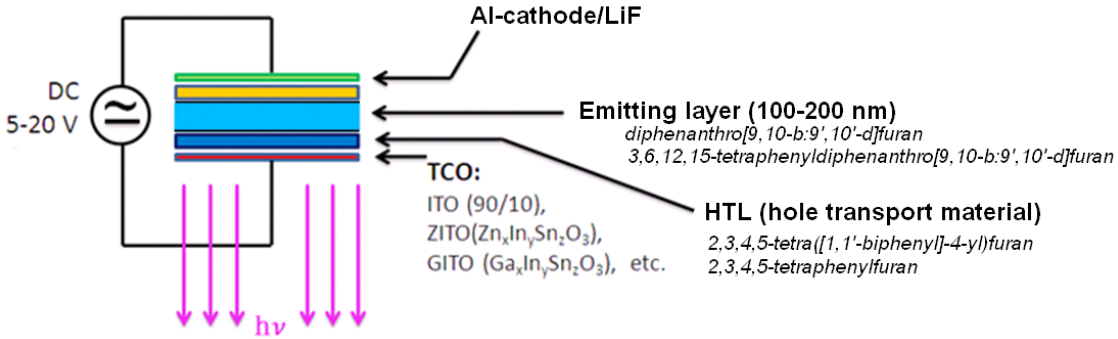


Fig. 1. Rough scheme of the multilayer structure of the investigated OLED prototype.

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This work was supported by F.A.S.I.E. foundation, grant START № 1074ГС1/21867 (2016).

Synthesis of the 5-ethynyl-2'-deoxyuridine boron cluster conjugates

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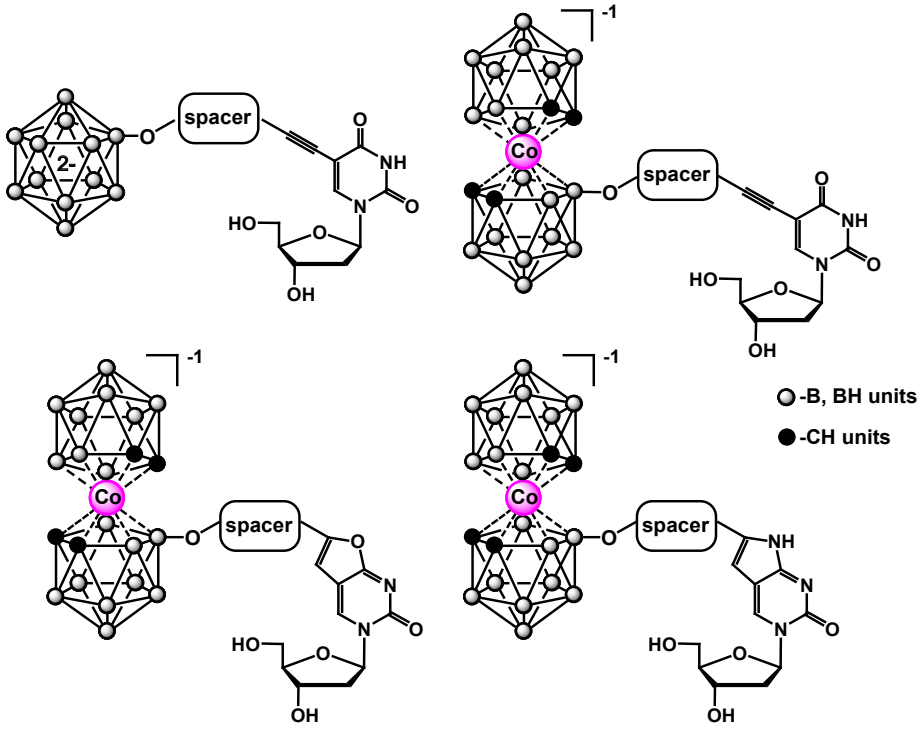
Our continious interest aims towards design of nucleoside conjugates with different boron clusters. Representative appilications of these conjugates include boron carriers for the boron neutron capture therapy (BNCT) of tumors, antiviral agents, RedOx-labels, inhibitors of the blood platelets aggregation, etc [1]. On the other hand, various 5-alkynyl modified 2'-deoxyuridines have received particular attention because this kind of substitution at position 5 of the pyrimidine nucleobase often does not attenuate susceptibility to nucleoside metabolizing enzymes and does not impart any significant conformational changes in oligonucleotides incorporating the modified unit [2].

Among the numerous boronated nucleosides synthesized so far, 5-ethynyl-2'-deoxyuridines modified with boron clusters were barely studied. In this contribution we present synthesis and preliminary biological evaluation of novel conjugates of 5-ethynyl-2'-deoxyuridine as well as its cyclic derivatives containing a *closo*-dodecaborate, carboranes and cobalt bis(1,2-dicarbollide) boron clusters.



Two synthetic approaches towards these bioconjugates as well as study of their cytotoxicity in several cell lines and antiviral activity will be discussed.

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The synthesis of alkaloids analogues

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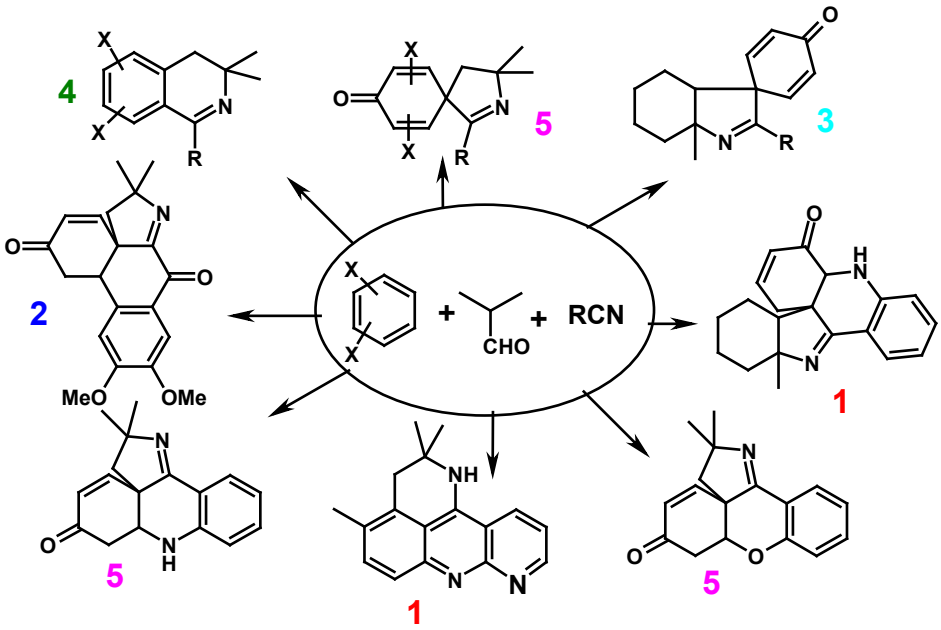

1. anticancer alkaloids analogues
2. morphinane alkaloids intermediates
3. indole alkaloids analogues (anyitumor activity)
4. isoquinoline alkaloids analoques (analgetic activity)
5. acrydine and xanthone analogues (antimicrobal activity)

The work was financially supported by grant of the RFBR 16-03-00561 and 16-33-00350-mol.

2,4,6-Trisubstituted pyrimidines: synthesis, transformations, optical and electrochemical properties

Shklyaeva E.V. [a,c], Antufieva A.D. [b], Bushueva A. Yu.[b], Vasyanin A.N. [c], Komissarova E.A. [b,c], Selivanova D.G. [b], Shurov S.N. [c], Sosnin E.A.[b], Abashev G.G.[b,c]

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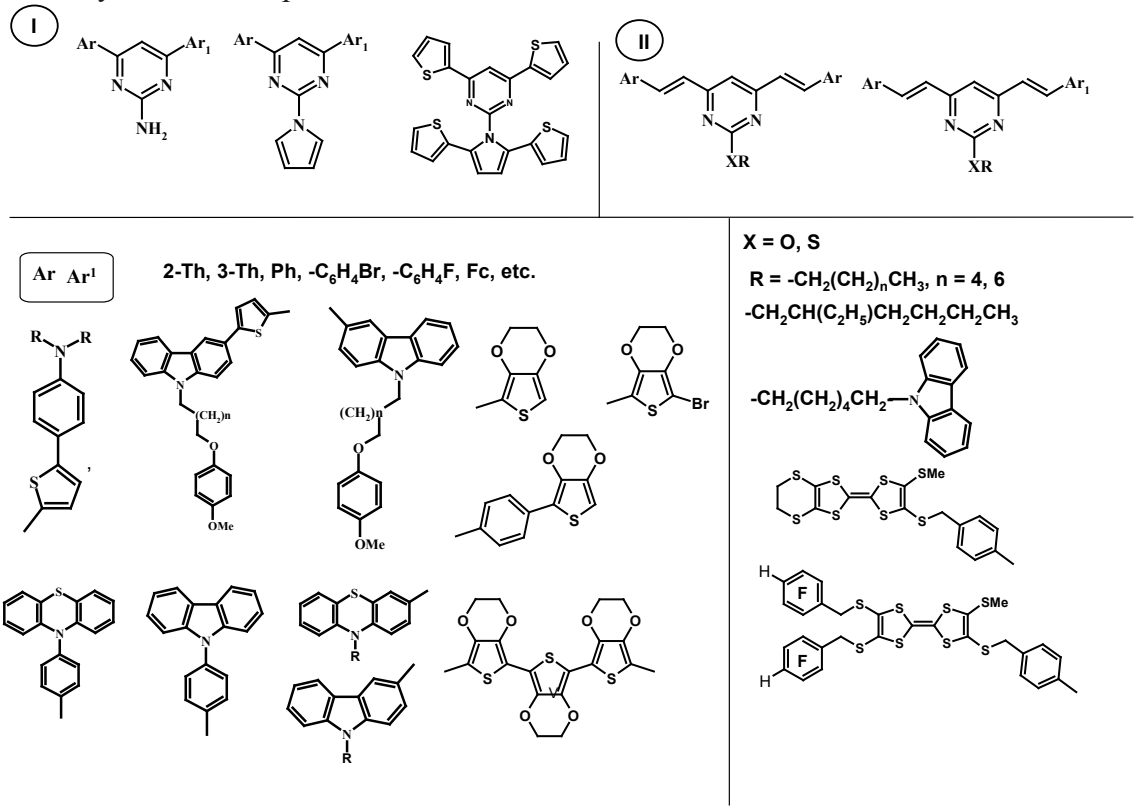
It is known that in the field of the creation of such electronic devices as OLEDs, solar cells *at al.* an important role belongs to the conjugated compounds, namely oligomers, polymers and so called "small molecules", which backbones include simultaneously electron-excessive heterocycles and electron-deficient heterocycles. Pyrimidine is one of the electron-deficient heterocycles, sometimes incorporated in such structures. This heterocycle can be easily formed and at the stage of its creation one can tune a set of substituents which combination could define properties of a future conjugated system. We have synthesized two series of 2,4,6-tirsubstituted pyrimidines (Fig. 1); some of them were polymerized electrochemically or via Gilch protocol.



All the prepared compounds were investigated from the point of view of optical and electrochemical properties. As a result, we have obtained the values of band gaps and Stokes shifts, the HOMO-LUMO energy values. For a number of compounds HOMO, LUMO and gap values were also obtained theoretically from DFT quantum calculations using B3LYP/6-311+G* basic set. As some of the synthesized compounds have revealed excellent film forming properties there prepared thin films, which surface structures were studied with the help of ASM, ETM and STM methods.

The work was financially supported by the Ministry of Education and Science RF (project No 012011461916) and by RFBR (projects 14-03-00341-a, 14-03-96003_Ural-a).

Original formulation and generic drug: equivalence instead of identity

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Modern pharmaceutics can solve almost all possible tasks assigned to it. Currently, there are thousands of drugs enable to treat the majority of diseases and pathologies successfully [1-3].

After the drug is no longer protected by patent, the copies of original product appear - generics from other manufacturers. This makes it possible to satisfy the market needs and reduce prices of the drug for the consumer.

The main problem of generic manufacturers is to proof the identity of their product to the original drug. The complex of physical and chemical methods of analysis is usually quite enough for small molecule drugs. In contrast, for products of biosynthesis, such as monoclonal antibodies, identity can not be achieved. Any attempt of reproduction results in a new drug. There is an intermediate option - complex macromolecular synthetic products, such as glatiramer acetate. For them the individual algorithms for certifying an identity are created and tested [4].

The presentation will discuss current requirements for active pharmaceutical ingredients (API) and the methods of establishing the identity of the structure and pharmacological action of generic drugs.

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New methods for carbon-carbon and carbon-heteroatom bond formation employing α-C-reactivity of nitronates

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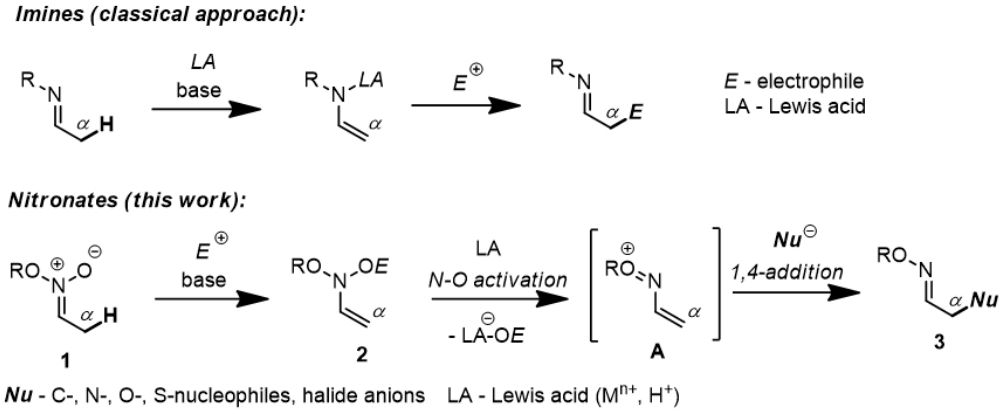
Reactions at α-carbon atom are probably the most synthetically important transformations of carbonyl compounds and imines. However, α-C-reactivity of their N,O-containing analogs (i.e. nitrones and nitronates) is much less explored. Considering the weak character of N-O bond, which can easily undergo homolytic and heterolytic cleavage, the α-C-reactivity of nitrones and nitronates can be expected to be more diverse than that of imines. This allows to design strategies, in which not only electrohiles, but also radicals and nucleophiles can be introduced to the α-carbon atom of nitrones and nitronates [1].



Scheme 1. Lewis acid-promoted α-C-H functionalization in nitronates **1**.

Here, we describe a general strategy for the functionalization of the α-carbon atom in nitronates **1** (Scheme 1) [2]. It involves the unprecedented Lewis acid-mediated addition of nucleophiles to bis(oxy) enamines **2**, which can be obtained *in situ* from nitronates **1** by the action of strong electrophilic agents with bases. The role of Lewis acid consists in activation of weak N-O bond in enamines **2** and its cleavage to form *N*-alkoxy-*N*-vinylnitrenium cations **A**. Being strong Michael acceptors cations **A** react smoothly with various C-, O-, N-, S-nucleophiles and halide anions providing α-substituted oximes **3** in result of formal S_N' substitution of O*E* group in bis(oxy)enamines **2**. This process is the most general approach to the synthesis of α–functionalized oximes and their cyclic ethers (isoxazolines and 1,2-oxazines) available to date.

In the presentation, the scope, mechanism and applications in total synthesis of the aforementioned nitronate α-C-H functionalization strategy will be discussed.

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Donor-Acceptor Cyclopropane Ring Opening with Nitrogen Nucleophiles: Small Ring Sacrifice Opening Routes to a Broad Variety of Azaheterocycles

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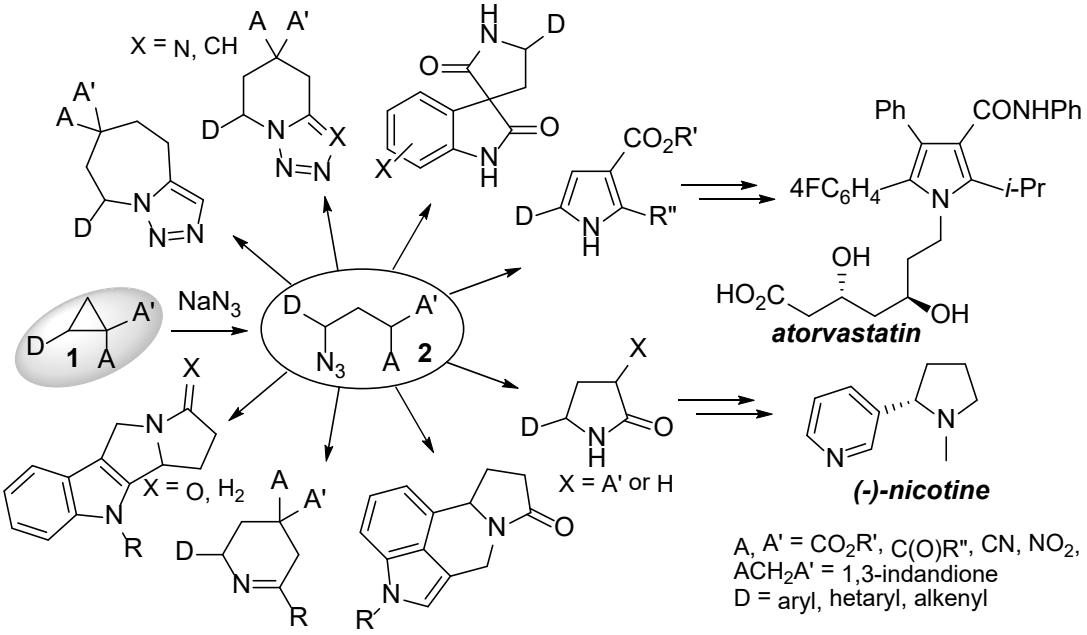
As a new general route to a broad variety of azaheterocycles, we have developed a synthetic strategy based on the donor-acceptor (D-A) cyclopropane ring opening with nitrogen nucleophiles leading to acyclic polyfunctionalized compounds bearing donor and acceptor groups, nitrogen containing reactive moiety as well as CH-acidic fragment. The subsequent intramolecular functional groups pairings, which can be performed directly or after preliminary modification(s), produce the target azaheterocycles.

In particular, D-A cyclopropanes **1** react with NaN_3 by the carbon atom bearing donor group and afford γ–azidocarbonyl compounds **2** which were further transformed into a large diversity of azaheterocycles, some of them are shown below. The proposed approach was applied to the total synthesis of (-)-nicotine and formal total synthesis of atorvastatin. On the other hand, nitroalkanes attack unsubstituted C(3) atom of D-A cyclopropanes furnishing β-(het)arylmethyl-γ–nitrobutyrates **3** which produce racetams with (het) arylmethyl group at β-position, after reductive cyclization.



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This work was supported by Russian Science Foundation (project 14-13-01178).

Solvent-free ozonolysis – large scale reactions and applications

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Ozonolysis is a well-known process which involves the reaction of ozone, usually with unsa-turated compounds, like alkenes, to form ozonolysis products (e.g. ozonides). Reductive decomposition of the ozonolysis products results in various compounds such as aldehydes. Such aldehydes and other compounds derived from reductive decomposition of ozonolysis products are valuable themselves (pheromones, drug precursors, etc.) and in the formation of resins and various polymeric materials.

Griegee proposed a mechanism of alkene ozonolysis which is widely accepted. It involves the formation of a primary ozonide A, with a rapid breakdown to zwitterion B and a carbonyl compound, followed by recombination to a secondary ozonide C which is relatively stable and survives at room temperature in most cases.

Further studies of ozonolysis revealed that protic solvents like water, alcohols and carboxylic acids can participate in the reaction. Participating solvents react with zwitterion B to form another zwitterion D with following proton transfer and formation of hydroxyperoxide E. The general agreement among researchers is that final major products are E and a carbonyl compound F.

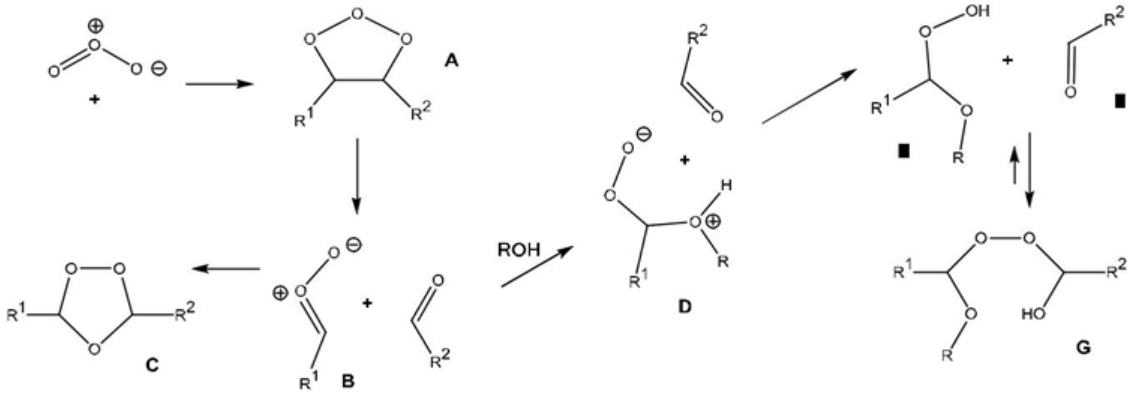

Fig.1. Ozonolysis mechanism

Our research utilised a participating co-reactant (water or alcohols) present in insufficient quantities to be deemed a solvent (from 0 to 20% w/w). The unsaturated oils, like rapeseed or Cashew Nut Shell Liquid (CNSL) were reacted with ozone at higher temperature than is usual for this reaction (0 to 80°C). It was found [1] that the final mixture of products contains very little aldehydes and the main components are peroxy hemi-acetals G. These were reduced to a mixture of aldehydes via catalytic hydrogenation, thus providing a cheap and renewable alternative to formaldehyde in the production of thermosetting resins. It was shown that CNSL being a mixture of phenolics containing a long unsaturated chain, can form a thermoset polymer itself (after ozonolysis), without additional nucleophiles.

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This work was supported by Department of Trade and Industry (DTI UK).

Unusual transformations of furans in heterocycles synthesis

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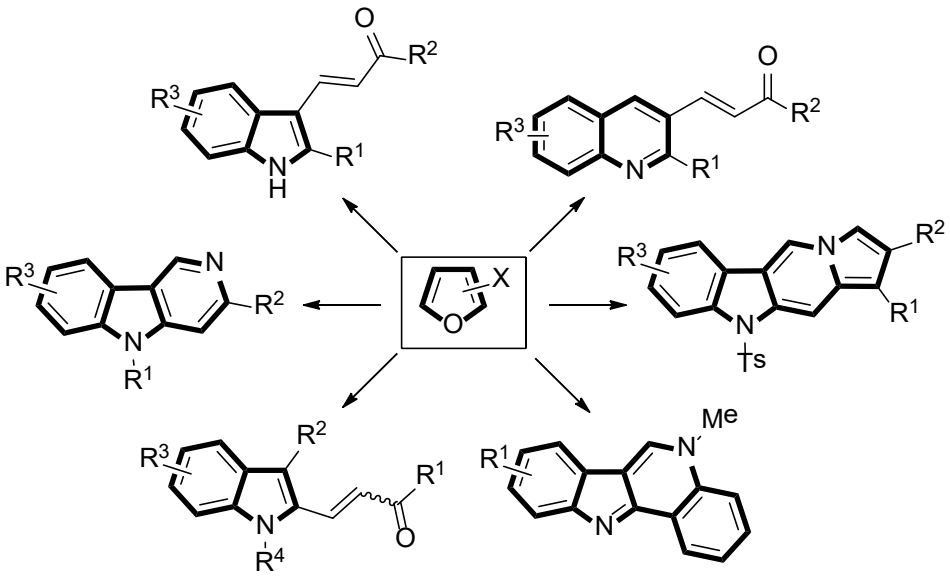
Due to low energy of aromaticity furan substrates may undergo chemical transformations which are unusual to those of arenes or other heterocycles. In such transformations furan nucleus may serve as masked 1,3 diene, enol ether or 1,4-dicarbonyl compound. This unique reactivity allows furans to be utilized in synthesis of a large variety of useful products, from alkanes to prostaglandines. Nitrogen-containing heterocycles are considered as ones of the most important among organic molecules, thus this is highly attractive to develop new synthetic routes toward such heterocyclic systems based on the utilization of so-called “furan platform”. That would provide an inexpensive way toward valuable objects exploiting products of biomass processing.

During the last decade we have developed general synthetic approaches toward functionalized heterocycles based on the furan rearrangement strategy. Recent results, discussion on mechanisms of specific transformations along with the scope and limitations of furan rearrangements into diverse polysubstituted heterocycles will be given.



This work was supported by Ministry of education and science of the Russian Federation (project № 4.246.2014/K) and the Russian Foundation for Basic Research (grant number 16-03-00513).

Highly selective heterocyclic polydentate N-donor ligands for separation of lanthanides and actinides. Computer-aided design, synthesis and coordination properties

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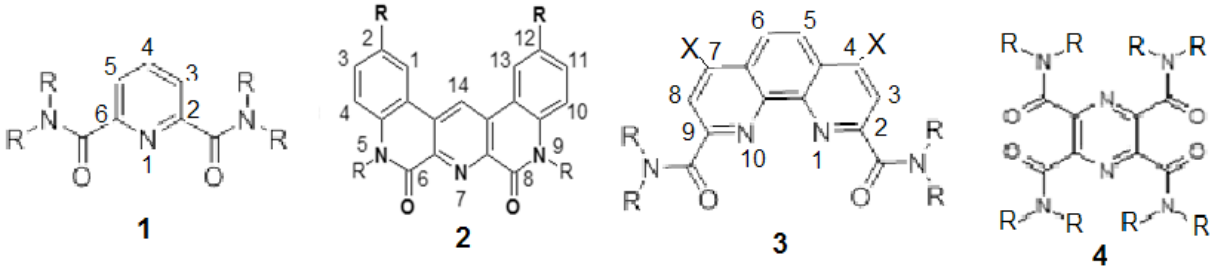
Development of high-tech separation of REE and minor actinides (Am, Cm, Np) in the processing of HLW in the construction of a closed nuclear fuel cycle and to produce high-purity rare earth compounds are among the strategic objectives of the country. Creating highly selective extractants for such processes is a challenge due to the exceptional similarity of chemical properties of these *4f*- and *5f*- elements. Quantum-chemical modeling (DFT, ab initio functional PBE and hybrid functionals PBE (0) and B3LYP, relativistic full electron TZ-basis, PRIRODA code) used to simulate structures and properties of lanthanide complexes and actinides with several series of N-heterocyclic ligands containing oxygen and nitrogen donor centers. Structures **1**, **2**, **3** and **4** having the highest characteristics (selectivity factors, thermodynamic stability of complexes) were selected as basic platforms for the synthesis. The synthesis of series of selected compounds with various substituents R and X, and their complexes with lanthanides has been performed. The ligands and complexes were characterized by UV-vis, IR, NMR, MS and XRD. The results of theoretical prediction verified in the extraction experiments on the model systems. The prospects of the use of new extractants in the development of viable technologies are discussed.



1 **2** **3** **4**

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Access to Pyridazines *via* Modified Hydrazones of Thiohydrazides

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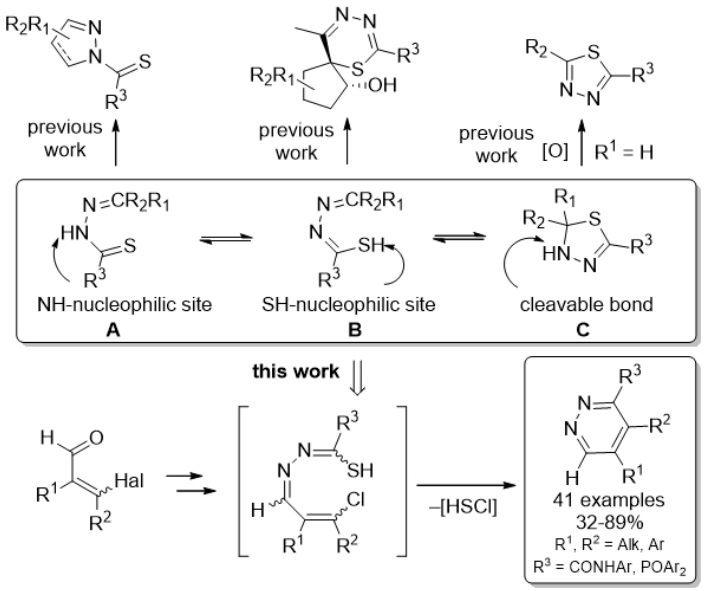

Scheme 1. Reactivity of monothiohydrazides hydrazones

In contrast to classical hydrazones, hydrazones of thiohydrazides exist as three isomers provided by an extra C=S group (Scheme 1). The thiol-thione tautomers **A**,**B** possessing NH- and SH-nucleophilic sites and cyclic thiadiazoline structure **C** equilibrate in solution thus efficiently extending the number of hydrazones of thiohydrazides possible chemical transformations.[1] Recently we elaborated a flexible approach to unknown 1,3,4-thiadiazoles, pyrazolines and spiro[1,3,4]thiadiazine with selective control of nucleophilic heterocyclization patterns of hydrazones of oxamic acid thiohydrazides.[2]

Here we report the new hetrocyclization of α,β-unsaturated hydrazones of thiohydrazides towards pyridazines.[3] A series of 3-carboxamide- and 3-diphenylphosphine oxide-substituted pyridazines were obtained in moderate to excellent isolated yields (32-89%). The synthetic value of this method was demonstrated by efficient synthesis of unique steroidal pyridazines of androstene and estrane series with cytotoxicity against the cell lines MCF-7 and MDA-MB-231. The mechanistic rationalization of the observed cyclization using UV spectroscopy, real-time ^{1}H NMR monitoring and computational studies (B3LYP/6-311+G(d,p), B3LYP/3-21+G(d,p) и B3LYP/6-31+G(d,p)) was performed.

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Photocatalytic C-F bond activation in polyfuorinated arenes

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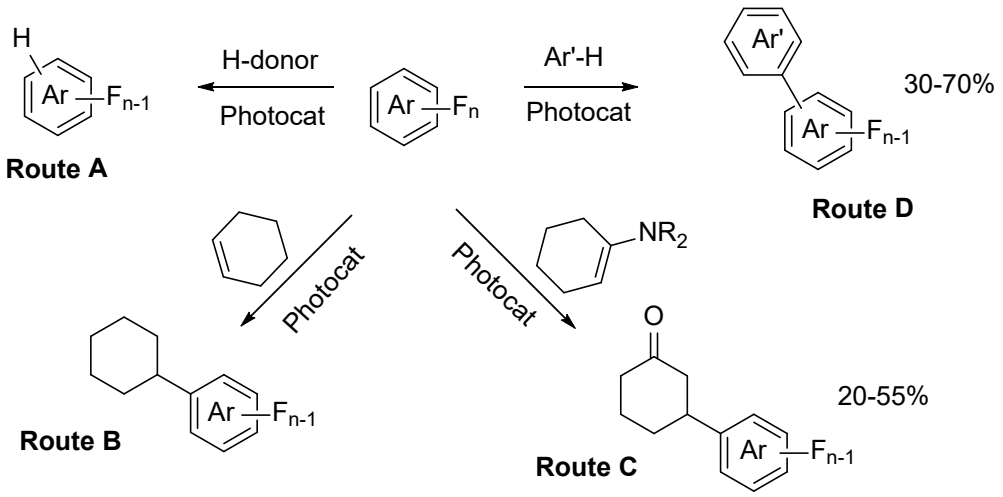
Polyfluorinated aromatics are of great interest to materials science as well as the medical chemistry, pharmaceutical and agrochemical industries and yet are often difficult to access. One of the main routes to multifluorinated arenes is nucleophilic substitution of fluorine atoms or hydrodefluorination in readly available perfluoroarenes. Catalytic methodologies for C-F bond functionalization have also been suggested [1]. Recently visible light photocatalytic hydrodefluorination (Scheme 1, route A) [2] and defluoroalkilation (Scheme 1, route B) [3] approaches utilising $Ir(ppy)_3$ has been described as an effective tool for perfuoroarenes derivatization.

We started our work with studies of perfluoroarenes interaction with trialkylamines which are known to undergo α-C-H- functionalization under photocatalytic conditions. However, we found NMe_3, NEt_3 and NBu_3 to lose one alkyl group yielding N,N-dialkylamino substituted polyfuoroarene. In case of Ph-NMe_2 we oserved only benzene ring perfluoroarilation products. Other electron-rich aromatics readly undergoes perfluoroarilation in similar photocatalytic conditions as well (Scheme 1, route D). We also investigated an interaction of cyclohexanone enamine with perfluoroarenes under $Ir(ppy)_3$ photocatalysis. The enamine was found to form β-perfluoroarylation product which gave corresponding β-arylated ketone after aquaous work up (Scheme 1, route C). Possible mechanisms of the trasformations will be discussed on the basis of competition kinetics experiments.



Scheme 1.

The applications of heterogeneous photocatalysts such as TiO_2, CdS and ZnS for C-F functionalization will be discussed.

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Oxidation of Dibutyl Sulfide by Oxygen of Air under Visible Light Catalyzed by C_{70}

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Oxidation of organic sulfides is an important stage of many organic synthesis procedures requiring introduction of sulfoxide or sulfone moieties. Obtaining high yields and selectivities with utilization of cheap non-toxic reagents is the way to improve the present ways of carrying out oxidation of sulfides. We undertook research on optimal conditions for oxidation of dibutyl sulfide (DBS) with oxygen of air at room temperature over visible light irradiated fullerens present in catalytic amounts. Previously the effect of irradiation wavelength was investigated [1] and we unexpectedly found that the rise in irradiance increased quantum yield of the oxidation reaction.

In the present research the influence of concentrations of the reagents (air flow, DBS concentration, C_{70} concentration) is investigated. Addition of ethanol into the initially toluolic reaction mixture greatly increased the rate of oxidation and allows obtaining almost pure dibutyl sulfoxide with quantitative yield. Without ethanol addition, several by-products are usually obtained such as dibutyl sulfone, dibutyl disulfide and butyraldehyde. Fig. 1 demonstrates the effect of addition of ethanol on the rate of DBS photooxidation. One can see that addition of moderate amounts of EtOH increased the rate by over an order of magnitude. The reaction became so fast that it took less than an hour to finish it at $[DBS]_0$ = 0.27 M.

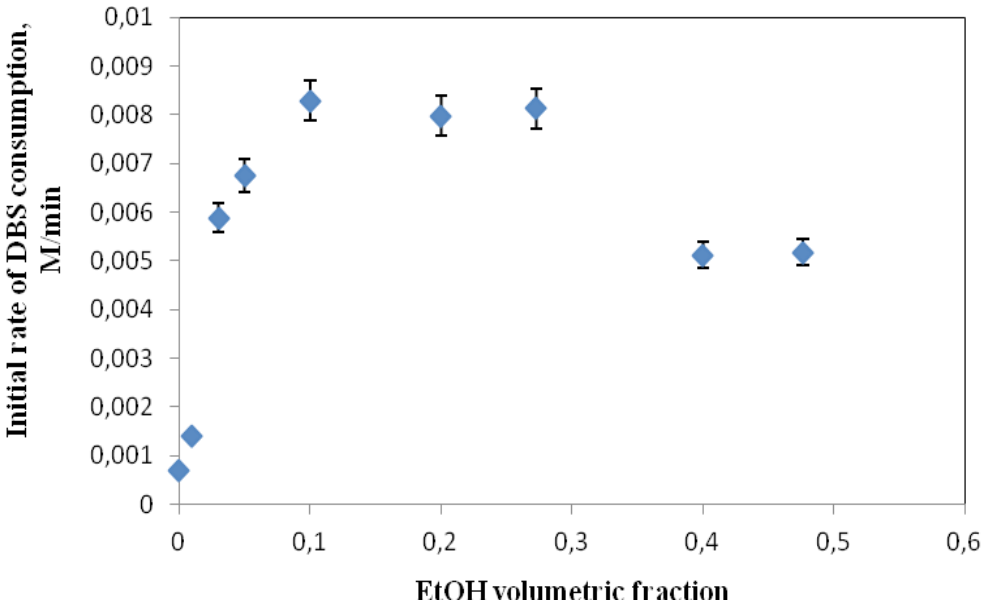

Fig. 1. Rate of DBS oxidation as a function of EtOH fraction in the reaction mixture.

Optimization of such parameters as DBS initial concentration, EtOH concentration, C_{70} concentration and air flow rate allowed obtaining pure sulfoxide as the sole product. Possible mechanism of the oxidation reaction with participation of singlet oxygen is suggested and will be discussed. The reaction can be up-scaled with utilization of solar light and ambient field reactors.

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Policy Management and Recent Development on Transgenic Technologies

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Fellow of Royal Society Chemistry UK

Patent and trade secret are the main choices for intellectual property protection on transgenic technologies, which is an integrated application in combined with biotechnology, microbiology, genetics and chemical engineering. The products can be generated through bioprocess by applying microorganisms, plants, and animals. Genetic transformation, metabolic pathways and biological process are involved in plants, animals and DNA scale to produced translation medicine, nutrition, and food. In 1985, Diamond v. Chakrabarty confirmed the patent protection of man-made microorganism; in 1087, the approval of onco-mouse set up the first transgenic animal patent.

The characteristic for plants development to be improved through innovative approach include yield, disease and insect tolerance, salt-tolerance, the ability to fix nitrogen, and tolerance to environmental stress, such as extreme temperature. Statistically, there were up to 40 percent of crop-loss insurance claims are due to heavy or moderate drought. The commercial biotech crop designed focused more to resist stressful environmental conditions rather than pests and herbicides, though the most well-known traits are herbicide tolerance and pesticide resistance.

Competing with transgenic technology, the 'marker assisted selection' gives the new hope with less fear from the unpredictable consequences if the climate-tolerant crops can be developed by using conventional breeding methods with new genetic information. As farmers start to suffer from herbicide tolerant 'super weeds' due to growing GM herbicide tolerant crops, likewise to the use of GM pest resistant crops to create Pesticide resistance. For this moment, 'Drought-tolerance trait and cannot be delivered by engineering a single gene into a plant, remain the most complex challenge. International agreements like International Undertaking on Plant Genetic Resources for Food and Agriculture in 1983, Convention on Biological diversity in 19913 and International Treaty on Plant Genetic Resources for Food and Agriculture in 2004 are involved in regulation human behaviors which may challenge God's creation.

In this paper, we analysis the development of technology trend on leading genetic modified crop, such as soybean, corn, rapeseed, cotton, and rice. In addition, we also explore the technology competency of leading companies with intellectual property analysis, including Monsanto, Bayer CropScience, DuPont Pioneer, Dow AgroSciences, etc. Hope to provide guidance and protocol for industry to learn from this paper, aiming for better development and outcome to improve crop safety and quality supply with safety for human being.

Key words: transgenic, patent litigation, patent licensing, industry alliance

New antiviral agents based on camphor scaffold. The steps from chemistry to medicine.

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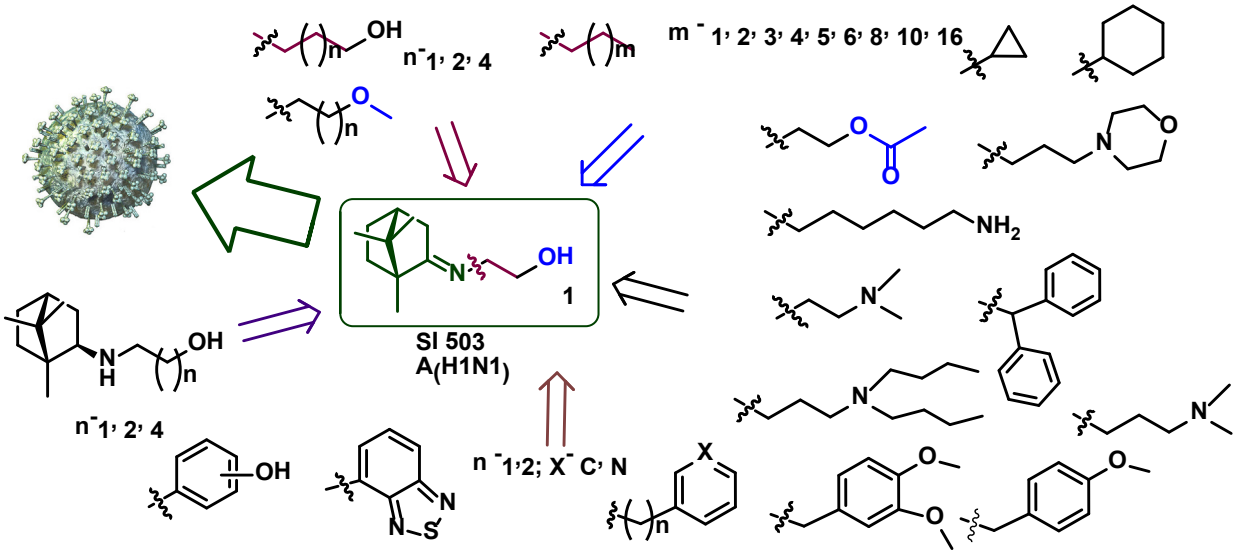
The search and development of novel agent against influenza virus is an important challenge for medical science and health care around the globe. We previously reported the synthesis and antiviral activity of compounds based on camphor [1, 2]. Now we have tested a set of new imino-derivatives of camphor for their inhibiting activity against pandemic influenza virus A (H1N1). As a result, we have synthesized and tested for antiviral activity more than two hundred substances. The therapeutic index of compound **1** is over 100 times higher than that of the reference compounds [3].



Camphor derivatives should be considered prospective for further development as potential antiviral able to overcome the resistance of currently circulating viruses to amantadine and rimantadine. The synthesis was optimized using factorial experiment. We developed a method of detection **1** in plasma using MS and the method was validated. The pharmacokinetics has been studied in preclinical trials. We have demonstrated high level and broad range of inhibiting activity of camphor derivative **1** against influenza viruses (H1N1, H3N2, H5N2, B) that is based on inhibition of viral hemagglutinin and is the most prominent on early stages of virus replication.

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YOUNG SCIENTISTS SESSION

Ruthenium(II)–phenanthrolines bearing polyamine receptors: synthesis and metal ion recognition

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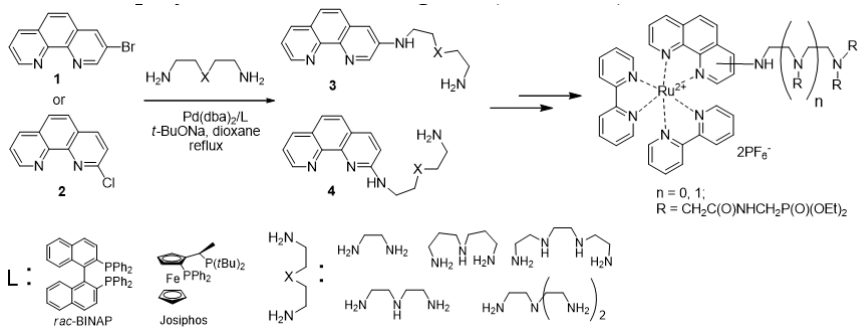
Design of optical chemosensors is one of the most important research axes in the development of diagnostic systems that covers various areas of human activities including clinical toxicology, environmental bioorganic chemistry and waste management. To develop optical sensors or probes, ruthenium complexes with 2,2'-bipyridines and/or 1,10-phenanthrolines seem to be of interest due to their appropriate photophysical properties. However, chemosensors based on these complexes are still scarcely investigated as compared to those containing organic signaling unit.

In this work a general synthetic approach to ruthenium(II) complexes with polyamine substituted 1,10-phenanthrolines is described. Amination of readily available 3-bromo-1,10-phenathroline (**1**) and 2-chloro-1,10-phenanthroline (**2**) with different polyamines was investigated (Scheme 1).



Scheme 1.

Polyamines react with 2-chloro-1,10-phenanthroline (**2**) under non-catalytic conditions (K_2CO_3, DMF, 140°C). However, the selective functionalization of primary amino group by chloride **2** in polyamines possessing primary and secondary amino groups can be achieved only under palladium catalysis conditions. The amination of less reactive 3-bromo-1,10-phenathroline (**3**) proceeds smoothly only under the catalytic conditions. The influence of the ligand and bases on the reaction outputs will be discussed.

Next, thus obtained compounds were *N*-functionalized with hydrophilic phosporous-containing substituents and introduced in the reaction with *cis*-$Ru(bpy)_2Cl_2$ to prepare chelators possessing emissive properties (Scheme 1). The sensing properties of these chelators with respect to environmentally-relevant metal ions were studied by using UV-vis and fluorescence spectroscopy.

The work was performed in the frame of French-Russian Associated Laboratory "LAMREM" and financially supported by the RFBR (grant N 12-03-93107) and CNRS.

10h-phenothiazines synthesis using double C-H functionalization of arenes

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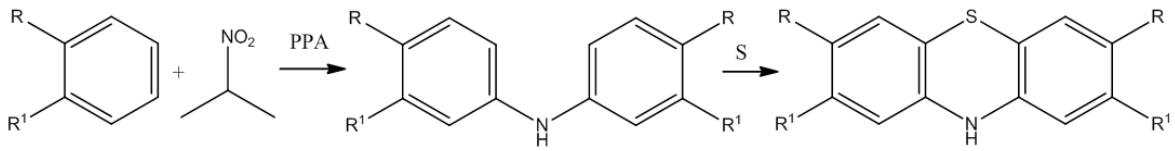
Phenothiazine one of a class of drugs used to control mental disorders. Phenothiazines reduce psychiatric disorders without causing addiction or euphoria. They are widely used to treat the symptoms of persons suffering from schizophrenia, psychotic depression, the manic phase of manic-depression, and organic psychoses. The phenothiazines suppress or eliminate such symptoms as hallucinations, delusions, agitation, and disordered thinking. It acts by blocking dopaminergic transmission within the brain. Also can be used also in the treatment of certain types of porphyria and with other medicines in the treatment of tetanus. Anticholinergic, antipsychotic, antihistamine, anti-arrhythmic action has been demonstrated. A wide spectrum of biological activity determining interest in the constant search for new methods of synthesis of such compounds. Classic methods of synthesis include the using of sometimes inaccessible diarylsulphides and diarylamines.

As was shown in our laboratory indoles interaction with 2-nitropropane in PPA medium leads to formation of diarylamines from available arenes in high yields. It was shown that sulphur reaction with diarylamines leads to formation of corresponding phenothiazines so we found that we can use this approach for creation of *in-one-pot* synthesis. Indeed reaction of arenes with 2-nitropropane in PPA with subsequent addition of sulphur proceeds as functionalization of 4 C-H bonds leading to formation of desired 10H-phenothiazines.



Scheme 1. One-pot synthesis of 10h-phenothiazines

This project was supported by grants from the Russian Science Foundation (grant #14-13-01108)

Reactivity of diazoazoles and azolyl diazonium salts towards 3-azolyl enamines

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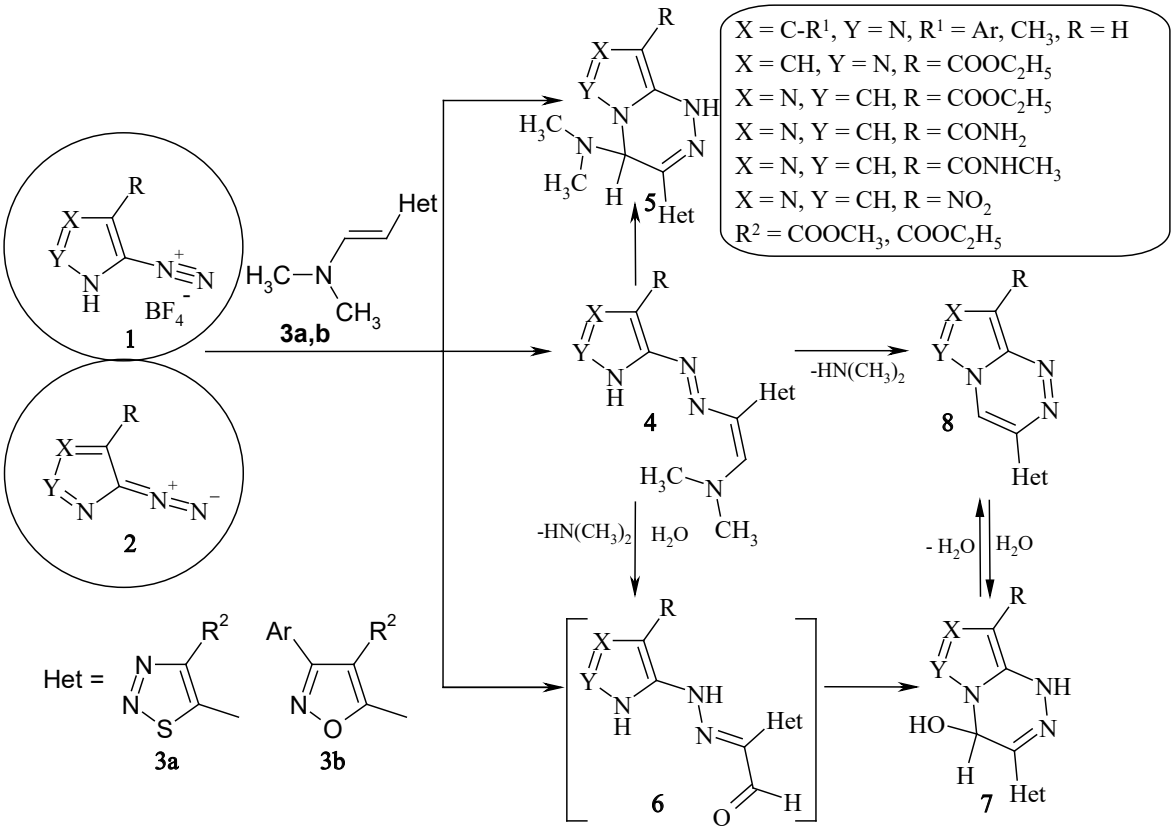
It is known that heterocycles bearing diazo function readily react with enamines. Two plausible routes of this interaction such as *C*-azo coupling or cycloaddition strategy are assumed. It is important to note that there is no mention of isolated and characterized intermediates of the process hitherto.

In the current research we have carefully studied the reaction of 3-substituted pyrazole-5-diazonium salts **1**, ethyl 5-diazopyrazole-4-carboxylate and 4-substituted 5-diazoimidazoles **2** with enamines **3** containing isoxazole and thiadiazole moieties.



It is found that the form of diazo component does not affect the structure of the final products. Actually, treatment of either 3-substituted pyrazole-5-diazonium salt **1** or 5-diazopyrazoles **2** bearing weak electron donating groups with enamines **3a,b** gives exclusively aromatic compounds **8** in excellent yields. On the other hand, introduce of the electron withdrawing groups in the molecules of both diazopyrazole and diazoimidazole derivatives leads to formation of 3-4 component mixture of products. 3-(4'-R-1,2,3-Thiadiazolyl)-1,4-dihydro-4-dimethylaminoazolo[5,1-*c*][1,2,4]triazines **5** in reaction with **3a** and 3-(3'-R-4'-R'-isoxazolyl)-1,4-dihydro-4-hydroxyazolo[5,1-*c*][1,2,4]triazines **7** in reaction with **3b** are isolated as main products along with azo intermidiates **4** and corresponding 4-R-5-(3',3'-dimethyltriazen-1'-yl)azoles. Our experimental data strongly suggests that we are dealing with azo coupling mechanism in this research.

Authors thank the Ministry of Education and Science of the Russian Federation (State task 4.1626.2014/K) and RFBR (grant № 14-03-01033) for financial support.

Spacer-armed bis-pyridyltriazole – new versatile ligands for coordination chemistry

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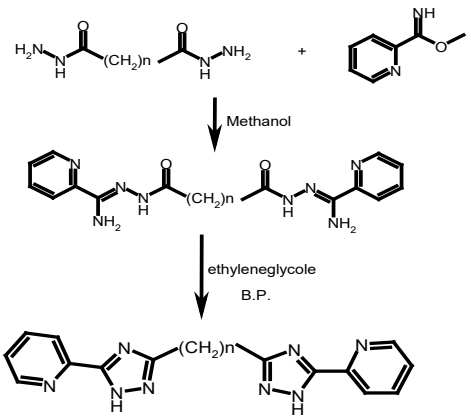
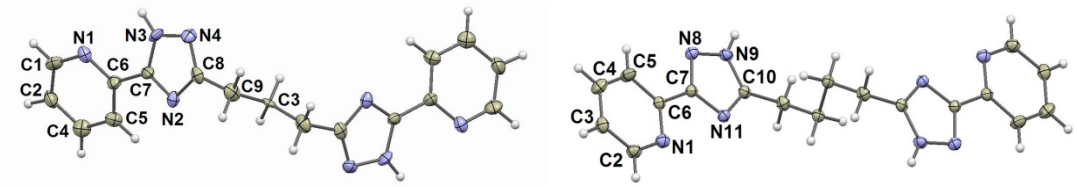
The use of the 1,2,4-triazole moiety as a part of ligand systems has gained considerable attention in recent years. A common strategy to gain some control of the coordination behaviour of small heteroatom rich systems like 1,2,4-triazole is to introduce aditional substituents carrying additional donor atoms thus creating bi- or terdentate binding sites which enhance the stability of the resulting complexes due to the chelate effect. Introducing flexibilty into bridging ligands can introduce an extra element of uncertainty into the formation of coordination compounds with controled properties. Ward and co-authers described numerous examples of polyhedral cages based on relatively simple bis(pyrazolyl-pyridine) bridging ligands and transition metal dications. Surprisenly other spacer-armed pyridylazoles are considerably rare. Here we describe sinthes, structure of new specer –armed ligands - bis-pyridyltriazole.



L^n n = 0-4

A series of new bistriazoles was prepared by a two-step reaction of 2-cyanopyridine and dihydrazide of oxalic malonic, succinic, glutaric or adipic acids. Heterocycles were fully characterizeted by various techniques such as elemental analysis, FTIR, NMR and UV-Vis spectroscopy. X-ray structures of L^3 and L^4 were determined.



The diffuse reflectance spectra of solid samples and electronic absorption spectra of methanol solutions of title triazoles contain two intensive bands with maxima at 240-244 nm and 275-282 nm assigned to π–π* transitions in triazole and pyridine rings. Bis-pyridyltriazole exhibit photoluminescence under UV irradiation. The position of the emission maximum and quantum yield for solid samples vary depending on the excitation wavelength, undergoing bathochromic shift with increasing excitation wavelength. Notably shift to longer wavelengths of the emission maximum from 347 to 398 nm and increasing the quantum yield (from 3 to 18%) increase in polymethylene chain length

This work was supported by Russian foundation for basic research (project № 16-03-00386) and Ministry of education and science of Russian Federation (project № 3874).

Synthsis and reactions of adamantyl-containing isocyanates and isothiocyanates

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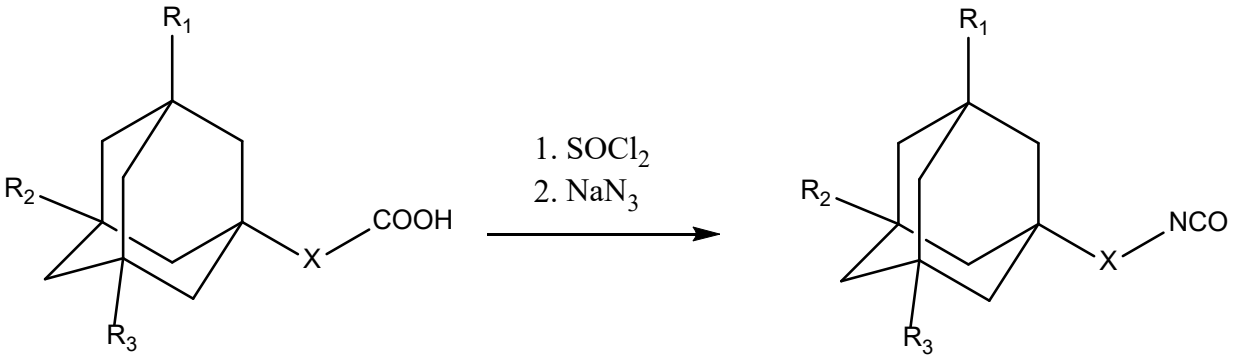
Adamantyl-containing ureas and thioureas are potent human soluble epoxide hydrolase (sEH) inhibitors. Inhibition of this enzyme by highly selective inhibitors leads to vasodilation and inflammatory pain relief. It makes soluble epoxide hydrolase a promising target in therapy of hypertension and inflammation. Moreover sEH inhibition could be used to treat renal diseases, Parkinson, Alzheimer and cancer.

Despite of more than 3000 sEH inhibitors of adamantine series were synthesized as for now, most of them were made from 1-adamantane isocyanate. General formula of such compounds is Ad-NH-C(O)-NH-R, где where Ad – 1-adamantyl. Thus the impact of substituents in adamantane and spacers between adamantane and urea group was not investigated.

One of the easy ways to acquire ureas and thioureas is interaction of iso- and isothiocyanates with amines. To synthesize ureas with substituents in adamantane and spacers between adamantane and urea group we developed new adamantyl-containing iso- and isothiocyanates.

First approach assumes synthesis of isocyanates by the Curtius reaction. Known method was improved to exclude possible explosiveness (Scheme 1).



Scheme 1. Preparation of adamantyl-containing isocyanatrs. R_1 = H, CH_3, CH_2-CH_3, $CH(CH_3)_2$; R_2 = H, CH_3; R_3 = H, CH_3; X = -, CH_2

Second approach is the reaction of 1,3-dehydroadamantane with various iso- and isothiocyanates. And finally we discovered that adamantyl-containing isothiocyanates could be synthesized by the reaction of amines with phenylisothiocyanate.

Those isocyanates and isothiocyanates were used to develop new series of ureas and thioureas. Inhibitory activity (IC_{50}) was investigated at Department of Entomology and Nematology University of California Davis.

Synthesized ureas show high inhibitory activity towards sEH. IC_{50} of lead compounds are < 0.5 nM. IC_{50} of best thiourea was 8.2 nM which is very good result for thioureas.

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Versatile Catalytic System for Selective Markovnikov-Type Hydrothiolation

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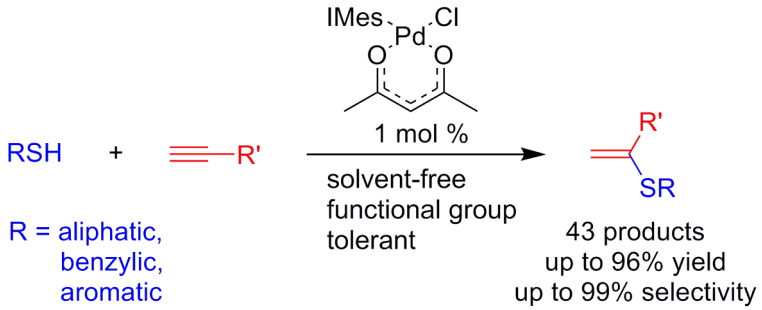

Alkyne hydrothiolation is a direct way of vinyl sulfides synthesis. Vinyl sulfides act as starting materials for heteroatom-functionalized polymers, which find a broad application in high-performance engineering plastics, optics, optoelectronics, network polymers, etc. The addition reaction to unsaturated bonds is the best atom-economic approach to access the target monomers.

In the study we developed an efficient catalytic system for selective formation of vinyl sulfides from different substrates. We found that Pd-NHC complexes catalyze hydrothiolation irrespective the thiols nature. In optimized reaction conditions evaluation of various alkynes and thiols proved high activity of the catalyst. All of the products were obtained in high yields. Interesting feature of the catalytic system is its compatibility with a wide temperature range (from 35 to 100 °C).

We have found that reaction of [IMesPd(acac)Cl] catalyst precursor with thiols (RSH) leads to the formation of unstable catalytically active species [IMesPd$(SR)_2$] and stable catalytically inactive dimer [IMesPd$(SR)_2]_2$. The mechanism of catalytic cycle involves the following steps: 1) alkyne coordination and insertion into the Pd-S bond; and 2) protonolysis of Pd-C bond with the thiol. Detailed mechanistic picture and substrate scope will be presented and discussed.

References

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This work was supported by Russian Science Foundation (RSF Grant No. 14-50-00126).

Reaction of arylboronic acids with 5-aryl-3-substituted-2-thioxoimidazolin-4-ones

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Recently, 2-thiohydantoin and its derivatives have attracted scientists attention[1]. By modification of 2-thiohydantoin fragment, analogs of biologically active substances and natural alkaloids can be produced. While S-alkylation of 2-thiohydantoin derivatives is a well known transformation [2], arylation of sulfur atom is mentioned only in a single publication [3]. We have optimised the conditions of arylation of 5-arylmethylene-3-substituted-2-thioxoimidazolin-4-ones with boronic acids in presence of copper acetate(II) (Scheme 1).

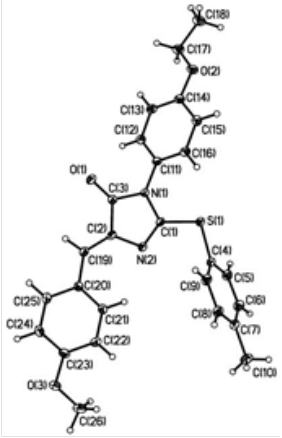
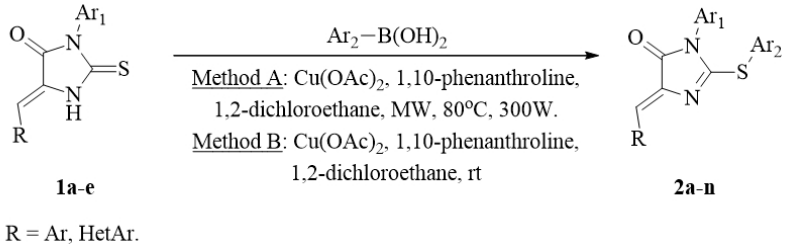


Fig. 1. The structure of the product **2f** was confirmed by X-Ray analysis.

We have obtained a number of novel compounds with yields 57 – 85%. We have developed a new method of synthesis of 3-substituted-2-thiogydantoins without using microwave irradiation. In case of 5-hetarylmethylene-2-thioxoimidazolin-4-one the process of alkylation by 1,2-dichloroethane became predominant. Subsequntly we decided to use more polar and aprotic solvent, such as DMF. 5-thiophenemethylene-2-thioxoimidazolin-4-one was taken, the yield after 12h without microwave irradeiation was 50%.

The final stage of our study was to test all the resulting compounds for antitumor activity. To test the binding affinity, the cell lines of human prostate cancer LNCaP (p53 expressing) and PC-3(not expressing p53) and breast cancer cells were taken. MTS-test [4] was used. LECH-4 cells were taken to test the toxicity of our compounds, no activity was observed. The results will be presented on the poster.



R = Ar, HetAr.

Scheme 1. General synthesis of 5-aryl-3-substituted-2-thioxoimidazolin-4-ones.

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This work was supported by RSF Foundation №14-34-00017.

1-Ethoxypentenynones in the synthesis of nitrogen heterocycles

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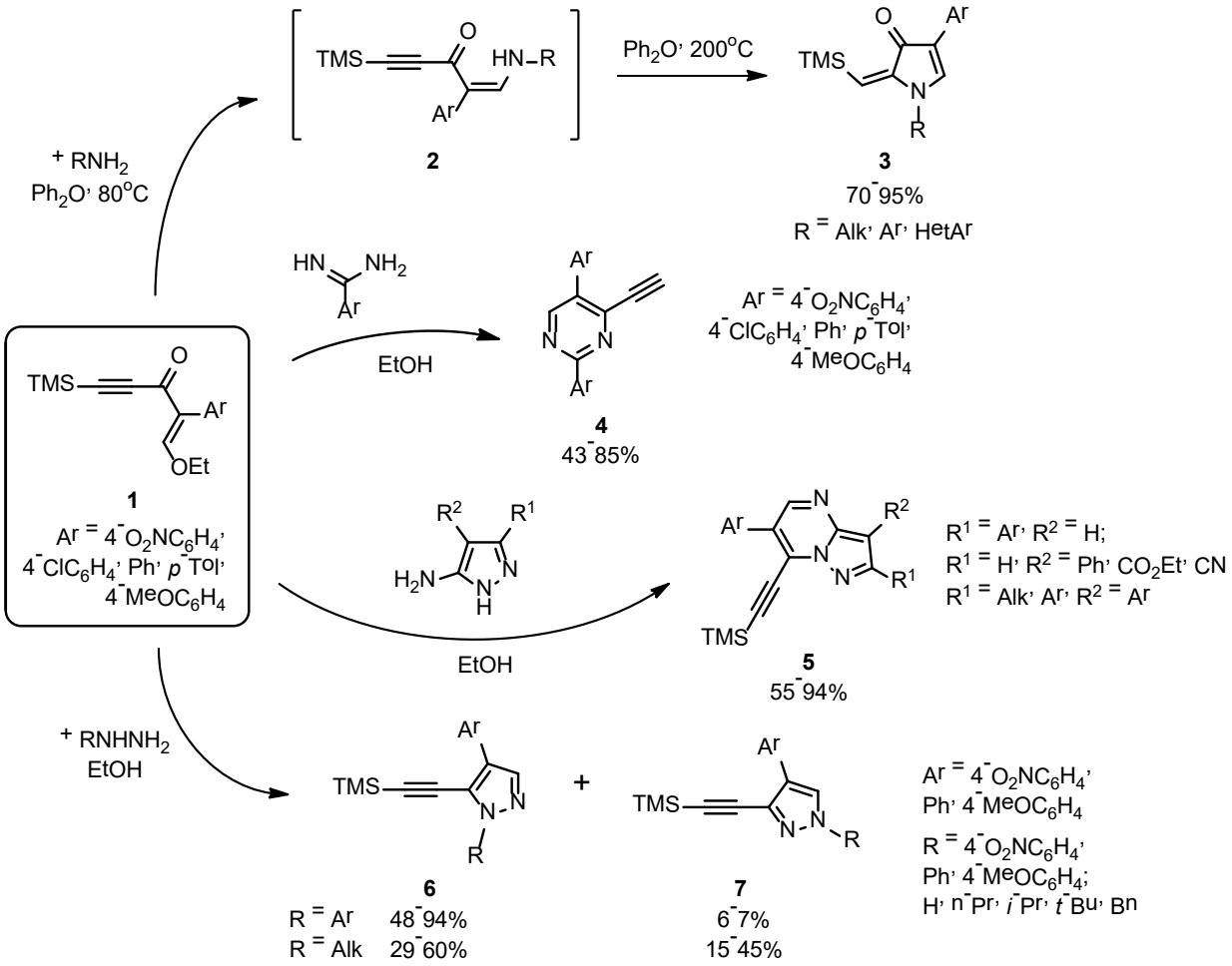
Chemistry of acetylenic compounds has been one of the major issues in synthetic organic chemistry over the last decades. Recently we have developed an approach to acetylenic ketones **1** based on easily accessible starting materials. These compounds contain three electrophilic centers and therefore they can be used for the synthesis of various heterocycles.



The reactions of enynones **1** with mono- and binucleophiles generally proceeded smoothly with high yields and regioselectivity. The triple bond of compounds **1** remained intact in reactions with hydrazines [1], amidines [2] or aminopyrazoles, and corresponding acetylenic heterocycles **6**/**7**, **4** and **5** were obtained. However, unusual regioselectivity of intramolecular addition to the triple bond was observed when amines were used to afford pyrrolone derivatives **2** [3].

References

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[3] Golubev, P.R.; Pankova, A.S.; Kuznetsov, M.A. *J. Org. Chem.* **2015**, *80*, 4545-4552.

This work was supported by a grant of the President of Russian Federation № MK-5965.2016.3.

3-Hetaryl-2-quinolones from 2-hetaryl-2-indolylnitroetanes

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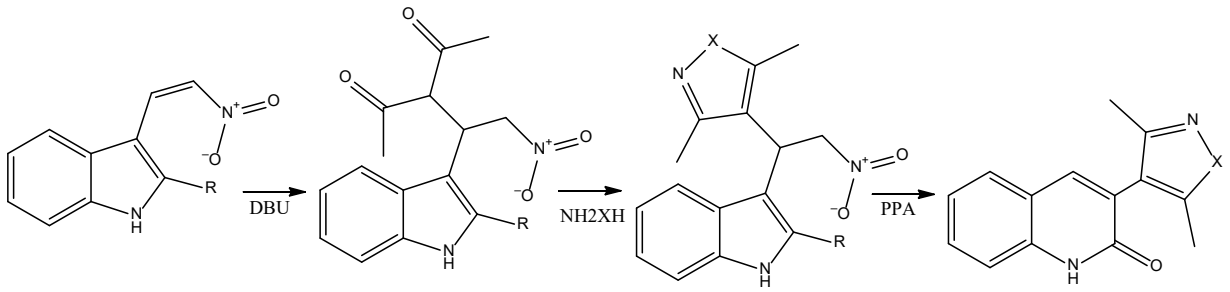
Alkaloid related species are compounds of great interest in terms of biological activity studies. Such an interesting class is 3-Hetaryl-substituted 2-quinolones. However, known methods for preparing of such compounds often include preparation of difficult to obtain starting compounds.

We found that these compounds are ready available from 2-hetaryl-2-indolylnitroetanes by the transannulation reaction of 2-hetaryl-2-indolylnitroetanes to 3-hetaryl-2-quinolones that was shown recently in our laboratory. The transformation proceeds with high yields and provides a wide range of 2-quinolones, using available starting materials. This project is dedicated to the synthesis of 2-hetaryl-2-substituted indolylnitroetanes using a simple sequence: Michael reaction-heterocyclisation followed by transannulation to 3-hetaryl-2-quinolones. Indeed, interaction of nitrovinylindoles with acetylacetone in presence of base and reaction of obtained dicarbonyl compound with NH_2OH or NH_2NH_2 gives us 2-hetaryl-2-indolylnitroetanes as semi-product. Reaction of the last in polyphosphoric acid leads to formation of decired 3-hetaryl-2-quinolones in good yeields.



Scheme 1. Synthetic sequence

We thank Russian Foundation for Basic Research (grant # 16-33-60108 мол_а_дк), and grant from the President of the Russian Federation for Young Scientists and Leading Science Schools (МК-5733.2015.3) for the financial support of this work.

Synthesis of new amphiphilic *p-tert-butyl*thiacalix[4]arenes derivatives in *1,3-alternate* stereoisomeric form via CuACC reactions

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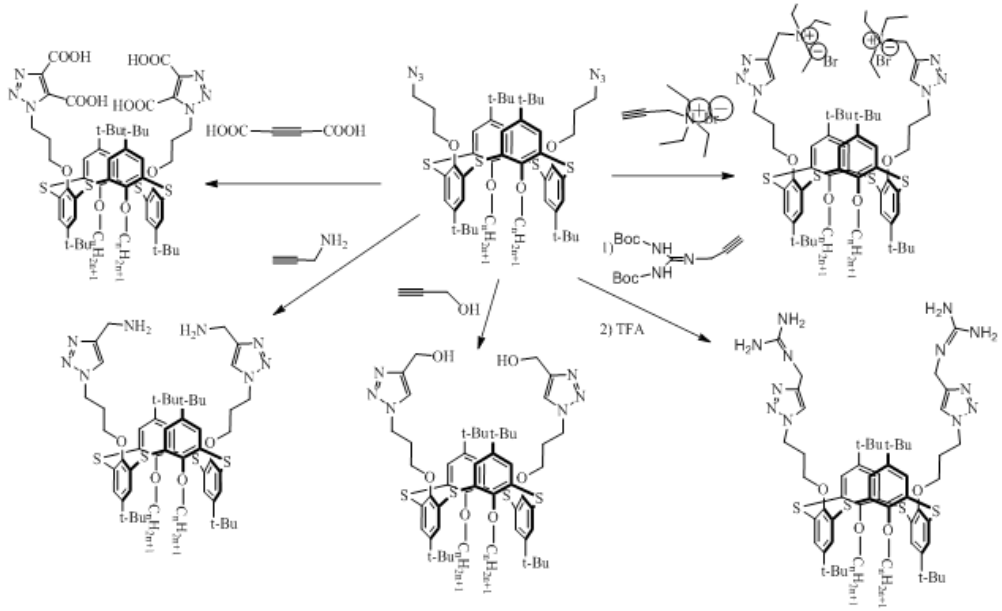
Calix[n]arenes are macrocyclic compounds consisting of four to eight phenolic units linked together via methylene bridges or S, O and other atoms. They have been found to be effective as complexing agents, substrate delivery systems, molecular receptors and components of molecular devices.

Introduction of azide groups in calixarene platform significantly extends the synthetic potential thereby allowing wide series of amphiphilic thiacalixarenes *via* click reactions.



Herein we have obtained a universal strategy for the synthesis of *p-tert*-butylthiacalix[4]arene derivatives containing different alkyl substituents and azide moieties at the lower rim in *1,3-alternate* stereoisomeric form. CuACC reactions of these compounds with different alkynes gave triazole-containing products with different functional groups. Molecules containing ammonium or guanidinium moieties are of a great interest due to their usage in recognition and/or condensation of the different biopolymers (DNA, BSA).

We are grateful for the financial support of RSF № 14-13-01151.

Synthesis of multitopic ligands based on imidazole and triazole using phenylene linker

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Coordination polymers and metal–organic frameworks (MOF), constitute an interdisciplinary field with its origins in inorganic and coordination chemistry that has expanded rapidly during the last two decades, and is now also attracting the interest of chemical industry. Compounds bearing several heterocyclic moieties can act as multidentate ligands for MOFs [1]. Constant design of new MOFs is stimulated by their high capacity for gas storage [2], photo-physical properties [3], sensor capabilities [4] and excellent catalytic performance [5]. Previously, we have successfully used tetra(pyrazol-1-yl)derivatives for the preparation of coordination polymers and molecular complexes [6, 7]. Here we report the synthesis of new bitopic ligands based on imidazole and triazole using phenylene linker (*Fig. 1.*).

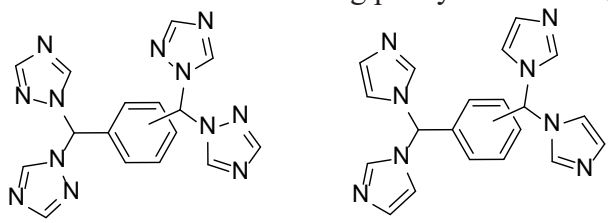
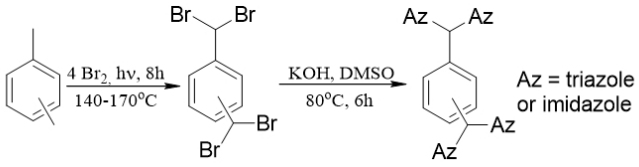


Fig. 1.

For this, o-xylene and p-xylene were radically brominated into the side chains to give 1,3-bis(dibromomethyl)benzene and 1,4-bis(dibromomethyl)benzene. Further, substitution reactions with brominated xylenes and imidazole or 1,2,4-triazole in a superbasic medium (potassium hydroxide – dimethyl sulfoxide) were carried out (*Scheme 1*). DMSO was removed under vacuum at 100°C. The residue was treated by ethyl acetate in a Soxhlet extractor to extract the organic products, which were then analyzed by NMR.



Scheme 1.

In summary, we have obtained the bitopic ligands 1,4-bis(di(imidazol-1-yl)methyl)benzene, 1,3-bis(di(imidazol-1-yl)methyl)benzene, 1,4-bis(di(1,2,4-triazol-1-yl)methyl)benzene and 1,3-bis(di(1,2,4-triazol-1-yl)methyl)benzene.

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New copper (I)-containing catalysts based on functionalized silicagel and their use in CuACC catalysis

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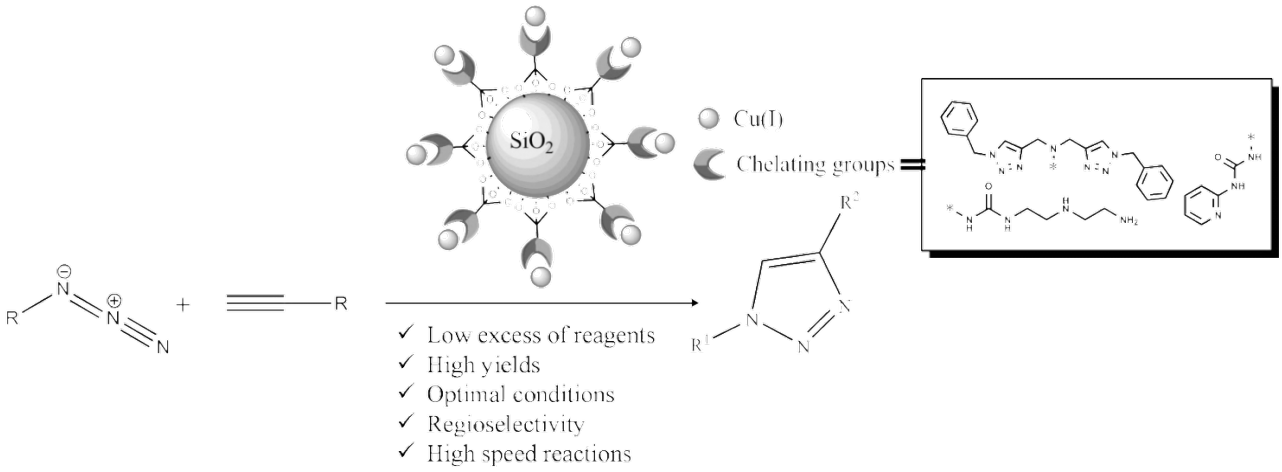
At last decade flow chemistry became very powerful instrument in organic chemistry. Due to conducting reactions and syntheses in stream it can achieved better selectivity, safety and outputs compared to reactions carried out in the flask. Although flow reactors are used in organic chemistry for a long time, their use for the reactions catalyzed by copper has only became relevant in the past few years. There are a large number of chemically important reactions of organic compounds catalyzed by copper. Besides reaction of azide-alkyne cycloaddition (CuAAC), macrocyclisation conducted through 1,3-dipolar cycloaddition, and some cross-coupling reactions, such as Sonogashira or Ullmann reactions are also catalyzed by copper. For carrying out abovementioned reactions complex compounds and salts of monovalent copper are used. In the literature there are many examples of copper complexes used as homogeneous catalysts, weakness side of which is low conversion of the substrate and difficulty in operation and cleaning and the catalyst regeneration. Furthermore it is known that the copper salts (i) used in the reaction are toxic. Thus, one of the promising directions in catalysis is heterogenization of corresponding copper (I) complexes on surface support. Such catalysts can be recycled by simple filtration, thereby minimizing toxic waste after the reaction and also can be used in flow reactors. Thus, in this work we have obtained new “heterogenized” copper-containing catalysts based on silicagel support which showed a great conversion in CuACC reactions made both in flow and batch conditions.



Scheme 1.

We express gratitude Russian Foundation for Basic Research (grant No. 16-33-00336 mol_a) for financial support.

1,3-Dicarbonyl compounds in the synthesis of mono- and bicyclic 1,2,3,4-tetrahydropyridines and hexahydropyrimidines by Mannich type reaction

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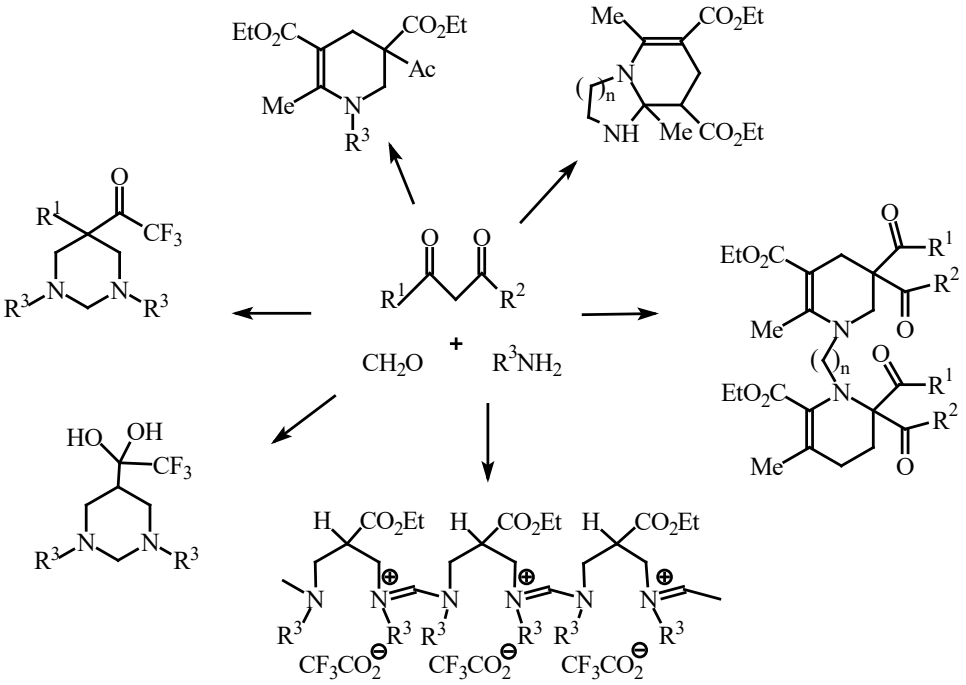
This paper presents the results of research in the synthesis of nitrogenous heterocycles on the basis of 1,3-dicarbonyl compounds by the Mannich type reaction. We have studied the interaction of fluorine-containing 1,3-dicarbonyl compounds (ethyl 4,4,4-trifluoroacetoacetate, 1,1,1-trifluoro-2,4-pentanedione, 1,1,1,5,5,5-hexafluoroacetylacetone) with formaldehyde and natural amino acids. The reactions proceed at room temperature in acetate buffer (AcONa-AcOH, pH 4). The yields and composition of the reaction products formed depend on the nature of the initial amino acid [1]. Novel fluorinated derivatives of 1,3-hexahydropyrimidine and oligomer of regular structure promising as ligands for asymmetric catalysis by metal, broad-spectrum drugs and ionic liquid.



Scheme 1.

Composition of hemiacetals formed by the reaction of paraformaldehyde with aliphatic alcohols in the presence of catalytic amounts of Et_3N was studied and the effect of the nature of hemiacetals on the yield and composition of the products of their condensation with acetoacetic ester and primary amines under the Mannich reaction conditions was examined. Mono- and bicyclic 1,2,3,4-tetrahydropyridine derivatives have been synthesized in up to 98% yield by one-pot three-component condensation of ethyl acetoacetate with methoxymethanol and primary amines (diamines) in methanol in the presence of *tert*-butyl alcohol.

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Oxidative furan-to-indole rearrangement. A new approach to 2-(2-acylvinyl)indoles

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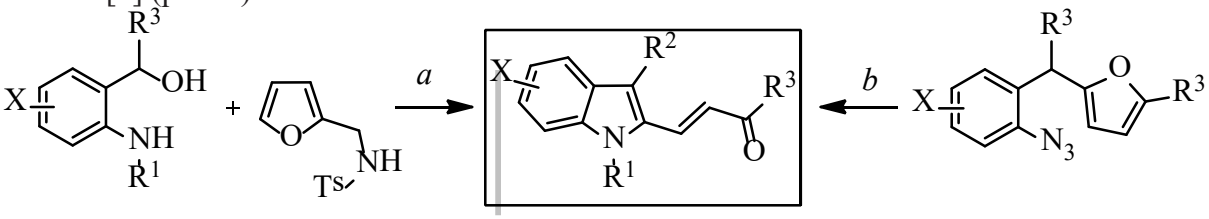
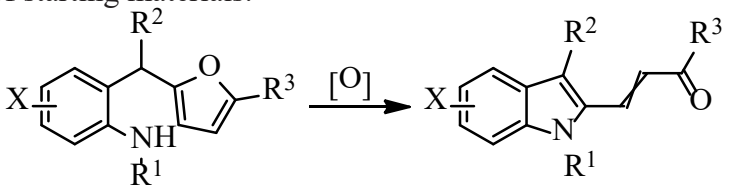
Indole core is present in an enormous number of natural products and biologically active compounds. There is manifold of synthetic approaches toward indole derivatives, however an interest in the development of new synthetic routes to highly substituted indoles bearing functionalities, which might be utilized in further transformations, has not waned.

Recently we developed several methods toward 2-(2-acylvinyl)indoles based on the furan dearomatization strategy. We showed that a domino reaction of *N*-tosylfurfurylamine with 2-(*N*-tosylamino)benzyl alcohols afforded 2-(2-acetylvinyl)indoles with excellent *E*-selectivity [1] (path a). (*E*)-2-(2-Acylvinyl) indoles may be also produced by thermolysis of 2-(2-azidobenzyl)furans followed by DMAP-induced isomerization [2] (path b).



In our ongoing study we found that oxidative recyclization of 2-(*N*-tosylamino)benzylfurans afforded 2-(2-acylvinyl)indoles with good to excellent yields and high *Z*- or *E*-selectivity depending on the electronic properties of starting materials.



19 examples, up to 90%
either Z- or E-isomer, dr > 49:1

Scope and limitations of this new reaction along with discussion on the mechanism of the oxidative recyclization of 2-(*N*-tosylamino)benzyl furans and potential applications of obtained products will be given.

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Copper-catalyzed synthesis of benzylfurans and benzofurans

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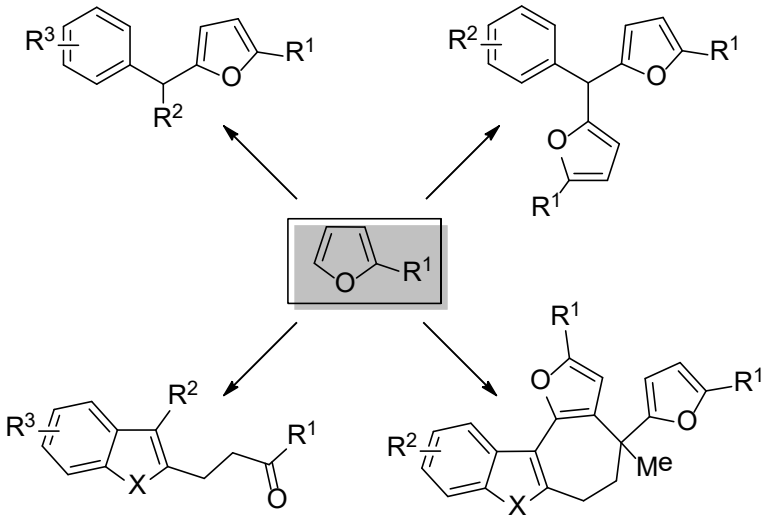
Furan chemistry is a field of a tremendous upgrowth. Furan substrates are widely used in the synthesis of useful products due to their versatile chemical properties. Evidently, the development of new efficient synthetic protocols toward functionalized furans is a topical task for chemical science. One of the oldest and most frequently applied method for aromatic ring functionalizations is the Friedel-Crafts reaction. However, this approach has limitations in case of furan substrates due to their lability in the presence of acids.

Recently we found that inexpensive copper salts may catalyze benzylation of furans with subsequent rearrangement of products to polyfunctionalized heterocycles.



Aspects of copper-catalyzed benzylation/rearrangement reactions of furans in the synthesis of polysubstituted heterocycles will be discussed.

This work was supported by Ministry of education and science of the Russian Federation (project № 4.246.2014/K).

Solvolysis Reactions in Condensed Tetrazolo-1,3,5-triazine Series

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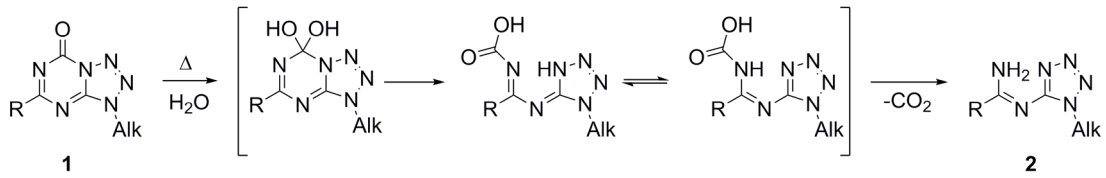
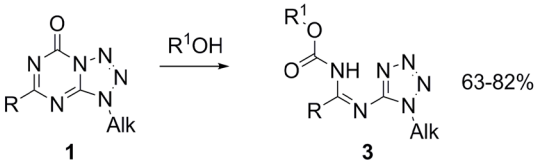
Earlier, it was shown that alkylation of aminosubstituted tetrazolo[1,5-*a*]-1,3,5-triazinones proceeded to give a mixture of 5-aminosubstituted 3-alkyltetrazolo[1,5-*a*]-1,3,5-triazine (N-alkylation), 2-aminosubstituted 6-alkoxy-4-azido-1,3,5-triazine (O-alkylation) together with (1-alkyltetrazol-5-yl)guanidine as the product of hydrolysis of the N-alkylated product [1]. Herein, substituted 3-alkyltetrazolo[1,5-*a*]-1,3,5-triazines **1** were examined under solvolysis conditions using water and a number of alcohols as solvents. Heating of suspension of **1** in water gave a colorless solution, and after evaporation of the reaction mixture, corresponding guanidines **2** were obtained in almost qualitative yields. The course of the reaction could be represented as follows.



1 **2**

R = NHPr, $N(CH_3)_2$; $N(CH_2)_2O$; $C(NO_2)_3$; Alk = CH_3; Bu; Allyl

Action of alcohols was similar to water and proceeded *via* addition of the corresponding alkoxy group to the carbonyl carbon atom following by the 1,3,5-triazine cleavage. The reaction proceeded smoothly at room temperature and gave corresponding carbamates in good to high yields.



1 **3**

R = NHPr, $N(CH_3)_2$; $N(CH_2)_2O$; $C(NO_2)_3$
R^1 = Me; Pr; Pr^i; tetrahydrofurfuryl; propargyl; Bn
Alk = CH_3; Bu; Allyl

Occuring of the reactions under mild conditions makes it possible to use this reaction as an approach to the synthesis of 1,5-disubstituted tetrazoles.

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Direct enantioselective synhesis of indolylacetohydoxamic acids

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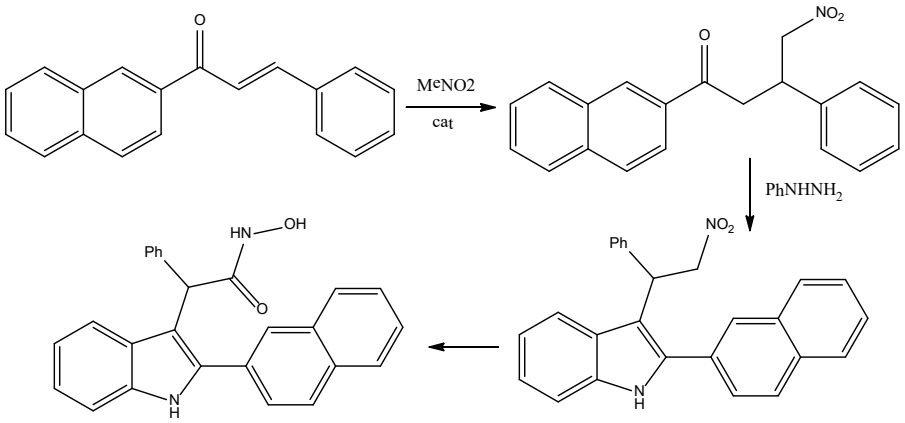
Synthesis of enantiopure organic compounds is one of the most important problem in organic and pharmaceutical chemistry. These compounds is widespread in the nature but has fixed position of structural elements. Preparation using division of enantiomers by physical methods, mainly by column chromatography is associated with the loss of half of the mass in the form of unnecessary isomer in par with the complexity of the selection of chromatographic separation systems. Also such experiments are hard to scale up. For these reasons, these approaches significantly inferior to directed enantioselective synthesis using chiral catalysts.

In our laboratory we have found high biological activity against certain types of cancer cells on indolylacetohydroxamic acids. The next target in this work is to obtain pure anantiomers of these compounds and investigate activity of such compounds. To solve this problem we proposed sequence: high-enantioselective Michael addition of nitromethane to α, β-unsaturated carbonyl compounds followed by Fischer reaction and isomerization of nitro compounds to acetohydroxamic acid. First step shows quantative yields but Fisher synthesis has turned a little bit complicated. Most of catalysts for this step don't work or can isomerise nitrocompound into hydroxamic acid that is associated with racemization. Racemisation can be avoided in case of BF_3/AcOH system that leads to formation of desired nitrocompound with good yields.



Scheme 1. Synthetic sequence

This project was financially supported by the Russian Foundation for Basic Research (grant # 16-33-60108 мол_а_дк).

Synthesis and antitumor properties of novel 4,11-diaminoanthra[2,3-*b*]furan-5,10-diones

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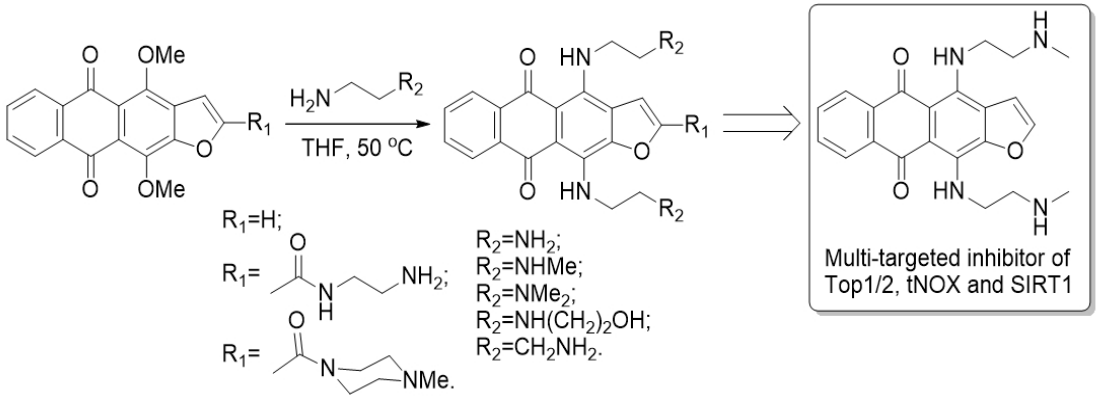
The arene/hetarene-fused derivatives of anthracene-9,10-dione have a high potential for development as antitumor agents [1],[2]. Among heteroarene-fused anthracenediones, 1,4-diaminoanthraquinone annelated with furan cycle is especially promising scaffold for the search of novel anticancer agents. Previously, it was found that the substituents at the position 2 of the heterocyclic moiety of 4,11-diaminoanthra[2,3-*b*] furan-5,10-diones strongly influenced the antiproliferative and Top1 inhibitory potencies [3]. In the present study we reported the synthesis and antitumor properties of a series of novel 4,11-diaminoanthra[2,3-*b*] furan-5,10-diones and analyze SAR for this chemotype.

Using the nucleophilic substitution of 4,11-methoxy groups by primary amines a series of new 4,11-diaminoanthra[2,3-*b*]furan-5,10-dione derivatives with different side chains and substituents at the position 2 was synthesized. Selected 2-unsubstituted derivatives showed high antiproliferative potency on a panel of mammalian tumor cell lines including multidrug resistance variants. Compounds utilized multiple mechanisms of cytotoxicity including inhibition of Top1/Top2-mediated DNA relaxation, reduced NAD^+/NADH ratio through tNOX inhibition, suppression of a NAD^+-dependent Sirtuin 1 (SIRT1) deacetylase activity and activation of caspase-mediated apoptosis. Here, for the first time, we report that tumor-associated NADH oxidase (tNOX) and SIRT1 as important cellular targets of antitumor anthracene-9,10-diones.



Scheme 1. Discovery of 4,11-diaminoanthra[2,3-*b*]furan-5,10-diones with multiple action.

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Synthesis of BODIPY derivatives library for liquid phase fluorescent sensorics

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BODIPY or Boron-dipyrromethene fluorescent dyes are known to have unique photophysical and chemical properties such as high quantum yields, sharp adsorption and emission spectra, small Stokes shift etc. [1] Being slightly modified, these luminophores may demonstrate precise sensitivity to vast range of important physical and chemical parameters in solution, such as dynamic viscosity and pH. [2]

At the same time these substances are quite resistant to photochemical destruction and aggressive chemical environment. Such unique properties are tending BODIPY to be desirable core compound for complex biomedical labels and optoelectronic materials.

Current work is focused on synthesis and investigation of new 8-functionalized BODIPY derivatives for specific analytical purposes. Discussed compounds include luminophores with aliphatic systems, proton and electron pair donor systems, aromatic substituents in bridge position (R in figure 1).

Tris- and bis- BODIPY domains connected via bulky triphenylamine spacer are obtained are presented for the first time.

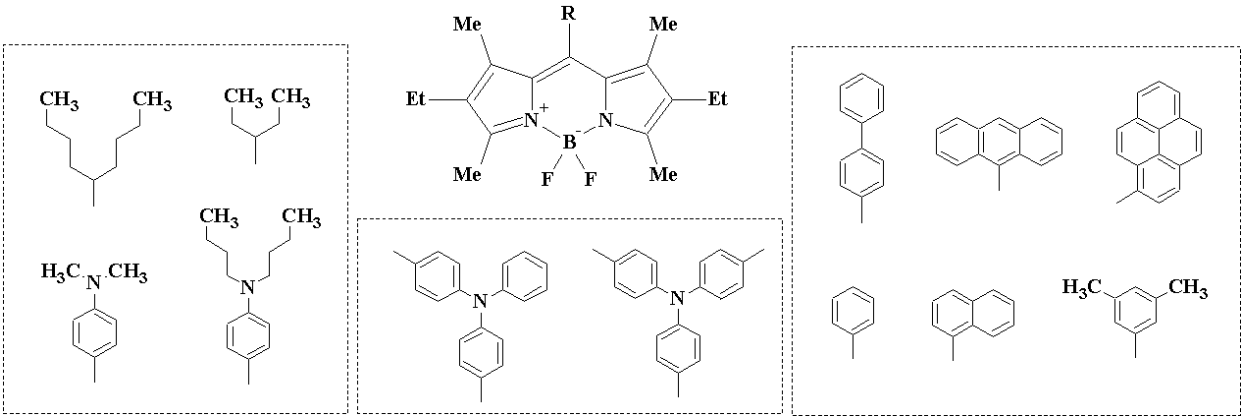

Fig. 1. Alkilated BODIPY core with 8-position marked as R (top-center) and groups successfully implied (dashed rectangles)

Obtained structures vere approved via CHN analysis, IR, NMR and UV-Vis (absorption and emission) spectroscopy. Stated compounds have demonstrated desirable callback to specific solution properties. Specific data and the most important practical results are to be stated in presentation.

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Lanthanide-catalyzed oxidative C-O coupling dicarbonyl compounds with malonyl peroxides

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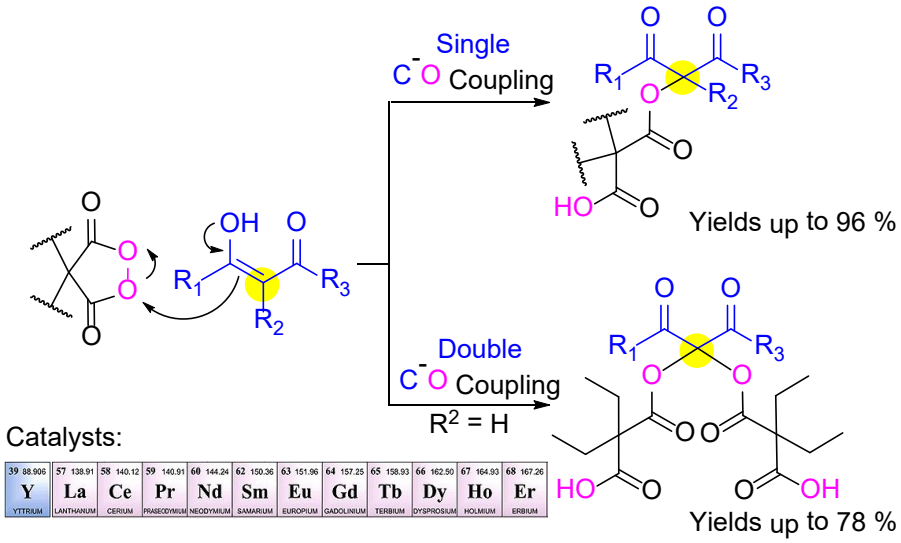
In the past decade, the cross-coupling reaction has attracted much attention because the formation of the new bond occurs with high atom efficiency and no functional groups are required [1]. Of the four main types of coupling reactions (C–C, C–N, C–P, and C–O), the oxidative coupling to form the C–O bond between the partners has been less well studied probably because of side oxidation and fragmentation reactions. In this context, cyclic diacyl peroxides were used in the 1950s to 1970s extensively in oxidation reactions, an area of peroxide chemistry that experiences currently a renaissance.

The lanthanide-catalyzed oxidative C–O coupling of 1,3-dicarbonyl compounds with diacyl peroxides, specifically the cyclic malonyl peroxides, has been developed (Scheme 1) [2]. An important feature of this new reaction concerns the advantageous role of the peroxide acting both as oxidant and reagent for C–O coupling.



Scheme 1.

It is shown that lanthanide salts may be used in combination with peroxides for selective oxidative transformations. The vast range of lanthanide salts (La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Y) catalyzes oxidative C-O coupling much more efficiently than other used *Lewis* and *Bronsted* acids. This oxidative cross-coupling protocol furnishes mono and double C–O coupling products chemo-selectively in high yields with a broad substrate scope.

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The synthesis of new isoxazolidines by 1,3-dipolar cycloaddition reaction of tricarbonyl chromium-/manganese complexes of nitrones and its free analogs with alkenes

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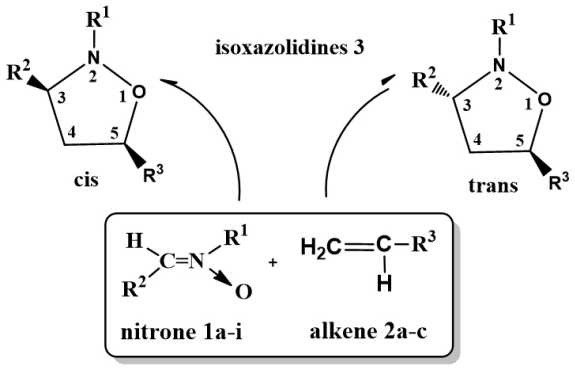
It is known that reactions of 1,3-dipolar cycloaddition between C,N-disubstituted nitrones and unsymmetrical alkenes not always have full regio- and stereoselectivity and often lead to the formation of the mixture of heterocyclic products - isoxazolidines. The use of compounds containing $Cr(CO)_3$- and $Mn(CO)_3$-substitutes are very attractive for increasing selectivity of different processes, because these groups are bulky and have electron-withdrawing properties. In order to obtain a number of new individual complexes of isoxazolidines by 1,3-dipolar cycloaddition and to establish the influence of tricarbonylmetall groups on the selectivity of this process, we carried out a series of reactions between free nirtones (**1a-c**) with η^6-(styrene)tricarbonylchromium (**2a**) or η^5-(vinylcyclopentadienyl)tricarbonylmanganese (**2b**), and coordinated nitrones (**1d-i**) with free alkene (**2c**). The reaction occurred in toluene in sealed glass tubes at a temperature of 80 °C in accordance with the **Scheme 1**. The formed derivatives – isoxazolidines (**3**) were isolated, purified and characterized by HPLC, UV, IR, ^{1}H NMR – spectroscopy, mass spectrometry and X-ray diffraction.



Scheme 1

1: R^1 = Me, R^2 = Ph (**a**);
R^1 = t-Bu, R^2 = Ph (**b**); R^1 = R^2 = Ph (**c**)
R^1 = Me, R^2 = Ph[$Cr(CO)_3$] (**d**);
R^1 = t-Bu, R^2 = Ph[$Cr(CO)_3$] (**e**);
R^1 = Ph, R^2 = Ph[$Cr(CO)_3$] (**f**);
R^1 = Ph, R^2 = Cp[$Mn(CO)_3$] (**j**);
R^1 = t-Bu, R^2 = Cp[$Mn(CO)_3$] (**h**);
R^1 = Ph, R^2 = Cp[$Mn(CO)_3$] (**i**);

2: R^3 = Ph[$Cr(CO)_3$] (**a**);
R^3 = Cp[$Mn(CO)_3$] (**b**);
R^3 = Ph (**c**).

Scheme 1

It is found out that the all reactions proceed with full regioselectivity with the formation of C(5)-substituted isoxazolidines **3**, but stereoselectivity was differ. The reactions of free nitrones (**1a-c**) with coordinated alkenes (**2a,b**) gave the mixture of isoxazolidines (cis- and trans- **3**) with predominantly cis-configuration. And processes between tricarbonyl chromium/manganese complexes of nitrones (**1d-i**) with styrene (**2c**) led to the formation only one product - cis-substituted isoxazolidine.

This work was done under the task of Ministry of Education and Science of Russian Federation (Proj. 736) and supported by Grant of President of Russian Federation (Proj. No MK-7578.2015.3).

Furyl-tethered amines as intermediates in synthesis of 1,2-annulated pyrroles

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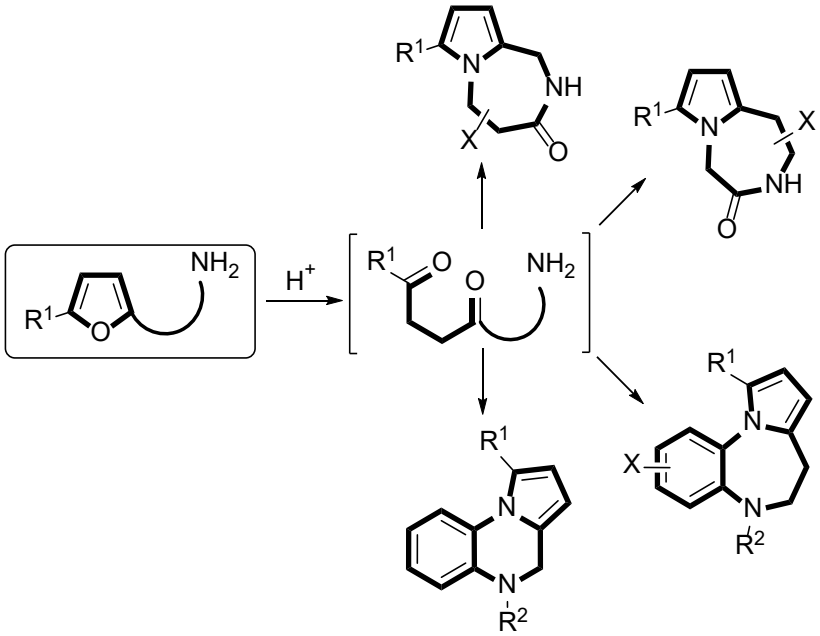
Substituted furans are widely used as starting compounds in the synthesis of biologically active molecules. In the presence of Bronsted acid furans containing amine functionality can undergo ring opening/intermolecular Paal-Knorr reaction affording annulated nitrogen-containing heterocycles [1]. Based on this reactivity of furan substrates, we developed simple and efficient synthetic protocols toward pyrrolo[1,2-a][1,4]diazepines, pyrrolo[1,2-d][1,4]diazepines, pyrrolo[1,2-a][1,5]benzodiazepines and pyrrolo[1,2-a]quinoxalines.



Scope and limitations of this type of the amine-tethered furans rearrangements to azaheterocycles will be discussed.

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[1] Trushkov, I.V.; Uchuskin, M.G.; Butin, A.V. *Eur. J. Org. Chem.* 2015, *14*, 2999.

This work was supported by Ministry of education and science of the Russian Federation (project № 4.246.2014/K).

POSTER PRESENTATIONS

Cyanine dyes of the basis of 2-mercaptobenzotellurazole

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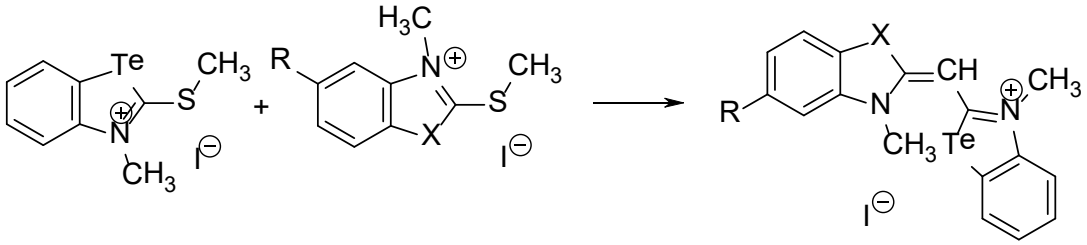
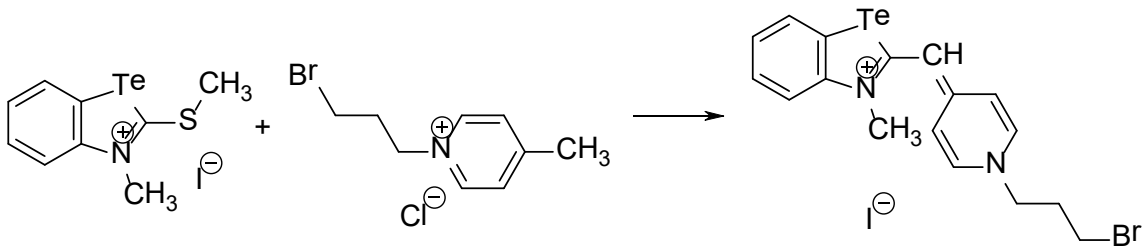
Chemistry of organochalcogen compounds is rapidly developing field of organic chemistry. This is due both to the interest in these compounds in terms of basic research and a wide range of possibilities of their applications. Serious interest in terms of biological activity are fluorescent probes used in studies of cells, membranes and lipoproteins compounds mostly belong to the class of mono- and trimethine dyes.

We have previously reported the synthesis of 2-mercaptobenzotellurazole and studied the reactivity of heterocyclic by nitrogen and tellurium atoms.

In the continuation of the study of chemical properties of 2-mercaptobenzotellurazole we attempt to synthesize cyanine dyes, especially since similar cyanine dyes were synthesized from 2-metilbenzotellurazolium, and they were described a number of benzochalcogenazoles and 4-methylpyridine salts. Thus, it was reported that S-CH_3 - group as a group SO_3H, located in the second position in benzochalcogenazoles is a good "leaving" group capable of being replaced by other groups like -NH-NH_2 to form cyanine dyes by interaction with different azole compounds.



1) X=O, R=H, 2) X=S, R=H, 3) X=Se, R=H, 4) X=Se, R=OCH_3



Scheme 1. Synthetic sequence

Ureas as Amination and Carbamoyl Amination Reagents for S_NH and S_NAr Reactions in 1,3,7-Triazapyrene Series

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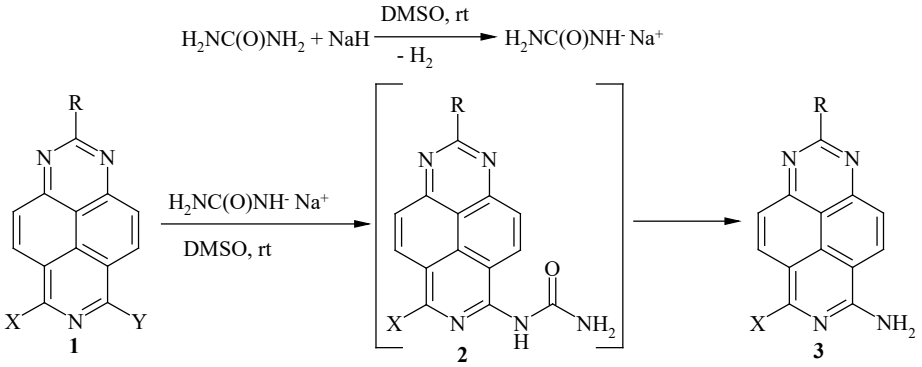
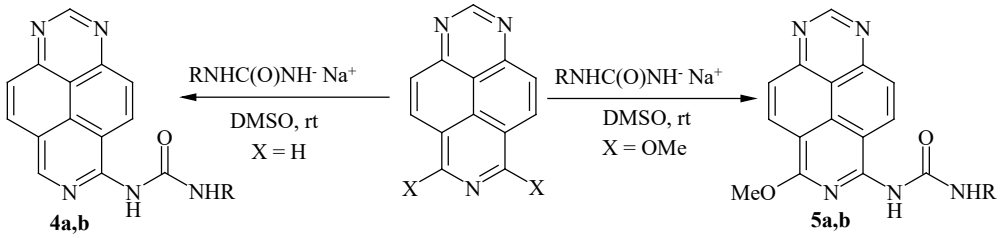
In the course of the study S_N reactions in 1,3,7-triazapyrene series we have been interested to test the possibility S_N carbamoyl amination reaction of this heterocycle using urea anion as the nucleophilic reagent. The last one was generated by action of sodium hydride in anhydrous dimethyl sulfoxide. The use of DMSO makes it possible to carry out S_NH and S_NAr reactions with 1,3,7-triazapyrenes (**1**) at room temperature. As it turned out, the reaction products obtained after water addition in both cases were appropriate 1,3,7-triazapyren-6-amines (**3**) instead of expected 1,3,7-triazapyren-6-yl-urea (**2**).



R = H, Me; X = H, Ar, OAlk, $N(Alk)_2$; Y = H, OAlk

As expected, use of the phenyl urea instead of urea itself in the reaction with 1,3,7-triazapyrene led to same primary amine**.** The postulated pathway for the compounds **3** formation is discussed in the report.

Other results were obtained upon using mono substituted ureas containing bulky substituents, such as *tert*-butyl-urea and (1,1-dimethyl-pentyl)-urea. When these ureas were used in the reaction with 1,3,7-triazapyrene the first products of the earlier unknown S_NH alkyl carbamoyl amination **4a,b** were obtained whereas in the case of 6,8-dimethoxy-1,3,7-triazapyrene the products of S_NAr alkyl carbamoyl amination **5a,b** were isolated.



R = ^{t}Bu (**a**), $C(CH_3)_2(CH_2)_3CH_3$

Thus, the ureas depending on the structure can be useful for the nucleophilic amination or carbamoyl amination of π-deficient heterocycles.

This project received financial support from the Ministry of Education and Science of the Russian Federation in the framework of the State Assignment to the Higher Education Institutions № 4.141.2014/K.

Heterogeneous Jørgensen-Hayashi catalyst

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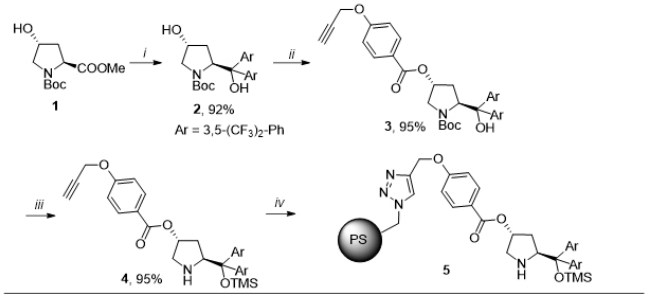
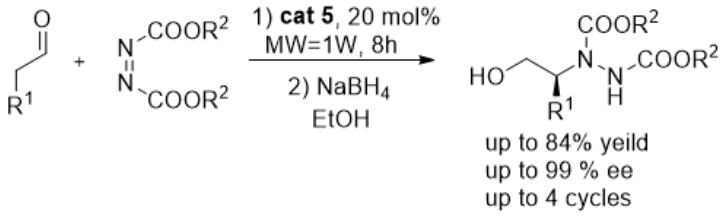
The immobilization of Jørgensen-Hayashi catalyst onto Merrifield resin was achieved using simple and reliable click-reaction. For this purpose, corresponding "clickable" prolinol **4** was synthesized *via* a 3-step procedure in an overall 83% yield (Scheme 1).



Scheme 1.

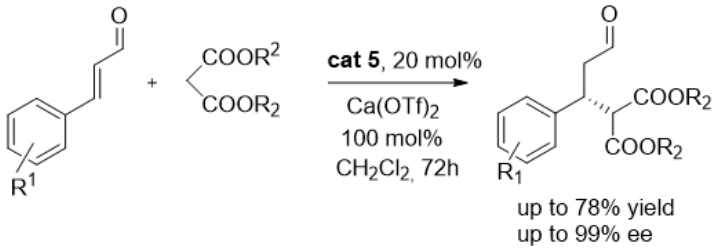
The catalytic activity of polymer-immobilized diarylprolinol **5** was studied in the reaction of aliphatic aldehydes addition to azodicarboxylates (Scheme 2).



Scheme 2.

Reaction products were obtained in high yields (up to 84%) and with excellent enantioselectivity (up to 99% *ee*). The catalyst **5** can be repeatedly used at least in 3 cycles without loss of enantioselectivity .

The same catalyst **5** in combination with $Ca(OTf)_2$ also provides high yields (up to 78%) and enantiomeric excesses (up to 99% *ee*) in the reactions of malonates addition to unsaturated aldehydes (Scheme 3).



Scheme 3.

The procedure provides easy separation of heterogeneous organocatalyst and allows to use nontoxic calcium salt as co-catalyst.

This work was supported by RFBR (grant # 12-03-93107).

N, *N*-bis-(dimethylfluorosilylmethyl)amides of *N*-organosulfonylproline and sarcosine: synthesis, structure and stereodynamic behaviour

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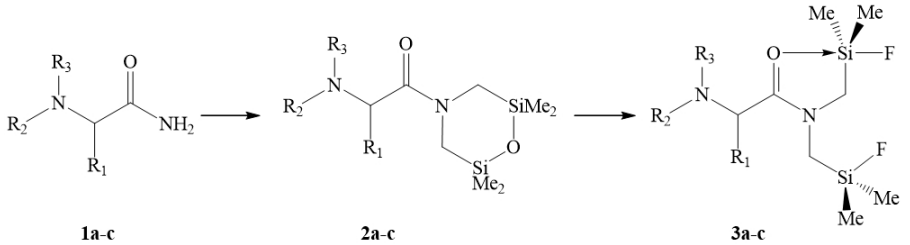
New difluorides $R_3R_2NCH(R_1)C(O)N(CH_2SiMe_2F)_2$ (**3a**–**c**) with one pentacoordinate and one tetracoordinate silicon atoms were synthesized by silylmethylation of amides $R_3R_2NCH(R_1)C(O)NH_2$ (**1a-c**), subsequent hydrolysis of unstable intermediates $R_3R_2NCH(R_1)C(O)N(CH_2SiMe_2Cl)_2$ into 4-acyl-2,6-disilamorpholines $R_3R_2NCH(R_1)C(O)N(CH_2SiMe_2O)_2$ (**2a**–**c**) and the reaction of the latter compounds with $BF_3{\cdot}Et_2O$. The molecular structures of **2a**, **2c** and **3a** were determined by XRD analysis. According to IR and NMR data, the O–Si coordination in solutions of these compounds was weaker than in the solid state due to effective solvation of the Si–F bond. The absence of spin-spin coupling constants $^3J_{HF}$ of the methyl groups at Si^V and their retention at Si^{IV} indicates a significant weakening of the Si–F bond at pentacoordinate silicon, which favours its ionization. A permutational isomerisation involving an exchange of equatorial methyl groups at the pentacoordinate Si atom in complexes **3a**–**c** was detected, and its activational parameters were determined by ^{1}H DNMR. Negative $\Delta S^{\#}$ values for the dynamic processes is indicative of the dissociation mechanism, which is confirmed by quantum chemical calculations.



Scheme 1. [Synthesis of N, N-bis-(dimethylfluorosilylmethyl)amides]

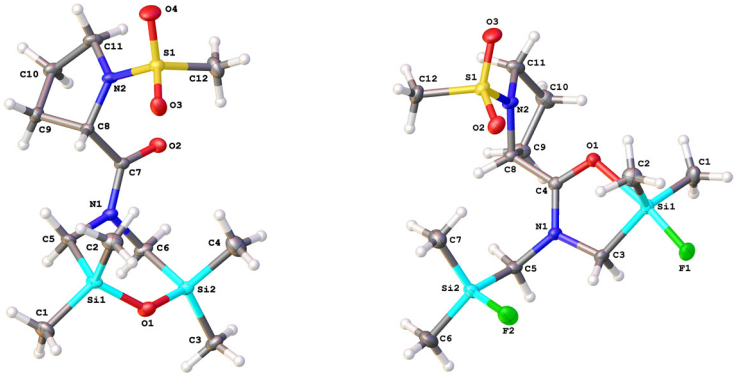


Fig. 1. [Molecular structure of **2a** and **3a**]

This work was supported by Russian Foundation for Basic Research № 16-33-00956, 13-03-01084 and 16-03-00957.

Fluorescent dyes based on the 4-styryl-1,8-naphthalimide: synthesis and spectral properties

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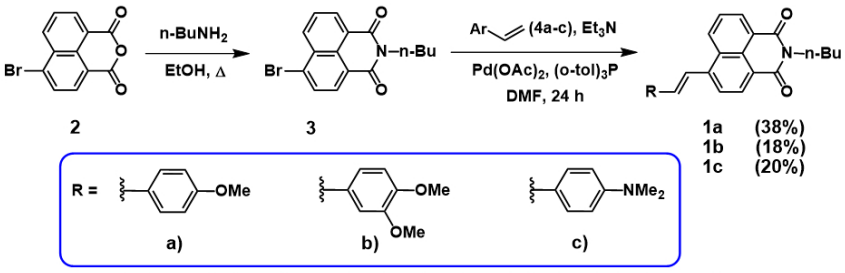
Currently, methods of optical fluorescence spectroscopy are of great importance in biological and biomedical research. With the advent of fluorescence microscopy organic luminophores have been used as molecular probes, imaging reagents and sensors allowing the study of biological macromolecules. Derivatives of 1,8-naphthalimide are practically important class of organic luminophores which is used in many areas of science and technology such as optical bleaching, fluorescent defectoscopy, conversion of solar energy, creation of optical memory elements and electroluminescent devices. Because its intensive fluorescence in the visible spectrum, high photostability and relative simplicity of the synthetic ways to directed modification of the molecule structure such compounds are attractive for the use as fluorescent dyes for applications in biology and medicine.



Scheme 1. [Synthesis of 4-styryl-1,8-naphthalimide derivatives]

Scheme 1. [Synthesis of 4-styryl-1,8-naphthalimide derivatives]

In this paper we present the synthesis and study of spectral and luminescent properties of 4-styryl-*N*-butyl-1,8-naphthalimide derivatives, containing styryl moiety with one methoxy group (**1a**), two methoxy groups (**1b**) and *N,N*-dimethylaminogroup (**1c**). Compounds **1a - c** are characterized by long-wave absorption band whose maximum shifts bathochromic at transition from methoxy substituted derivative **1a** to dimethylamino substituted naphthalimide **1c**, and intensive fluorescence in the visible spectrum. All the compounds show significant solvatochromism and solvatofluorochromism.

This work was supported by Russian Foundation for Basic Research № 16-33-00581.

Metal Free DIRECT C-H Functionalization of 1,3,7-triazapyrene

Avakyan E. K. ,[a] Amangasieva G. A.,[a] Shmelkova E. S.,[a]
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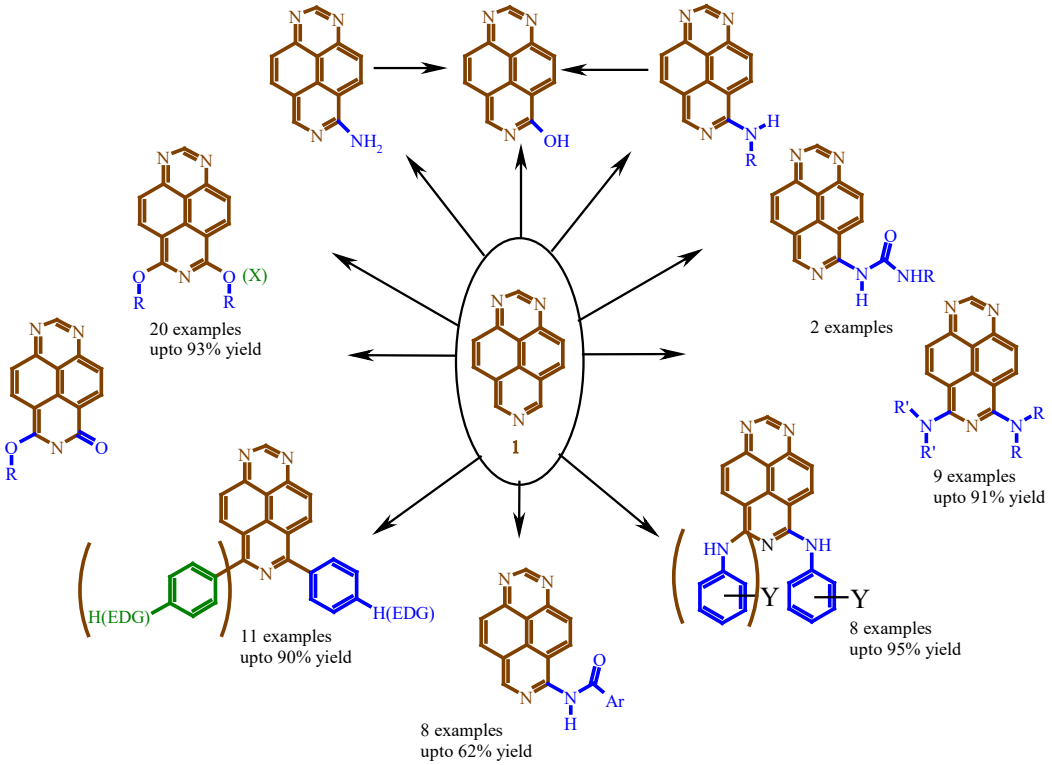
Oxidative substitution in electron-deficient (hetero) aromatic compounds, via the nucleophilic substitution of hydrogen, is a methodology that has made significant progress in last period [1]. It does not require prior introduction of classical leaving groups into the aromatic substrate or reagent molecule, or the use of costly catalysts or ligands.

Summarizing the results of our studies, we can state that peri-fusion of carbo- and heterocycles in molecule 1 determines specific chemical properties of this compound, such as unusually facile oxidative nucleophilic substitution of hydrogen (ONSH). The transformation was promoted only through the use of bases (or mineral acides) in the presence of oxidants and gave 1,3,7-triazapyrene derivatives in moderate to high yields.



So, reactions of oxidative alkoxylation, hydroxylation and amination of the 1,3,7-triazapyrenes give corresponding products in aqueous medium. It also able to undergo tandem nucleophilic substitution.

Products of arylamination and arylation are synthesized with a high yield by using a protic solvent system. Reactions with amides and ureas proceed in anhydrous DMSO solution at room temperature without protection from the air.

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This project received financial support from the Ministry of Education and Scienceof the Russian Federation in the framework of the State Assignment to the Higher Education Institutions № 4.141.2014/K.

Synthesis and antitumor activity of 4-arylidene-2-(arylthio)-1H-imidazol-5(4H)-ones

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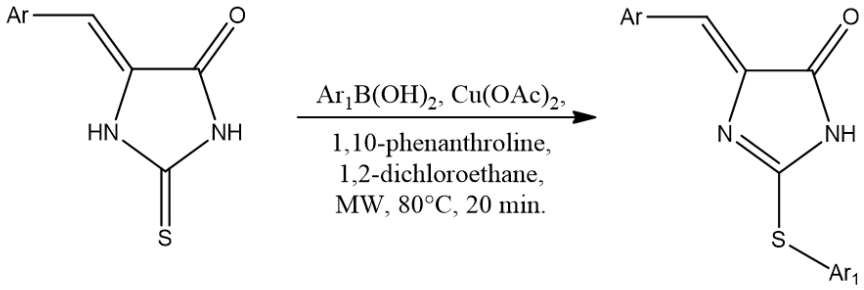
glebaver@gmail.com

Thiohydantoin and its derivatives attract scientists attention due to their diverse biological effects. In particular, some of them show antitumor activity[1]. The S-alkylation of 2-thiohydantoin moieties is a well known reaction[2]. However, arylation of the sulfur atom is described only in a single patent[3].

Thiohydantoin androgen receptor antagonists, such as enzalutamide[4] and apalutamide[5], are used for the treatment of prostate canser. In these compounds, the aryl substituents are located on the nitrogen atoms of the 2-thiohydantoin moiety. By using the S-arylation reaction of 5-aryliden-2-thioxoimidazolin-4-ones with arylboronic acids, we have made a step forward in design of antitumor thiohydantoin derivatives (Scheme 1).



1 a-c **2 a-f**

Scheme 1. General synthesis of 4-arylidene-2-(arylthio)-1H-imidazol-5(4H)-ones.

A number of novel compounds have been obtained with yields 71 – 82%. The structure of the products was confirmed by NMR and HRMS analysis.

A structure-activity relationship study was carried out on the resulting compounds. The cell lines of human prostate cancer LNCaP (p53 expressing) and PC-3(not expressing p53) and breast cancer cells were taken. MTS-test [6] was used. LECH-4 cells were taken to test the toxicity of our compounds, no activity was observed. The results will be presented on the poster.

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Novel Transformations of Substituted 6-R-pyridones-2

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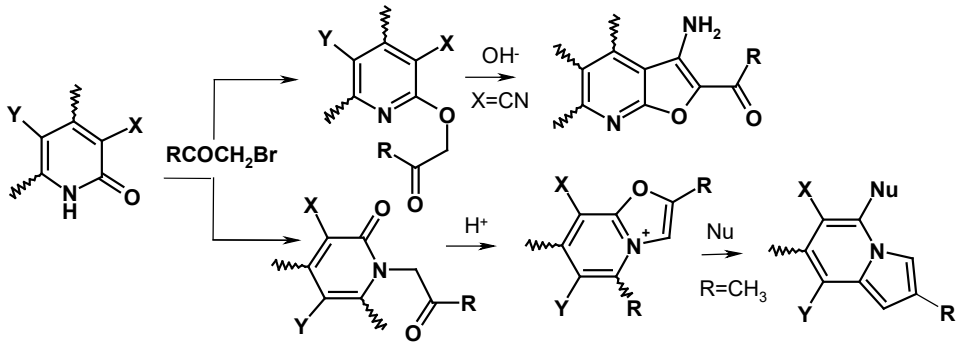
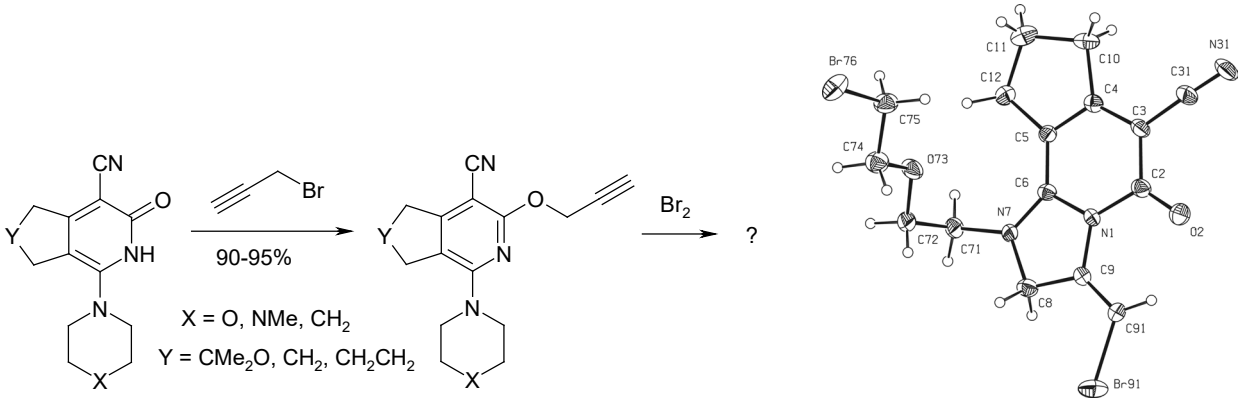
We have investigated by using X-ray methodology the behavior of 6-R-pyridones-2 with different substituents toward the action of phenacyl bromides [1]. Particularly, we have examined the cases of X or Y = CN, $CONH_2$, COOMe, COMe. The results are presented on the Scheme 1.



Scheme 1.

Additionally we have examined the behavior of 6-R-pyridones-2 [2] toward the reaction with propargyl bromide and further action of halogens (Scheme 2). In one case very unusual product of ring transformation was observed.



Scheme 2.

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This work was supported by Russian Foundation of Basic Research (grant No. 15-53-05064).

Continuous Flow Selective Hydrogenation of Functionalized 7-azabicyclo[2.2.1]hepta-2,5-dienes

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Laboratory of High Technologies, Ltd.
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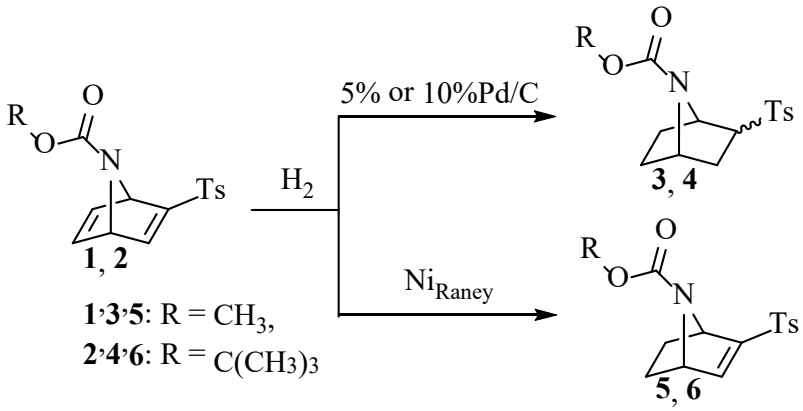
The selective hydrogenation of cyclic diene systems is an important tool in the synthesis of promising biologically active compounds [1].

Herein we present the investigation of hydrogenation for a series of N-alkoxycarbonyl-2-tosyl-7-azabicyclo[2.2.1]heptadienes **1**,**2** which results in a selective or complete reduction of the diene system depending on the conditions applied.

Hydrogenation reactions were carried out in a flow reactor H-Cube Pro [2,3] with 10% Pd/C, 5% Pd/C and Raney nickel catalyst composition in cartridges and 100% release of hydrogen in a hydrolytic cell. All substrates were used as 0.05 M solutions in methanol. During the investigation we have screened different temperatures of the catalytic cell (10 - 150 °C), system pressure (1 - 100 bar) and flow rate (0.3 - 2.0 mL/min) to determine the optimal conditions of synthesis.

It was found that the hydrogenation at 25° C on 5% Pd/C and 10% Pd/C at a flow rate of 0.5 to 2.0 mL/min, yields the complete hydrogenation products **3**,**4**. At the same time the reaction under catalysis of Raney nickel at a flow rate of 1 mL/min and 25°C results in a selective hydrogenation of one double bond **5**,**6**.



Complete control of chemo- and regioselectivity, observed in these reactions, combined with quantitative chemical yields renders this methodology synthetically superior to the previous methods.

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Synthesis novel derivatives of the N-[(adamantan-1-yl)methyl] anilines by reductive amination of adamantane-1-carbaldehyde

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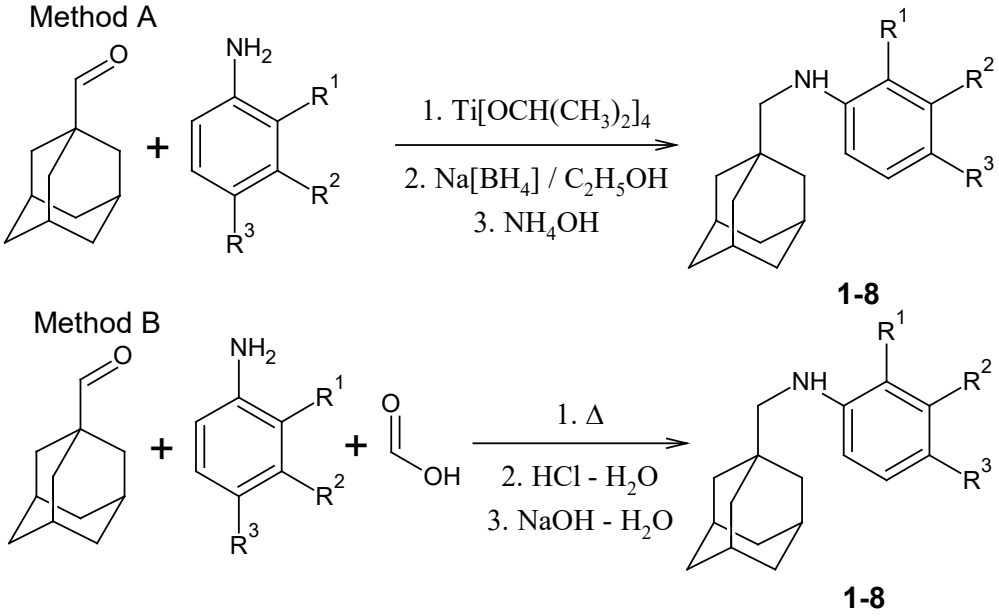
The *N*-[(adamantan-1-yl)methyl]anilines derivatives (**1-8**) that could potentially obtain an importance as novel conformationally flexible structural analogues adaptogen "Bromantane", were synthesized by us by reductive amination of adamantane-1-carbaldehyde with corresponding aromatic amines. The reactions were carried out in accordance with the schemes:



Scheme 1.

Where:

$R^1 = R^2 = R^3 = H$ (**1**); $R^1 = R^2 = H$, $R^3 = CH_3$ (**2**); $R^1 = R^2 = H$, $R^3 = I$ (**3**); $R^1 = R^2 = H$, $R^3 = OH$ (**4**); $R^1 = R^2 = H$, $R^3 = NO_2$ (**5**); $R^1 = H$, $R^2 = NO_2$, $R^3 = H$ (**6**); $R^1 + R^2 = (CH)_4$, $R^3 = H$ (**7**); $R^1 = H$, $R^2 + R^3 = (CH)_4$ (**8**).

Since comparative analysis of the two methods has led us to the conclusion that in most cases the Leuckart–Wallach reaction (method B) is a preferred method of making the derivatives *N*-[(adamantan-1-yl)methyl]anilines, we examined the effects of the conditions of the present reaction on the yield and composition of its products. At the same time, reductive amination using the system "$Na[BH_4]$ - $Ti[OCH(CH_3)_2]_4$" relevant in the case of having in a structure of the original amine of functional groups sensitive to formic acid.

This work was supported by the RNF, grant № 16-13-00100.

Intramolecular cyclization in the line propargil-substuted benzimidazoles

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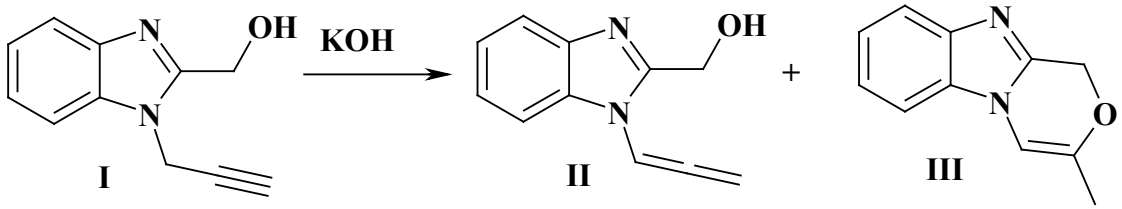
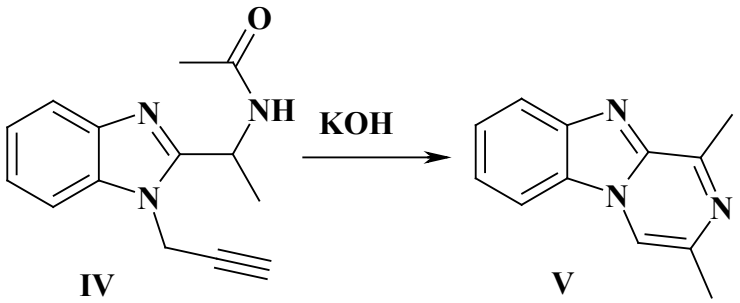
While studying acetylene-allen regrouping in the alcoholic alkalin in the line of the derivatives of 1-prop-2-ynyl-1H-benzoimidazoles in the case (1-prop-2-ynyl-1H-benzoimidazol-2-yl)-methanol (I) from reactionary weight two products according to PMR-spectroscopy as (1-propa-1,2-dienyl-1H-benzoimidazol-2-yl)-methanol (II) and 3-Methyl-1H-2-oxa-4a,9-diazafluorene (III) are identified. The formation of 3-Methyl-1H-2-oxa-4a,9-diazafluorene is also described (III) in the work of Essassi E.M. [1].



Scheme 1. Synthsis (1-propa-1,2-dienyl-1H-benzoimidazol-2-yl)-methanol (II) и 3-Methyl-1H-2-oxa-4a,9-diazafluorene (III).

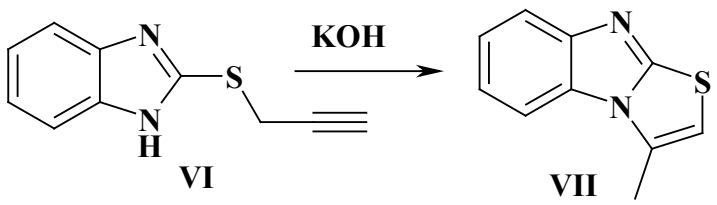
In this regard the process of the transformation of propargilic radical in the alkaline medium of a number of the derivatives of benzimidazole containing the free nucleophilic center is examined. It is determined that in the case of N-[1-(1-Prop-2-ynyl-1H-benzoimidazol-2-yl)-ethyl]acet-amide the main product of reaction is 1,3-Dimethyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyra-zine but the mechanism of the formation of it is not clear enough.



Scheme 2. Synthsis 1,3-Dimethyl-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine

In case of β-and γ- position of the nucleophilic center relatively to imidazole cycle the typical acetylene-allen regrouping of 1-prop-2-ynyl radical not followed by cyclizations takes place.

According to the similar scheme the cyclization of the 2-prop-2-ynylsulfanyl-1H-benzoimidazole which results to the product of 3-methylbenzo[4,5]imidazo[2,1-b]thiazole proceeds. The nitrogen of imidazolt ring acts as the reactionary center.



Scheme 3. Synthsis 3-Methyl-benzo[4,5]imidazo[2,1-b]thiazole

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Synthesis and biological testing of novel inhibitors of protein-protein interaction p53-MDM2 on the base of dispirooxindolones

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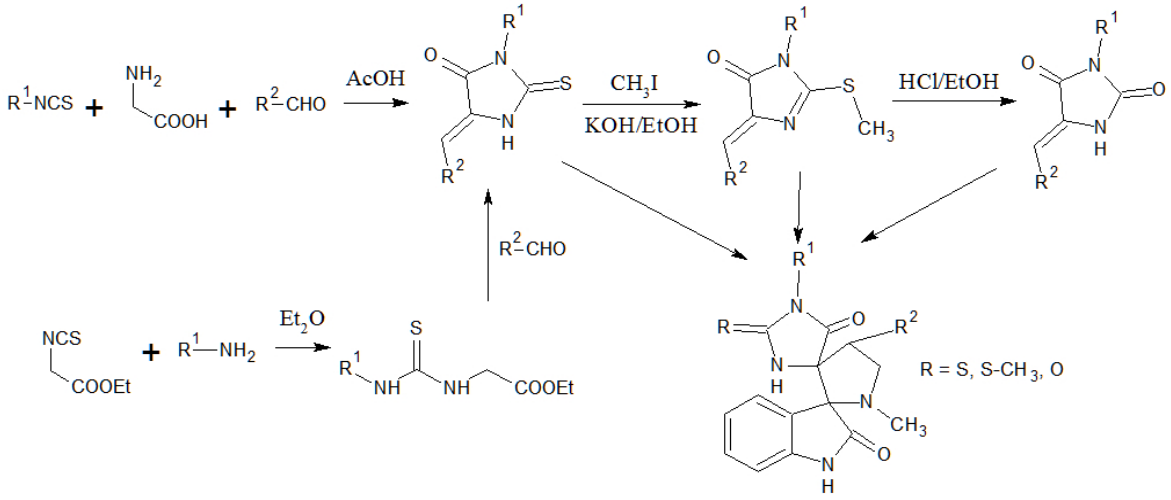
In this paper the synthesis and biological testing of new potential inhibitors of protein-protein interaction p53-MDM2 are discussed. It is known [1] that p53 protein is involved in the cell cycle by inactivating the DNA chain if it is damaged. The protein MDM2 binds with p53, resulting in the formation of cancer cells.

Previously [2], in our group the new molecule showing the potential inhibitor activity was found. On the base of the studies of interaction p53-MDM2 in this paper a series of novel compounds - potential inhibitors of MDM2 is discussed.

This compound can be obtained by the reaction of 1,3-dipolar cycloaddition from isatins, sarcosine and different types of 5-arilmethyliden substituted hydantoins. These compounds can be obtained with high yield from commercially available reagents and do not require special purification techniques.



A study of toxicity of these substances on cell lines PC3, LNCap, HCT p53$^{(+,+)}$ and HCT p53$^{(-,-)}$ is discussed.

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Synthesis, Structure and SOD-like Activity of Copper (II) Complexes containing a variety of heterocyclic substituents

Barskaya E.S.[a], Shcherbacheva E.V.[a], Tarakanova A.S.[a], Beloglazkina E. K.[a], Majouga A.G.[a,b], Zyk N.V.[a]

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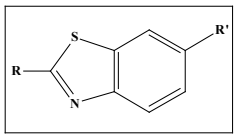
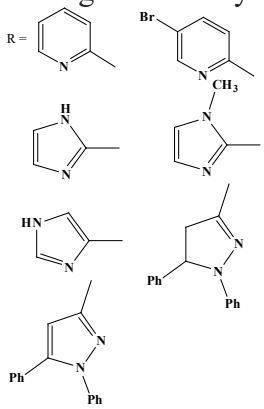
Superoxide dismutase, catalase, and other antioxidant enzymes protect the body from constantly produced highly oxygen radicals. They play a crucial role in almost all of the antioxidant protection of cells anyhow in contact with oxygen.

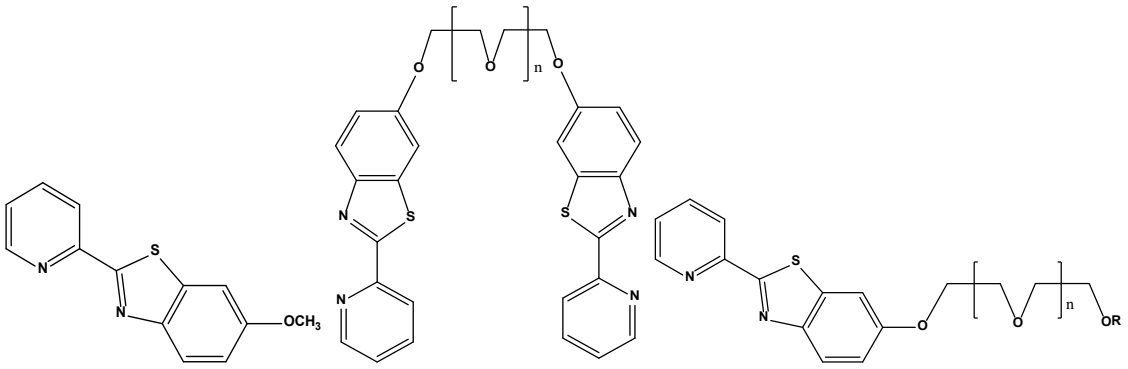
In recent years there have been many studies showing that lack of SOD leads to many disorders and diseases such as diabetes, ischemia, cataract, Parkinson's disease, cancer. Accordingly, medicaments based on these enzymes are of great interest. However, the enzyme preparations have some drawbacks, the main of which are small and instability of their lifetimes in biological systems, which limits their successful application. Therefore there is a need for low molecular weight SOD analogs capable of reducing superoxide anion with sufficient efficiency and are stable in biological systems. Moreover, these molecules are required to have analogues small dimensions and be sufficiently hydrophobic to pass through the plasma membrane, but at the same time possess hydrophilic regions to enhance solubility. Currently, a large number of known copper complexes exhibiting SOD activity, with different ligands. According to recent work showing the highest activity complexes with ligands comprising aromatic nucleus.





An important task is to expand the base of coordination compounds with various aromatic and heterocyclic substituents and the study of their catalytic properties and SOD activity.

We have developed the methods for the obtaining of Cu(II) coordination compounds with various benzothiazolyl and benzimidazolyl substituted pyridines, imidazoles and pyrazoles and also studied the effect of various hydrophilic fragments in benzothiazole ring on solubility and SOD activity of the corresponding coordination compounds.



This work was supported by Russian Foundation for Basic Research (Project № 16-03-00931-a).

The design of the effective procedure for the Z-isomers retinoid analogs preparation

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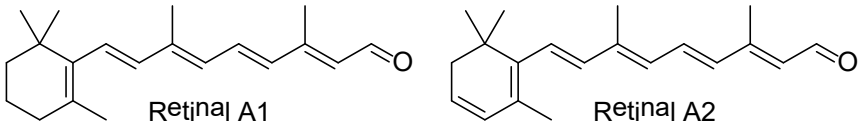
The retinoid isomers play the key role in functioning processes in retinal proteins — bacteriorhodopsin, halorhodopsin, tundra-rhodopsin, visual pigments and others, as well as in the retinoic acid nuclear receptors. Upon absorption of light quantum the isomerisation of the definite double bond initiates a cascade of events needed for the generation of the physiological or chemical responses. Individual retinoid *Z*-isomers are mostly unavailable due to their low thermal and photostability, and their spontaneous isomerization into more stable *E*-isomers while stored. The study of retinal derivatives from retinal proteins of different species aids in understanding their function, which is important both for fundamental sciences and for application in medicine. The determination of the exact structure of retinal derivatives in the chromophoric groups is a complicated task, since possible retinal derivatives are present in the nanogram quantities, and the use of traditional identification methods is impossible. In our opinion, the comparison of retention time (t_R) values of the studied samples with t_R values of synthetic standards by analytical HPLC is the most suitable identification method for the retinal derivatives. However, the individual isomers preparation of retinal and its analogs as the standard samples is a highly sophisticated and labor-intensive task, because only few substances are commercially available. Therefore, the effective synthetic procedures for the preparation of retinal derivatives series as HPLC standards is required for such experiments, although their syntheses are quite complicated. All known synthetic routes could be divided into two groups: a) stereoselective synthesis of given retinoid isomers [1]; b) synthesis of the most available single isomer or isomer mixture followed by photo- or thermoisomerization and isolation of required isomers from the reaction mixture with preparative HPLC.



We studied HPLC separation process of natural retinal (A1) and its 3,4-didehydroderivative (A2) *Z*-isomers in the isocratic mode with use of single normal phase analytical HPLC column or a system of two such columns connected consistently. The photostationary *Z*-isomer mixtures were prepared by *all-E*-isomers photoisomerization in acetonitrile. The model mixtures for the separation were: 1) *all-E*-retinal and *all-E*-3,4-didehydroretinal mixture; 2) photostationary retinal *Z*-isomers mixture; 3) photostationary 3,4-didehydroretinal *Z*-isomers mixture. This method has been tested on retinal and 3,4-didehydroretinal model mixtures, and high reproducibility has been shown. The application of two sequentially connected columns was found to increase the difference in retention times of substances having similar chromatographic mobility and thus allows increasing the precision of HPLC peak correlation. The developed analytical protocol for the retinal derivatives structure determination by HPLC was successfully approved for the several visual pigments, bacteriorhodopsin, and tundra-rhodopsin [2].

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This work was partly supported by RFBR Grant (project № 16-04-01264a).

The design of the effective procedures for direct modification of the spiropyran molecule

Belikov N.E., Demina O.V., Melnikova I.A., Lukin A.Yu., Shumsky A.N., Levin P.P., Varfolomeev S.D., Khodonov A.A.

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A promising way for the new hybrid photoactive/photocontrollable systems and materials design consists in the covalent binding of the photochromic probes via their covalent "immobilization" on various substrates, e.g. polymers, lipids, proteins and quantum dots. Developing the new generation of photochromic probes containing substituents with appropriate functional group type will be required for the implementation of this procedure. Indoline spirobenzopyrans are one of the most studied photochromic compound classes. The structure of possible target substrates defines the nature of the reactive anchor group. Spectral properties and photochemical parameters of spirobenzopyrans depend significantly on the nature of the substituent present in the defined part of the molecule, hence, the targeted variation of substituents' nature allows to search directly for new photochromes with given photochemical properties and various stimulus-responsive structural elements.

Previously we have studied the spirobenzopyran formylation process under the Duff reaction conditions and the influence of different substituents in the pyran cycle on its regioselectivity. The Duff formylation of photochromic spiropyrans having electron-acceptor substituents in the pyran part of molecule (R: 6-NO_2; 8-NO_2; 6-CHO; 6-CO_2Et; 6-CO_2H) was found to mainly proceed to C5'-position of indoline fragment. As the result we developed a new synthetic method for the key carbonyl precursor - 5'-formyl-6-nitrospiropyran derivative by direct formylation of 6-nitrospiropyran, in one step with 86% yield under the Duff reaction conditions [1]. The synthetic application potential of these precursors for targeted modification of the photochrome molecule at 5'-position has been significantly broadened by the application of well-known synthetic procedures (Wittig and Horner-Emmons olefination; nucleophilic addition to the carbonyl group with a family of reagents, possessing an active methyl or methylene groups; reductive amination; [3+2] cycloaddition reaction and others) [2-6].

As the result of this study we developed a number of effective synthetic procedures for four series of new 5'-substituted spirobenzopyrans, which contain the targeted choice of reactive anchor group nature by direct one-step procedure for introduction of substituents of different nature [2-6]. The spirobenzopyran derivatives were prepared in the preparative amounts; their structure was characterized by a number of physical-chemical analysis methods.

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Synthesis of novel anticancer drugs based on dispiro compounds of different N,O-containing heterocyclic fragments

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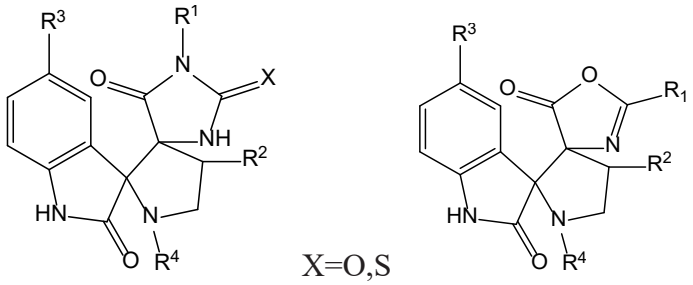
Synthesis of non-peptide small-molecular inhibitors for blocking p53-MDM2 interaction is an actual problem and new strategy in anti-cancer drug design. P53 is a tumor suppressor and plays key role in controlling of cell cycle and apoptosis. MDM2 is endogenous oncoprotein and cellular inhibitor of p53. Thus, small-molecular inhibitors binds to MDM2 whereby released p53 activating process of destruction of the tumor cells. Inhibitors of MDM2 containing spiro-oxindole core are relatively new class of biological active compounds which had ability for effective blocking of the interaction between p53 and MDM2 [1].

In our group we have developed synthetic approaches for preparation of spiro-oxindoles from commercially available reagents using 1,3-dipolar cycloaddition reactions [2]. As starting materials isatins, N-substituted amino acid and 5-arylmethylene-2-thiohydantoins, 5-arylmethylene-2-hydantoins and 1,3-oxazalones derivatives were used. As the result, the compounds containing two spiro-fused cyclic fragments of different nature were obtained [3]:



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This work was supported by Foundation… РФФИ, проект № 16-33-60166.

Redox transformation of 3-(3-oxo-1,3-diphenylpropyl)chroman-2,4-dione with the participation of oxidized hydrogen sulfide

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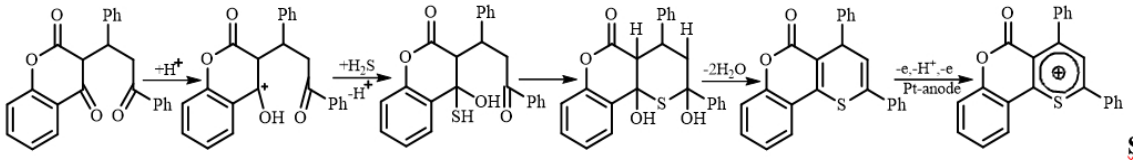
In this work the new synthesis metod of heterocyclic system containing coumarin and thiopiran fragments is discussed. The biological value of these compounds is very high: antibacterial, vasodilator, antimutagenic and antitumor activity. Previously, we investigated the reaction of hydrogen sulfide with 1,5-dicarbonyl compounds with alkyl and aryl substituents in mild conditions [1,2]. The redox activation of H_2S contributed to obtaining of corresponding thiopyrans without the use of mineral or organic acids.

The reaction of 3-(3-oxo-1,3-diphenylpropyl)chroman-2,4-dione with hydrogen sulfide was conducted in conditions of electrochemical one-electron oxidation stage of H_2S to the radical cation at a platinum electrode in organic solvents. The oxidation potential of a reagent is lower at 0,6B than substrate potential. The redox activation of hydrogen sulfide is only possible during electrolysis while substrate is in molecular form.

The electrochemical reaction of 3-(3-oxo-1,3-diphenylpropyl)chroman-2,4-dione with hydrogen sulfide was investigated in CH_3CN, CH_2Cl_2 and solvent mixture CH_3CN:CH_2Cl_2 (1:1). at a temperature 25°C for 1,5h. The cyclization of 3-(3-oxo-1,3-diphenilpropil)chroman-2,4-dion in the presence of H_2S (fig.1) is possible due to the fragmentation of the radical cation with cleavage of the proton. The reaction proceeds according to the scheme:



Scheme 1.

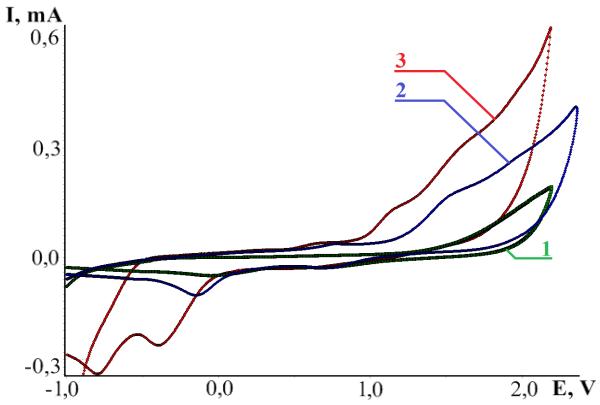


Fig. 1. CVA of the oxidation: 1 – substrate, 2 – substrate at the present of H_2S, 3 – reaction products of H_2S with substrate (CH_3CN:CH_2Cl_2 (1:1), Pt-anode, Ag/AgCl, 0,1 *n*-Bu_4NClO_4, C = $5 \cdot 10^{-3}$ M)

The resulting thiopyran (1,72-1,82B) is able to oxidize at the electrolysis potential and this leads to forming of thiopyrilium salt (-0,38-(-0,46B)). The thiopyran's yield depends on the nature of organic solvent and it reaches a maximum using CH_3CN:CH_2Cl_2 (1:1). The ration of the two reaction products (the thiopyran and thiopyrilium salt) was about the same. The dimer (1,24-1,36B) has been as an unwanted product. The conversion of 3-(3-oxo-1,3-diphenylpropyl)chroman-2,4-dione to sulfurcontaining heterocyclic compounds varies from 41 to 70% in different organic media.

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Polymer composites based on epoxy resin with added carbon nanomaterials

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Using modern achievements of nanotechnology can improve the properties of polymer composite materials is an important task in the field of new materials new nanocomposites. Polymer composites based on epoxy resin with added multilayer graphene and carbon nanotubes (CNTs) obtained using physical and mechanical effects on the suspension of CNTs were studied by electron microscopy. Composites tensile and flexural strength were studied. Insertion of 0.1 weight % of CNTs into polymer matrix resulted in the composite tensile strength increase to 84±4.1 MPa (35% increase as compared to initial composites). Obtained reinforcement exceeded all the available literature reinforcement data for epoxy composites based on epoxy resins. Multilayer graphen were less effective in composite tensile and flexural strength improvement as compared with CNTs. Insertion of CNTs into a polymer matrix increased glassy temperature and was not influence the composites thermal stability. Surface of composites cuts was studied by electron microscopy technique. The reinforced composites can be applied in the different application.

Acknowledgements.
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Cyclopropanes Nitrosation – Advances in the Synthesis of [NO]-Heterocycles

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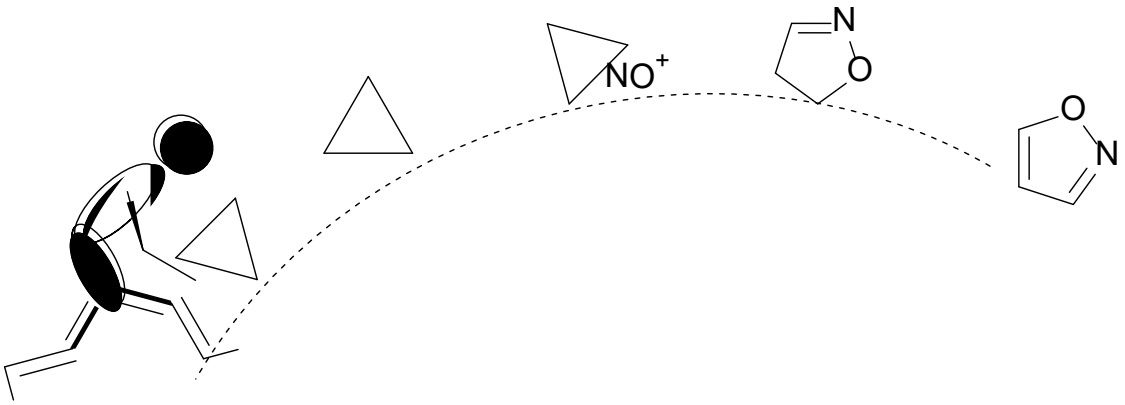
Cyclopropanes nitrosation is a direct route to the construction of [NO]-heterocycles. Some of them, namely, isoxazole and isoxazoline derivatives, every year find more wide application as objects for pharmacological investigations. They exhibit antibacterial, antiasthmatic, antirheumatic and other pharmacological activities and are active principle of some drugs different in their function. In addition, isoxazole/isoxazoline derivatives are widely used in multi-step organic synthesis [1,2]. A significant share of success in electrophilic nitrosation of cyclopropanes is determined by the possibility of a stable carbocationic intermediate formation. Nitrosation of arylated cyclopropanes proceeds, as a rule, *via* benzyl carbocation leading to the formation of 5-arylisoxazolines [3]. In the case of 1,1-dihalocyclopropanes dihalomethyl cation turns out to be the most stable. As a result of the following heterocyclization and spontaneous aromatization under reaction conditions 3-aryl-5-haloisoxazoles are formed [4].



Our studies in the field of cyclopropanes nitrosation are aimed at:
development of new available and efficient nitrosating reagents/systems
determining the scope and limitations of the reaction;
clearing up factors influencing chemo- and regioselectivity of the reaction;
application of haloisoxazoles in organic synthesis;

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The Prilezhaev Oxidation of Kinetic and Thermodynamic Products of the Tandem IMDAF Reaction between DMAD and 1,3-Bis-furyl Dienes

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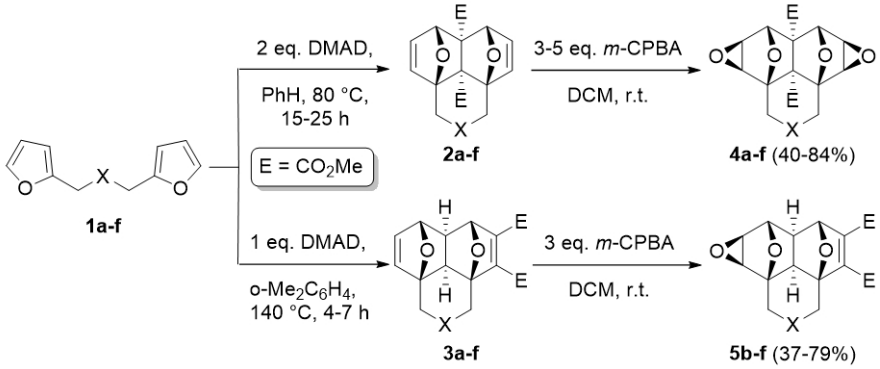
Within the framework of this communication, the rare example of total chemoselectivity in the tandem intramolecular Diels-Alder furan (IMDAF) reaction was demonstrated. The IMDAF reaction between dimethyl acetylenedicarboxylate (DMAD) and *bis*-furyl dienes at 25-80 °C leads to the pincer-adducts (**2**) – the kinetic products [1]. On the contrary, at thermodynamic reaction control (140 °C) the domino-adducts (**3**) are formed only.

In our precedent papers [2-4] the synthesis and chemical transformations of the similar IMDAF reaction adducts were described in detail. Here the Prilezhaev oxidation of diepoxynaphthalenes **2a-f** and **3b-f** is discussed.



Scheme 1. X = S (**a**), O (**b**), N-$COCF_3$ (**c**), N-Ac (**d**), N-Bz (**e**), N-Boc (**f**); for **4a** X = SO_2.

Tri- and tetraepoxides **4a-f** and **5b-f** are formed at mild reaction conditions and in rather good yields. It should mention some features of the reaction: the domino-adducts **3** can be oxidized chemoselectively and the oxidation of sulfur-containing compound **1a** is accompanied by the oxidation of the sulfur atom to the sulfone **4a**.

Highly symmetric oxidation products **4** are of interest to study their spatial structure by X-Ray analysis, and for the subsequent synthesis of polyfunctionalized naphthalene derivatives.

The structure of products **4d** and **5d** (X = N-Ac) was unambiguously established based on its *X*-ray analysis data.

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Development of Synthesis of Ciprofloxacine Analoques on 1,4-Dioxide Quinoxaline Scaffold

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Fluoroquinolones is a group of antibacterial agents with outstanding safety and efficacy profile which widely used for the treatment of a wide range of infectious diseases. Nevertheless it has been reported that new fluoroquinolone-resistant strains of microorganisms are formed [1]. So the development of new fluoroquinolone-based antibacterial agents with advanced *chemotherapical* properties is actual. Derivatives of quinoxaline 1,4-dioxides is another well known class of bioactive compounds potent against bacteria, fungus and tumor cells [2].

The aim of our research was development of scheme of preparation of new analogues of fluoroquinolones based on 1,4-dioxide quinoxaline scaffold. The structure of the target molecule (**1**) have been generated *via* «scaffold-hopping» approach by the hybridization of pharmacophore groups of fluoroquinolone Ciprofloxacin and quinoxaline 1,4-dioxide Olaquindox (Fig. 1).

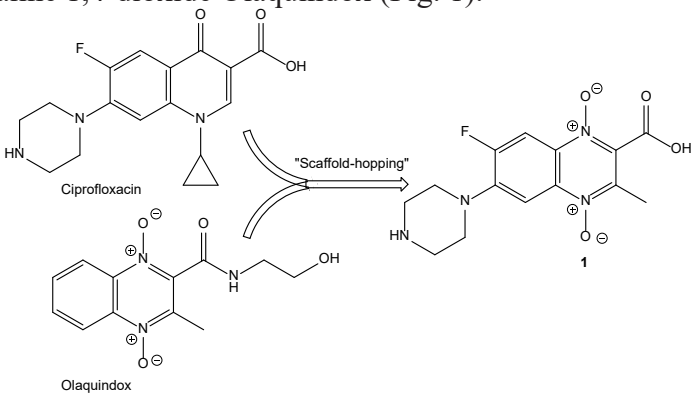
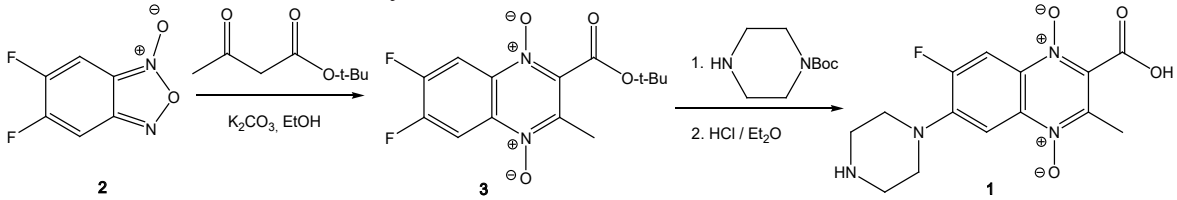


Fig. 1. Design of quinoxaline 1,4-dioxide **1** *via* «scaffold-hopping» approach

For the preparation of **1** three steps synthetic route was developed. On the first stage 2-(*tert*-butoxycarbonyl)-6,7-difluoro-3-methylquinoxaline 1,4-dioxide (**3**) was prepared by Beirut reaction of 5,6-difluorobenzofuroxan (**2**) [3] with *tert*-butyl acatoacetate in the presence of potassium carbonate. At the final steps flourine atom in the position 6 of quinoxaline **3** was substituted with 1-Boc-piperazine and a subseqent protecting groups clevage (Boc- and *tert*-Bu-) to gave target compound **1**. Thus, our synthetic studies led to development of the preparation of bioactive compounds of new chemotype, biological properties of which are still under way.



Scheme 1. Synthesis of target molecule **1**

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Furan amidoalkylation as a route to functionalized furfurylamines

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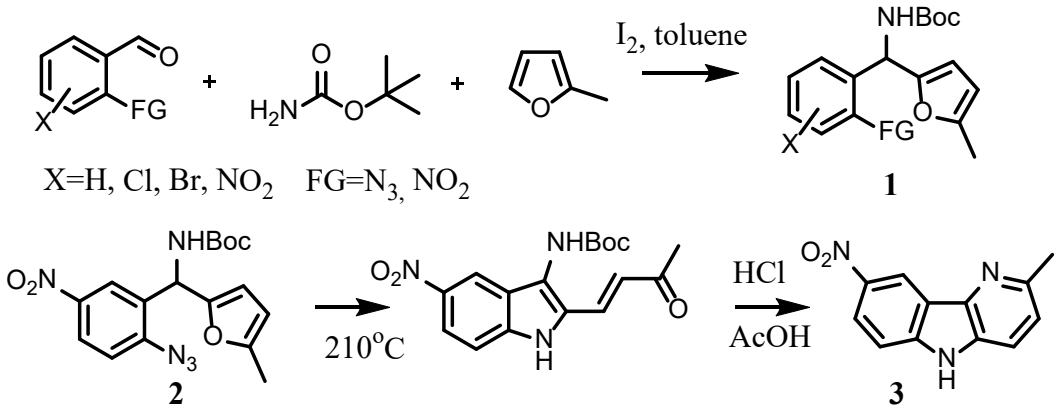
Amidoalkylation of aromatic compounds is a versatile method for the synthesis of branched amines due to intrinsic multicomponent nature and benign reaction conditions[1,2]. Amidoalkylation can be readily adopted to the synthesis of variety of furfurylamines. We have found that this three-component condensation operates equally well with benzaldehydes substituted with azido or nitro-group in ortho-position. Obtained furfurylamines **1** are precursors for the synthesis of benzannelated heterocycles. This methodology was showcased with one-pot transformation of 2-azidobenzylfuran **2** into δ-carboline **3** according to recently developed indole synthesis[3].



Scheme 1. Amidoalkylation of silvan wih ortho-functionalised benzaldehydes.

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Reagents for Storage and Regeneration of Nonstabilized Azomethine Ylides: Spiroanthraceneoxazolidines

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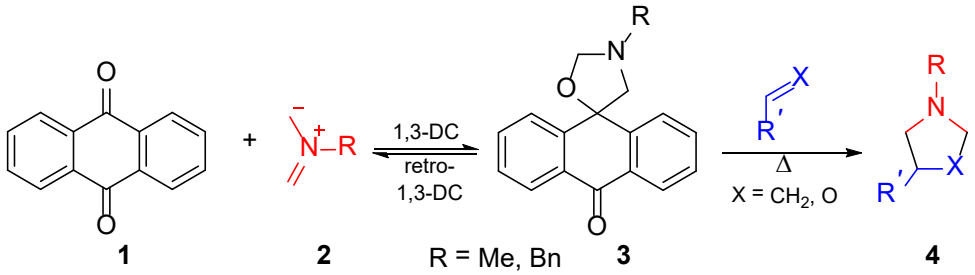
Anthraquinone **1** readily reacts with nonstabilized azomethine ylides **2**, derived *in situ* from N-substituted glycine and formaldehyde to give 10*H*-spiro[anthracene-9,5'-oxazolidin]-10-ones **3** in quantitative yield [1]. The latter possess an unusual ability to undergo a cycloreversion and to eliminate the dipole **2** in the presence of another dipolarophile at 120–150 °C. The sequence of retro-1,3-DC/1,3-DC was examined on a number of substrates such as carbonyl compounds and electron-poor alkenes. All tested dipolarophiles smoothly reacted with spirooxazolidines **3** to give cycloadducts **4** in moderate to high yields (41–92%).



The proposed method for the generation of the ylides from spiroanthraceneoxazolidines, obtained from anthraquinone, possess a number of obvious advantages over the interaction between dipolarophiles with sarcosine and formaldehyde. First, an absence of formed water and of the necessity to remove it from the reaction medium. Second, performing syntheses in *o*-xylene instead of toxic benzene (the best solvent for obtaining 5-aryloxazolidines by azeotropic method). Third, the possibility to obtain high concentration in a reaction mixture.

Furthermore, another promising feature of the proposed method for the generation of nonstabilized azomethine ylides from spiroanthraceneoxazolidines **3** is to provide the opportunity to carry out the reactions at high temperature. We demonstrated that implementation of the [3+2] cycloaddition in a sealed vial at 210 °C in a microwave reactor allows to obtain cycloadducts with low reactive dipolarophiles such as benzophenones, styrene, and sterically hindered alkenes with good conversions and in moderate yields (20–56%).

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Photocyclization of Diarylethenes Comprising an Imidazole Moiety

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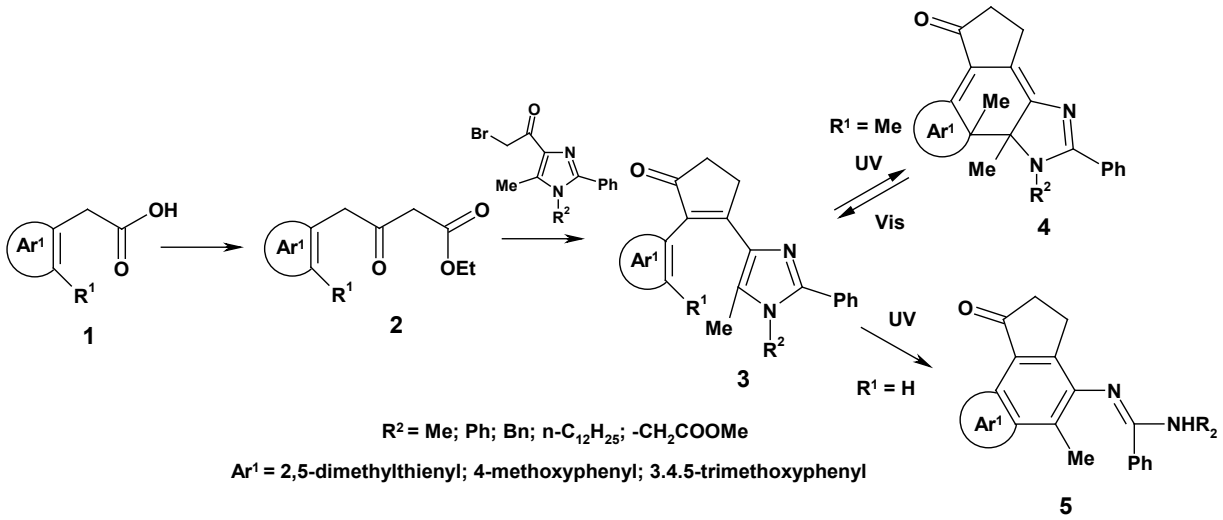
Organic photochromic compounds are widely investigated for the development of different high-tech materials. Diarylethenes are of a great interest among photochromic compounds due to a high thermal stability of the metastable photoinduced form and fatigue resistance. Recently, in our laboratory the first photochromic diarylethenes based on cyclopent-2-en-1-one series with azole derivatives as aryl moieties have been developed. It was found that the photochromic properties of these diarylethenes strongly depend on the nature of the azole residue. In particular, it was shown that the use of imidazole derivatives as aryl moiety leads to an increasing the thermal stability.

The goal of this work is to synthesize and study the photocyclization reactions of diarylethenes bearing an imidazole moiety. The synthesis of diarylcyclopent-2-en-1-ones comprising imidazole residues was carried out according to the method developed by our research group, and it involves the synthesis of ketoesters **2** by following alkylation with bromoketones of an imidazole series and the intramolecular cyclization. A series of non-symmetrical 2,3-diarylcyclopent-2-en-1-ones **3** were prepared.



Scheme 1. Synthesis and photocyclization of 2,3-diarylcyclopent-2-en-1-ones

In this work the photochromic properties and the photocyclization reaction of the prepared 2,3-diarylcyclopent-2-en-1-ones have been studied. It was found that there are two alternative transformations: either reversible photochromic isomerization (R^1 = Me), or photorearrangement reaction (R^2 = H) depending on the substituent at the reaction center of diarylethene's molecule.

In this contribution we will also discuss the some mechanistic aspects of these transformations.

This work was financial supported by the Russian Foundation for Basic Research (RFBR) Grant № 15-03-05546.

Highly-Efficient Nanocarbon-Modified Zeolite Materials for Removal Heavy Metal Ions

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Zeolites – microporous framework alumosilicates – are very promising natural materials due to their high technological parameters and the absence of adverse environmental impacts while employing them on a large scale in various fields. Since these materials are easily machined (followed by fractionation), highly resistant to weak alkaline and weak acidic media, do not swell in water and exhibit good molecular-sieve, adsorption and mechanical properties, they can be successfully used as adsorbents in water and wastewater treatment.

However, in many cases, it is required to achieve an extremely high degree of water and wastewater treatment (e.g., by considerably decreasing heavy metal levels in drinking water or wastewater effluents) to reduce environmental and human health risks. One of the most widely known heavy metal ions is nickel (Ni^{2+}), which take place in the domestic and technical wastewater. Commonly used zeolites often cannot allow for fulfilling this objective completely due to their insufficient adsorption capacity.

In this regard, to improve their adsorption capacity for heavy metal ions in aqueous systems, they can be modified with carbon nanotubes (CNTs). The latter possess unique mechanical and physicochemical properties and have a rather large surface area which makes them a very efficient adsorbent material.

The present work describes a procedure for modifying zeolite with differend kinds of CNTs (synthesized over catalysts obtained through sol-gel (SG) and thermal decomposition (TD) techniques) and presents a comparative kinetic study of the adsorption of nickel ions on non-modified and nanomodified zeolites.

It was found that adsorption equilibrium in the systems is achieved after 450 sec of the process, and the nanomodified zeolites present higher adsorption capacity compared to the non-modified one (295 mg/g – CNTs-SG, 270mg/g – CNTs-TD, and 260 – non-modified). The nickel adsorption was successfully (R^2>0.98) fitted to the pseudo-second-order, Elovich, and intraparticle diffusion kinetic models for all the adsorbents, thereby confirming the chemical nature of the process and the pore diffusion as rate-limiting step. It should be noted that the chemical nature of the nickel adsorption stands for the availability of more active sorption sites able to adsorb more nickel ions.

Considering the aforementioned results, the CNTs-modified zeolite can be employed as an adsorbent in water and wastewater treatment processes for effectively removing heavy metal ions from aqueous solutions.

The present research was supported by the Ministry of Education and Science of the Russian Federation (Project No. 16.711.2014/K).

N-, C- and O-adamantilation of azoles by 1,3-dehydroadamantane

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Adamantyl-containing heterocyclic compounds with nitrogen atoms in the ring are of great interest, either from the point of synthetic organic chemistry, or their practical application. From a wide range of physiologically active adamantane derivatives more than half are the nitrogen-containing heterocycles, including the class of azoles [1].

The promising way of synthesis hard to gain adamantyl-containing azoles is to use as a starting material strained bridged [3.3.1] propellanes. In a practical and scientific point of interest of such propellanes there is tetracyclo [3.3.1.1.3,7.0.1,3] decane (1,3-dehydroadamantane, 1,3-DHA). The presence of volatile propellane bond connecting inverted quaternary carbon atoms, makes these compounds extremely reactive in addition reactions to various compounds with mobile proton.

We have carried out the reaction of 1,3-DHA with rows of azoles:

- 1*H*-pyrazole and 1-R-, 3 (5) -R-, 4-R-, 3,4-R,R-, 3,5-R_1,R_2-, 3,4,5-R_1,R_2,R_3 -derivatives;
- 1*H*-imidazole and 2-methyl-1*H*-imidazole, 2-methyl-benzimidazole;
- 1*H*-1,2,4-triazole and 3-R-, 3,5-R,R-derivatives;
- 5-methyl-1*H*-tetrazole;
-3,5-R_1,R_2-isoxazole and 3-R_1-5-R_2-4,5-dihydroisoxazol-5-carboxylic acids.

The structure of initial azoles (1*H*-pyrazoles, 1*H*-imidazoles, 1*H*-1,2,4-triazoles, 1*H*-tetrazoles) had a different nature and quantity of substituents, allowing widely influence on the acid-base properties. Azoles contained either the electron-donating (methyl-, 1-adamantil-, amino groups) or electron-withdrawing substituents (phenyl, trifluoromethyl, bromo, chloro, iodo, nitro, hydroxy and carboxy).

It is found that the structure of the synthesized in specific cases adamantyl-containing azoles depends on the structure of initial azole and his acid-base properties, the presence of tautomeric transformations, reaction conditions, nature of the solvent in reaction. While carrying out the reactions we mentioned preferential formation of N-adamantilated azoles products (1*H*-pyrazoles, 1*H*-imidazoles, 1*H*-1,2,4-triazoles, 1*H*-tetrazoles). In some cases, there was the formation of the C-adamantilated products 1*H*-pyrazoles by carbon atoms heteroaromatic cycle (8-28%) and alkyl substituents (4-19%). Adamantilation of N-substituted azoles by 1,3-DHA proceeds on the cycle heteroaromatic carbon atoms and functional groups.

In the case of presence in the structure of the heterocyclic compounds the carboxy group (3-R_1-5-R_2-4,5-dihydroisoxazol-5-carboxylic acid), 1,3-adamantilation this compounds by 1,3-DHA proceeds exclusively thereon to form esters.

Thus, the method developed by introducing the adamantane skeleton into the structure of azoles produces adamantyl-containing heterocyclic compound in one step in a short time under mild conditions and with sufficiently high yields of products.

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Synthsis of adamantyl-containing isothiocyanates

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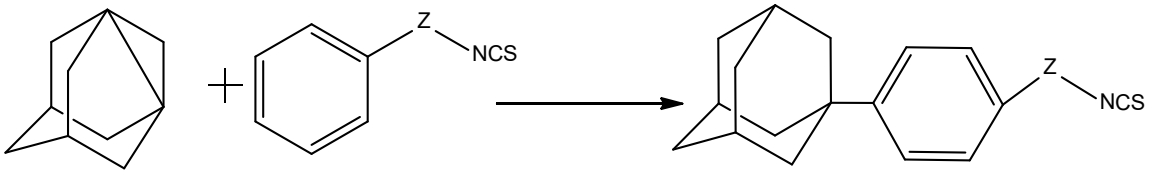
Adamantyl-containing isothiocyanates are of great interest as promising intermediates for the synthesis of biologicaly active compounds.

Thioureas acquired from 1-adamantyl isothiocyanate are potent soluble epoxide hydrolase (sEH) inhibitors. This enzyme inhibition by highly selective inhibitors are followed by vasodilatation and inflammatory pain relief. Thus sEH is the promising target in the therapy of hypertension and inflammation. Moreover sEH inhibition may be used to treat asthma, renal failure, Parkinson, Alzheimer and cancer.

Besides there are many adamantyl-containing thioureas synthesized by now, most of them were made from 1-adamantyl isothiocyanate. Thus the structure-activity relationship of substituents in adamantane part as well as spacers between adamantine and thiourea group were never investigated before.

To produce thioureas with substituents in adamantine part or spacers between adamantane and thiourea group one have to synthesize new adamantly-containing isothiocyanates.

Our first approach is the interaction of aromatic isothiocyanates with 1,3-dehydroadamantane.

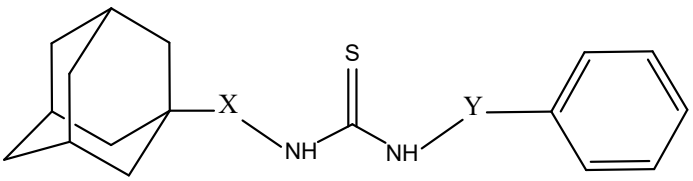


Z = -, CH_2, CH_2-CH_2;

1-Adamantyl isothiocyanate was synthesized from isothiocyanic acid by the same reaction with 1,3-dehydroadamantane.

Another approach for the synthesis of adamantyl-containing isothiocyanates is the interaction of adamantyl-containing amines with phenylisothiocyanate. This reaction when carried out in toluene doesn't lead to thiourea.

New adamantyl-containing thioureas were synthesized and investigated as human soluble epoxide hydrolase inhibitors:



X= -CH(CH_3)-, Y= - (I); X= -(CH)CH(C_2H_5)-, Y= - (II); X= -CH(CH_3)-, Y= -CH_2- (III); X= -(CH)CH(C_2H_5)-, Y= -CH_2- (IV); X= -CH(CH_3)- , Y= -CH_2-CH_2- (V); X= -(CH)CH(C_2H_5)-, Y= -CH_2-CH_2- (VI).

Activity of synthesized compounds against sEH (IC_{50}) were investigated by the kinetic fluorescent method at University of California Davis. For the first time thioureas with IC_{50} under 10 nM were synthesized.

This work was supported by RFBR (project # 16-33-00172 mol_a)

Preparation of β-ketosulphones under Fenton reaction conditions

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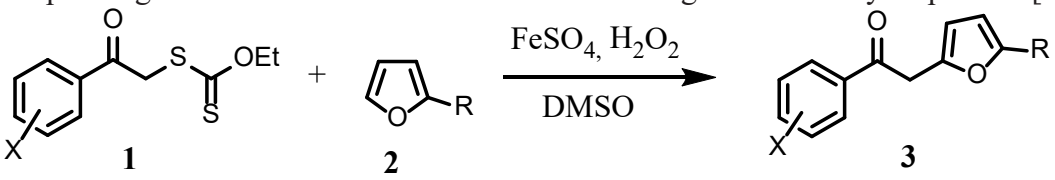
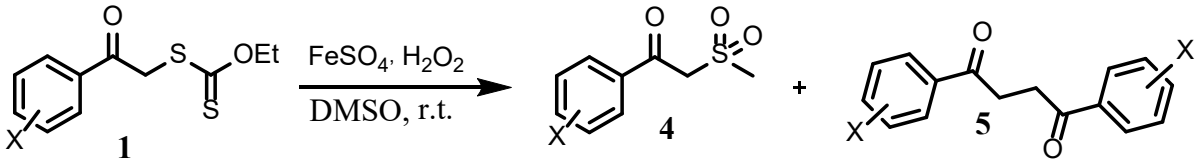
Recently we reported the method of synthesis of furphuryl(aryl)ketones **3** by phenacylation of furans **2** with the corrresponding xantates **1** under the action of Fenton reagent in dimethylsulphoxide[1].



Side products sulphones **4** and symmetrical 1,4-diketones **5** that invariably accompanied the formation of ketones **3** became principal products when the reaction was performed without furan substrate. Optimization of the reaction conditions allowed for the preparation of sulphones **4** in practically useful yields.



Phenacylsulphones are valuable active methylene compounds widely utilized in the synthesis of various oxygen- and nitrogen containing heterocycles therefore their new methods of synthesis are desirable. Our new protocol for their synthesis features ready availability of starting phenacylxantates or phenacyliodides, employment of cheap and non-toxic DMSO as a source of sulphur, short reactions times (up to 30 min), easy isolation of target compounds avoiding chromatography and due to simplicity will be complementary to the existing methods.

1. P.N. Chalikidi, T.A. Nevolina, M.G. Uchuskin, V.T. Abaev, A.V. Butin Chem. Heterocyclic Comp., 2015, 621

Financial support for this work was provided by the Ministry of Education and Science of Russian Federation (project № 2754)

Synthesis of 6-(e)-2-aryl(hetaryl)-1-ethynyl-4-pyrimidinoles and 3-[1-(2,4,5-trisubstituted-4-pyrimidinyl)methylidene]-1-methyl-2-indolinones

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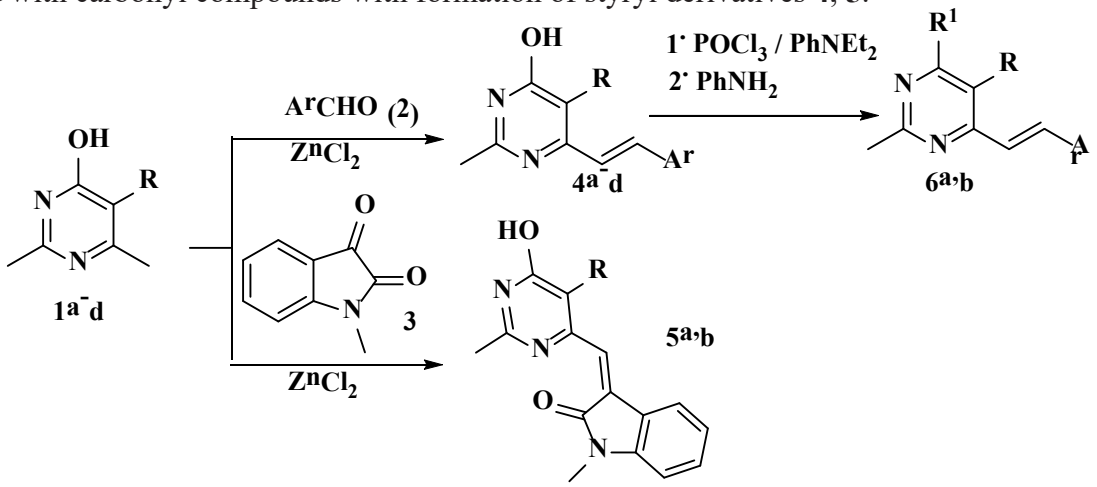
Substituted pyrimidines are traditionally considered as prospective models in the search for new compounds for medicine and engineering. In continuation of our work in the synthesis and transformations of functionally substituted pyrimidines [1-3], we have synthesized a series of 6-styrylpyrimidines – heterocyclic analogs of stilbenes aimed at further studying their biological and photochromic properties. Synthesis of the target compounds was carried out by fusion (in the presence of $ZnCl_2$) of 5-R-2,6-dimethyl-4-pyrimidinoles **1** and aromatic aldehydes **2**, or 1-metilizatin (**3**). Under the described conditions 6-methyl group, exhibiting increased acidity is easily condensed with carbonyl compounds with formation of styryl derivatives **4**, **5**.



1^{a-d}: $R^{-}(CH_2)_2COOH$ (a), $CH(CH_2)_4$(b), $(CH_2)_3Me$ (c), $CH_2{}^{-}2,4Me_2C_6H_3$ (d)

4^{a-d}: $R^{-}(CH_2)_2COOH$, $Ar^{-}2^{-}OH^{-}C_6H_4$ (^{a}), $4^{-}OH^{-}C_6H_4$ (b), $3^{-}C_4H_4N$ (c), $R^{-}CH_2{}^{-}2,4^{-}Me_2C_6H_4$, $Ar^{=}4^{-}NO_2C_6H_4$ (d)

$5^{a,b}$: $R^{=}CH(CH_2)_4$ (^{a}), $(CH_2)_3Me$. $6^{a,b}$: $Ar^{=}4^{-}NO_2C_6H_4$, $R^{=}CH_2{}^{-}2,4^{-}Me_2C_6H_3$, $R^{1=}Cl$ (^{a}), NHPh (b)

Condensation of aldehydes and 3-pyridincarbaldehyde with pyrimidines results in formation of E-isomers of 6-styryl derivatives while similar condensation of 5-cyclopentyl- and 5-butyl-pyrimidines **1b,c** with 1-metilizatin leads to formation of a mixture of two isomers in the ratio of 9:1. Chlorination followed by aminolysis of compound **4d** results in its transformation to 4-phenylamino derivative **6b**, that demonstrates the possibility of additional functionalization of compounds for creation of libraries of compounds of this series.

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The work has been fulfilled within the framework of the “Program of development of Russian-Armenian University 2014-2016”.

Synthesis of new hydrazine-based bis-heteroaromatic ligands

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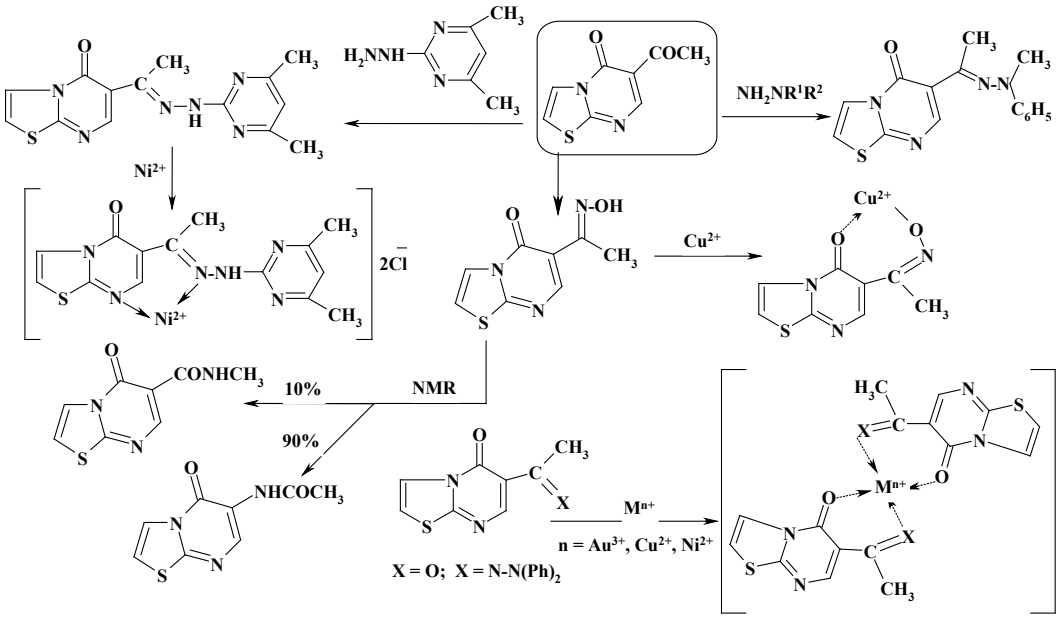
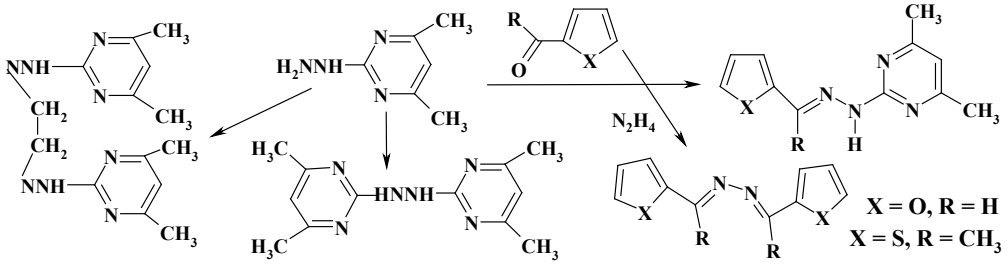
The presence of two or more fragments in the molecule capable of complexation is known to result in stable metal complexes. The latter have a number of useful properties of practical value [1,2]. Therefore, research in this direction is quite intensive worldwide [3].

We have synthesized a number of polydentate ligands combining in the molecule fragments of pyrimidine, furan, thiophene, thiazolo[3,2-a]pyrimidine bound by either N-N hydrazine fragment or N-O oxime bridge.



The target models were obtained on the basis of 6-acetyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one or 4,6-dimethylpyrimidine.



Complexes of some synthesized compounds have been synthesized.

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The work has been accomplished within the program 13-1D334 of the State Committee of Science of the Ministry of Education and Science of the RA, as well as in the framework of the “Program of the Development of Russian-Armenian University 2014-2016”.

Possible Applications of the 3D Printing Technology in Chemical Laboratory

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Fig. 1. Test-Tubes with Screwed Caps Created on 3D Printer.

Application of 3D printing can open new horizons for chemists as it allows to create necessary equipment on-demand. In this study we have examined the most popular and inexpensive technology of 3D printing (FDM - Fused Deposition Modeling) in routine chemical research. Simple printer construction and its easy maintenance in group with diversity of available construction materials makes FDM technology very attractive.

In the present study the question of applicability of the printed labware to chemical needs is discussed. We have chosen widespread in laboratory practice test-tube format (Fig. 1) for initial study. Its chemical stability and impermeability were tested prior carrying out chemical synthesis. The performance of FDM-printed test-tubes was evaluated on the example of cross-coupling Suzuki-Miyaura and hydrothiolation reactions. Advantages and disadvantages of the printed reactionware from ABS, PLA, PETG and PP thermoplastic materials will be presented and discussed.

This work was supported by Foundation RNF 14-50-00126.

3-Aminothieno[2,3-*b*]pyridines as Versatile Buildng Blocks for Polyheterocycles

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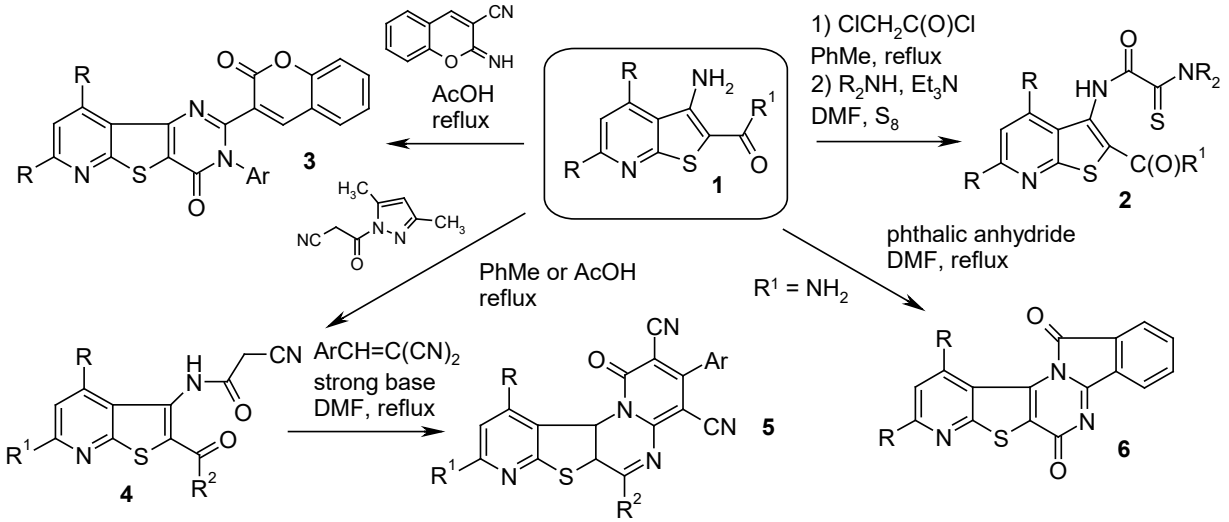
3-Aminothieno[2,3-b]pyridines are known to exhibit a broad spectrum of biological activity and were recognized as valuable reagents for heterocyclic synthesis [1-3]. In continuation of our studies on the synthesis of polyheterocyclic ensembles starting from thienopyridines, we have undertaken a systematic study of the reactions of thienopyridines **1** with a couple of electrophilic agents.

3-Aminothienopyridines **1** could be easily N-acylated with $ClCH_2C(O)Cl$ and cloroacetamides obtained were converted into monothiooxamides **2** by the known procedure [4,5] based on the reaction with sulfur and active amines in the presence of a base. Upon treatment with 3-cyano-2-iminocoumarins, thieno[2,3-b]pyridines afforded coumarins **3** through the cascade recyclization [6]. 1-Cyanoacetyl-3,5-dimethylpyrazole is the most convenient and useful reagent for cyanoacetylations [7]. When thienopyridines **1** were treated with cyanoacetylpyrazole, cyanoacetamides **4** were obtained in 60-80% yields. The obtained compounds **4** reacted with arylmethylidene malononitriles under harsh conditions to give 7-thia-5,8,11c-triazabenzo[*c*]fluoren-1-ones **5**. 7-Thia-5,8,11c-triazaindeno[1,2-*c*]fluorenes **6** were obtained from *domino*-type condensation of thienopyridines **1** with phthalic anhydride.

Scheme 1.



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This work was supported by Russian Ministry of Education and Science (State Assignment to Higher Education Institutions, project No. 547).

Synthesis of thieno[2,3,4-*gh*]perimidine from 1*H*-perimidines and 1,8-diaminonaphthalene

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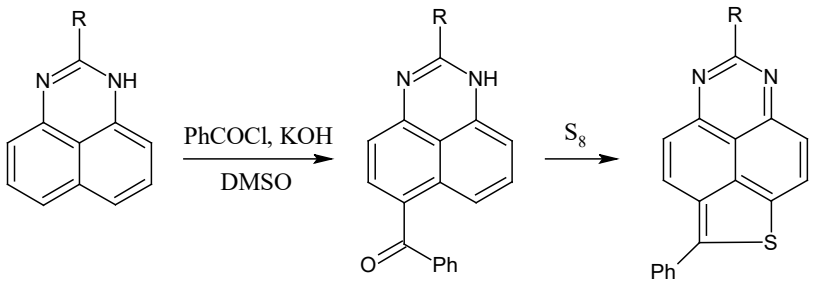
Thiophene and derivatives are undoubtedly of great importance as compounds of high biological activity [1-3], and materials possessing useful applied properties [4].

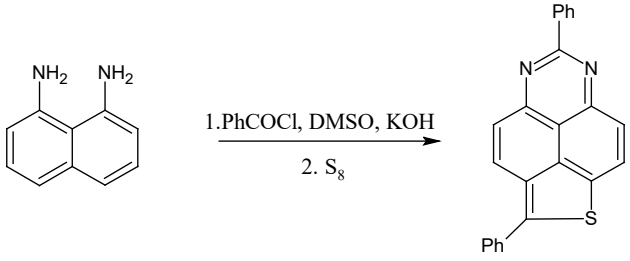
We have previously reported the synthesis of thieno[2,3,4-*gh*]perimidine under the reaction conditions of Willgerodt-Kindler [5], this method has one drawback because it requires prior benzoylation of the source azaphenalenes. In this paper we present a new modified method for peri-annulaton of a thiophene ring to perimidines. It is a multicomponent reaction of both 1*H*-perimidine and benzoyl chloride with alkali and dimethyl sulfoxide followed by the addition of sulfur.



R=H, Me, Ph

Probably, the reaction proceeds via benzoylation step under Schotten-Baumann reaction conditions, followed by a peri-annulation of the thiophene ring. The reaction yield was 63-78%.

It is known that 2-phenylperimidine can be formed from 1,8-naphthylenediamine and benzoyl chloride, so we decided to combine this reaction with previous one. As it turned out, instead of 2-phenylperimidine one can use its predecessor 1,8-diaminonaphthalene. In this case the use of a 3-fold excess of benzoyl chloride is required. The reaction yield was 57%.



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Approaches to the synthesis of monomers for poly(imide siloxane)s preparation

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Polyimides (PI) – are one of the most important large-tonnage polymers. These polymers are applicable in very many branches of modern technology and industry : electronics, functional materials for spacy industry, nanotechnology and many others. However, one of the most important drawback of PI implementation is difficulties of its processing to final product due to rigid polymer structure. This obstacle can be circumvented by incorporation rigid PI and flexible polydimethylsiloxane (PDMS) chains, which can be considered as block copolymer poly(imide siloxane) (PIS). PIS diblock and multiblock copolymers with different monomers nature and polymerization degrees are ideal candidates for controlling interfacial properties between silicon substrates layered with thin films for wide variety applications. These high Tg materials offer an approach for obtaining reduced moisture absorption and low stress interfaces.

PIS copolymers have been reported as early as 1966 when pyromellitic dianhydride (PMDA) was reacted with an amine and terminated siloxane dimer to form the poly(amic acid) precursor followed by curing to yield the imide (Fig.1) [1]. Several approaches for preparing these materials have emerged to date, but none of them cannot be used for preparing well-ordered PIS block-copolymers [2].

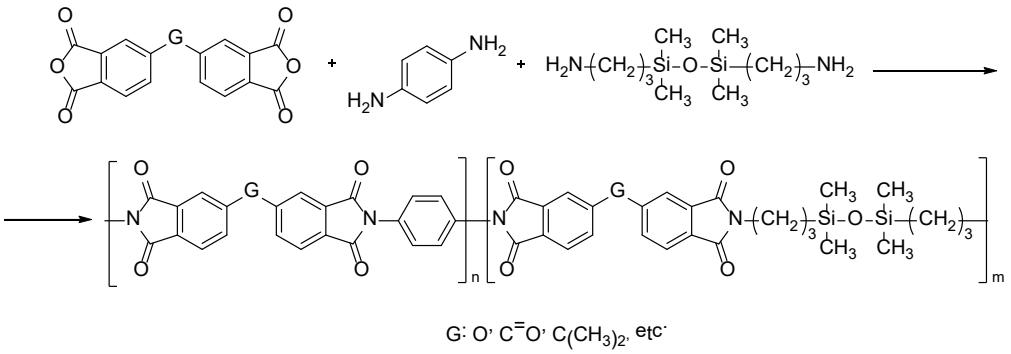

Fig. 1. Typical synthetic route of randomly segmented PIS

We offer novel 3-step methodology of PIS preparation by using hydrosililation reaction between vinyl containing nitroaromatic monomers **M1-M3** (Fig.2) and telehelic two functional hydride-PDMS as a key step. For these purposes the strategy of synthesis series of vinyl containing nitroaromatic monomers **M1-M3** was developed.

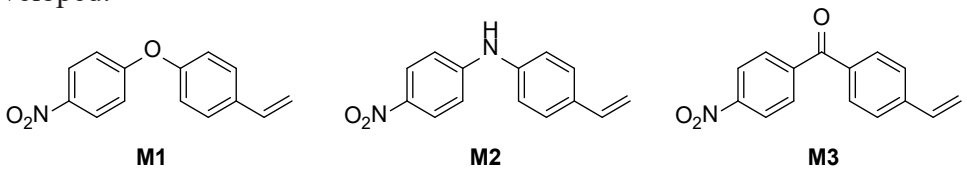

Fig. 2. The structures of vinyl containing nitroaromatic monomers

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Synthesis of the new alternating copolymers with dithienodicianovinyl acceptor units

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Nowadays, the development of new high-efficient conjugated polymers – is one of the most substantial aspects of the organic photovoltaic. For the last few years power conversion efficiency (PCE) of polymers based organic solar cells (OSCs) 10% barrier has been passed [1] and now is going to be continuous. Despite of the large number of publications, one cannot always find the most effective polymer because of many requirements: optimum frontier orbitals levels (HOMO/LUMO) for the best correlation to fullerene acceptor's energy levels, narrow band gap, high charge transfer mobility, wide absorption spectrum in UV-vis light, high solubility in organic solvents.

One of the most popular approach for development of the polymer with the above-mentioned requirements is to insert alternating donor and acceptor blocks in the polymer chain. By varying the number and electronegativity of these blocks, the HOMO/LUMO levels and band gap can be fine-tuned.

The aim of this research was the synthesis of 2 alternating conjugated polymers with dithienosilol (**Me_3Sn-DTS-dec**) as donor block and two novel acceptors: dithienodicianovinyl **(2T-DCV)** and its analog – cyclopentadithiophene-dicianovinyl (**CDPT-DCV**) as acceptor block (Fig. 1).

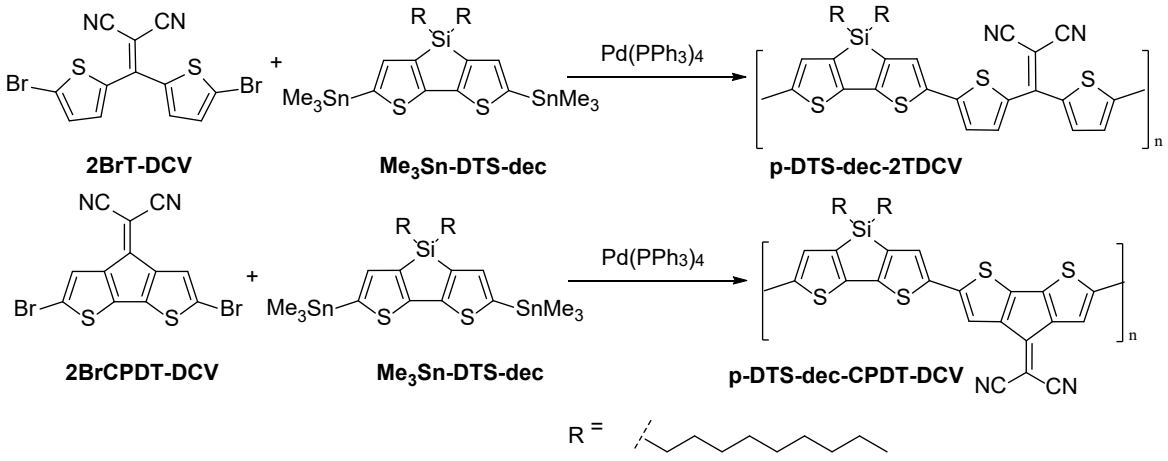

Fig. 1. Synthesis of the two copolymers with dicianovinyl thiophene-consisted acceptors

During the first period of this work, the synthetic methodology of 2Br-2T-DCV and 2Br-CDPT-DCV bifunctional monomers was performed started on 2-bromothiophene. Moreover, donor fragment Me_3Sn-DTS-dec was synthesized and purified by preparative chromatography. All of the intermediates were isolated and characterized by HPLC, NMR and element analysis. After that, the synthesis of two new polymers p-DTS-dec-2T-DCV и p-DTS-dec-CPDT-DCV was done by Stille cross-coupling protocol. Both polymers were isolated, purified and fractionalized.

References

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4,5-Bis(dimethylamino)quinolines: unusual trends of protonation

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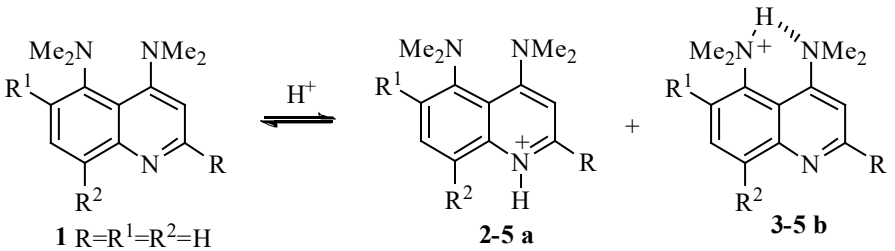
It is well known that protonation of conjugated aminoazines occurs exclusively at the exocyclic nitrogen atom (aza-group). A classical example is 4-dimethylaminopyridine widely using as a catalyst for transacylation reactions. In the present work we aimed to clarify the question: is it possibly under some circumstances to achieve protonation of the side NMe_2 group. For this we have synthesized a number of derivatives of yet unknown 4,5-bis(dimethylamino)quinoline **1** as a heterocyclic analogue of 1,8-bis(dimethylamino)naphthalene ("proton sponge"). Notably, that to the beginning of our work there were reported no representatives of 4,5-diaminoquinoline at all. We performed a multistep synthesis of compounds **2–5** and studied their structural, spectral and electronic characteristics focusing mainly on their basicity and protonation trends.

The main conclusions of our work are as follows. 1) In accord with the electron-accepting nature of the aza-group, compounds **2–4** display somewhat lower basicity (pK_a 6.3–7.2, DMSO) than 1,8-bis(dimethylamino)naphthalene (pK_a 7.5, DMSO). 2) Basicity of **5** (pK_a 7.7, DMSO) is the largest among all known derivatives of 4,5-bis(dimethylamino)quinoline and even slightly exceeds that of the parent "proton sponge". This can be attributed to the "buttressing effect" exhibited by the 6-MeO group. 3) The most important observation is a dual protonation of amines **2–5**. While compound **2** in solutions and in the solid state forms exclusively quinolinium cation **2a**, its counterparts **3–5** demonstrate simultaneously the azine and the proton sponge behavior. Thus, in solutions **3–5** are protonated producing equilibrium amounts of cations **a** and **b**; the maximum percentage of anilinium form **b** is observed for diamine **5**. In the solid state, the protonated salts of **3** and **5** exist only as anilinium forms **3b** and **5b** with the proton chelated by the *peri*-NMe_2 groups while **4** in the solid state gives the quinolinium salt. Besides, stable double salts **6** with picrate and perchlorate anions unprecedented for the azines with conjugated aza and NMe_2 groups have been obtained and thoroughly studied.

Thus, for the first time we have disclosed the conjugated aminoazine representatives capable to be protonated at exocyclic dialkylamino groups.

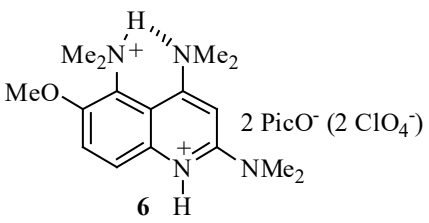


1 R=R^1=R^2=H
2 R=R^2=Me; R^1=H
3 R=NMe_2;R^1=H; R^2=Me
4 R=NMe_2; R^1=H, R^2=OMe
5 R=NMe_2; R^1=OMe; R^2=H

2-5 a

3-5 b

Salt	Solvent	a / b, %
2·PicOH	CD_3CN	100 / 0
	DMSO-d_6	100 / 0
3·PicOH	CD_3CN	50 / 50
	DMSO-d_6	45 / 55
4·$HClO_4$	CD_3CN	89 / 11
	DMSO-d_6	77 / 23
5·$HClO_4$	CD_3CN	13 / 87
	DMSO-d_6	59 / 41



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This work was supported by the Russian Foundation for Basic Research (grant 14-03-00010).

Peparation of enantiopure indolylacetohydoxamic acids

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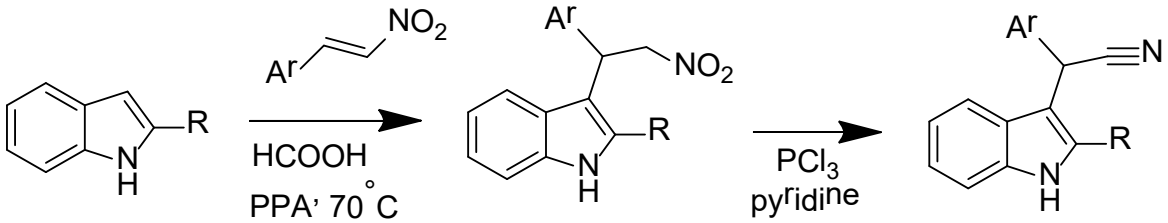
Development of synthetic approaches to alkaloid-mimics embedding the indolyl moiety is one of the central themes of contemporary organic and medicinal chemistry. Such interest caused by various biological activity of species with this fragment. Thousands of synthetic compounds as well as alkaloid were shown. This is a reason why interest in a these compounds and synthetic routes will never go out.

We have recently found the 2-aryl-2-(3-indolyl)-acetohydroxamic acids have significant activity against glioma, melanoma, esophageal, and many other cancer lines intrinsically resistant to apoptosis induction and poorly responsive to treatment with traditional proapoptotic drugs. In our present work we decided to study indolylacetonitriles related to these compounds. Starting from indoles and β-nitrostyrenes, we needed catalyst for alkylation to be fully compatible with a sensitive indole moiety and reducting agent that used in the second step. We found that formic acid is perfect as catalyst. This allows us to perform transformation as *in-one-pot* process using the addition of PCl_3/pyridine system to reaction mixture. This reducts nitrogroup and decomposes formic acid.



Scheme 1. Synthetic sequence

This project was supported by grants from the Russian Science Foundation (grant #14-13-01108)

Copper-catalyzed Michael addition of furans to α,β-unsaturated carbonyl compounds

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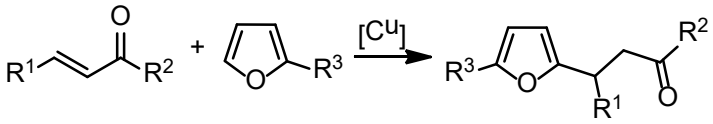
Michael reaction is a powerful instrument for building organic molecules. Since the discovery of this reaction, a lot of its variations was developed.

Existing methods of addition of furans as nucleophiles to Michael acceptors have significant disadvantages, such as use of expensive catalysts [1] or specific conditions [2].

Our group has developed a simple and efficient synthetic method towards β-furylketones based on the Michael addition of furans to α,β-unsaturated carbonyl compounds under catalysis by inexpensive copper(II) salts.



Scope and limitations of the newly developed approach along with potential synthetic application of the obtained products will be discussed.

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This work was supported by RFBR (grant № 16-33-00101) and Ministry of education and science of the Russian Federation (project № 4.246.2014/K).

Synthesis of calix[4]arene derivativs with azide groups on the upper rim using Cu(I)-mediated substitution reaction

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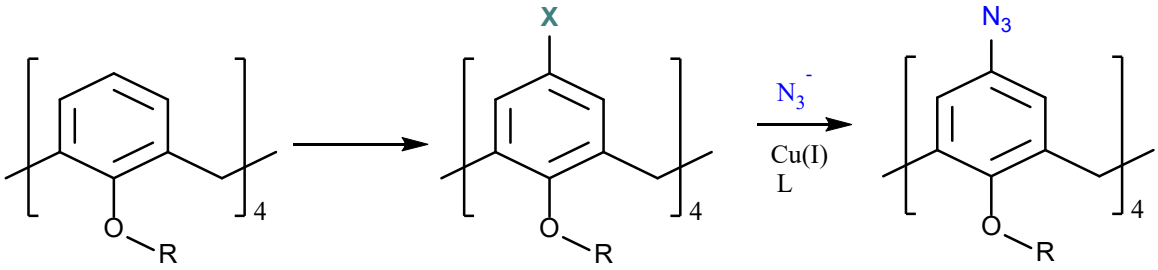
The unique structure and diversity of the stereoisomeric forms of calix[4]arene derivatives have led to their wide application in supramolecular chemistry. Classical calix[4]arene can be modified *via* chemical transformations of its upper and lower rims. Four hydroxyl groups on the lower rim can be used for further functionalization using alkylation reactions [1]. The upper rim can be modificatied using general methods common for aromatic compounds. Also calix[4]arene has a hydrophobic cavity wich also can bind different 'guests' *via* hydrophobic interactions. Therefore calix[4]arenes are widely used in recognition of anionic, cationic and uncharged substrates [2].

Organic azides are good starting material for the synthesys of many nitrogen-rich structures such as aziridines, triazoles, triazines, and others [3, 4]. In our work we carried out the synthesys of tetra-substituted calix[4]arene derivatives containing azide groups on the upper rim using Cu(I) – mediated aromatic nucleophilic substitution. The effect of supporting ligand, solvent and exess of reagents was discovered. Obtained azides were successfully used in CuACC reactions with some model alkynes.



Scheme 1.

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Asymmetric Michael/Friedel-Crafts indole alkylation catalyzed by magnesium iodide-PyBox comlexes

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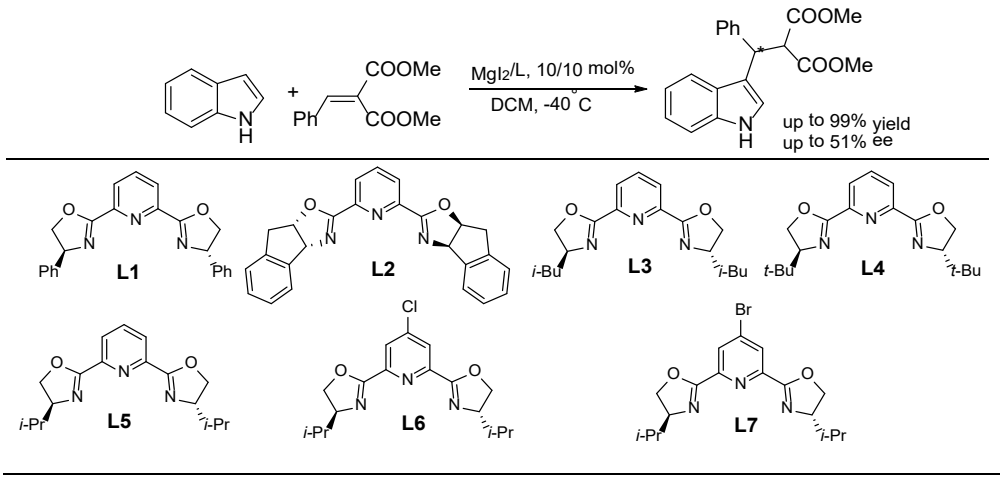
Michael/Friedel-Crafts indole alkylation with electron-deficient olefins has received great attention due to its potential application for synthesis pharmaceutically valuable molecules. For the asymmetric indole alkylation with Michael aceptors complexes of chiral bisoxazoline ligands with copper, zinc, nickel and scandium salts are used [1-3]. We have demonstrated that the reactions of indoles with arylidenmalonates are catalyzed by magnesium salts.



Scheme 1.

The optimization of conditions was performed using the reaction of indole with dimethyl benzylidenemalonate. To achieve asymmetric induction a variety of PyBox ligands was used. (Scheme 1).

Table 1

Entry	L	Yield, %	ee, %
1	L1	trace	nd
2	L2	trace	nd
3	L3	83	13
4	L4	99	32
5	L5	99	41
6	L6	82	47
7	L7	99	51

It was demonstrated, that ready available ligands L5-7, derived from L-valinol, provide excellent yield (up to 99%) and good enantioselectivity (up to 51% ee) (Table 1).

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The synthesis of 2-substituted 1,2,3-triazoles bearing azido group

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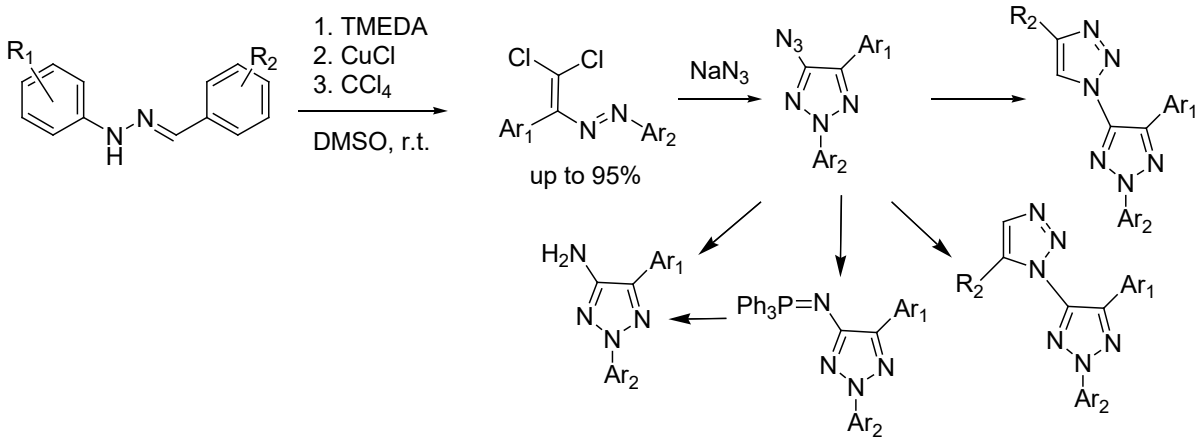
We studied the reaction of N-substituted aromatic hydrazones with CCl_4 in the presence of CuCl as a catalyst. As a result, we have found a new catalytic reaction, which allows to create carbon-carbon double bond. We have found that this transformation occurs with the formation of 4,4-dichloro-1,3-diaryl-1,2-diazabutadienes-1,3 and developed a general method for their preparation. The reaction has universal character and allows to synthesize diazenes containing both donor and acceptor substituents in the aromatic ring with high yields.

The presence of conjugated π-electron system with acceptor azo group and the presence of two chlorine atoms open unique opportunities for application of these synthetic substrates. Thus, reaction with sodium azide proceeds as tandem transformation including formation of bis-azides, followed by elimination of a nitrogen molecule, and cyclization to form unknown 4-azido-2,5-diaryl-1,2,3-triazoles. The presence of the azide group offers the possibility of their further modification of these unique compounds (Scheme 1).



Scheme 1. Synthetic potential of 2,5-diaryl-4-azido-1,2,3-trazoles.

Synthesis and Cytostatic Properties of Polyfunctionalized Furanoallocolchicinoids

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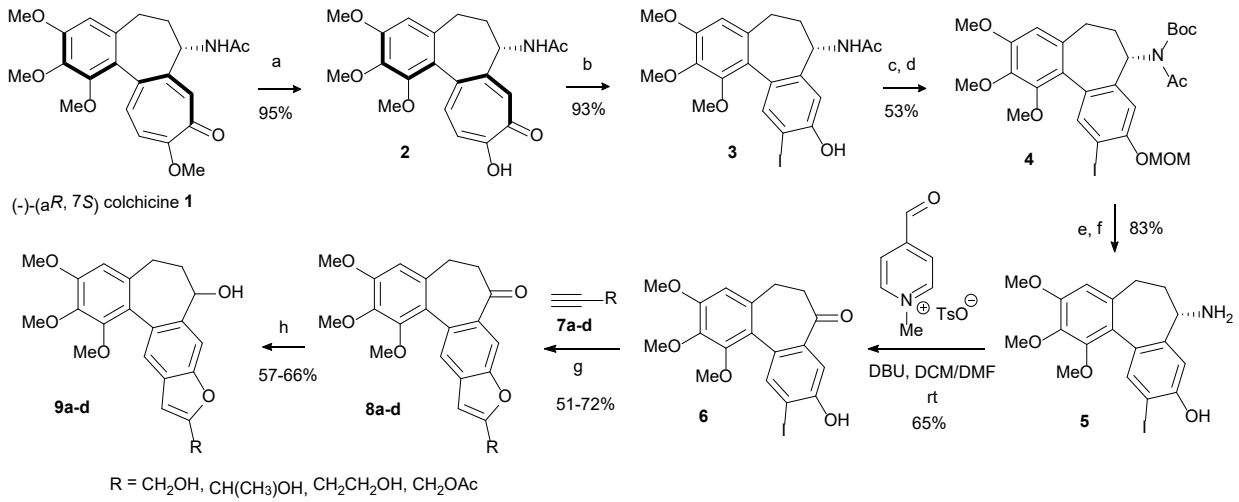
A series of furan-based allocolchicinoids was prepared from commercially available colchicine *via* a nine-step reaction sequence (Scheme 1). Cytostatic activity, cell cycle arrest, apoptosis, tubulin and F-actin expression were studied *in vitro* in 2D and 3D cultures of normal and tumor epithelial keratinocytes, endothelial and mesenchymal cells. Among prepared furanoallocolchicine analogues, **8a** and **9a** demonstrated the most pronounced anti-cancer activity. These compounds induced two types of effects: (a) induction of cell cycle arrest in the G2/M phase as a direct consequence of effective tubulin binding (metaphase effect) and (b) pronounced cell stress (as evidenced by the overexpression of tubulin and F-actin), which was caused by the hyperpolarization of mitochondrial and lysosomal membranes (intrephase effect).



Scheme 1. Synthesis of furanoallocolchicinoids **9**. *Reagents and conditions:* (a) 0.1 M HCl, AcOH, 100 °C, 3 h; (b) NaOH, I_2, KI, H_2O, 0-5 °C, 2 h; (c) MOMCl, DIPEA, DCM, 0-20 °C, 20 h; (d) Boc_2O, DMAP, TEA, MeCN, reflux, 26 h; (e) NaOMe (20 mol%), MeOH, r.t., 1.5 h; (f) HCl, EtOH, r.t., 20 h; (g) $Pd(OAc)_2$ (0.05 mol%), CuI (0.1 mol%), AcOK (3 equiv.), Ph_3P (0.15 mol%), MeCN, 70 °C 4-6 h; (h) $NaBH_4$, THF/H_2O/EtOH, r.t., 1-2 h.

Acknowledgements
Chemical synthesis was supported by the Ministry of Education and Science of The Russian Federation, grants 4.619.2014/K, 02.B.49.21.0003 and by the Russian Foundation for Basic Research, 14-03-91342. Biological studied were supported by the Program "Nanotechnologies & Nanomaterials" of the Russian Academy of Sciences and by the Russian Foundation for Basic Research, 16-03-01093. MSC were generated and studied under the support by the Russian Scientific Foundation, grant 14-25-00179.

Formaldehyde hemiacetal derivatives in the synthesis of hexahydropyrimidines and tetrahydropyridines

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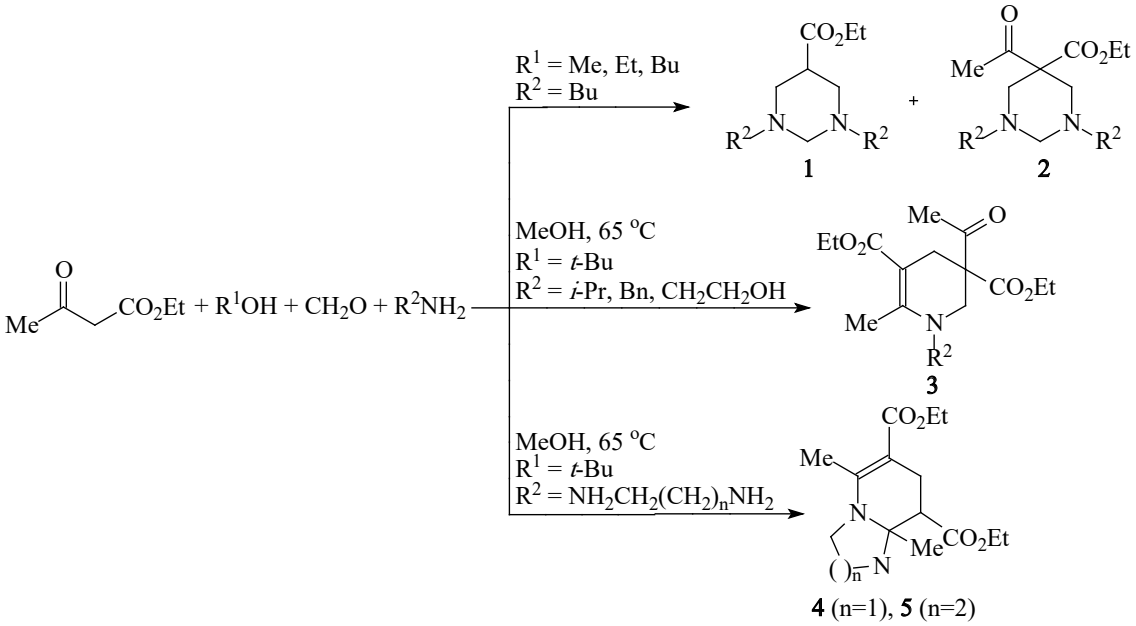
In this paper we studied the composition of hemiacetals formed in the reaction of paraformaldehyde with aliphatic alcohols (MeOH, EtOH, *i*-PrOH, BuOH and *t*-BuOH) in the presence of 3.8 mol. % Et_3N and the effect of the nature of hemiacetals on the yield and composition of the products of condensation with acetoacetic ester and primary amines (*i*-$PrNH_2$, $BuNH_2$, $BnNH_2$, $HOCH_2CH_2NH_2$) in a Mannich reaction. Et_3N catalyzed reacting of paraformaldehyde with aliphatic alcohols was carried out at 20 °C for 24 h at molar ratios CH_2O : alcohol = 1:1, 3:4, 1:2, 1:4. [1]. Interaction of acetoacetic ester with $BuNH_2$ and hemiacetals $RO(CH_2O)_nH$ on the basis of primary alcohols (molar ratio CH_2O : ROH = 1 : 1, R = Me, Et, Bu) by boiling for 5 hours gives a mixture of ethyl 1,3-dibutylhexahydropyrimidine-5-carboxylate **1** and ethyl 5-acetyl-1,3-dibutylhexahydropyrimidine-5-carboxylate **2** with 69-82% yields.



Scheme 1.

Based on these studies, we have proposed a one-pot method for the synthesis of diethyl 1,2,3,4-tetrahydropyridine-3,5-dicarboxylate by reacting acetoacetic ester with methoxymethanol and primary amines. The reaction proceeds at a molar ratio 1: 3: 2 in the presence of tert-butanol at 65 °C for 5 hours and gives selectively mono- and bicyclic diethyl 1,2,3,4-tetrahydropyridin-3,5-dicarboxylates **3**, **4**, **5** with yields of up to 98%. Synthesized nitrogenous heterocycles are promising as biologically active compounds possessing antieczematic, fibrinolytic, spasmolytic and antiviral activity and may also act as inhibitors of membrane permeability and calcium channel activators.

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A Facile Access to Functionalized 2,3-Dihydrofurans and Their Application in the Synthesis of Five-membered Heterocyclic Systems

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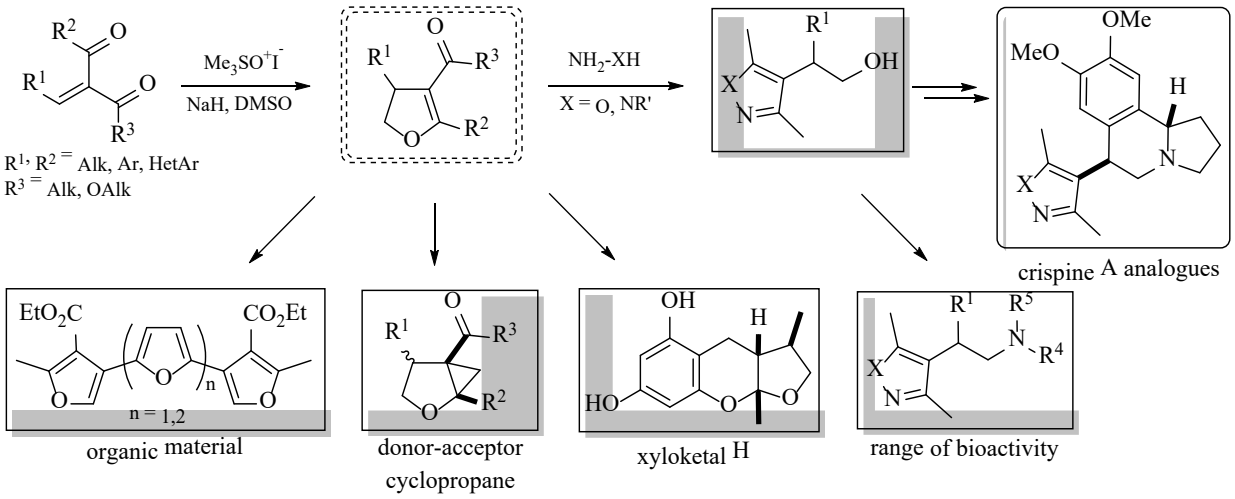
Five-membered heterocycles are an essential part of numerous natural compounds, pharmacological agents and functional materials. In this regard, a discovery of new efficient and selective methods allowing a rapid assembly of these structures is still highly desired.

Herein we report an original straightforward approach to polysubstituted 2,3-dihydrofurans *via* a reaction between Corey ylide and α,β-unsaturated ketones which proceeds as (4+1)-annulation in contrast to common (2+1)-annulation leading cyclopropane derivatives [1]. Ready availability and variability of the reagents as well as mild reaction conditions allowed us to synthesize a wide range of 3,4,5-trisubstituted 2,3-dihydrofurans.

Easy modifiability of the dihydrofuran ring, the C-C double bond as well as side substituents makes the obtained 2,3-dihydrofurans synthetically significant precursors for producing potentially useful structures, including natural and pharmacologically valuable compounds. We have described simple synthetic pathways based on the elaboration of 2,3-dihydrofurans into more complex structures *via* oxidation, cyclopropanation reactions, and ring closure–ring opening domino reactions with hydrazines and hydroxylamine affording multisubstituted furans, cyclopropa[*b*]tetrahydrofurans, pyrazoles and isoxazoles [1,2]. The present methodology has been successfully applied in the synthesis of natural products, such as xyloketals, 2,4-dimethylfuran-3-carboxylic acid whose *α*-L-rhamnopyranosides, isolated from culture broth of *Streptomyces* sp., was shown to inhibit *α*-hydroxysteroid dehydrogenase, as well as oligofurans which are considered as promising materials for solar cells, OLEDs and OFETs.



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This work was supported by Russian Foundation for Basic Research (project 15-33-20442).

Novel Perhalogenated Porphyrazines and Their Al^{III}, Ga^{III} and In^{III} Complexes

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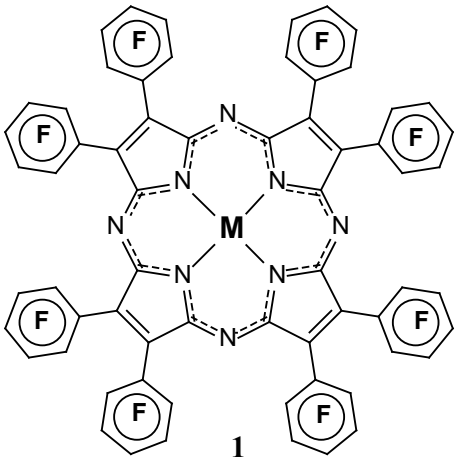
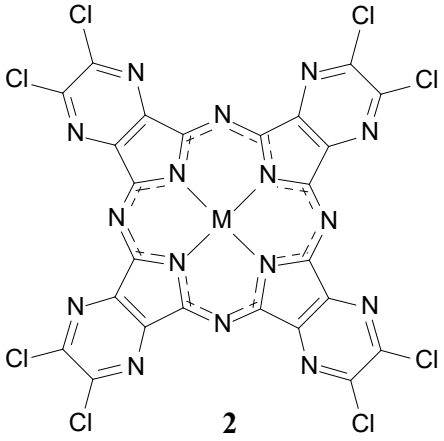
Tetrapyrrolic macrocycles, especially phthlocyanines and their metal complexes, are widely used as perspective materials for molecular electronics [1]. Introduction of strong electron-acceptor substituents and fragments into the porphyrazine macrocycle should significantly increase its electron-deficiency, that might be especially interesting for design of new materials with enhanced *n*-conductivity for organic electronics. Recently, we have prepared for the first time perfluorinated octaphenylporphyrazine ($F_{40}OPhPAH_2$) [2] and perchlorinated tetrapyrazinoporphyrazine ($Cl_8TPyzPzH_2$) [3]. Here we report on synthesis, spectral and electrochemical study of the complexes of these perhalogenated porphyrazines with the aluminum subgroup metals.



1

[$F_{40}OPhPAM$]



2

[$Cl_8TPyzPAM$]

M = Al(OH), Ga(OH), In(OH)

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Branching reagents for multiple alkyne incorporation

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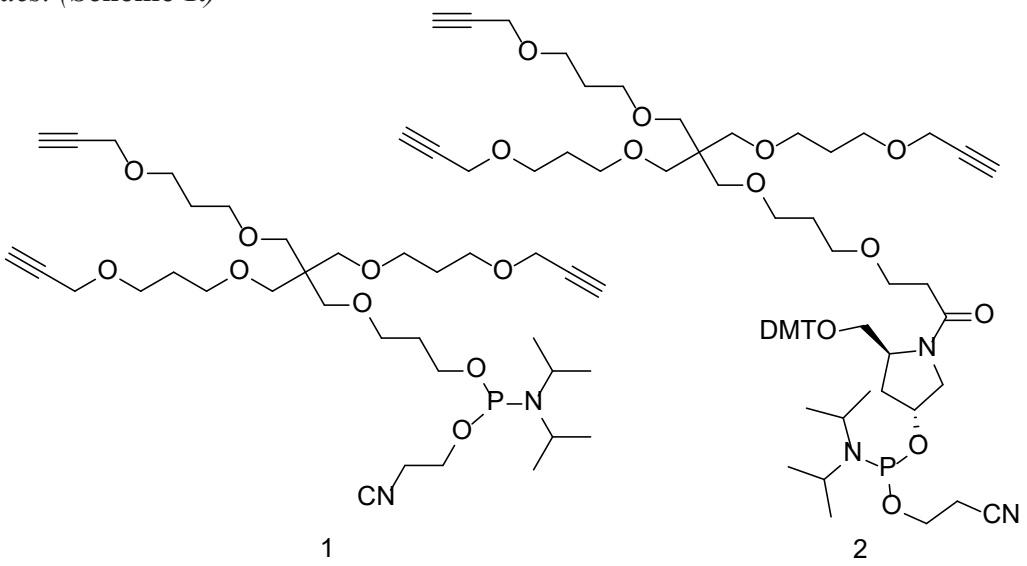
Modifications with branching reagents are often used for oligonucleotide's triplex stabilization, incorporation of specific groups for transportation into a cell, a multiple fluorescent dye tagging, conjugation with peptides, etc [1, 2].

The pentaerithrite based branching reagents are conformationally flexible and may carry up to three different modifications. So, herein, we suggest the application of such reagents having three alkyne groups for the *oligonucleotide's tagging.*

We have synthesized amidophosphite reagents **(1)** and **(2)** suitable for *automatic* synthesis of *oligonucleotides. (***Scheme 1.***)*



Scheme 1.

Particularly amidophosphite reagent **(1)** was used for 5'-end modification of oligonucleotides whereas compound **(2)** was more universal and allowed modification to any position along with multiple incorporation into the oligonucleotide's chain. Moreover in the case of compound **(2)** for 5'- modification the final oligonucleotides could be easily purified using trityl-on oligonucleotide purification technology.

The structures of the amidophosphite reagents **(1)** and **(2)** *were confirmed* by ^{1}H, ^{13}C and ^{31}P NMR spectra.

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Synthesis of Azide Precursor for the Preparation of New Biomolecule-Based Clusters

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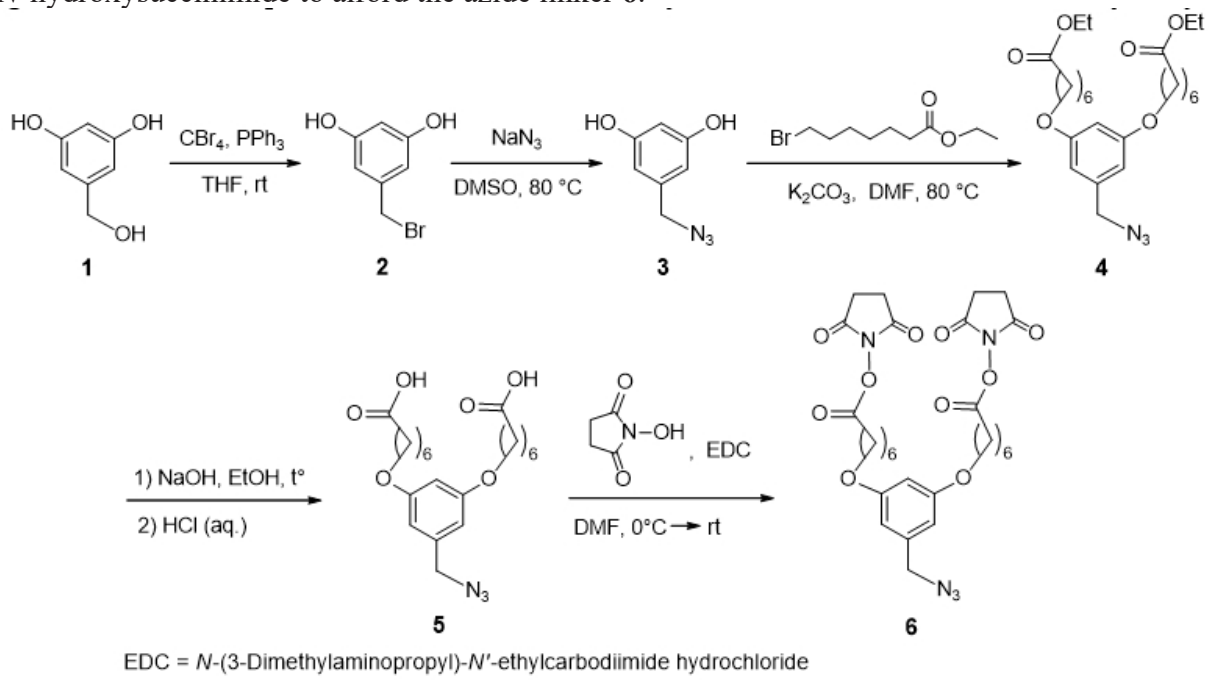
In this work we developed method for the synthesis of organic azide **6**, which is precursor for the preparation of series of homogeneous and heterogeneous azide-containing biomolecules, e.g., peptides or glycans. Synthesis of compound **6** commenced with the bromination reaction of a commercially available 3,5-dihydroxybenzylalcohol **1**, followed by treatment of benzyl bromide **2** with sodium azide (scheme 1). Alkylation of the phenolic hydroxyl groups of compound **3** was performed with ethyl 7-bromoheptanoate to give ester **4**. After saponification of ester **4**, dicarboxylic acid **5** was condensed with *N*-hydroxysuccinimide to afford the azide linker **6**.



EDC = *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

Scheme 1. Multistep synthesis of azide precursor **6**

On the next stage precursor **6**, containing azide group and two activated carboxylic groups, was reacted with two different biomolecules (peptides or glycans) in order to obtain homogeneous and heterogeneous azide-containing biomolecules and further perform their immobilization on cluster templates. These biomolecule-based clusters will be systematically investigated for the interaction with target cells both *in vitro* and *in vivo*.

This work was performed within the Russian Government Program of Competitive Growth of Kazan Federal University.

Interaction of 3-trichloromethyl-1,2,4-triazines with 1-mopholinocyclopentene and aryne intermediate

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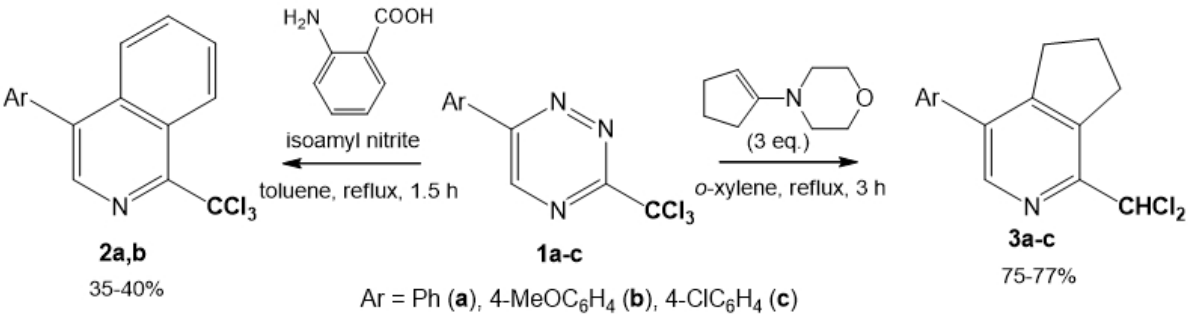
Pyridine derivatives bearing di- or trichloromethyl groups at the α-position are of considerable interest from the standpoint of their easy subsequent conversion into the corresponding carboxylic acids or aldehydes *via* the short-step synthetic protocols. Furthermore, e.g., α-dichloromethylpyridines widely used as plant growth regulators, fungicides etc.

In this work we used the "1,2,4-triazine" strategy for preparation of pyridines and isoquinolines bearing di- or trichloromethyl group at C1- or C2-position correspondingly as a result of reaction with various dienophiles, such as 1-morpholinocyclopentene and aryne intermediate.



Scheme 1

In part, interaction of 3-trichloromethyl-1,2,4-triazines **1** [1] with 1,2-dehydrobenzene resulted in the expected products **2** (Scheme 1). However we found that the reaction of **1** with enamine did not resulted in the expected 1-trichloromethyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridines, but the only products was α-dichloromethyl derivatives **3**.

[1] Kozhevnikov, D. N.; Kataeva, N. N. ; Rusinov, V. L.; Chupakhin, O. N. *Russ. Chem. Bull.* 2004, 53, 1295.

This work was supported by Russian Science Foundation (Ref. # 15-13-10033), by Act 211 of the Government of the Russian Federation (contract № 02.A03.21.0006) and by Council for Grants of the President of the Russian Federation (grant no. MK-3079.2015.3).

Oligomers with 2-pentyl-1,3-dioxolane groups based on 3,4-(1,2-phenylenedioxy)thiophene

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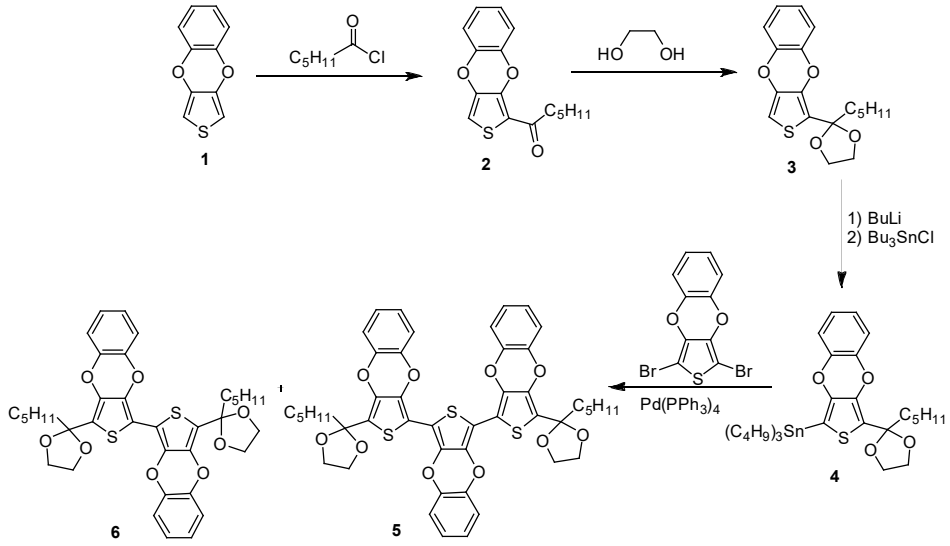
Poly(3,4-ethylenedioxythiophene) (PEDOT) is a very stable conjugated polymer [1] with a high conductivity. It has been used in a variety of applications for organic electronics. Previously, it was synthesized new series of precursors in which the ethylene bridge of EDOT has been replaced by a phenyl ring – 3,4-(1,2-phenylenedioxy)thiophene (PheDOT). The significantly lower HOMO level of PheDOT oligomers compared with their EDOT analogues thus opens the possibility to synthesize p-conjugated systems stable in ambient conditions and which can be solubilized by appropriate alkyl chains while preserving the compact packing organization needed to ensure high charge-carrier mobility [3].

The dimer and trimer of 3,4-phenylenedioxythiophene (PheDOT) with 2-penthyl-1,3-dioxalane groups have been synthesized (Scheme 1). Unlike the parent systems based on 3,4-ethylenedioxythiophene (EDOT), these compounds are quite stable under atmospheric conditions. The electronic absorption spectra of di- and tri-PheDOT exhibit a well-resolved vibronic fine structure indicative of self-rigidification of the conjugated structure by noncovalent intramolecular sulfur–oxygen interactions.



Scheme 1. Synthesis of dimer and trimer with 2-penthyl-1,3-dioxalane groups.

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Adamantane aminopolycarboxylic acids via ritter reaction

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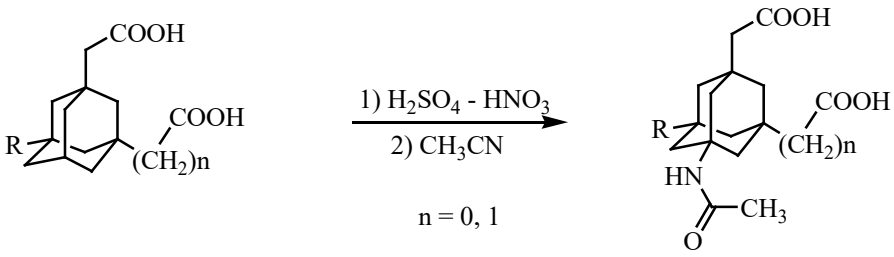
Development of the effective methods of introducing some functional groups in deactivated cage compounds is difficult because of its carbonium ions low stability.

We were realized the approach to synthesis of adamantane aminopolycarboxylic acids, which can be considered as the GABA analogues. These amino acids could be used as a base to design the high molecular complexity ensembles.

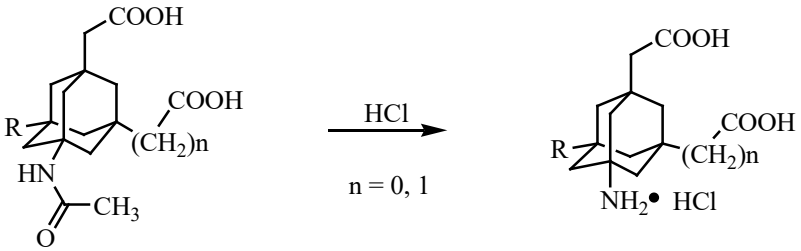
Initially the parent polycarboxilic acids (1a-f) reacts with acetonitrile in Ritter reaction conditions to form the corresponding N-acetamido derivatives (**2a-f**). For successful oxidation of tert C-H bond the 5 eq of nitric acid is needed. Reaction was carried out at room temperature. Products of Ritter reaction (**2a-f**) was obtained in 42-90% yelds.



1a-f **2a-f**

R=H, n=0 (1a, 2a), n=1 (1b, 2b); R=Me,n=0 (1c, 2c), n=1 (1d, 2d); R=Et, n=0 (1e, 2e), n=1 (1f, 2f).

Compounds (**2a-f**) were hydrolised to corresponding amino acids (**3a-f**) in concentrated hydrochloric acid. Amino acids (**3a-f**) were obtained in 18-81% yelds.



2a-f **3a-f**

R=H, n=0 (1a, 2a), n=1 (1b, 2b); R=Me,n=0 (1c, 2c), n=1 (1d, 2d); R=Et, n=0 (1e, 2e), n=1 (1f, 2f).

The compounds that were obtained could be used as building blocks in conformationally constrained peptidomimetic synthesis.

This work was supported by the Russian Ministry of Education and Science within basic part of government assignment for scientific research (2014/199-1078) and by Russian Foundation of Basic Research (agreement 14-03-97075).

Interaction of 3-Aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with Thioacetamide

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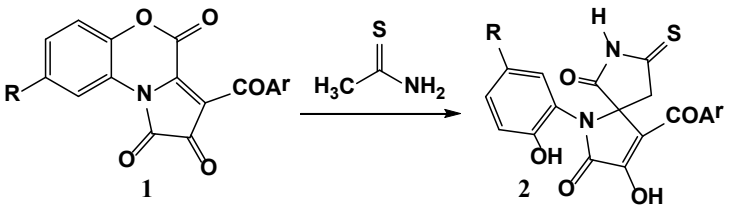
Interaction of hetareno[*e*]pyrrole-2,3-diones (1*H*-pyrrole-2,3-diones [*e*]-annelated with different azaheterocycles) with various CH,NH and NH,SH binucleophiles is the key step to diverse fused, spiro-bicyclic and bridged heterocyclic systems which are inaccessible or hardly accessible by other ways. Many of these heterocyclic systems are found to show useful properties. Reactions of hetareno[*e*]pyrrole-2,3-diones with thioacetamide have not been studied.

We found that interaction of 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **1** (1*H*-pyrrole-2,3-diones [*e*]-annelated with benzoxazin-2-one moiety) with thioacetamide resulted in formation of 4-aroyl-3-hydroxy-1-(2-hydroxyphenyl)-8-thioxo-1,7-diazaspiro[4.4]non-3-ene-2,6-diones **2**. The structure of compounds **2** was proved by XRD analysis (Fig. 1).



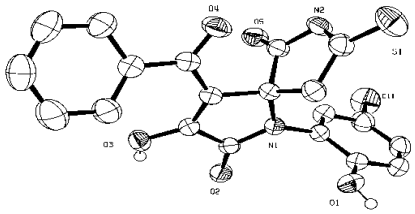


Fig. 1. Molecular structure of 4-aroyl-1-(5-chloro-2-hydroxyphenyl)-3-hydroxy--8-thioxo-1,7-diazaspiro[4.4]non-3-ene-2,6-dione according to XRD data

Apparently, the first stage of the interaction involved nucleophilic attack of activated CH group of the thioimidol form of thioacetamide on the C^{3a} atom of pyrrolobenzoxazinetriones **1** followed by subsequent intramolecular attack of NH_2 group of thioacetamide pattern on lactone carbonyl group of benzoxazine cycle and C^4–O^5 bond opening.

Compounds **2** are heterocyclic analogues of Amathaspiramides A-F (Fig. 2), isolated from the marine bryozoan *Amathia wilsoni* (Fig. 3). Amathaspiramides A-F exhibit significant antimicrobial, antiviral, and cytotoxic activity.

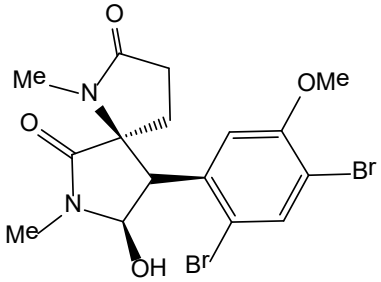


Fig. 2. Amathaspiramide B

Fig. 3. The marine bryozoan *Amathia wilsoni*

We investigated the antimicrobial activity of the synthesized compounds **2**. We found that two of them exhibited an inhibitory effect against *S. aureus* at a concentration of 1000.0 mg/ml.

This work was supported by the Ministry of Education of the Russian Federation (project 965).

Reduction of the prooxidant activity of heavy metal compounds at presence of porphyrin with phenolic fragments

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Earlier in vitro experiments we have found the promotion of lipid peroxidation (LPO) of Russian sturgeon's sperm in the presence of CH_3HgI, $HgCl_2$, $(C_4H_9)_3SnCl$ and $CdCl_2$ [1]. The purpose of this work was to study the influence of *meso*-tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenyl)porphyrin (R_4PH_2), and its analogue, which does not contain 2,6-di-*tert*-butylphenolic antioxidant groups ($TPPH_2$), on the level of secondary LPO products accumulation within 24 hours, which form a colored complex with thiobarbituric acid (TBARS) in the sperm of Russian sturgeon (*Acipenser guldenstadti Brandt*) in the presence of CH_3HgI, $HgCl_2$, $(C_4H_9)_3SnCl$ and $CdCl_2$.

It was shwon in this work that promotion of sperm lipid peroxidation by toxicants was reduced by additives of R_4PH_2 at 29 - 100%, by additives of $TPPH_2$ - at 13-50% (Fig.). The highest inhibitory effect was found for R_4PH_2 in respect to $HgCl_2$ - in the presence of this toxicant and R_4PH_2 the concentration of TBARS in Russian sturgeon's sperm decreased 2 times compared to a case without porphyrin addition.

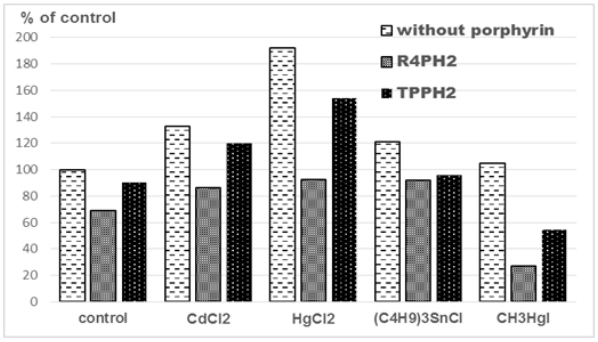

Fig. 1. The effect of porphyrins in the pro-oxidant activity of the compounds of heavy metals in reactions of sturgeon sperm lipid peroxidation. Control - TBARS concentration in Russian sturgeon's sperm without additives. Concentration of the compounds in the incubation medium is 0.1mM.

R_4PH_2 evens promoting activity of all toxicants, $TPPH_2$ - only for organic derivatives of mercury and tin, in the presence of inorganic salts and $TPPH_2$ the level of TBARS remains above the control case without additives.

Thus, it was shown that a porphyrin, containing sterically hindered phenolic groups, was characterized by higher efficiency of prooxidant activity reduction for heavy metal compounds in the reactions of sturgeon sperm lipid peroxidation compared to the porphyrin, containing no antioxidant groups. It is obvious that the increase of R_4PH_2 antioxidant activity compared to $TPPH_2$ was caused by 2,6-di-tert-butylphenolic substituents and was associated with the reversibility of the phenoxy radical formation processes on the periphery of the porphyrin ring.

References

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This work was supported by RFBR (Grants № 14-03-00578, 16-03-00334)

New carbazole-containing naphthodithiophenes for photovoltaic

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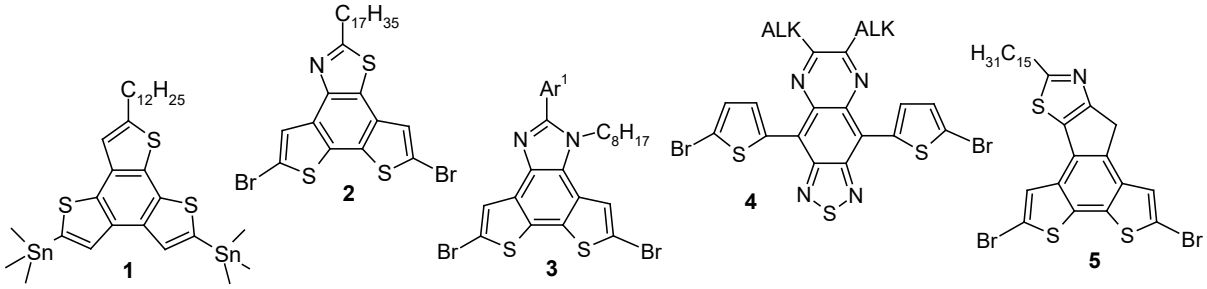
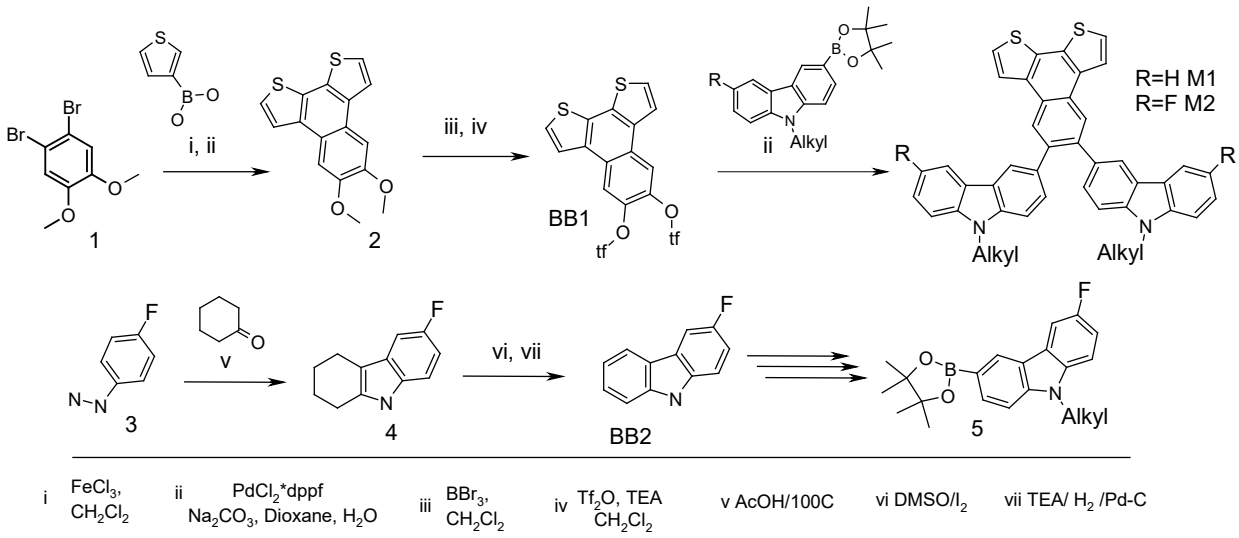
Much effort was aimed at developing organic solar photovoltaic cells (SPCs) in recent decades [1]. Earlier we developed new benzodi- and trithiophene-containing monomers 1-5 as promising "building blocks," and new narrow-band donor–acceptor conjugated polymers were synthesized on the basis of these monomers as an electroactive material for the solar photovoltaic cells [2].

Scheme 1



Further to this direction we have developed approaches to preparation of the new carbazole-containing naphthodithiophenes M1 and M2, which will be used further as a weak donor fragments of narrow-band donor–acceptor conjugated polymers (figure 1).

Fig.1



Structure of M1 and M2 are confirmed by elemental analysis, IR spectroscopy, ^{1}H and ^{13}C NMR. Convenient routes for synthesis of compounds BB1 and BB2 in multigram amounts.

References:

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Convenient synthesis of fused 1,2,3-dithiazoles

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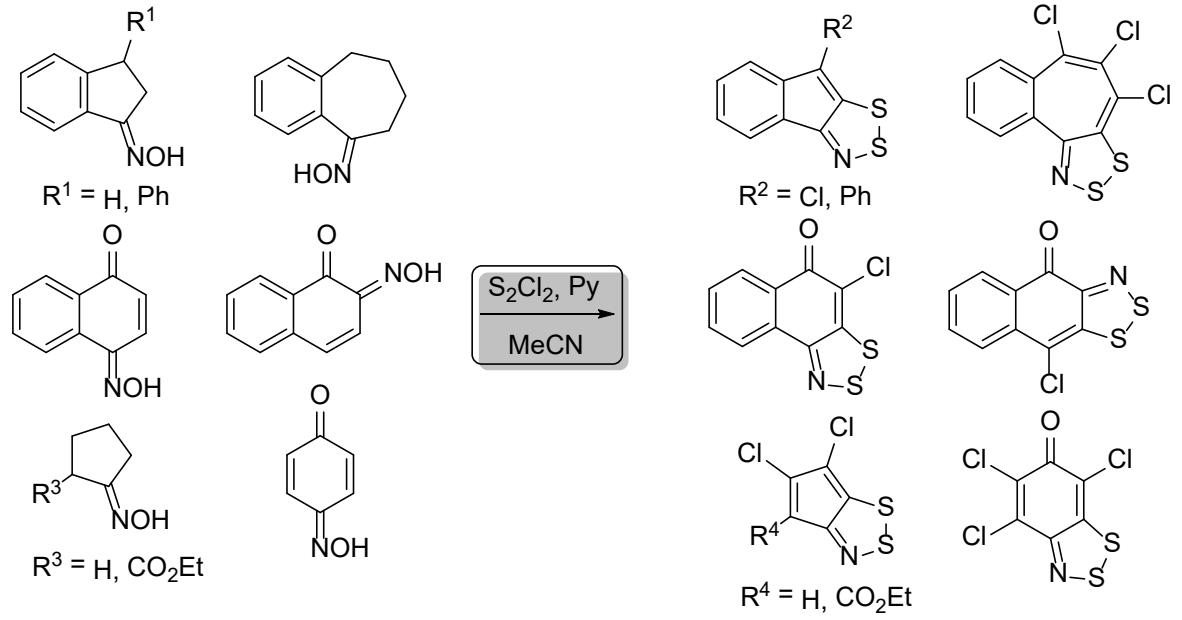
Among the five-membered heterocycles containing nitrogen and sulfur atoms, 1,2,3-dithiazoles are important compounds due to their unusual physical properties, biological activity and various transformations of their derivatives [1]. Fused 1,2,3-dithiazoles are of special interest as the precursors of stable radical anions. Benzofused 1,2,3-dithiazoles can be easily prepared from aromatic amines by Herz reaction. The most applicable synthesis for 1,2,3-dithiazoles fused with other carbo- or heterocycle are the reaction of cyclic oximes with sulfur monochloride in the presence of organic bases. Various bases including *N*-ethyldiisopropylamine and triisobutylamine were investigated, and no general procedure was established; also in all cases careful and repeated purification by column chromatography in silica was required.

We have found that treatment of cyclic oximes with sulfur monochloride and pyridine in acetonitrile at room temperature gave 1,2,3-dithiazoles fused with various cycles, such as indene, naphthalenone, cyclohexadienone, cyclopentadiene and benzoannulene, in high (90%) to low (7%) yields. In all cases, the yields of 1,2,3-dithiazoles obtained are equal or superior to those when other bases were employed. The heterocycles can be easily isolated from the reaction mixtures without purification by chromatography in silica.



The structure of 4-chloro-5*H*-naptho[1,2-*d*][1,2,3]dithiazol-5-one was strictly confirmed by X-ray analysis. The reaction mechanism was proposed and the key intermediate -1,2,3-dithiazole-3-oxide was isolated. The described experimental procedure may serve as an efficient basis for synthesis of 1,2,3-dithiazoles fused with both carbo- and heterocycles.

References
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This work was financially supported by the Russian Science Foundation (grant no. 15-13-10022).

Organic chemistry of iron(III) bis(1,2-dicarbollide)*

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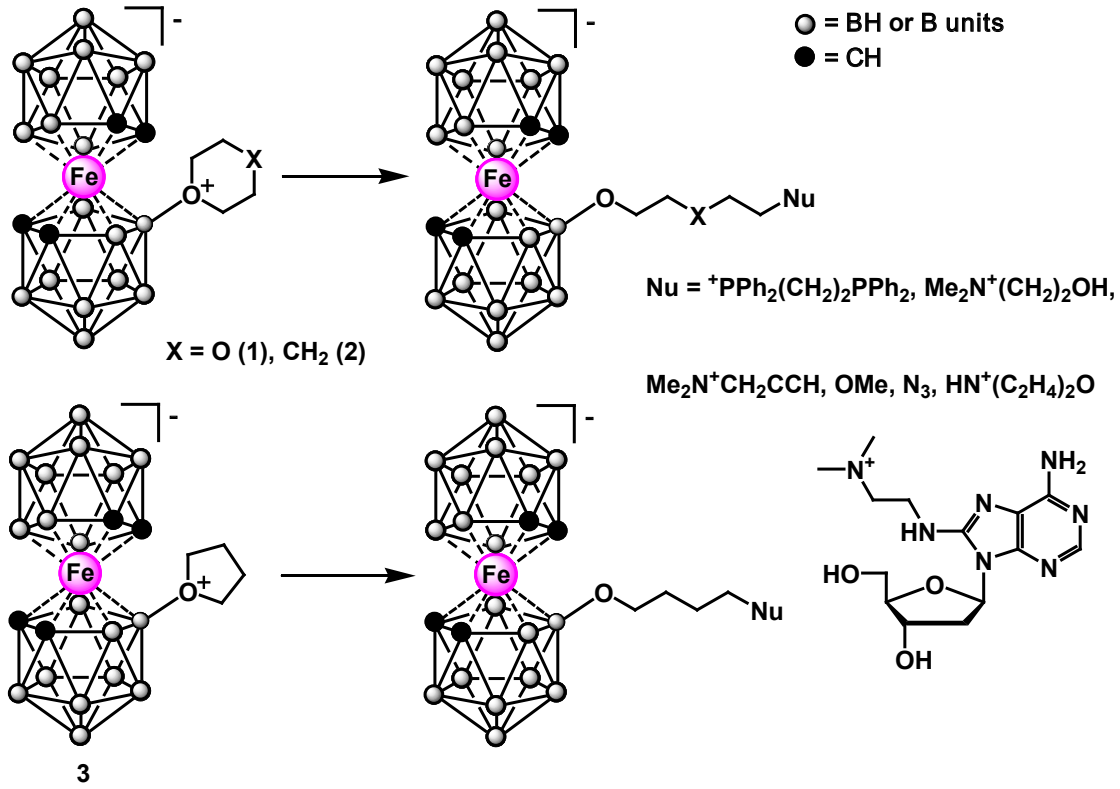
Synthesis of paramagnetic (8-O(CH_2CH_2)$_2$O-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)-3,3'-Fe (**1**) was reported previously [1]. We synthesized two novel paramagnetic oxonium derivatives of iron(III) bis(1,2-dicarbollide) (**2**, **3**). These compounds were found to be a versatile synthons for preparation of various organic derivatives of this metallacarborane [2] using ring-cleavage approach (Scheme 1).



Scheme 1.

This approach was successfully applied for the preparation of conjugates with nucleosides as potential antiviral agents.

References

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*In memory of Dr. Irina Lobanova

This work was supported by Russian Foundation for Basic Research (14-03-00042), stipendium of the President of Russian Federation (SP-1023.2015.4) and Russian Science Foundation (14-13-00884).

Synthesis of ethyl 5'-([2,2':6',2''-terpyridin]-4'-yl)-3-hexyl-[2,2'-bithiophene]-5-carboxylate

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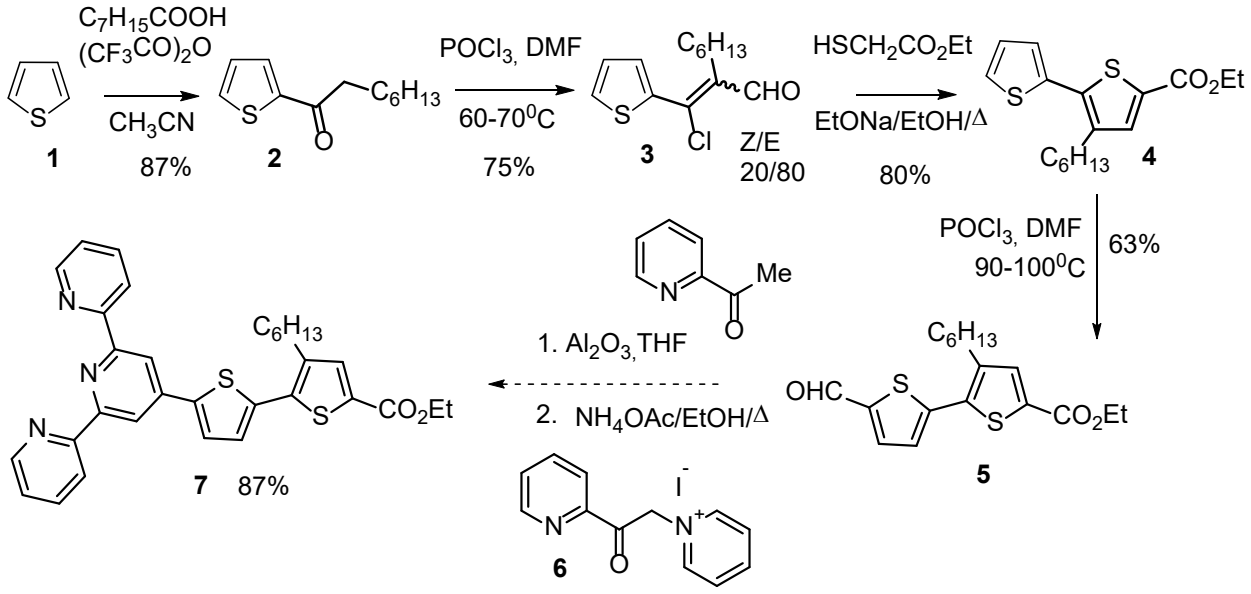
Derivatives of 2,2':6',2''-terpyridines are widely used as ligands in coordination chemistry. They are popular materials for fabrication of organic light emitting diodes, sensors, solar cells, ect. [1].



Scheme 1.

Recently, we have proposed a simple method for the preparation of 3-substituted-2,2-bithiophen-5-carboxylic acids and esters [2-6]. A compound **4** was used for the synthesis of ethyl 5'-formyl-3-hexyl-[2,2'-bithiophene]-5-carboxylate **5** (Scheme 1). 2,2':6',2''-Terpyridine 7 was obtained by Kröhnke reaction compound **5**, piridiniume salt **6** and 2-acetylpiridine with good yield.

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Coordination compounds Co II), Cu(II), Cu(I) based on imidazol-4 -ones with antitumor activity

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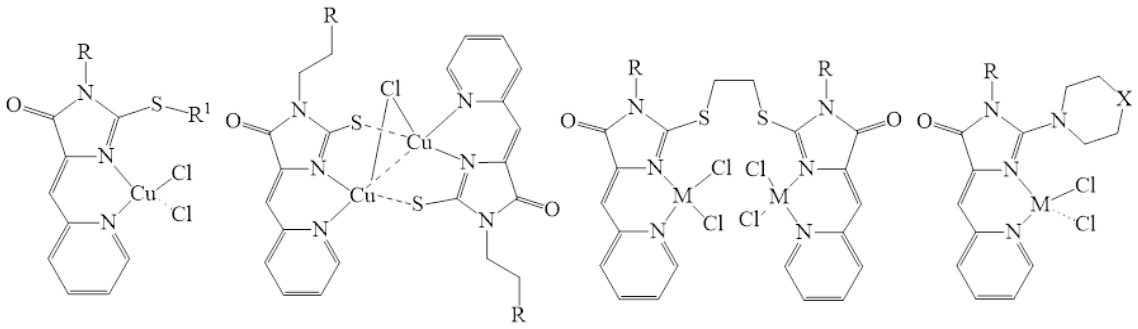
2-Thiohydantoins, 2-alkylthioimidazolones, 2-aminoimidazolones derivatives are known to possess various biological activities.

We have developed synthetic approach to coordination compounds of Co (II), Cu (II), Cu (I) based on functionalized derivatives of 2-*thiohydantoines, 2-alkylthioimidazolones, 2-aminoimidazolones* and have thoroughly investigated physical - chemical properties of obtained compounds.

Coordination compounds of the following structural types have been synthesized in this work:



R = Alk, Ar; M = Co, Cu; X = O, CH_2

Cytotoxicity of synthesized ligands and coordination compounds towards tumor MCF-7, SiHa, HEK-293, A-549 cells was assessed using the MTT procedure. All obtained coordination compounds possess cytotoxicity comparable to currently used in clinical practice cisplatin and doxorubicin.

Confocal microscopy demonstrated the ability of the coordination compounds of Cu (II), (I) to penetrate the cell membrane and accumulate in the cell nucleus. Also, the possibility of use of synthesized Co (II) coordination compounds as oligonucleotide delivery vehicles has been demonstrated.

One of the coordination compounds obtained is currently at stage 1 of preclinical trials as a drug for breast cancer treatment.

The work was supported by the RSF grant №14-34-00017.

Transformations of Chromones and Their Structural Analogues into Fluorescent Products under UV-Irradiation

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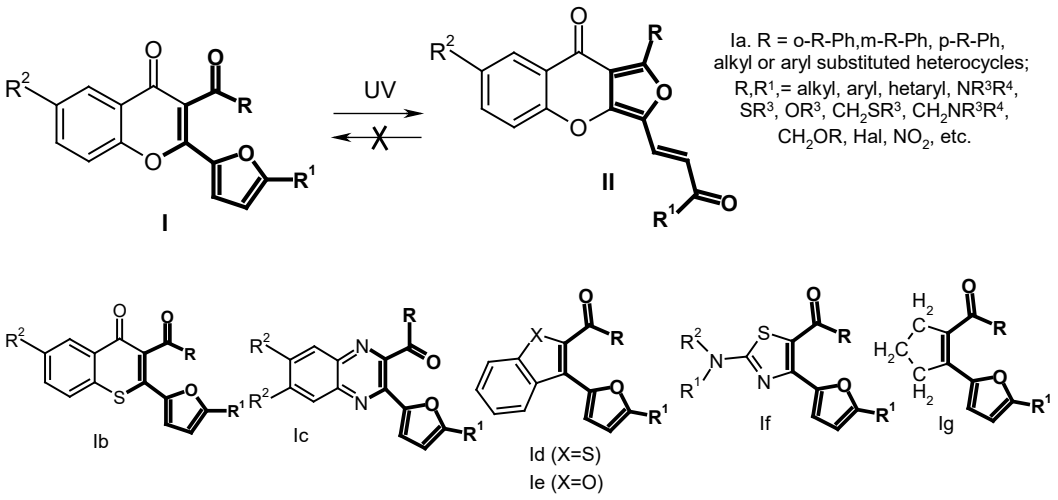
In recent years, the prospects of an increase in the capacity of data storage media (up to 1 Terabytes/ cm^3) are related to the development of multilayer light-sensitive optical discs using light-sensitive organic compounds for data recording and readout. Preparation of the effective compounds, which undergo photochemical transformations providing 3D operative and archival optical memory with ultra-high storage capacity due to non-destructive fluorescence readout, is one of the key problems of molecular electronics.

Earlier it has been demonstrated that UV-irradiated acylchromones Ia that show no fluorescence irreversibly rearrange into fluorescent furano[3,4-b]chromenones II. We have synthesized a wide range of benzopyranes Ia. Based on the latter, we have developed multilayered recording media for optical discs of the WORM type [1].



This work is devoted to development of methods for synthesis and the study of the photochemical properties of their analogues Ib-g. Structures and fluorescent properties of photoarrangement products II have been investigated as well. It was shown that the rearrangement I → II has a common character for all I containing the 2-(2'-furyl)vinyl ketone system. The formation of fluorescent compounds under light exposure can be considered as a powerful approach for designing of information systems and, in particular, multilayer optical discs.

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The work was supported by the Russian Foundation for Basic Research (projects #14-03-00431 and 15-03-09274).

Aza-Henry reaction with fluorinated imines

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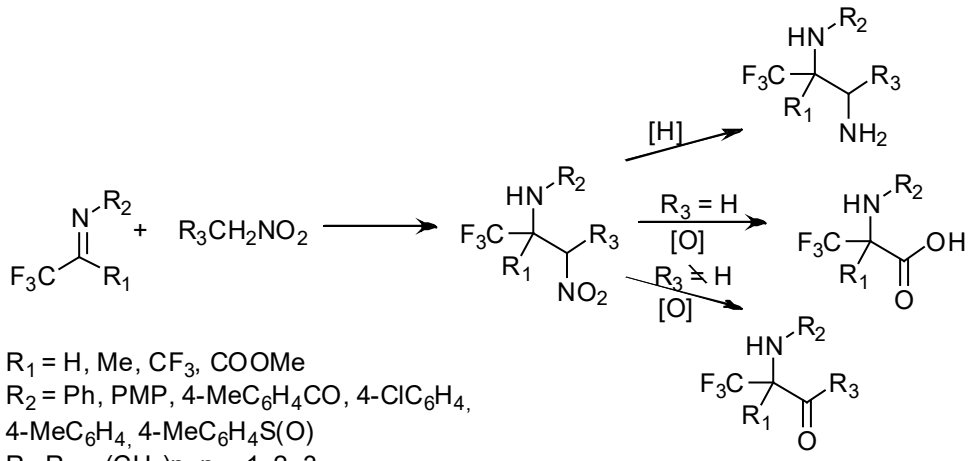
The importance of fluorinated organic compounds for medicine and modern material science is commonly known. The psychotropic and neuroleptic drugs, as well as many antiviral medications, most often bear fluorine atom. Nearly 25% of all pharmaceuticals contains in its structure fluorine atom or CF_3-group. At the same time fluoroorganic compounds are rarely occur in nature. The use of reagents, which allow to introduce fluorine or fluorinated groups directly, is limited. Thus the fluorine-containing building block method is steel the most widely used tool for preparation of molecules bearing fluorine atom or fluorinated fragment at certain place in structure. Trifluoromethyl substituted imines are interesting substrates for this purpose.

The reactions that allows to create of carbon-carbon bond with fluorinated imines lead to the attractive structures containing not only CF_3-group but also amino group. The Aza-Henry reaction involves the nucleophlic addition of nitroalkanes to imines and leads to β-nitroamines formation, both nitrogen-containing functional groups could be easily converted into various organic classes. [1].



R_1 = H, Me, CF_3, COOMe
R_2 = Ph, PMP, 4-MeC_6H_4CO, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeC_6H_4S(O)$
R_1-R_2 = $(CH_2)n$, n = 1, 2, 3

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This work was supported by the Russian Science Foundation (RSCF) (grant number 15-33-70009 mol_a_mos).

Nucleosides bearing closo-dodecabarate anion $[B_{12}H_{12}]^{2-}$. Synthesis and biological investigation

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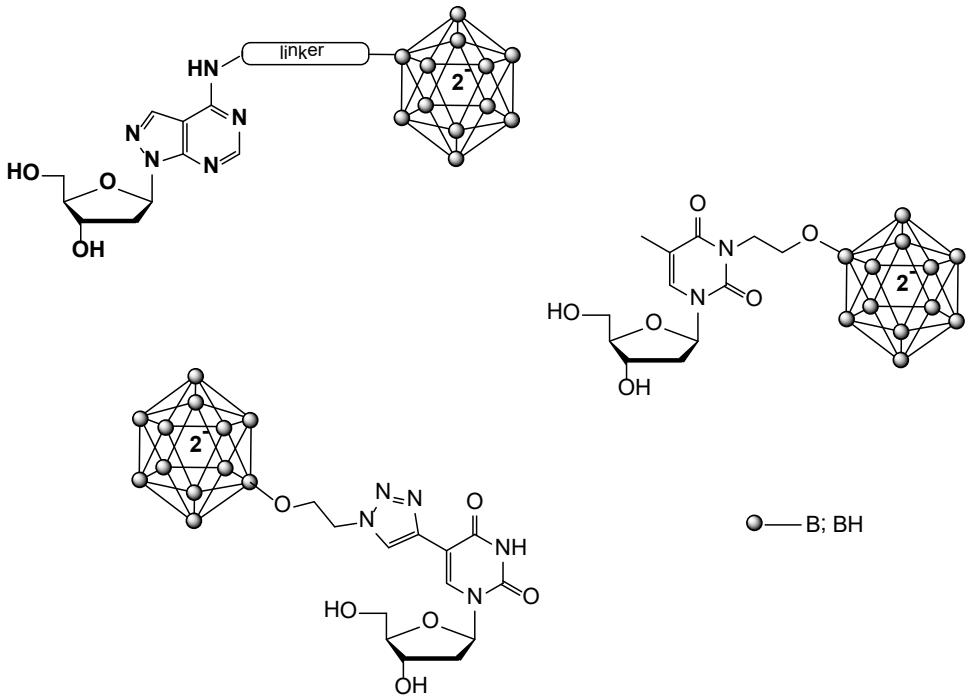
Nucleosides are building blocks for ribonucleic (RNA) and deoxyribonucleic (DNA) acids. Thus they are widely used as suitable tools in molecular biology, biotechnology and medicine. Boron cluster modified nucleosides constitute attractive subfamily. Representative applications include anticancer[1] and antiviral agents[2], purinergic receptors modulators[3] or redox labels for DNA/RNA probes[4]. In addition, 7-deaza-8-aza-2'-deoxyadenosine and its derivatives are often used as nucleic acids modification as shape mimics of their parent purine nucleosides[5].

Herein we report synthesis of novel thymidine and uridine bearing closo-dodecaborate anion and first examples of 7-deaza-8-aza-2'-deoxyadenosine joined with $[B_{12}H_{12}]^{2-}$ moiety via two types of linkage.



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This work was partially supported by Russian Foundation for Basic Research (Grant 14-03-00042).

Synthesis of optically pure 5-menthyloxy-2(5*H*)-furanone derivatives

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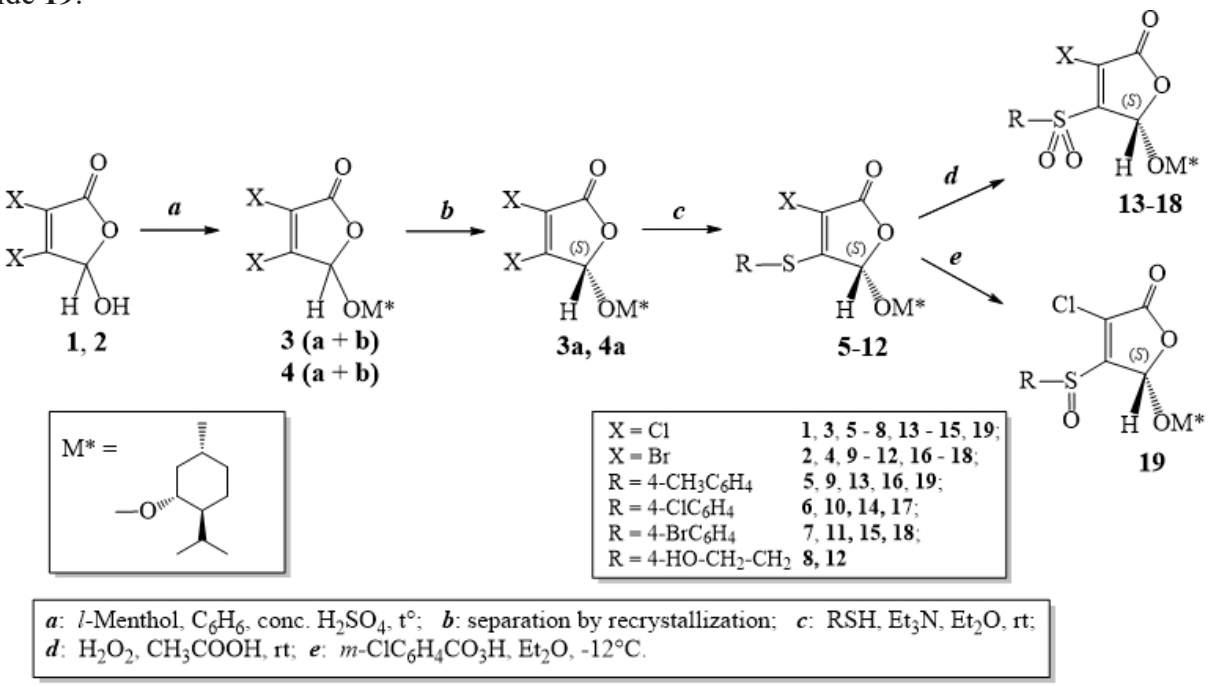
2(5*H*)-Furanones represent an important class of five membered heterocyclic compounds that have attracted significant attention over the years due to their occurrence in nature and their high synthetic utility as versatile intermediates for the construction of highly functionalized heterocycles. The wide range of biological properties and potent pharmaceutical applications have entailed continuous interest in the development of new methods for the synthesis of optically active 2(5*H*)-furanone derivatives.

In this work the optically active 2(5*H*)-furanones with *l*-menthol auxiliary have been synthesized and their biological properties were investigated. On the first step reactions of 3,4-dihalogen-2(5*H*)-furanones **1** and **2** with *l*-menthol were performed under acidic conditions; in both cases the mixture of diastereomers was initially obtained and then individual stereoisomers **3a** and **4a** were isolated by recrystallization. Reactions of stereoisomers **3a** and **4a** with different thiols in the presence of triethylamine afforded novel 4-substituted thioethers **5**–**12**. Oxidation reactions of thioethers **5**–**11** with 33% solution of hydrogen peroxide and *meta*-chloroperbenzoic acid resulted in the formation of optically pure sulfones **13**–**18** and sulfoxide **19**.



The antimicrobial activity of the synthesized compounds **3**–**19** against various bacteria was studied. One of the menthol-containing compounds efficiently repressed the biofilm formation by *S. epidermidis* and *S. aureus* with MBIC of 1 μg/ml. The CC_{50} for skin fibroblasts and MCF7 cell was found to be 8 and 48 μg/ml, respectively.

The work was supported by the Russian Science Foundation (project No 15-14-00046)

Synthesis of chiral octahydrochromens containing an amine nitrogen atom

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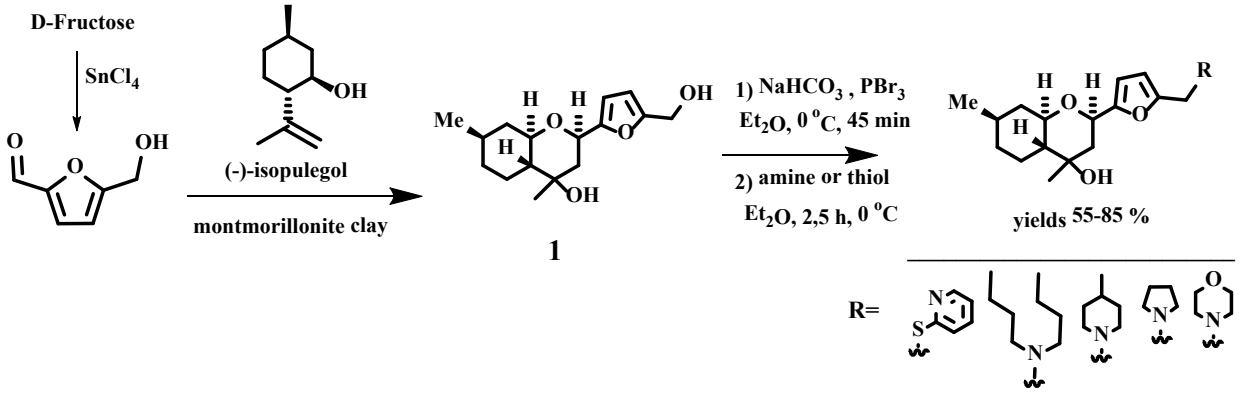
It was found earlier that reaction between isopulegol and heteroaromatic aldehydes in the presence of montmorillonite clay led to formation of compounds with octahydrochromen framework [1]. Some products demonstrated promising biological activity including analgesic one [2].

Heteroaromatic aldehydes containing different donor and acceptor substitutes with the exception of amine nitrogen compounds can be used for the reaction. The exception can be explained by the deactivation of acid sites of the catalyst. At the same time, amine nitrogen compounds are known to exhibit different physiological activities.

The goal of this work is the synthesis of nitrogen containing derivatives of chiral octahydrochromen compounds based on (-)-isopulegol and sugar-derived hydroxymethylfurfural. The target chiral heterocyclic products were synthesized through intermediate compound **1**.



Scheme 1. Synthesis of chiral octahydrochromens containing an amine nitrogen atom

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This work was supported by the Russian Science Foundation, grant N 15-13-00017.

Synthesis of stable 1,4-diionic organophosphorus compounds from the reaction between triphenylphosphine and diaroylacetylene in the presence of 4,5-disubstituted-2,3-furandiones

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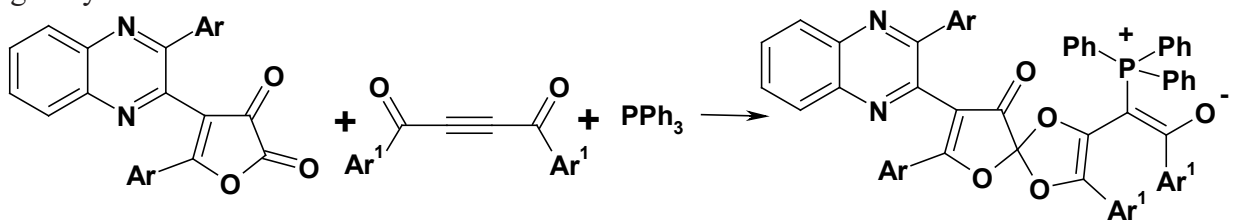
Organophosphorus compounds are synthetic targets of interest, not least because of their value for a variety of industrial, biological, and chemical synthetic uses [1]. As a result, a large number of methods have appeared describing novel syntheses of organophosphorus compounds. A number of reactions have been observed which involve diionic phosphorus compounds as elusive transient species [2]. In all of the reactions in which this diionic system is postulated, the betaine cannot be isolated but appears to occur as an intermediate on the pathway to an observed product. Researchers [3] have described the synthesis of stable diionic compounds from the reaction between triphenylphosphine and acetylenedicarboxylic acid in the presence of N–H heterocyclic compounds.

We demostrated first a simple one-pot reaction between triphenylphosphine and diaroylacetylenes the presence of 4,5-disubstituted-2,3-furandiones **1a-d**, leading to 1,5-diionic phosphorus betaines **3a-d** in fairly good yields.



1a-c **2a-c** **3 a-d**

1: Ar= C_6H_5 (a); 4-$CH_3C_6H_4$ (b); 4-$C_2H_5C_6H_4$ (c).
2: Ar^1=C_6H_5 (a); 4-$CH_3C_6H_4$ (b); 2,4-$(CH_3)_2C_6H_3$ (c).
3: Ar=C_6H_5, Ar^1=C_6H_5 (a); Ar=C_6H_5, Ar^1=4-$CH_3C_6H_4$ (b); Ar=4-$CH_3C_6H_4$, Ar^1=4-$C_2H_5C_6H_4$ (c); Ar=4-$C_2H_5C_6H_4$, Ar^1=C_6H_5 (d).

The structure of compound **3b** was unambiguously confirmed by single-crystal X-ray diffraction (**Fig. 1**).

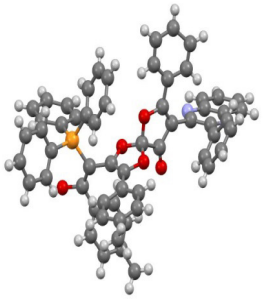


Fig. 1 Molecular structure of compounds **3b.**

The mechanism of formation of betaines **3a-d** is under discussion.

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This work was supported by grant RFBR 14-03-96012.

Synthesis of 2,2-bis-1,5,7-triazacyclopenta[cd]phenalenes

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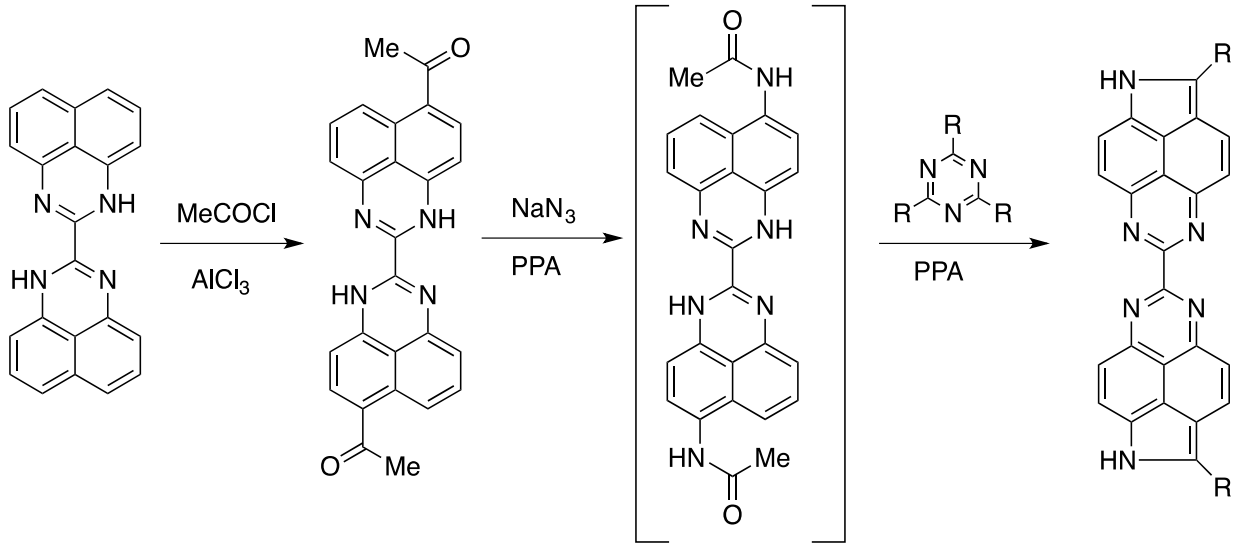
Chemistry of organic polyconjugated scaffolds has enjoyed increased attention during the last decade, which is primarily related to a great potential in the employment of such compounds in electronics and optoelectronics. In particular, there is a constantly growing interest in pyrene azaanalogs, which because of some structural features of their crystalline lattice and unusually low redox potential seem to be very promising materials for the production of organic semiconductor devices: light-emitting diodes, field-effect transistors and solar cells. Furthermore, the close attention paid to polyazapyrenes is related to the potential of their utilization as DNA intercalators, a basis for constructing so-called “molecular devices”, as well as their applications in coordination and supramolecular chemistry.

In present work we propose an approach to the synthesis of previously unknown class of such compounds 2,2-bis-1,5,7-triazacyclopenta[cd]phenalenes. This approach is based on the acylation of 2,2-bisperimidines and subsequent Schmidt reaction of carbonyl compounds.



Scheme 1. synthetic sequence

This project was financially supported by the Russian Foundation for Basic Research (grants: 16-03-00177a и 16-33-00483 мол_а).

Peculiarities of oxidative addition reactions of tri(*m*-tolyl)- and tri(*o*-tolyl)antimony with 2-nitrobensaldoxime and thiophene-2-carboxaldoxime

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It has been known that triphenylantimony dioximates and/or μ-oxo-*bis*[(oximato) triphenyl-antimony] are products of oxidative addition reactions between tri(*m*-tolyl)- and tri(*o*-tolyl)antimony and oximes. Our group pioneered in studying the reactions of tri(o-tolyl) and tri(m-tolyl) antimony with 2-nitrobensaldoxime and thiophene-2-carboxaldoxime in the presence of an oxidizing agent (hydrogen peroxide or *tert*-butil hydroperoxide) and we revealed the peculiarities of these interactions.

It has been found that the reaction of tri(*m*-tolyl) antimony with 2-nitrobensaldoxime in the presence of *tert*-butil hydroperoxide led to the formation of μ_2-oxo-*bis*[(2-nitrobensaldoxim ato)tri(*m*-tolyl) antimony] (*m*-$Tol_3SbONC_6H_4NO_2$-2)$_2$O. Using hydrogen peroxide as an oxidizing agent in the same conditions of reaction and irrespective of the molar ratio of the reactants (1:2:1 or 1:1:1), *bis*[(2-nitrobenzaldoximato)tri(*m*-tolyl)antimony] *m*-$Tol_3Sb(ONC_6H_4NO_2\text{-}2)_2$ was synthesized.

m-Tol_3Sb + $HONCHC_6H_4NO_2$-2 + t-BuOOH →
→ [*m*-$Tol_3Sb(HONCHC_6H_4NO_2\text{-}2)]_2O$ + t-BuOH + H_2O
m-Tol_3Sb + 2 $HONCHC_6H_4NO_2$-2 + H_2O_2 →
→ *m*-$Tol_3Sb(ONCHC_6H_4NO_2\text{-}2)_2$ + 2 H_2O

The interaction between tri(*o*-tolyl)antimony and 2-nitrobenzaldoxime and thiophene-2-carboxaldoxime irrespective of the oxidizing agent nature (hydrogen peroxide or *tert*-butil hydroperoxide) and the molar ratio of the reactants, leds to the formation of a single organoantimony product which is tri(*o*-tolyl) antimony dioximate. For example, *bis*[(thiophene-2-carboxaldoximato)tri(*o*-tolyl)antimony]:

o-Tol_3Sb+2$HONCHC_4H_3S$+ROOH → *o*-$Tol_3Sb(ONCHC_4H_3S)_2$+ROH+H_2O
R = *t*-Bu, H.

The molecular structures of the reaction products were determined by means of X-ray diffraction analyses.

Synthesis of ligands of the asialoglycoprotein receptor for targeted delivery to hepatocytes

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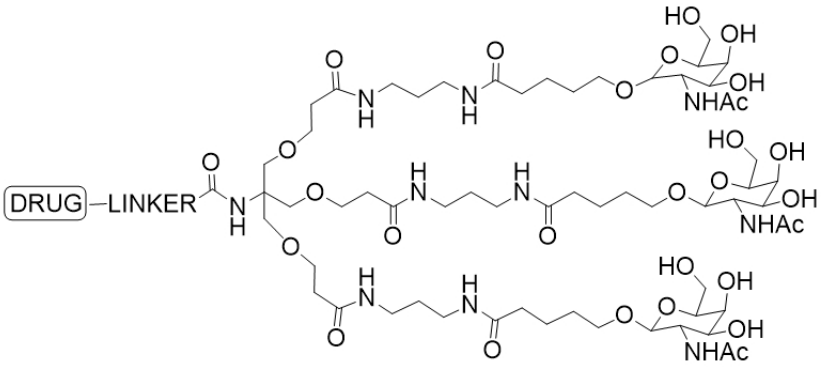
The asialoglycoprotein receptor (ASGPr) is highly expressed predominantly in hepatocytes. It facilitates uptake and clearance of glycoproteins, containing terminal D-galactose and *N*-acetylgalactosamine residues [1]. In view of its abundant presence on parenchymal liver cells, selective binding with carbohydrate moieties and ability to transport molecules through cell membrane, the ASGPr is widely used as a target in drug delivery studies [2].

Previously it was shown that tri-antennary ligands containing three *N*-acetylgalactosamine moieties demonstrate the highest affinity for the asialoglycoprotein receptor [3].



We investigated synthetic approaches to the aforementioned asialoglycoprotein receptor ligands, as well as preparation of new efficient structures. Biological testing of obtained compounds were evaluated on cell lines HepG2 and HuH7 with induced by biotin ASGPr.

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This work was supported by RSF, grant №14-34-00017.

New approach to the synthesis of pyrrolo[2,1-*a*]isoquinolines by the reaction of 1-aroyl-3,4-dihydroisoquinolines with symmetric alkynes

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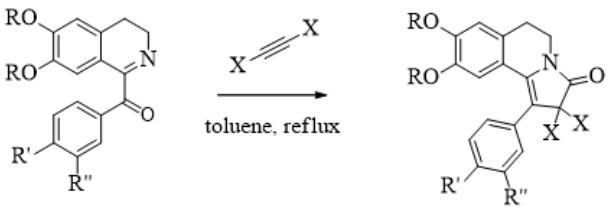
Pyrroloisoquinolines exhibit a broad range of biological activity which leads to increased interest in developing new approaches to the synthesis of these heterocyclic compounds. We have previously determined that a three-component reaction of 1-aroyl-3,4-dihydroisoquinolines with asymmetric activated alkynes and alkenes in alcohols leads to formation of pirroloisoquinolines with a functional group in the second position in good yields.

The reaction of 1-aroylisoquinolines **1** with symmetric alkynes flows through the rearrangement with the formation of pyrrolo[2,1-*a*]isoquinolines **2**. The structures of pyrrolo[2,1-*a*]isoquinolines **2** contain a lactam fragment and a geminal location of functional groups. The reactions occur under toluene reflux less than a day. Derivatives pirroloisoquinolines isolated by crystallization from the reaction mixture in good yields.



1 **2**

50-85%

R=Me, Et
R'=Me, Et, Cl
R''=Me, Et, H
X=CO_2Me, CO_2Et, CO_2Ph

Scheme 1.

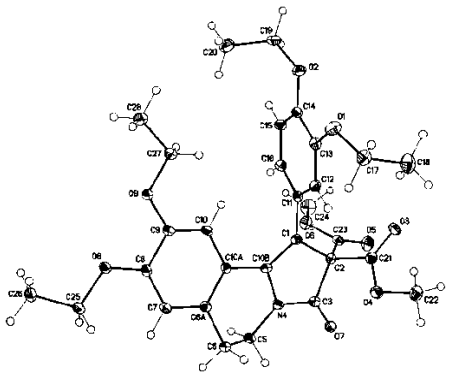


Fig. 1. Molecular structure of pyrrolo[2,1-*a*]isoquinoline **2**

This work was supported by the Russian Foundation for Basic Research (grant № 15-33-20187).

Synthesis and Studies of Symmetric Dibenzothienylcyclopentenes

Migulin V.A. [a], Krayushkin M.M. [a], Barachevsky V.A. [b], Kobeleva O.I. [b],
Novikov V.V. [c], Lyssenko K.A. [c]

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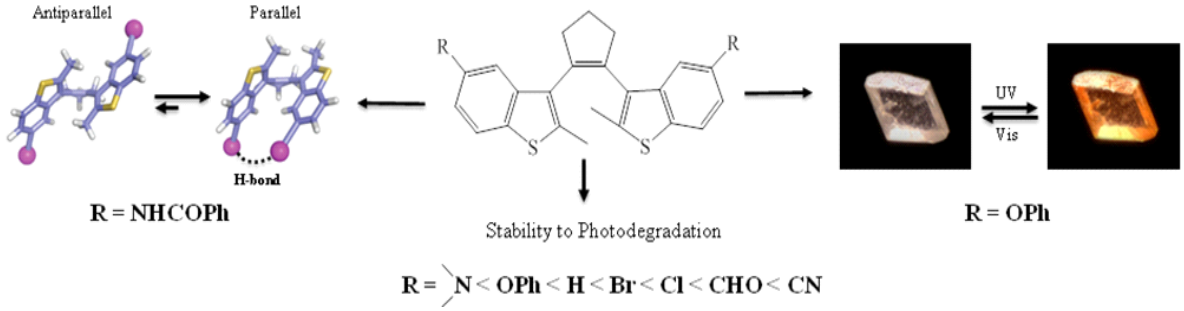
Synthetic approach to diverse 5,5'-substituted symmetric dibenzothienylcyclopentenes has been developed via straightforwardly accessible corresponding dibromide that could be considered as universal starting material for this purpose. The obtained compounds were profoundly studied in both solution and solid state in order to explore a dependence of photochromic properties of this class of dithienylethenes on the substituent in the benzothiophene ring [1].



NMR studies revealed that two distinct rotamers with antiparallel and parallel orientation of benzothienyl fragments existed in solution, interconversion of which could be completely suppressed at -50 °C. The ratio of two conformers was established to be dependant on both nature of the chemical substituent in the molecular core and a value of the dielectric constant of the solvent.

Moreover, symmetric dibenzothienylcyclopentenes also occupied either antiparallel or parallel conformation in the crystalline phase. It was found that the latter was controlled by intramolecular interactions of particular substituents in the benzothiophene rings, and hence could be predicted by DFT calculations for the isolated molecules. On the contrary, the antiparallel arrangement of the rings was being governed by different intermolecular interactions in the crystal packing, thus excluding the possibility of a predictive foresight towards photochromic properties in a single crystal. Photochromism of diphenoxy-substituted dibenzothienylcyclopentene was explained by intermolecular S…π and S…H contacts that were primarily responsible for this phenomenon by drawing the benzothiophene cycles together, and therefore, shortening the distance between two reactive centers, thus allowing the photocyclization reaction to proceed.

Overall, we have presented a comprehensive research for this class of dithienylethenes both in solution and solid state. The obtained data and observed regularities in photochromic behavior should greatly assist a researcher in this field in designing of future photochromic dithienylethenes.

Reference:

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1-aminophosphonates based on polyhedral oligomeric silsesquioxane

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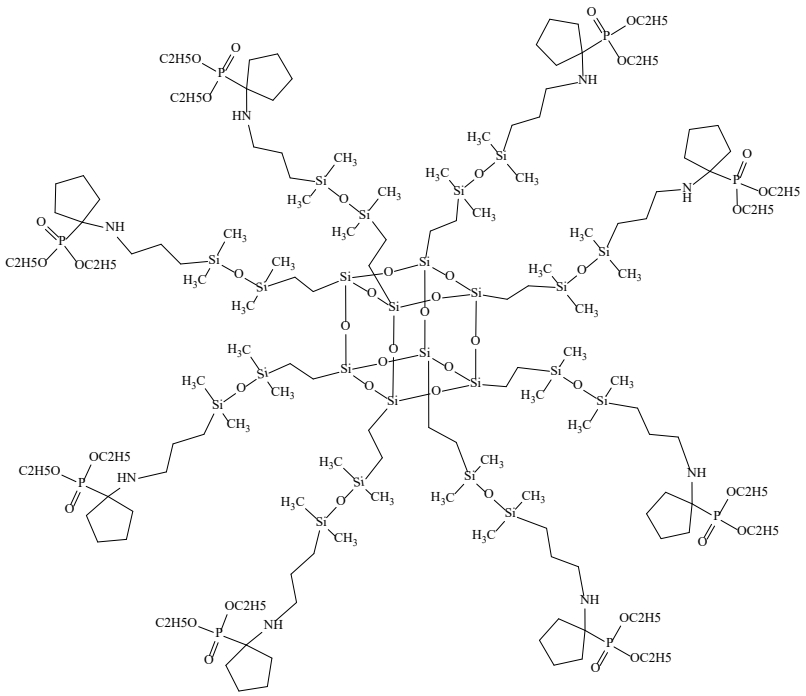
Polyfunctional organophosphorus compounds 1-aminophosphonates – are the objects of interest, from both scientifical and practical points of view. The molecule of such compounds contains fragments with the proton-acceptor (phosphoryl) and proton-donor (amino) group, what opens up possibilities for their use as the receptors for the recognition of biologically important objects, such as organic acids, amino acids, etc.

Polyoctahedral silsesquioxanes are unique three-dimensional nanobuilding blocks that can be used to create a wide variety of hybrid materials, where precise control of nanostructure and properties is required.

The synthesis of new compounds based on polyhedral oligomeric silsesquioxane containing aminophosphonate fragments and some physico-chemical characteristics of these products are going to be presented in this work.



Scheme 1. Scheme of 1-aminophosphonates based on polyhedral oligomeric silsesquioxane

Fluorescent detection of sulfonate SAS using new amphiphilic derivatives of Thiacalix[4]arene with Eosin Y

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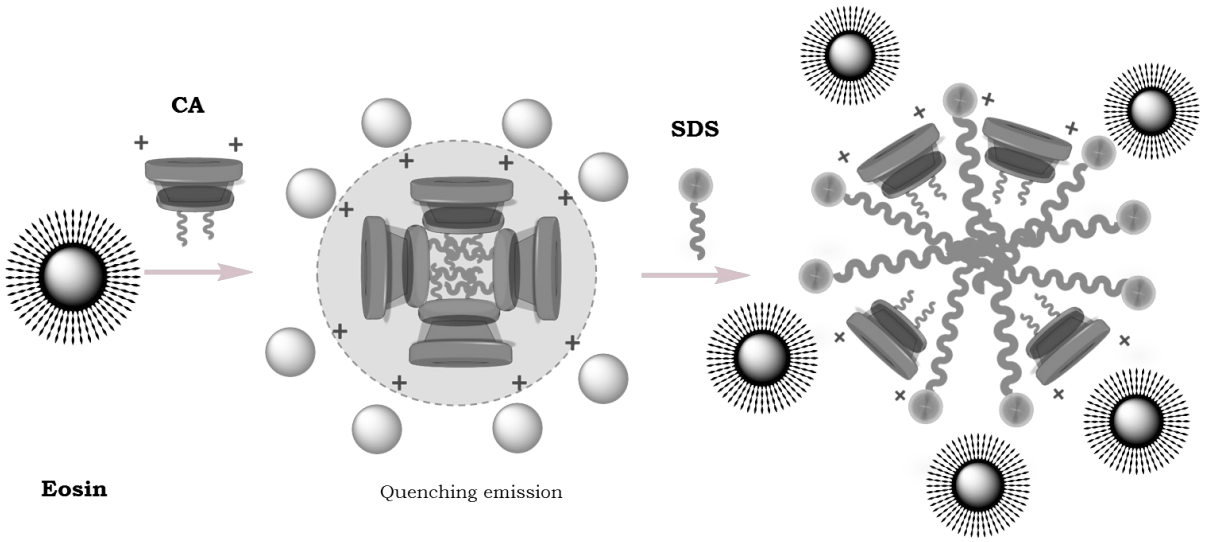
Amphiphilic derivatives of p-tert-butylthiacalix[4]arene were obtained by click reactions of the corresponding azido derivatives with N-proparhyl-N,N,N-triethylammonium bromide. Aggregation numbers, CMC and ζ-potential of calixarene and dye-calixarene aggregates were studied by DLS and fluorescent probe pyrene. A new fluorometric method for the determination of anionic surfactant sodium dodecyl sulfate (SDS) was proposed. The method is based on the binding competition between calixarene and the dye or surfactant. The calibration graph is linear at the concentration range of SDS from 0 to 3.5×10^{-4} mol L^{-1} with a detection limit 3.5×10^{-7} mol L^{-1}.



We thank the Russian Scientific Foundation for the financial support of this work (grant No. 14-13-01151).

New oxidizing reagents based on iodobenzenesulfonic acid

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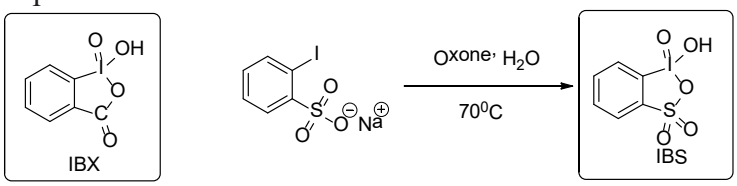
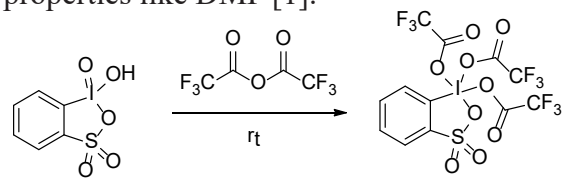
The chemistry of hypervalent iodine attracts a great interest and nowadays this field is developing rapidly [1]. Especially interesting is such a reagent as 2-iodoxybenzenesulfonic acid (IBS), however, there are some problems with isolation of this product [2, 3]. It is known IBS is a much more reactive oxidant than IBX and its derivatives [2]. We have improved the method of preparation of IBS [3], and for the first time have isolated pure IBS.



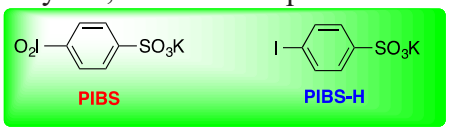
Scheme 1. Preparation of IBS [3]

Also we have prepared sulfoanologue of Dess-Martin Periodinane (DMP) and investigated its oxidative properties. We prepared the IBS derivative according to the following procedure. This analogue has potentially powerful oxidizing properties like DMP [1].



Scheme 2. Preparation of DMP's analogue

Also we proposed an alternative variant of a stable strong oxidant, potassium 4-iodylbenzenesulfonate (PIBS), which has been obtained by oxidation of 4-iodobenzenesulfonic acid using Oxone in water. Furthermore, the active agent (PIBS-H) can be recovered from the reaction mixture efficiently and recycled back to PIBS in 67% overall yield, which corresponds to the principles of Green chemistry. [4]



Scheme 3. Use of PIBS in electrophilic addition reactions [5]

In the present communication, we report the use of PIBS as an efficient and recyclable reagent for iodination of alkenes, alkynes and ketones leading to the corresponding aliphatic iodides [5].

Acknowledgment. This work was supported by a research grant from the Ministry of Education and Science of Russian Federation (project "Science" No. 4.2569.2014/K).

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Supported copper nanoparticles in catalysis of C-C and C-heteroatom bonds formation

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Renaissance of Ullmann chemistry has led to the fact that copper catalysis has become a good alternative to palladium catalysis, especially in cross-coupling reactions of formation carbon-carbon and particularly carbon-heteroatom bonds [1,2]. On the other hand, the transition from homogeneous catalysis by palladium complexes to the use of PdNPs nanoparticles with various soft and hard supports has shifted the boundary between homogeneous and heterogeneous catalysis and caused a chain reaction in the application of the nanometallic catalysts, including copper-based nanocatalysts [1].

The advantages of such copper nanocatalysts are the absence of ligands, easy separation from the reaction products, ability to recycling and low cost. However, problems with using of CuNPs significantly increase already existing difference in the mechanisms of catalytic action of homogeneous palladium and copper complexes [2], because oxidation film on the CuNPs surface has copper in two oxidation states: Cu(I) and Cu(II). There is a complex interaction substrate - CuNPs - Cu(I)/Cu(II).

In this work we have investigated how such catalyst system manifests itself in different cross-coupling reactions: the formation of the C-S, C-N and C-C, as well as in case of formation of the same bond C-N, but with different substrates (among azole) (**Figure**), and when using different supports for CuNPs (TiO_2, C, zeolite and MK-10).

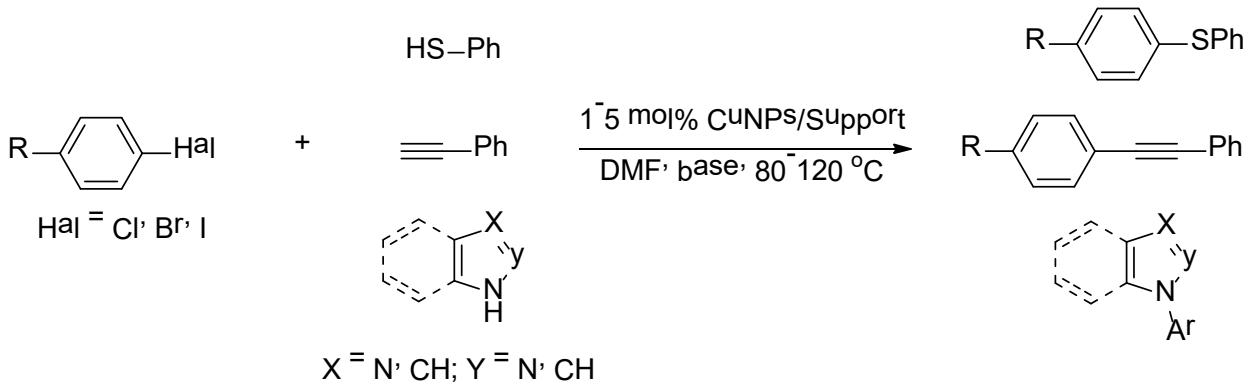

Figure. CuNPs-catalyzed cross-coupling aryl halides with thiophenol, phenylacethylene and series of azoles.

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A convenient synthesis of α-amino acids by Michael addition of N-nucleophiles to nitroalkenes

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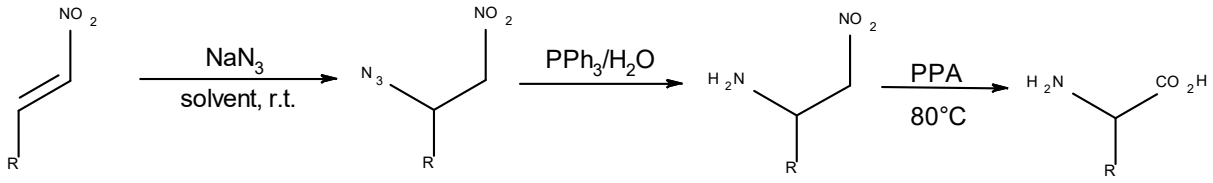
Despite the existence of large number well-established synthetic routes to the both natural and unnatural alpha-amino acids [1], a new convenient and practical way of preparation such compounds would be still welcome by the general chemist community. Herein we would like to report our results on the development of the synthesis of α-amino acids by Michael addition of azides to nitroalkenes followed by direct conversion of nitro to carboxyl group (Nef reaction). This procedure is found to be quite general with the obtained yields ranged from good to moderate.



Scheme 1. Synthesis of α-amino acid derivatives via aza-Michael / Nef sequence

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The $Zn(OAc)_2$-acorbic acid catalyzed 1,3-dipolar cyloaddition of arylazides and alkynes

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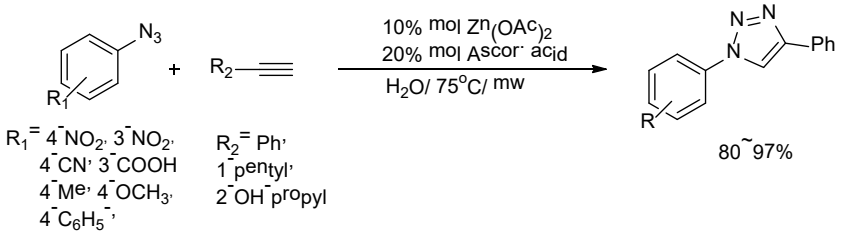
1,4--substituted 1,2,3-triazoles have a wide application in the organic synthesis, medicinal chemistry [1], material chemistry[2] and drug synthesis [3,4]. The common procedure for synthesis of 1,4-substituted-1,2,3-triazoles is direct interaction of terminal alkyne with azides in presence of Cu-containing catalyst (Cu(OAc), $CuSO_4$ or nanomaterials and zeolites containing copper) [5-7]. Nevertheless, this method does not allow to obtain desired products from internal alkynes. The promising alternative to Cu-catalysts are Zn-containing catalytic systems, which are able to synthesize triazoles from internal alkynes [8].

We found that $Zn(OAc)_2$ is a conventional alternative to known catalytic system for synthesis of 1,4-substituted 1,2,3-triazoles. The proposed procedure includes simple 1,3-dipolar cycloaddition of arylazides and alkynes in the presence of 10 mol % of zinc acetate and 20 mol % of ascorbic acid under microwave irradiation. Corresponding method allows to synthesize a wide range of substituted triazoles with high yields. The method demonstrates high tolerance to the functional groups in alkyne and azide moieties.



Thus, we developed new conventional procedue for preparation of 1,4--substituted 1,2,3-triazoles.

Acknowledgment. This work was supported by a research grant from the Russian Foundation for Basic Research №. 16-33-00348 mol_a.

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Synthesis of functional derivatives of thiophene

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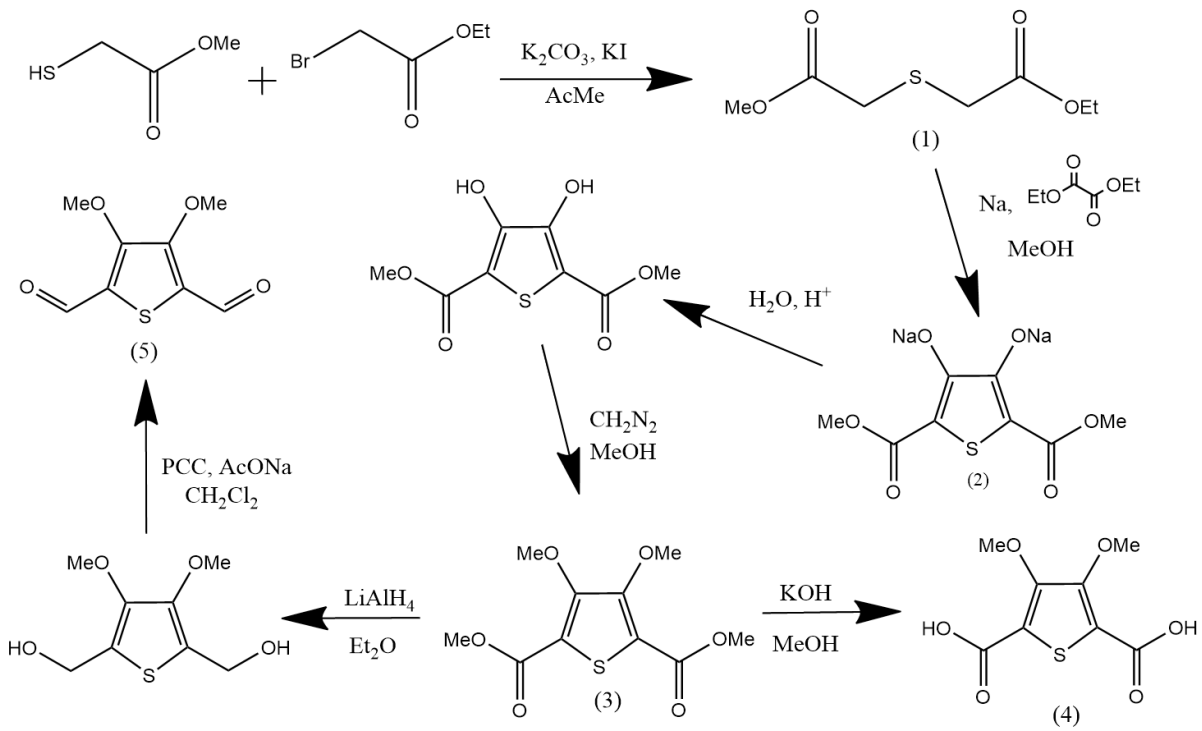
One of the promising areas of scientific research is the synthesis and determination of the physical and chemical properties of substances, capable of forming conjugated polymers of the following formula: $(\text{-X-D-A-D-})_n$ (where D is electron-donating fragment, A is electron-accepting fragment, X is cyclic system). Derivatives of heterocyclic compounds, thiophene in particular, act as donor fragments in most cases.

At the initial stage the goal was set: to synthesise thiophene nucleus, which contains functional groups (carboxyl and carbonyl groups) capable of further polycondensation transformations.



Scheme 1.

Simple precursors, i.e. thioglycol acid and ethyl ester of bromoacetic acid initially yielded Compound **1**. Further therefrom by reaction with diethyl ester of ethanedioic acid in sodium methylate medium we have obtained basic Compound **2** which is disubstituted thiophene. At the next stage of hydrolysis followed by methylation of the resulting hydroxyl groups (methylation with diazomethane) yielded Derivative **3**. On the basis of preisolated/preseparated Compound **3** it was possible to obtain Compound **4**: thiophene compound with two carboxyl groups in positions 2,2' resulting from alkaline hydrolysis of complex ester groups. Compound **5** has been synthesized as well, which is a difunctional thiophene derivative though with aldehyde groups in positions 2,2'.

The structures of all the obtained compounds have been confirmed by array of the following techniques: IR-, ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry.

Fluorinated alkenes in the synthesis of practically useful compounds

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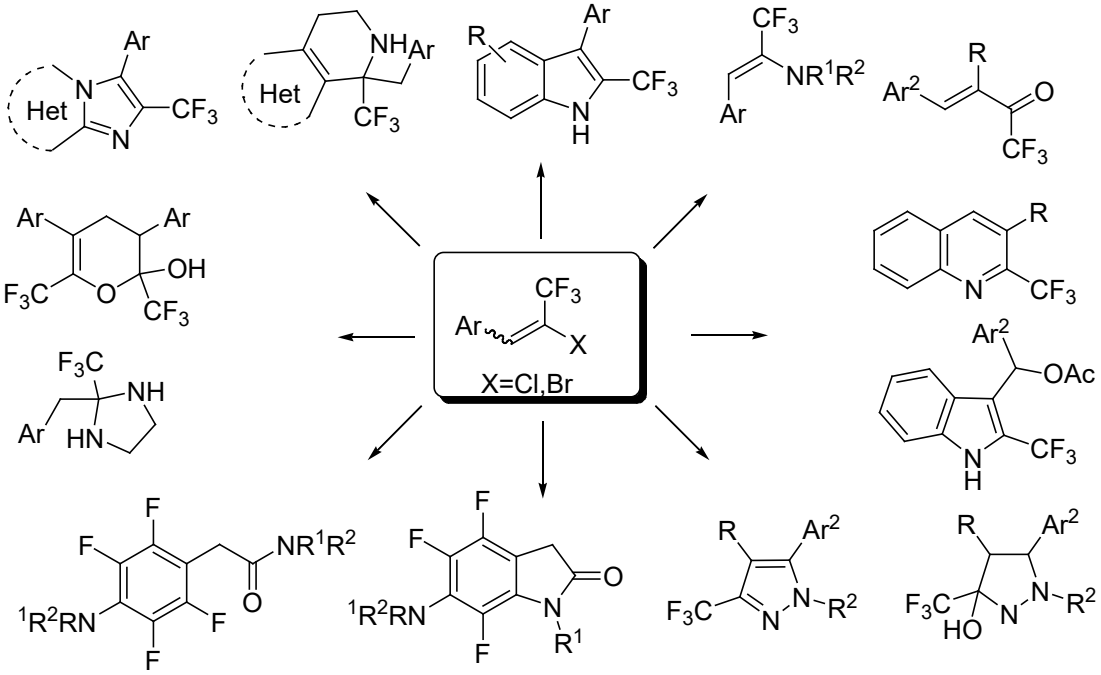
Organofluorine chemistry is one of the fastest growing area of modern organic chemistry, because of many fluorine-containing compounds have a high biological activity. To date, approximately 25-30% of all pharmaceuticals contain fluorine.[1] The great role of fluorinated compounds in agrochemistry and the material science can not be also overestimated. At the same time, known methods of direct introduction of fluorine or fluorinated moiety do not always posses enough selectivity and effectiveness. Hence, there is a great demand for the elaboration of new synthetic methods in this field.

Fluorinated functionally substituted olefins and acetylenes have a great potential for the construction of molecules having fluorine or perfluoroalkyl groups attached to desired position. Several years ago a novel catalytic olefination reaction was found by our group. *N*-Unsubstituted hydrazones of aldehydes and ketones transforms into alkenes $R^1R^2C{=}CXY$ under treatment with $CHal_2XY$ in the presence of catalytic amount of copper salts. This reaction allows to synthesize a variety of fluorinated alkenes and acetylenes using cheap and affordable freons. These fluorinated building blocks were successfully used in the synthesis of fluorinated heterocyclic compounds, which are perspective for medicinal chemistry.



This work was supported by Russian Science Foundation (grant no. 14-13-00083).

New chromone-containing ligands

Myannik K.A. [a], Yarovenko V.N. [a], Krayushkin M.M. [a], Levchenko K.S. [b], Beloglazkina E. K. [c]

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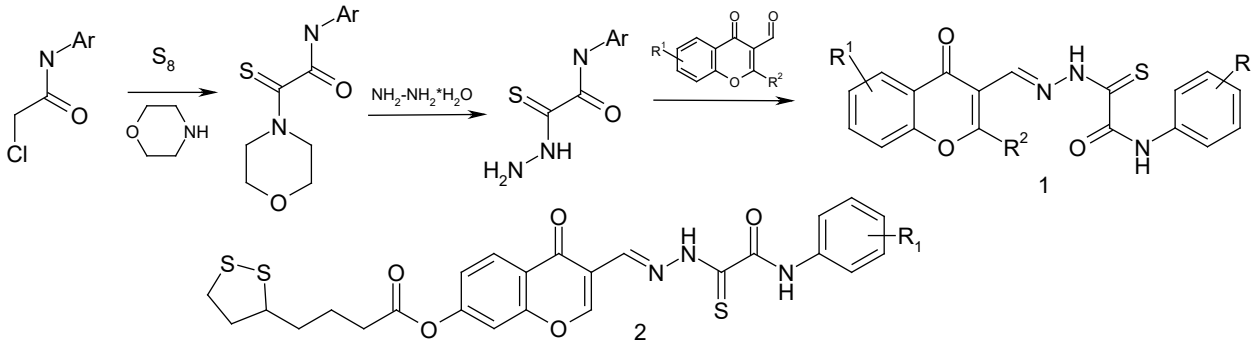
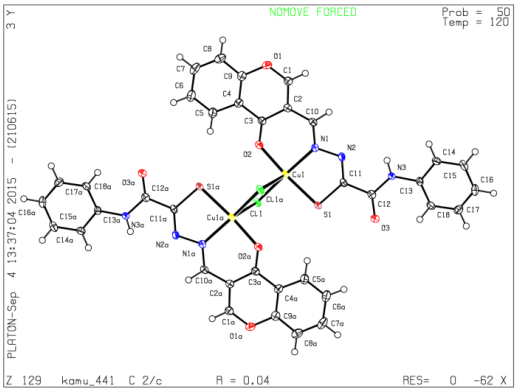
Chromone derivatives are of doubtless interest as bioactive compounds [1] and elements of recording media for multilayer optical discs of superhigh capacity [2]. We have shown previously that the replacement of hydrazide or thiohydrazide fragment for thioxydrazide of oxamic acid increases drug efficiency [3]. For now we have developed convenient method for the synthesis of new polydentante ligands on the basis of chromones containing thioxydrazides of oxamic acids **1** and bifunctional compounds **2** (scheme 1). They are capable of coordinating with transition metal ions and compound **2** can interact with gold nanoparticles.

Scheme 1



The structures of compounds **2** and **3** were established on the basis of spectral data and x-ray diffraction. For example, the crystal structure of the copper complex 3 is shown on figure 1.

Fig. 1. Absolute configuration of compound 3 with L_2CuCl_2 ($C_{36}H_{26}Cl_2CuN_6O_6S_2$)



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Unexpected cyclization during the synthesis of 1-aryl-1-deoxyconduritols F

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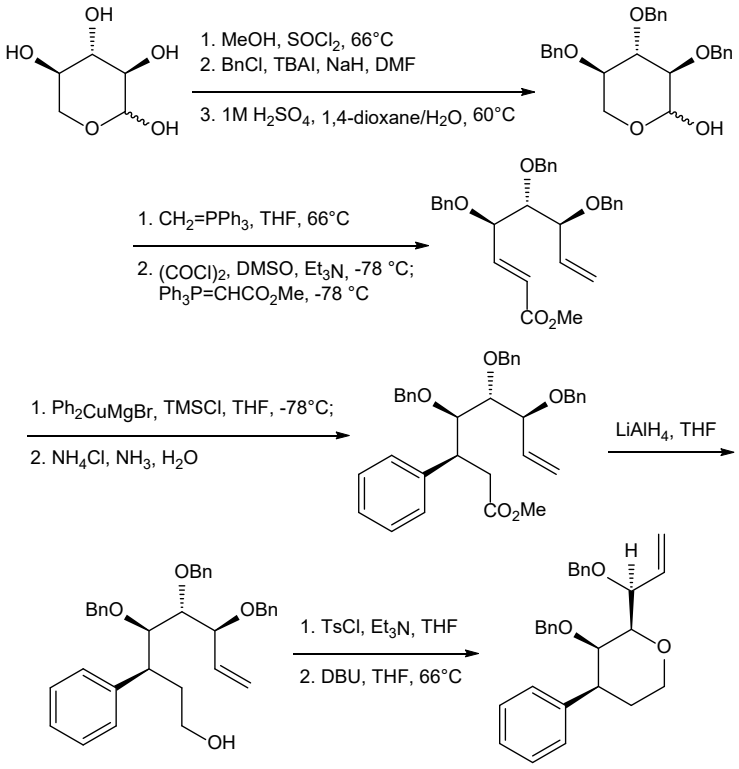
Novel synthetic approaches to the naturally occurring cyclitols and their analogs are of considerable importance due to diverse biological properties associated with these compounds. For example, inositols and their phosphate derivatives mediate intracellular signal transduction pathways.

Conduritol epoxides and aminoconduritols act as glycosidase inhibitors. Cyclophellitols are potent inhibitors of human immunodeficiency virus. Furthermore, the multifunctional nature and the stereochemical complexity of these compounds have made them convenient starting materials for the synthesis of more advanced structures.



Scheme. Synthetic sequence which led to an unexpected syclization

An efficient multi-gram synthesis of various 1-aryl-1-deoxyconduritols F was reported, which establishes a firm foundation for achieving a practical synthetic route to not only pancratistatin alkaloids themselves, but also their aryl analogs, paving the way for more systematic SAR studies of these promising anti-cancer agents [1].

All attempts to install a terminal double bond by the elimination reaction of primary tosylates, mesylates, triflates and halides with various bases failed. We found during the unexpected cyclization, the terminal protected hydroxyl as well as one of the benzyl group were both eliminated. Preliminary reports show that six-membered ring was formed. We are going to investigate further this conversion, install its mechanism and utilization for the synthesis.

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Synthesis of 4-Arylfuro[2,3-*f*]isoindol-5-ones by the IMDAV Reaction

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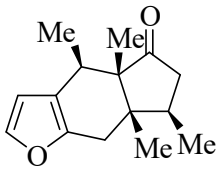
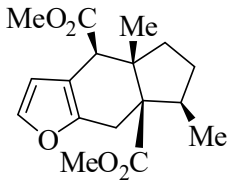
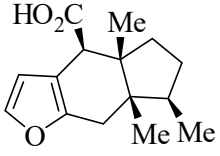
As it has been previously shown by our groups, the interaction of (3-furyl)allylamines with maleic anhydride leads to the formation of furo[2,3-*f*]isoindoles – the aza-analogs of pinguisane-type sesquiterpenes [1].



Pinguisone

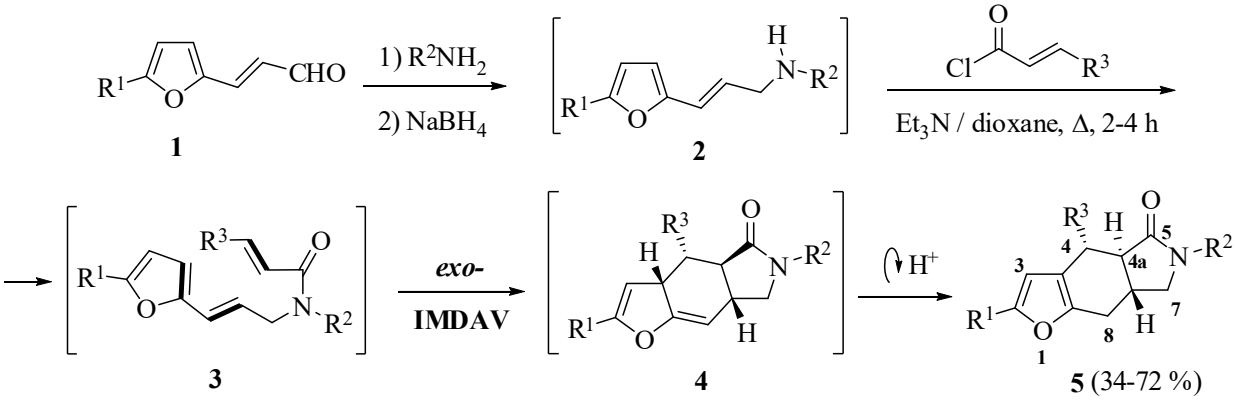


Bryopterin B



Deoxopinguison-15-oic acid

In this work 3-(2-furyl)allylamines **2**, easily available in two steps from furylacroleins **1** and primary amines, were studied in the tandem N-acylation / intramolecular [4+2]-cycloaddition reaction with furylacryloyl and cinnamoyl chlorides [2]. By using the domino reaction of 3-(2-furyl)allylamines **2** and arylacryloyl chlorides, various hexahydro-4*H*-furo[2,3-*f*]isoindoles **5** were synthesized efficiently under mild conditions. The domino sequence includes three steps: acylation of the nitrogen atom in allylamines, the intramolecular Diels–Alder cycloaddition in the resulting N-acryloylfurans **3** (IMDAV reaction), and the prototropic shift in the adducts **4** followed by recovery of aromaticity of the furan nucleus.



R^1 = H, Me; R^2 = C_6H_4-4-OMe, Ph, Bn; R^3 = 2-Furyl, Ph, C_6H_2-3,4,5-$(OMe)_3$ (6 examples).

The *exo*-cycloaddition reaction proceeded stereoselectively with the retention of the substituent R^3 configuration in products **4**,**5**.

References

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This work was supported by the Russian Foundation for Basic Research (RFBR) according to the research projects № 16-33-00389, 16-03-00125 and by the Ukrainian State Fund for Fundamental Research (grant F53.3/013).

STUDY OF METHYLATION OF HELIOMYCIN

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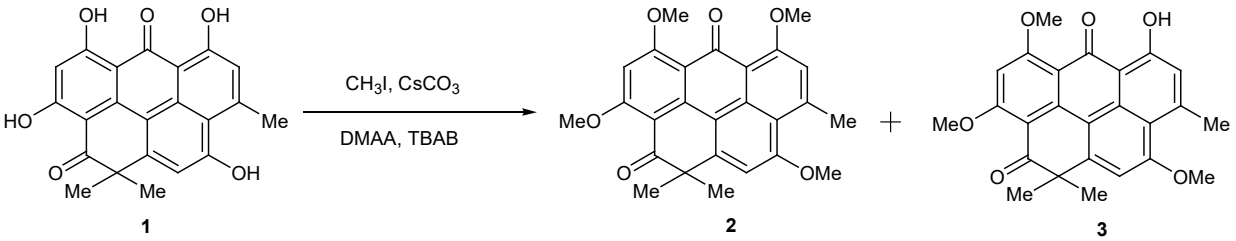
Heliomycin (resistomycin) is a potent antibiotic produced by *Actinomyces Flavochromogenes* discovered in 1950[th][1]. This antibiotic has great potential for the treatment of infection diseases. Heliomycin demonstrate wide spectrum of biological activity, including antibacterial, antifungal, antiviral and anticancer [1-4]. Mechanism of antibacterial activity of heliomycin realized through the blocking of RNA polymerases, which leads to a disruption of protein biosynthesis in the cells [4, 5]. Although heliomycin has a promising biological activities, some disadvantages of this antibiotic (the main of which is poor solubility) significantly limit its practical usage.

Despite of the unique biological properties of heliomycin, chemistry of this compound is very poorly understood to date. Thereby, the aim of our study was a development of methods of transformation of heliomycin and preparation of new semisynthetic derivatives with improved characteristics, perspective for the development of new chemotherapeutic agents.

So, as the initial step, possibilities of protection of hydroxyl groups of heliomycin (1) by the alkylation reaction have been investigated. Heating of compound **1** with excess of methyliodide and cesium carbonate in dimethylacetamide (DMAA) in the presence of tetrabutylammoniumbromide (TBAB) lead to the formation of 3,5,7,10-*O*-tetramethylheliomycin (**2**, Scheme) in good yield (85%). 3,5,10-*O*-Trimethylheliomycin (**3**) was isolated as a by-product in 10% yield. Decreasing of temperature of the methylation of heliomycin (**1**) leads to the formation of trimethyl derivative **3** as a main product.



Scheme. Synthesys of *O*-methyl derivatives of heliomycin **2**,**3**.

Structures of compounds **2** and **3** were confirmed by NMR spectroscopy and HR-MS spectrometry methods. Synthesized derivatives **2** and **3** have better solubility in organic solvents than the starting heliomycin **1** and can be useful for further development of the methods of its modification.

The reported study was funded by the Russian Foundation for Basic Research according to the research project № 16-34-60110.

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Synthesis of Bromo Derivatives of Oligomycin A

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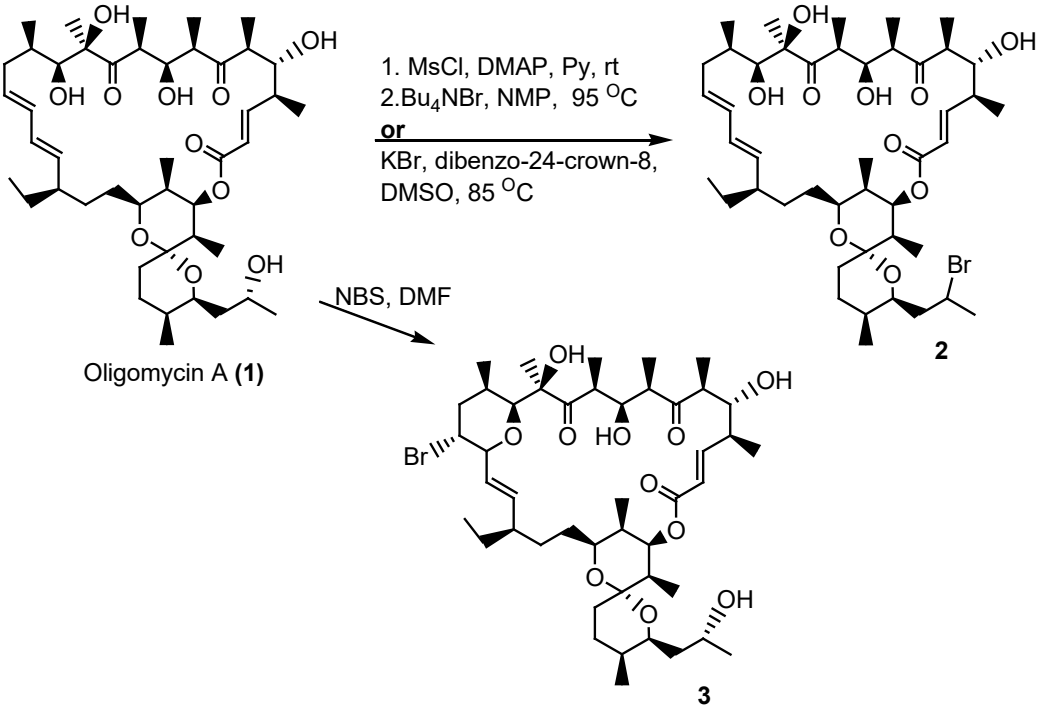
Oligomycins are produced by actinomycetes *Streptomyces* and belong to class of highly-substituted macrolide antibiotics [1]. Oligomycin A (**1**) inhibit F_1F_0 ATP-synthase, which is regarded as a molecular target for new drugs in the treatment of tumors and infections. In micromolar concentrations, oligomycin binds to F_0 c-subunit and blocks proton translocation [2]. Available data suggest the existence of some additional targets for action of oligomycin A to cells [3]. Preparation of new oligomycin A derivatives will provided searching of new biological targets and establishment of the detailed mechanism of cytotoxic activity of oligomycins.

In this key, bromo derivatives of oligomycin A (**1**) have been synthesized. 33-Bromooligomycin **2** was obtained in two steps: mesylation of **1** and subsequent substitution of mesyloxy group with *tetra*-butylammonium bromide or potassium bromide produced a mixture of two diastereomers 33-(*R*,*S*)-bromo-33-deoxyoligomycin A (**2**). Bromination of oligomycin A (**1**) by *N*-bromosuccinimide accomplished with cyclization of tetrahydropyrane ring and yielded a bromo derivative **3**. It has been shown, that modification of hydroxyl groups at C-13 and C-33 positions led to significant decrease of anti-actinomycotic activity of oligomycin A against *S. fradiae* ATCC-19069. Detailed spectra of biological activities of bromo-substituted derivatives **2** and **3** as well as selection of mutants *S. fradiae* resistant to bromooligomycins **2** and **3** will be evaluated.



Scheme 1. Synthesis of bromooligomycines **2** and **3**.

References

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Alkylation of 1*H*-1,2-diazaphenalenes.

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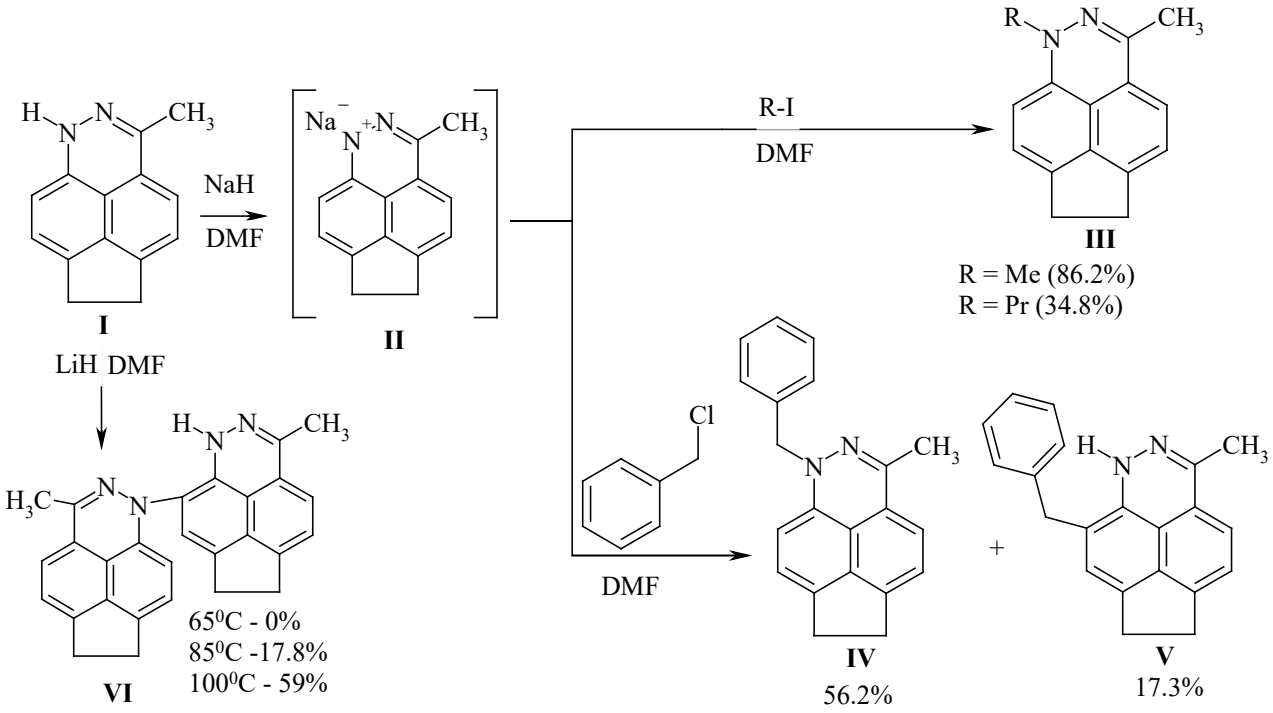
It has been shown that 1*H*-1,3-diazaphenalens based on acenaphthene (aceperimidine) were readily alkylated by haloalkanes on "pyrrole" nitrogen at reflux in an alcoholic potassium hydroxide solution [1]. However isomeric 1*H*-1,2-diazaphenalene (**I**) in the same conditions did not enter into the reaction. Just have failed other methods of alkylation: boiling in DMF with a haloalkanes, boiling in acetone with haloalkanes in the presence of potassium carbonate. In an attempt to find a workable methodology for the introduction of alkyl substituents on the "pyrrole" nitrogen atom, we have found that indoles easily and with high yields have been alkylated by haloalkanes using sodium hydride as the base [2] via the intermediate formation of the sodium salt (**II**). Since 1*H*-1,2-diazafenalenes are weak acids and are capable of forming salts with alkali metals, we conducted a reaction using sodium hydride in DMF cooled to 0^0C:



N-Substituted-1*H*-1,2 diazaphenalenes were obtained in good yields, in addition, by using benzyl chloride as the alkylating agent a reaction passed at C^9 – atom naphthalene nucleus (**V**).

Using lithium hydride as a base requires different conditions (heating to 85-950S for 3-5 hours) and leads not only to the formation of N-alkylation products (**III**), but also to the formation of dimer (**VI**). The yield of the dimer increases sharply with increasing temperature.

When tetrahydrofuran was used as a reaction solvent a reaction did not went neither with sodium hydride no lithium hydride.

The structures of the compounds are proved by ^{1}H NMR, IR and mass spectra.

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This research was supported by The Ministry of education and science of Russian Federation in the framework of the State Assignment for Research, project № 1895.

Trifluoroacetylation of 1,2-diazaphenalens.

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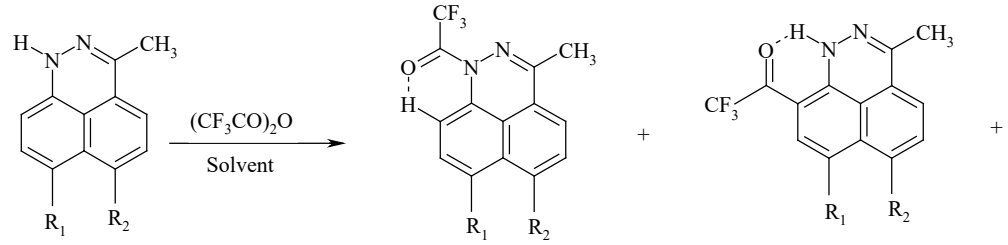
The trifluoroacetylation of aromatic compounds by trifluoroacetic anhydride is an electrophilic substitution which allows the introduction of a $COCF_3$ group into an activated substrate [1]. It was found, that pyrrole trifluoroacylated only on carbon [2]. Whereas, indole trifluoroacylated on nitrogen and carbon. But indol also gives dimerization product. Finaly, carbazole – only on nitrogen [3].

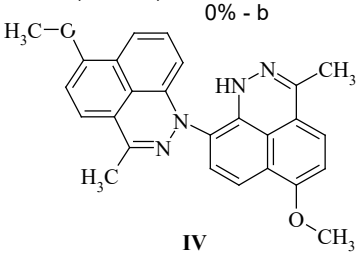
Based on these data, we have found, that acylation of 3-methyl-1H-1,2-diazaphenalens (**Ia,b**) with trifluoroacetic anhydride leads to the formation of products of N- (**IIa,b**) and C-acylation (**IIIa,b**) and also gives product of dimerization 3-methyl-6-methoxy-1H-1,2-diazaphenalen (**IV**).



Ia,b
$R_1 = R_2 = -CH_2-CH_2-$ (a)
$R_1 = H$, $R_2 = -OCH_3$ (b)
Solvent = DMF, CH_2Cl_2, $(CF_3CO)_2O$.

IIa,b
DMF: 38% - a
7% - b
CH_2Cl_2: 21% - a
4.5% - b(at 0°C)
(CF3CO)2O: 7.4% - a
0% - b

IIIa,b
DMF: 30% - a
14% - b
CH_2Cl_2: 60% - a
45.5% - b
(CF3CO)2O: 79.5% - a
86% - b



IV
DMF: 52% - b
CH_2Cl_2: 38% - b
(CF3CO)2O: 12% - b (at 39°C)

In the IR spectrum of (**IIa,b**) was no NH-group absorption band, but present absorption band of the carbonyl group. In 1H NMR spectrum filmed in CDCl3, were observed four signals of aromatic protons and the absence of NH proton signal. Proton signal H^9 is shown at 7.2 ppm against 6.05 m.d. the starting compound, this is indicating the presence of a strong intramolecular hydrogen bond.

In the IR spectrum of (**IIIa,b**) present broadened absorption band of NH-group at 3267 cm^{-1} and the absorption band of the carbonyl group at 1640 cm^{-1}. In the 1H NMR spectrum of this compound there are two doublet - H^4 and H^5 protons, multiplet of H^8 proton and NH-proton signal at 12.79 ppm, which also indicates the presence of a strong air force.

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This work was supported by Foundation…

Reactions of o-quinone methides with 1,2,4-triazoles and pyrazoles: access to condensed azolooxazines

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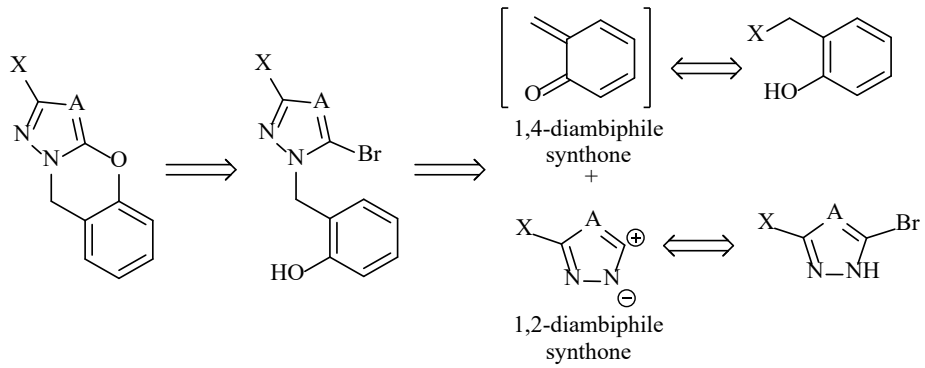
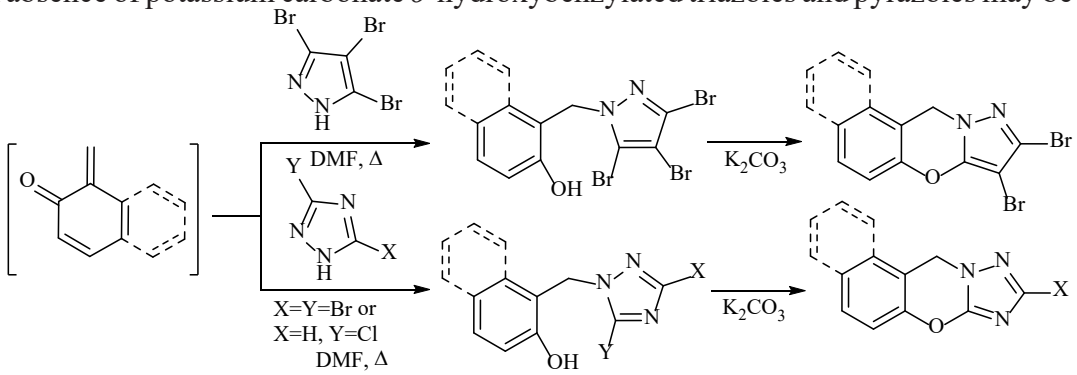
The cascade aza-Michael – intramolecular nucleophilic substitution reactions have great potential in developing new reaction pathways with high step economy to produce nitrogen-containing heterocycles but remain underdeveloped. *o*-Quinone methides (*o*-QM) can be efficiently used in these reactions as Michael acceptor. At the same time, in spite of numerous reports of aza-Michael reactions of *o*-quinone methides in biological systems, the exploitation of these pathways in the synthesis of heterocycles is limited to several reports.

As a part of our ongoing interest in developing new synthetic strategies for the construction of azolo-1,3-benzoxazines, we focused our attention on the reaction of *o*-QM with 1*H*-azoles. In case of presence of good leaving group such as halogen near nucleophilic nitrogen atom in azoles it may be considered as 1,2-diambiphile. Reaction of this type of azoles with *o*-QM as an 1,4-diambiphile leads to different azolo[1,3]benzoxazines.



It was found that condensation of 3-halo-1,2,4-triazoles and 3,4,5-tribromopyrazole with a series of *o*-QM precursors by heating equimolar quantities of the starting materials in DMF in presence of potassium carbonate gave triazolo- and pyrazolobenzoxazines in high yields.

In case of absence of potassium carbonate *o*-hydroxybenzylated triazoles and pyrazoles may be obtained.



The study was carried out with the financial support of the Russian Foundation for Basic Research (grant 16-33-00773 mol_a) and the Grant Council of the President of the Russian Federation (State Program for support of young Russian scientists, grant MD-5833.2016.3).

Synthesis of 1,5,7-triazacyclopenta[cd]phenalenes, by the reaction 1,4,8-triaminonaphtalene with aliphatinc nitrocompounds

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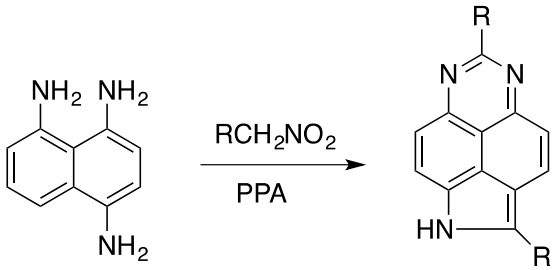
There are dozens of works devoted to the development of methods of synthesis polynuclear aromatic and heteroaromatic compounds, such as poliazapyrenes and similarly structured systems. Low availability of such compounds is determined, primarily by the lack of convenient methods of peri-annulation of carbocyclic and heterocyclic nuclei to phenalenes and azaphenalenes. The development of peri-annulation methodologies, namely, the search for new reagents, reagent systems and conditions conduce to the construction of both new and previously known heterocyclic systems.

Recently in our laboratory a new method for annulation of five-membered nitrogen-containing heterocycles on a basis of reaction of *ortho*-substituted anilines with nitroalkanes was shown. This method gives good yields of benzoxazoles and benzoimidazaoles in mild conditions.

Increasing the distance between the amino groups, such as using of *peri*-substituted naphthalene may provide a method of annulation of six-membered heterocycles. Indeed, the reaction of 1,4,8-triaminonaphthalene with nitroalkanes in PPA leads to corresponding 2,6-disubstituted 1,5,7-triazacyclopenta[cd]phenalenes. Sequential addition of two nitro compounds leads to the formation of 1,5,7-triazacyclopenta[cd]phenalenes with two different substitutients.



Scheme 1. synthetic sequence

This project was financially supported by the Russian Foundation for Basic Research (grants: 16-03-00177а и 16-33-00483 мол_а).

Synthesis and study of photochromic properties of unsymmetrical bis-spiropyrans

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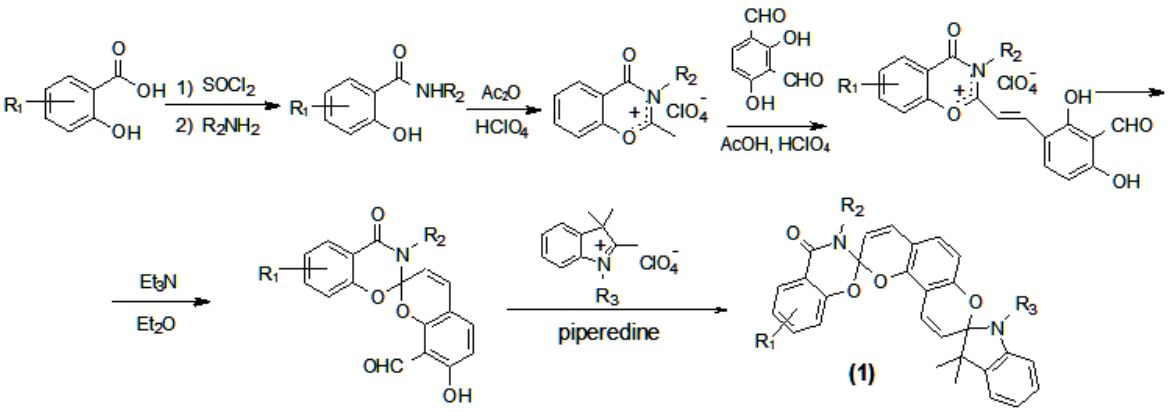
Spiropyrans represent one of the most interesting classes of photochromic compounds, which can undergo reversible photoisomerisation from spirocyclic form to a colored merocyanine form under activating irradiation. As easy tunable molecular switches SP have found diverse applications in the areas of chemosensorics, molecular electronics, non-linear optics, bio-imaging, control of cellular processes, photocontrolled drug delivery and in the development of dynamic smart materials [1]. Bis-photochromic compounds can exist as three or more isomers due to the presence of two potentially photoactive centers in molecule. That makes bis-photochromes promising prototypes of molecular switches for molecular electronics [2].

In this study a series of unsymmetrical indoline-benzoxazine bis-spiropyrans (1), in which the photoactive centers are conjugated through a common pyranochromene moiety, was synthesized by a multistage procedure. The structure of bis-spiropyrans was proven by the ^{1}H NMR, IR, and mass-spectroscopy.

All the obtained compounds demonstrate photochromic activity at room temperature. Photochemical study of the obtained compounds has shown that the modification of benzoxazine part with electron donating groups and bulky substituents near the spirocyclic carbon atom are the most promising directions for the stabilization of the once opened merocyanine isomers.



R_1 = : -H, 7-CH_3, 8-CH_3, 8-OCH_3; R_2 = -CH_3, -CH_2Ph; R_3 = -CH_3, -CH_2Ph, -CH_2CH_2OH, -CH_2CH_2COOH

Scheme 1. Scheme of synthesis of the unsymmetrical bis-spiropyrans

References

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This research was supported by The Ministry of education and science of Russian Federation in the framework of the State Assignment for Research, project № 1895.

Synthesis and structures of phenylpyrazole-based hypervalent phosphorous(III) compounds

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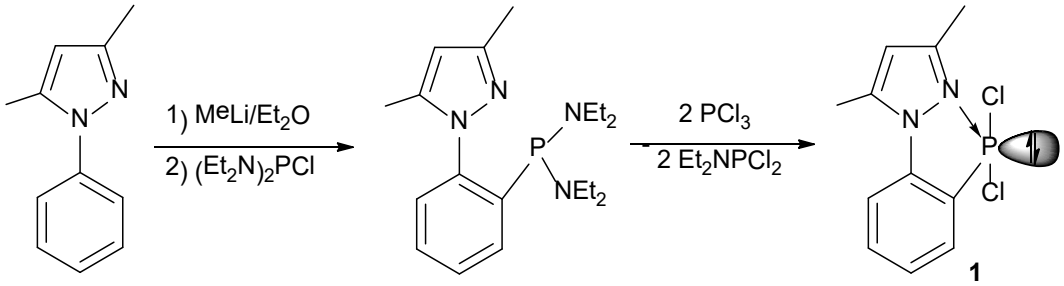
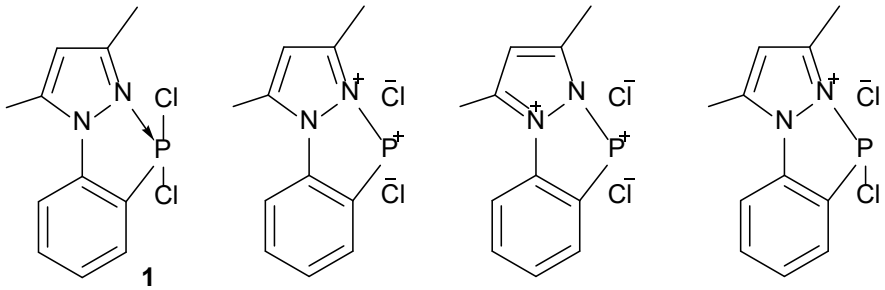
Hypervalent phosphorous(III) compounds play an important role in phosphorous chemistry and chemistry of heterocycles[1] and have attracted increased attention because of its unusual structure, bonding interaction and reactivity. Here, we report the formation and chemical properties of phenylpyrazole-based hypervalent phosphorous(III) compound **1** in a stepwise manner.[2]



X-ray diffraction analysis determined that 5-membered heterocycles of **1** adopt a nearly planar conformation. Trivalent four-coordinate phosphorous atom has disphenoidal geometry. Chlorine atoms occupy the axial position. Interestingly, the P-N bond length (1.775(1) Å) is in the range of P-N single bond distances. P-Cl bonds (P(1)–Cl(1) 2.3652(5) and P(1)–Cl(2) 2.3855(5) Å) are significantly longer then the sum of covalent radii and shorter then the sum of Van der Waals distances.

To better understand the bonding situation at P-atom in **1** DFT calculations at the (B3LYP)/6-31+G(d) level of theory were performed. NBO analysis reveals high charge separation between phosphorous (+1.078) and chlorine (–0.531) atoms. So, the canonical formulae of **1** can be represented with separated charges at P and Cl atoms with P-N covalent bonding.



The reactivity of **1** toward reducing and nucleophylic substrates will be discussed.

References

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[2] Kornev A.N., Sushev V.V., Panova Yu.S. et al. *Eur. J. Inorg. Chem.* **2015**, 2057.

This work was supported by Russian Science Foundation № 14-13-01015.

Synthesis of furo[2,3,4-*gh*]perimidines

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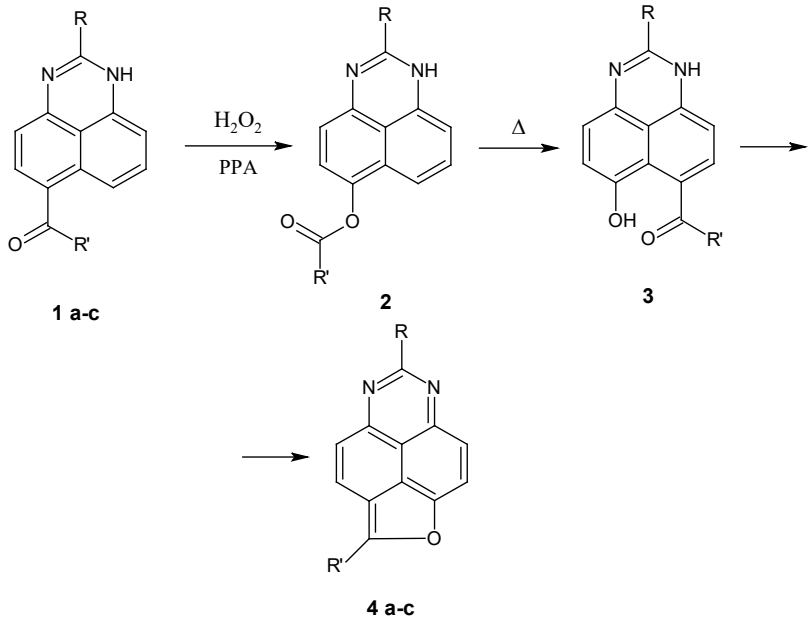
Organic compounds containing aromatic five-membered heterocyclic rings are widespread in nature and often play an important role in various biochemical processes. A wide range of biological activity of furan derivatives continues to attract the attention of synthetic chemists to this class of compounds.

Previously a method of synthesis of furo[2,3,4-*gh*]perimidines was discovered in our laboratory based upon the interaction of 4,5-diamino-1-naphthol with acylating reagents. Its disadvantage was a very low availability of the starting diamine. We decided to develop an alternative method of preparation of these compounds, which is based on the principles of C-H functionalization, based on available 6(7)-benzoylperimidine **1**. The method was based on the assumption of the feasibility of Baeyer-Villiger reaction of ketones with hydrogen peroxide in polyphosphoric acid (PPA). It was obvious that the formation of ester **2** and its conversion to ketone **3** as a result of Fries reaction followed by a furan ring closure would lead to the desired result. The reaction sequence is represented on the scheme below:



1,4 a R = H; R' =Ph; **b** R = Me; R' = Ph; **c** R = Ph; R' = Ph;

Indeed, the reaction of 6(7)-benzoylperimidines **1 a-c** with hydrogen peroxide in polyphosphoric acid (PPA) lead to the formation of furo[2,3,4-*gh*]perimidines **4 a-c**. The yield was 56-63%. The reaction was accompanied by a partial deacylation of ketones and a rerrangement to the 4(9)-acylderivative.

N-Benzyl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxamide chiral crystals and their analgesic properties

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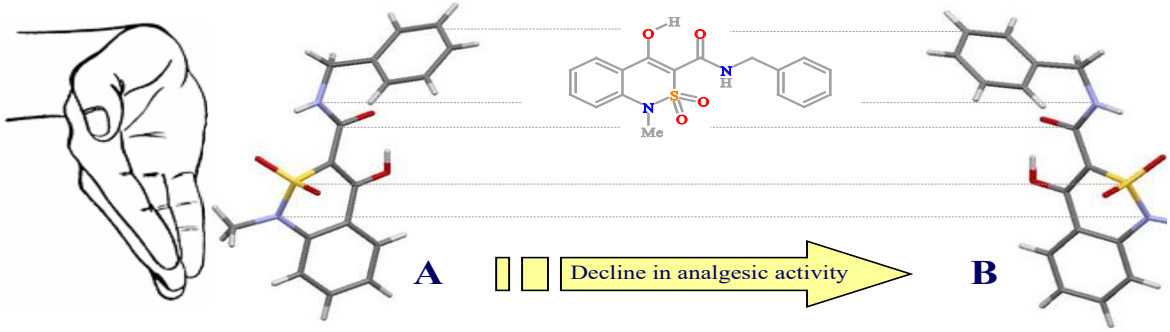
Previously the possibility of drugs to exist as different crystal modifications (their polymorphs) has been considered by scientists as a fun fact of nature. Later this phenomenon has begun to attract the attention more often due to development of the pharmaceutic industry. Significant differences in the properties of drug substances from different manufacturers, a sharp decline in biological activity, rapid loss of storage stability, increased water absorption, the sudden appearance of the chemical incompatibility of the ingredients in the multicomponent dosage forms, the deterioration of solubility and changes of flow ability are just some of considerable pharmaceutical, pharmacological and technological problems caused namely by polymorphism that producers have to face. As a result studying the drug polymorphic modifications has acquired special importance for pharmaceutical industry. It should be noted that in accordance with ICH guidance for industry practice of active pharmaceutical substances new drugs can obtain a state regulatory registration only for defined crystal form of the active compound in many countries. Therefore the activity of the pharmaceutical companies in detecting and describing as many polymorphs as possible increases sharply in addition to purely scientific interest and such researches are patented for their intellectual property protection.

Taking into account this trend we have performed the present study with the aim to obtain different polymorphic forms of *N*-benzyl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzo-thiazine-3-carboxamide (**I**), and to study peculiar properties of their crystal structures as well as to compare their pharmacological behavior.



Benzylamide (**I**) molecule does not contain a stereogenic atom, but intramolecular hydrogen-bonding interactions engender enantiomeric chiral conformations as a labile racemic mixture. It crystallized in a solvent dependent single chiral conformation within one of two conformationally polymorphic $P2_12_12_1$ orthorhombic chiral crystals: Form **A** and Form **B** (see Fig.). Each of these pseudo-enantiomorphic crystals contains one of two pseudo-enantiomeric diastereomers. Form **A** is obtained from methylene chloride and form **B** can be crystallized from *N,N*-dimethyl formamide, ethanol, ethyl acetate or xylene. Pharmacological studies with solid-particulate suspensions have shown that crystalline Form **A** exhibits almost four-fold higher antinociceptive activity compared to one for Form **B**.

Catalytic Friedel-Crafts alkylation in HFIP

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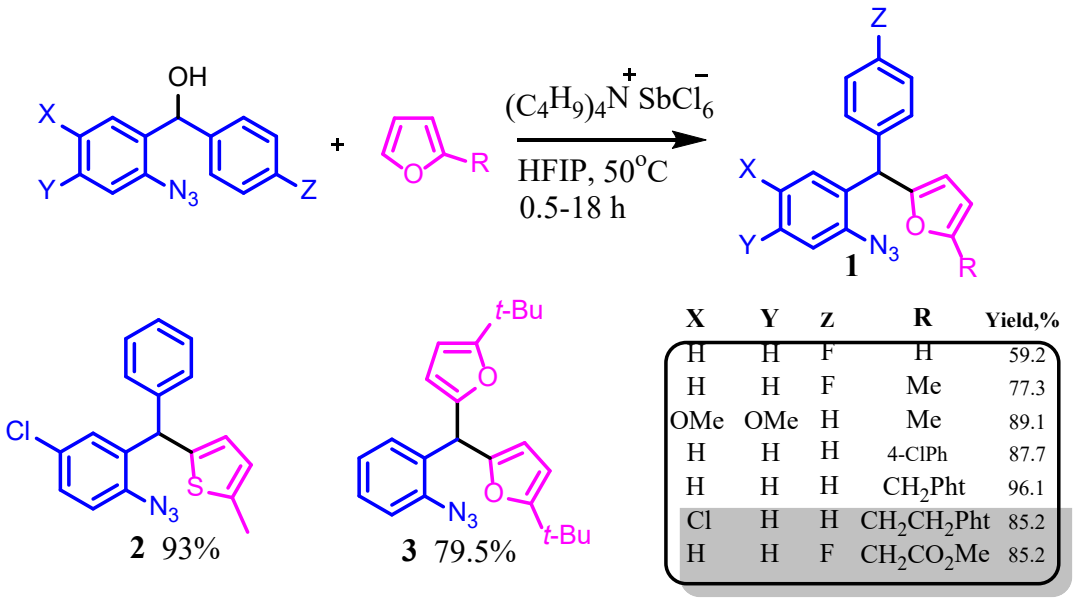
Dehydrative alkylation with activated alkohols is a current topic of high priority in synthetic organic chemistry [1]. Such straightforward C-C bond forming reaction is attractive due to atom economy, availability of alkohols and minimal impact on the environment as water is the only byproduct. The main problem in such Friedel-Crafts alkylations is activation of hydroxy group otherwise posessing poor leaving group ability. Common option in this case is a proper choice of the acid catalyst or alternatively the reaction solvent. An impressive achievments were made in the field under the auspices of perfluoroalcohols that lended themself as perfect medium for alkylation reaction. Due to multiple hydrogen bond formation, low acidity and high ionising power, perfluoroalcohols can activate alcohols without extra added catalyst [2].

Expanding the scope of our new indole synthesis [3] we attempted the synthesis of 2-azidobenzylfurans **1** in pure trifluoroethanol. We found that the reaction proceeded very slowly thus adversely affecting the yields of thermaly sensitive azides. However, employment of hexafluoroisopropanol (HFIP) in the presence of only 1% of tetrabutylammonium hexachloroantimonate dramatically reduced the reaction time and allowed for the preparation of a number 2-azidobenzylfurans in exellent yields. 2-Methylthiophene and 2-azidobenzaldehyde also entered the reaction, funishing the corresponding methanes **2** and **3**.



X	Y	Z	R	Yield,%
H	H	F	H	59.2
H	H	F	Me	77.3
OMe	OMe	H	Me	89.1
H	H	H	4-ClPh	87.7
H	H	H	CH_2Pht	96.1
Cl	H	H	CH_2CH_2Pht	85.2
H	H	F	CH_2CO_2Me	85.2

Scheme 1. Alkylation of furan derivatives in hexafluoroisopropanol

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This work was supported by Russian Foundation for Basic Research (grant № 13-03-01048 A, 16-03-00807 A)

Peculiarity of the Interaction of 2-Furylpyrrolidine with Maleic Anhydride

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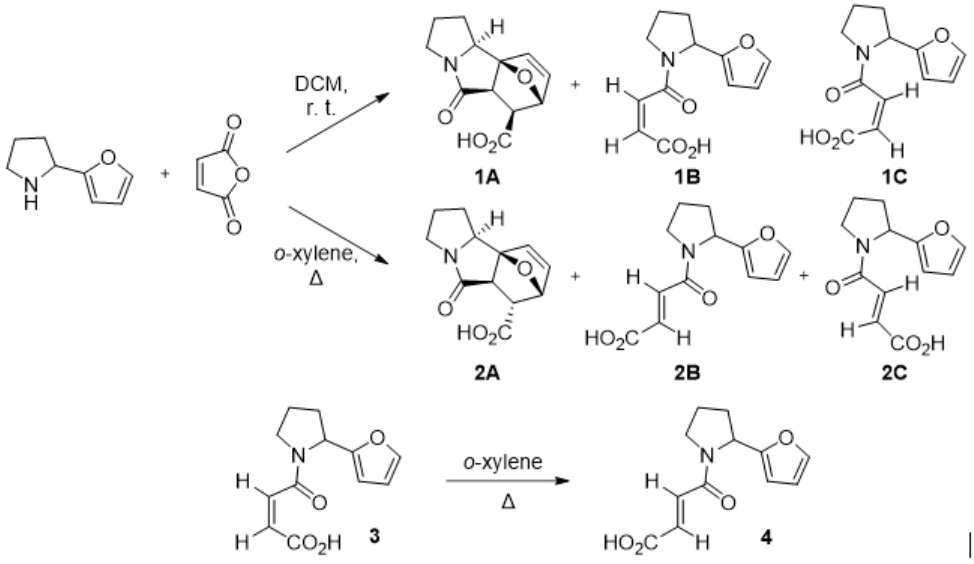
During the last decade our group is carrying out a systematic study of the reaction between anhydrides of α,β-unsaturated acids and α-furyl substituted azaheterocycles, to develop new approaches to isoindoles fused with other heterocycles [1-3]. A wide range of 6- and 7-membered α-furylazaheterocycles can be involved in this reaction [3], but our prelaminar attempts to apply this reaction to the condensed α-furyl pyrrolidines invariably ended in failure.

This study describes in detail the interaction of 2-furyl pyrrolidine with maleic anhydride.



	A	B	C	Total yield (%)
Ratio of products **1** (%)	68	12	20	85
Ratio of products **2** (%)	76	12	12	82

At room temperature, the reaction leads to the tautomeric mixture of the expected cyclic adduct **1A** and rotamers **1B**, **1C** (this mixture is in equilibrium in DMSO-d_6 solution, but in solid state only compound **1A** exists). In boiling *o*-xylene, the same reaction leads to a formation of the tautomeric mixture of isomer **2A** and rotamers **2B**, **2C**. Apparently, at high temperature the intermediate, N-maleinamide **3**, undergoes a *cis-trans* isomerization to give another intermediate **4**.

This work was supported by the Russian Science Foundation (project № 16-43-02009), and by the Indian DST Foundation project № DST/RSF/15/P-61.

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Mono- and Bisorganophosphorus Proline Derivatives with P-C-N Moieties

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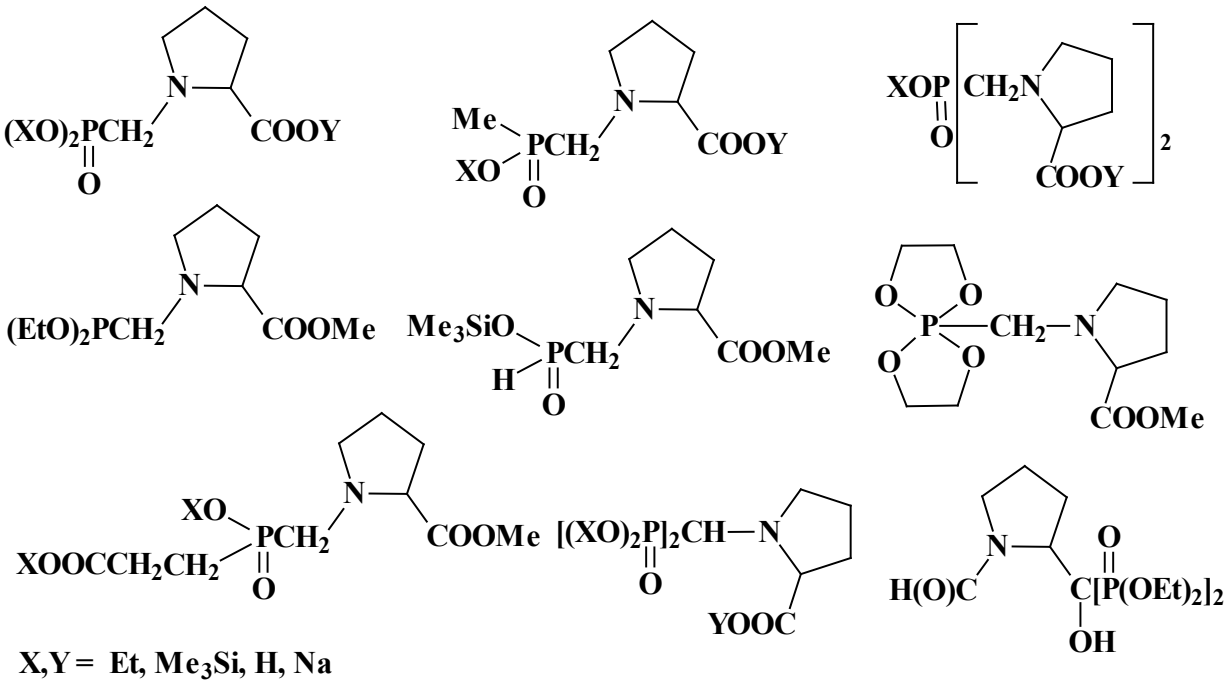
The functionalized organophosphorus derivatives of aminocarboxylic acids and their corresponding peptides are the perspective organophosphorus biomimetics of natural phosphates and hydroxy or amino acids. These compounds with nonhydrolysable P-C bonds interfere with various enzymatic processes and possess the antibacterial, antiviral, antibiotic, pesticidal, antitumor and enzyme inhibitory properties. Several organophosphorus containing peptides with proline moieties have attached attention in the capacity of the competitive inhibitors of human immunodeficiency virus protease [1]. Recently the organophosphorus derivatives of glycine, β-alanine and γ-aminobutyric acid with PCH_2N moieties have been synthesized by us [2]. We have developed a convenient two- or three-component aminomethylation of various PH-acids as the perspective method for synthesis of mono- and bisorganophosphorus proline derivatives with P-C-N moieties using proline or its highly reactive functionalized precursors. Trimethylsilyl-containing organophosphorus compounds easily react with methanol excess or with sodium methylate in methanol giving water soluble acids or their sodium salts in high yields.



Scheme 1. New Mono- and Bisorganophosphorus Proline Derivatives

So the unique synthesis of proline-containing organophosphorus acids and their derivatives with 3-,4- и 5-coordinated phosphorus starting from available reagents were developed by us. The resulting compounds are the promising synthons for preparation of various organophosphorus peptides with different arrangement of proline moieties as well as the perspective polydentate ligands and biologically active substances with versatile properties.

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Five-Membered Nitrogen-Containing Heterocycle Derivatives of Mono- and Diphosphonic Acids

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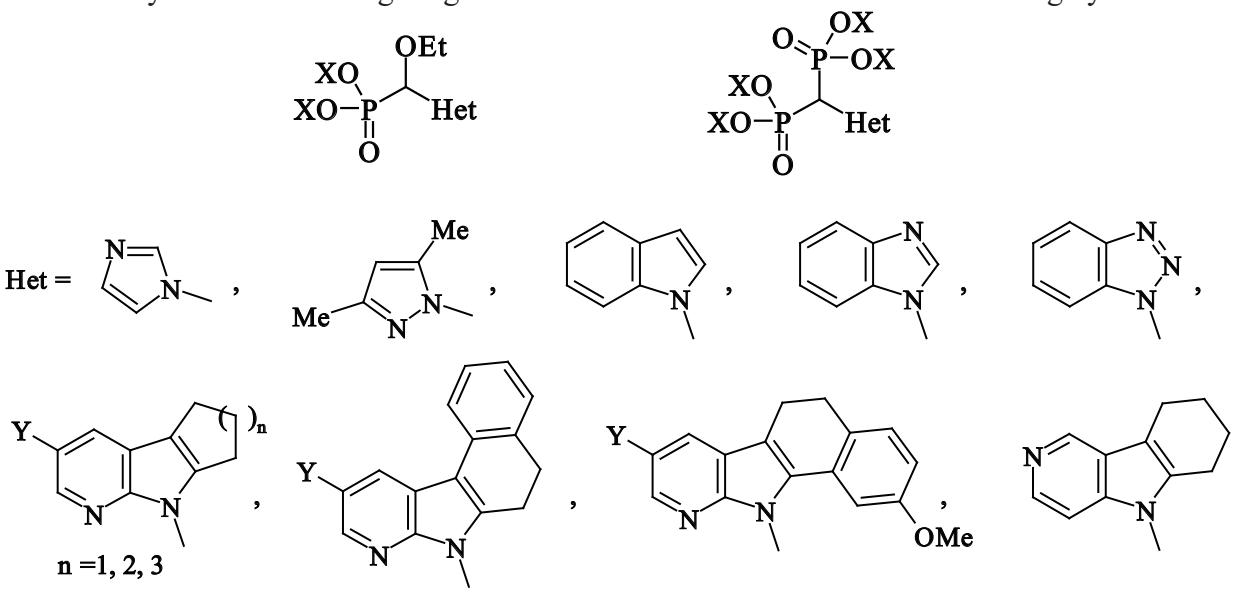
Functionalized organophosphorus acids and their derivatives with heterocyclic moieties are of great interest as effective chelating ligands and perspective bioactive substances with various properties. These acids are well-known biomimetics of hydroxyl (amino)carbonic acids and natural pyrophosphates, and some of them such as zoledronic, risedronic, and minodronic acids are widely used in medicine. We have synthesized the new functionalized mono- and diphosphonic acids and their derivatives including five-membered nitrogen heterocycles via two- or three-component aminomethylation of several trimethylsilyl esters of phosphorous acid [1] using as starting compounds recently available NH-heterocycles [2] and triethyl orthoformate.

Trimethylsilyl-containing organophosphorus compounds easily react with methanol excess or with sodium methylate in methanol giving water soluble acids or their sodium salts in high yields.



Scheme 1. New Organophosphorus Derivatives of Five-Membered Nitrogen Heterocycles

The resulting compounds are the perspective polydentate ligands and biologically active substances with versatile properties as well as the promising precursors for multitarget drug discovery.

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Synthesis of biologically active heterocyclic derivatives based on 4-(het)aryl-2,4-dioxobutanoic acids

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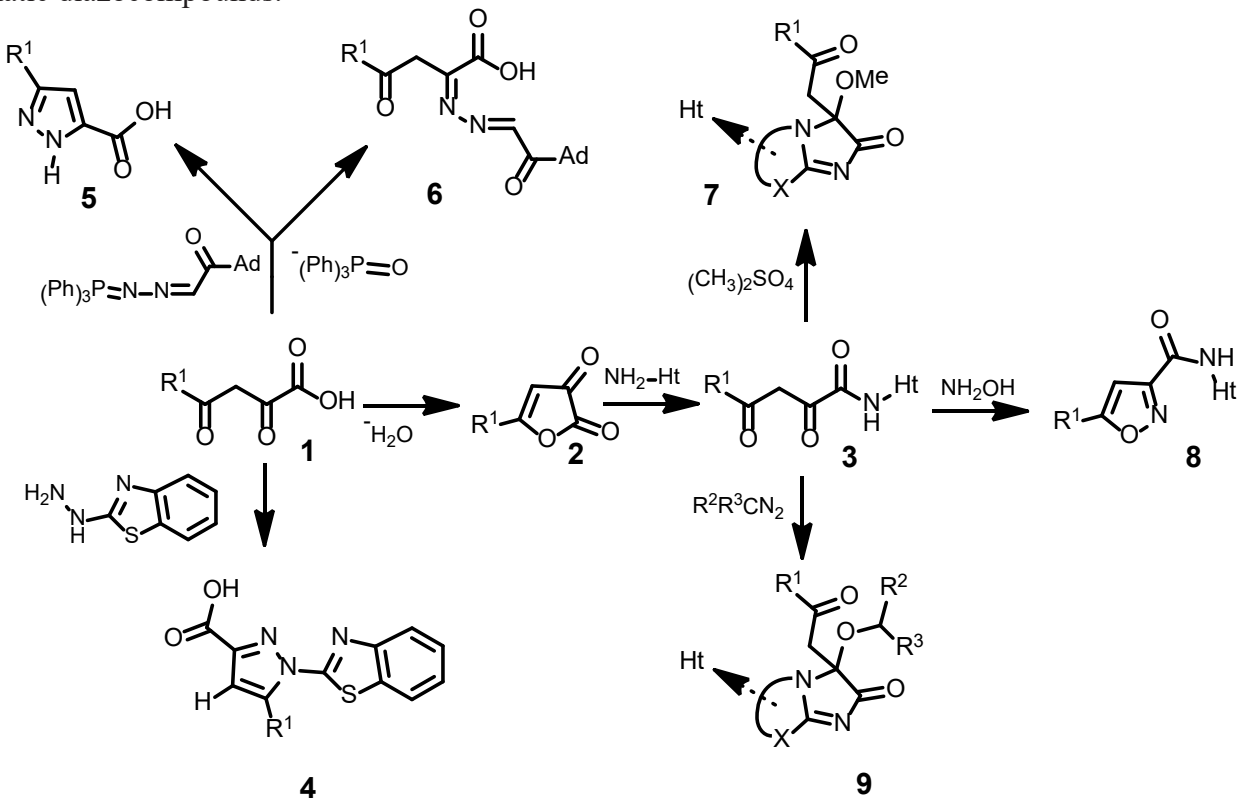
4-(Het)aryl-2,4-dioxobutanoic acids (**1**) and 5-(het)arylfuran-2,3-diones (**2**) are convenient synthetic objects for creating biologically active compounds possessing various types of pharmacological activities with low toxicity. It was of interest to modify the (het)arylpyruvate's original matrix by the introduction of new pharmacophore fragments, as well as initiate heterocyclization in molecular structure for creating original potential pharmaceutical substances. Corresponding pyrazoles **4** have been obtained by the action of 2-hydrazinobenzo[d]thiazole on initial acids. The known derivatives **5** can be formed by adding 1-adamantanoyl-2-(triphenylphosphoranylidenhydrazono)ethanone, thus decreasing the yield of the target acids **6**. Under the action of dimethyl sulfate hetarylamides of 4-(het)aryl-2,4-dioxobutanoic acid (**3**) form imidazole derivatives **7** having conjugate with the corresponding heterocyclic moieties. The reaction of amides **3** with hydroxylamine produced hetarylamides of 5-arylisoxazol-3-carboxylic acids (**8**). The products of intramolecular cyclisation **9** are formed from amides **3** due to interaction with aliphatic diazocompounds.



Scheme 1.

Structure of compounds **3-9** is confirmed by IR-, ^{1}HNMR-spectroscopy, as well as mass spectrometry. Acute toxicity, anti-inflammatory, analgesic, hypoglycemic, antimicrobial and anthelmintic activity of obtained compounds have been studied. The substances comparable and exceeding the potency of reference drugs have been discovered. The possible dependence of the biological action of the compounds on their chemical structure is discussed.

Search and structure elucidation of major metabolites of camphor-based antiviral drug

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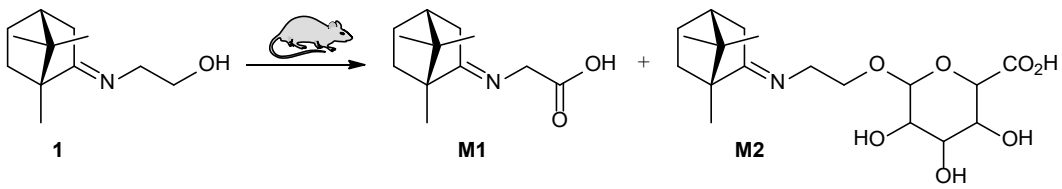
Recently we have developed a new class of camphor-based antiviral drugs. Leading compound, camphecin **1**, showed a wide spectrum of antiviral activity [1]. In this study, we investigated metabolism of **1** in rats by the analysis of their whole blood in comparison with control group of animals. Samples were prepared by the extraction of dried blood spots collected on Protein Saver Card (Whatman), and the analyses were carried out by HPLC-MS/MS (6500 QTRAP, Sciex) in Q1 and EPI modes scanning both positive and negative ions.

Analysis of chromatograms obtained in Q1 mode showed that blood samples taken from animals received agent **1** contained two major compounds forming molecular ions of masses 210.4 and 372.6 $[M+H]^+$. These compounds were absent in the blood of control group of animals and thus supposed to be camphecin metabolites (**M1** and **M2** correspondingly).

The molecular mass of **M1** (209.4) is 14 Da more than that of camphecin **1** (195.4), that may correspond to often met oxidation of primary alcohol group to the carboxylic acid [2]. Collision-activated dissociation of compound **M1** led to the formation of several groups of ions characteristic for fragmentation pattern of camphor. At the same time, the mass-spectrum of fragmentation of compound **M1** showed intensive ion with m/z = 164.3 Da, which corresponded to the loss of 46 Da and was not formed during fragmentation of camphecin **1**. This loss is often observed during ESI-MS/MS analysis of protonated aminoacids and corresponds to the elimination of molecules CO and H_2O [3]. In addition, many aminoacids do not form negative ions of $[M-H]^-$ kind, which also were not found in our experiments with compound **M1**.

Upon collision-activated dissociation of compound **M2** ($[M+H]^+$ = 372.6), fragment with m/z = 196.4 is formed, corresponding to the formation of protonated camphecin. The observed loss of mass of 176 Da is characteristic for glucuronides, which are often formed as metabolites *in vivo* [2]. Negative electrospray ionization of compound **M2** led to the formation of molecular ion $[M-H]^-$ with m/z = 369.6 showing the presence of carboxylic group in the structure.

Based on the literature and experimental data, we have concluded that the main metabolites of camphecin are carboxylic acid **M1** and glucuronide **M2**.



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Synthesis of HIV-1 capsid protein assebly inhibitor (CAP-1) and its analogues from biomass as starting material

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One of the most important unsolved problems of modern science and medicine is a search of effective anti-HIV drugs. In this area rapid synthesis of compounds-candidates and their structural analogues is of crucial importance. Recently, a compound with novel type of antiviral activity CAP-1 has been discovered [1].

The structure of CAP-1 was retrosynthetically subdivided into 5 sites, each of which can be variated independently in order to understand structure-property relationship (Fig. 1). We suggested effective synthesis of CAP-1 which allows flexible structural variation using cellulose as cheap and renewable starting material [2].

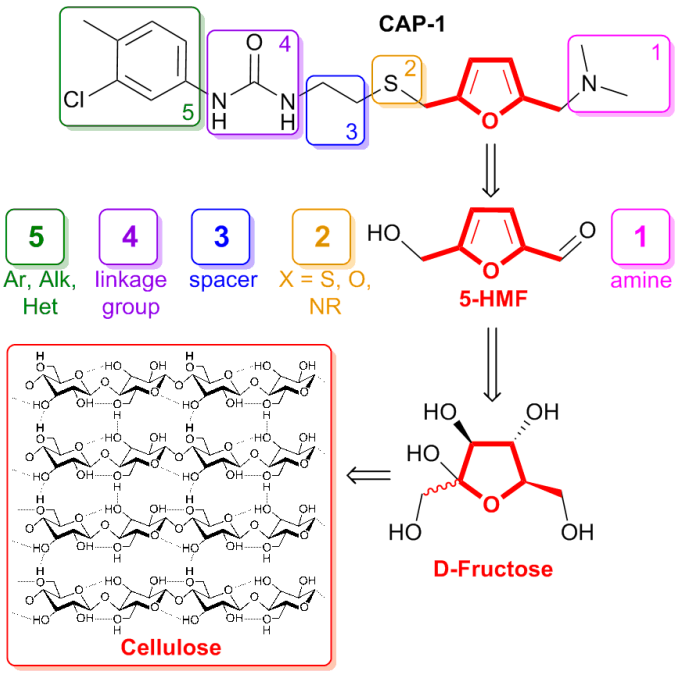

Fig. 1. Retrosynthetic analysis of CAP-1

In this work CAP-1 and its structural analogues were synthesized in good yields according to suggested synthetic scheme.

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This work was supported by Russian Science Foundation (RSF Grant 14-13-01030)

Synthesis and chemical transformations of 2-amino-1-(het) aryl-4-oxo-5-(2-aryl-2-oxoethylidene)-1*h*-4,5-dihydropyrrole-3-carboxamides

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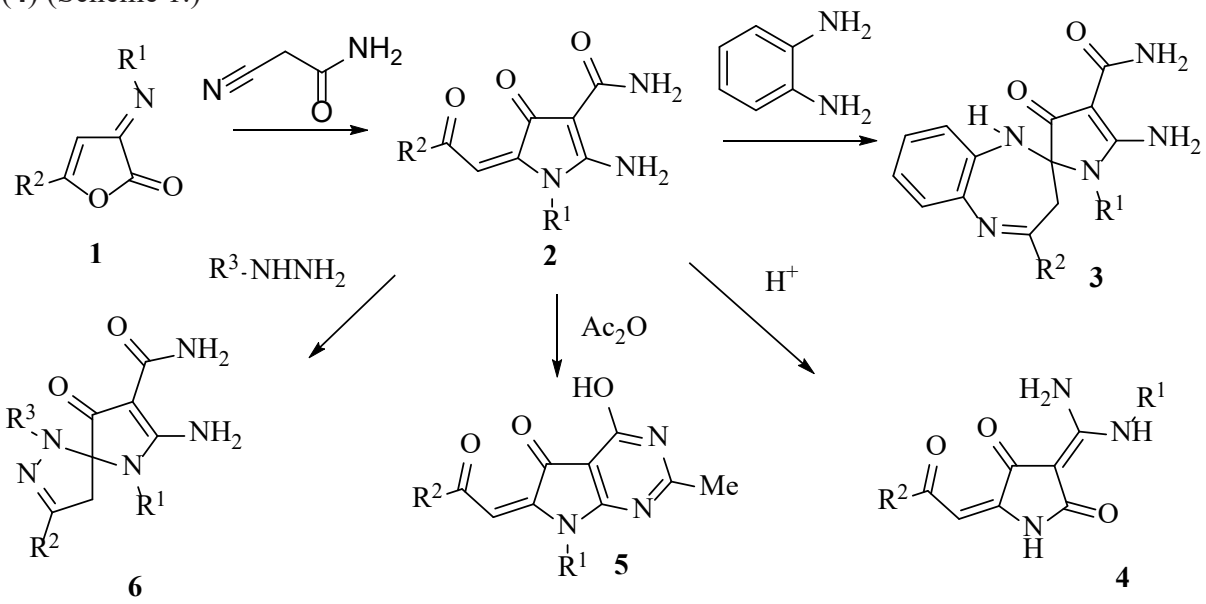
We formerly demonstrated the synthetic opportunities of 3-imino-3H furan-2-one(**1**) in the reactions with derivatives cyanoacetamide resulting in the derivatives of 2-amino-1-(aryl)-4-oxo-5-(2-oxo-2-arylethylidene)-1H-4,5-dihydropyrrole-3-carboxamide (**2**) [1]. The structure of compounds (**2**) underlies their rich synthetic opportunities. The presence of several electron-deficient and donor sites in the molecule of pyrroles (**2**) makes it possible to us to expect the formation of a variety of fused and *spiro* heterocyclic system under of nucleophile's and electrophiles attack. The reaction of 2-amino-1-(het)aryl-4-oxo-5-(2-oxo-2-arylethylidene)-1H-4,5-dihydropyrrole-3-carboxamide (**2**) with substituted hydrazine and o-PDA led to the corresponding spiropyrroles (**3,6**), with acetic anhydride led to the corresponding 4-hydroxy-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-ones (**5**). The intramolecular recyclization under the action Bronsted aicids of 2-aminopyrrole-3-carboxamide led to the corresponding pyrrolidine-2,4-dione (**4**) (Scheme 1.)



Scheme 1.

The structure of synthesized compounds has been proved by IR, ^{1}H, ^{13}C NMR, mass-spectroscopy and X-Ray analysis. The mechanism of reactions and biological activity of compounds **3-6** will be discussed.

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This work was supported by Foundation Russian Foundation for Basic Research (Grant No. 14-03-96016) and Grant from the President of the Russian Federation for Young Candidates of Sciences (No. MK-7061.2015.3)

Chemical composition of essential oils of herbs which were introduced in the Stavropol region.

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Essential oils were obtained by the exhaustive distillation method from several plants: *Melissa officinalis, Hyssopus officinflis, Monarda didyma, Lavandula angustifolia*. All of them were introduced in Stavropol region. Pharmacological and technological value of these oils stimulates research of dependence of chemical composition of the oil from habitat of the herb. Dry stock of medical plants containing essential oils from the collection of Stavropol Botanical Garden was used for the study.

Chemical composition of essential oils was obtained with gas chromatograph Shimadzu GCMS-QP2010 Ultra (The Program Built MS ROM Version: 1.06; GC ROM Version: 2.1030) using silica capillary column ($l - 35\ m, d - 0{,}25\ m$). Helium was the carrier gas. Chloroform was used as a solvent. Linear retention indices and mass spectrums were established for each component and compared with bibliography sources for identification. 37 components from 41 were identified for *Melissa officinalis* using this technique; *Hyssopus officinflis* - 27 from 37; *Monarda didyma* - 27 from 30; *Lavandula angustifolia* Miller - 42 from 48. The main components in the oils are:

Melissa officinalis L.	citronellol (35,5%) and geraniol (17%), citronellal (4%), benzyl alcohol, linalool >1%.
Hyssopus officinflis L.	pinokamfon (59%) and pinanediol (10,23%); β- pinene ~2%;
Monarda didyma	thymol (61%) and its methylester (9%), cymene (7,6%), γ-terpinene (3,4%), carvacrol (5,4%).
Lavandula angustifolia	linalool (31%), linalyl acetate (36%), α — pinene, borneol

2-Halogeno-2-CF_3-Styrenes in Friedel-Crafts Reaction with Arenes in the Superacid CF_3SO_3H

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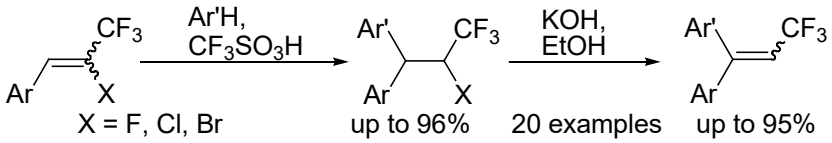
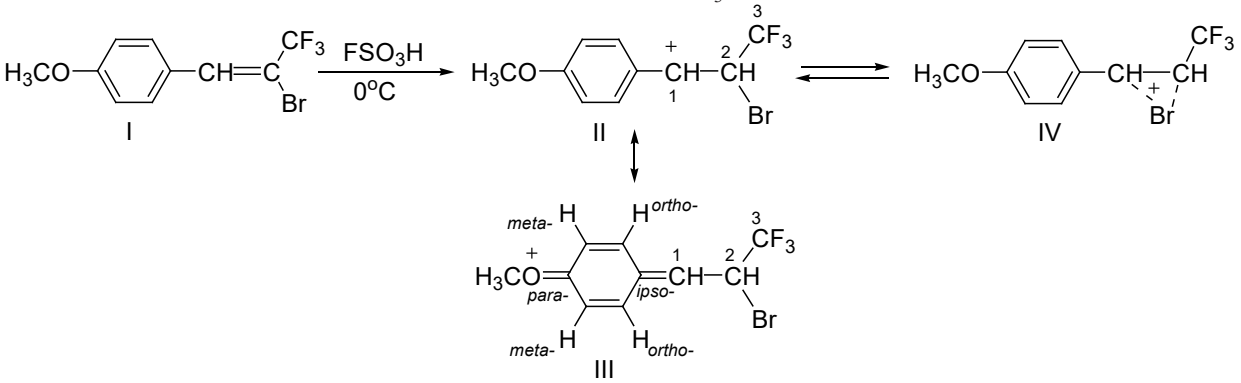
The reaction of 2-halogeno-2-CF_3 styrenes [ArCH=C(X)CF_3, X = F, Cl, Br] with superacid CF_3SO_3H resulted in the formation of the corresponding benzyl cations [$ArHC^+$–CH(X)CF_3]. These species were studied by NMR method. Subsequent Friedel-Crafts reaction of such benzyl cations with arenes Ar'H afforded diastereomeric 1,1-diaryl-2-halogeno-3,3,3-trifluoropropanes [Ar(Ar')CH–CH(X)CF_3] in high yields (up to 96%). The obtained halogenopropanes were easily transformed to the corresponding *Z-/E*-isomeric trifluoromethylated diarylethenes [Ar(Ar')C=CCF_3] (in yields up to 96 %) by dehydrohalogenation with base (KOH or *t*-BuOK).



Scheme 1. Hydroarylation of 2-halogeno-2-CF_3 styrenes in CF_3SO_3H.

NMR study of protonation of styrenes in superacids such as CF_3SO_3H and FSO_3H showed no protonation at temperature below -20°C we could see protonation of the double bond of alkenes, but oligomerization process takes place vigorously. We succeeded to record spectra only in the case of methoxyphenyl bromo-substituted alkene, which gave protonated species in FSO_3H at 0 °C.



Scheme 2. Protonation of *para*-methoxyphenyl bromo-substituted alkene.

This work was supported by Saint Petersburg State University, Saint Petersburg, Russia (grant № 12.38.195.2014), and Russian Science Foundation (grant № 15-33-50678).

Potential synthetic approaches for azolo[5,1-b]purines

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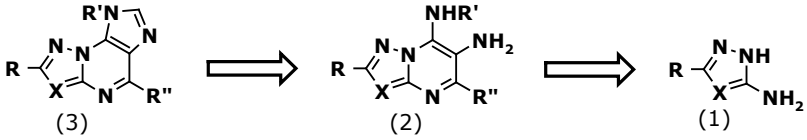
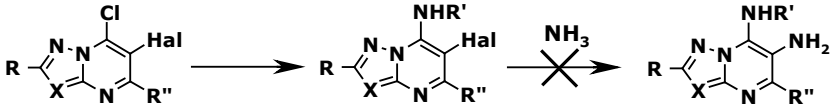
Triazolo[5,1-b]purines are least widespread structural analogues of natural nucleosides and nucleic bases of purine series. At the same time, known representatives of azolopurines exhibit a wide spectrum of antiviral activity, potency against rheumatoid arthritis, psoriasis, Alzheimer's and Parkinson's diseases, etc [1]. Despite the practical value, azolo[b]purines are very stingily represented in the chemical references due to their synthesis complexity.

We have proposed a synthesis strategy of purine precursors (2) based on the simple reagents such as amino-azoles (1) according to the following retroscheme.



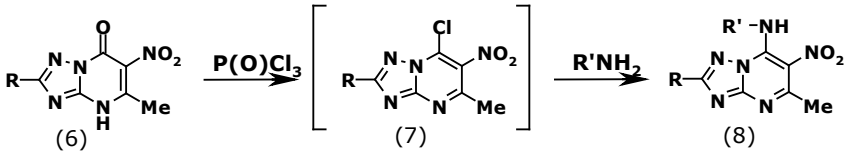
(3) (2) (1)

Firstly, we tried to synthesise diaminoderivatives throught 5,6-dihalogenheterocycles. Synthesis of aminohaloazolopyrimidines (5) was carried out with good yields, but further halogen substitution could not be realized even in rigorous conditions.



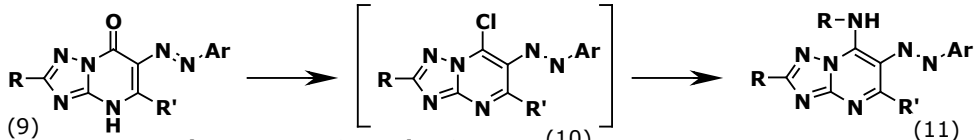
(4) (5) (2)

Reduction of arylazo-, nitro- or nitrozo-group is also used to produce amino fragment in 1,2,4-triazolo[1,5-a]pyrimidines. Chlorodeoxygenation of triazolopyrimidines (6) was used to obtain chloroderivatives (7) which were highly unstable and were converted into nitroaminotriazolopyrimidines (8) without isolation with poor yields.



(6) (7) (8)

Reaction of 6-arylazotriazolopyrimidines (9) with phosphoryl chloride in acetonitrile and subsequent treatment of intermediates (10) with primary amines gave desired products (11) in satisfactory yields.



(9) (10) (11)

R: a = H, b = Me, c = SMe, d = 3-Py

Our first attempts of azo-group reduction into amino-group in substrate (11b) were unsuccessful. However, we anticipate that the strategies described herein will pave the way for the diaminotriazolo[1,5-a] pyrimidines as intermediates in the synthesis of biologically active triazolo[5,1-b]purines.

References:

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We thank the Russian Federation Ministry of Education (project 2458) and Russian Scientific Foundation grant № 14-13-01301.

Synthesis of new 10*H*-indole[1,2-a]indolines and indole[1,2-a] quinolines based on sterically hindered 1,2-benzoquinones

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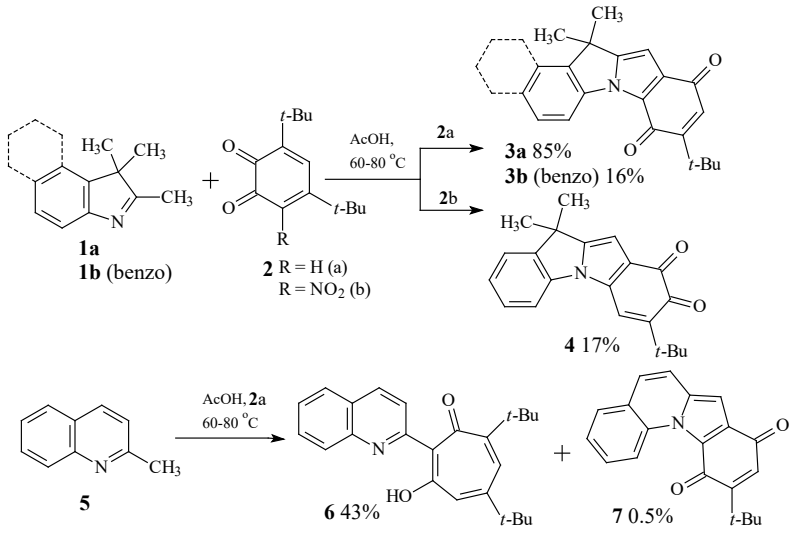
Reaction products of 2-methyl nitrogenous heterocyclic compounds with 1,2-benzoquinones depend on the nature of the heterocycle, its substituents, as well as on the nature of the 1,2-benzoquinone, and reaction conditions. We find that acid-catalyzed interaction of the 2,3,3-trimethylindoline **1** derivatives with 3,5-di(*tert*-butyl)-1,2-benzoquinone **2a** results in formation of 10*H*-indole[1,2-a]indoline-1,4-dione **3**. At the same time interaction of **1** with nitroquinone **2b** results in 10*H*-indole[1,2-a]indoline-1,2-dione **4**.



Reactions of 2-methylqiunolines with 1,2-benzoquinones **2** usually proceed with expansion of the *o*-quinone cycle and lead to 2-quinolin-2-yl-1,3-tropolones. In the case of absence of a substituent at the 8th position of 2-methylquinoline, the reaction of **5** with 1,2-benzoquinone **2a** results in formation of 1,3-tropolone **6**, as well as in moderate yield of 10-*tert*-butyl-indole[1,2-a]quinoline-8,11-dione **7**. The structures of the obtained compounds are confirmed by NMR ^{1}H, IR-spectroscopy, and mass-spectrometry. The structure of the compounds **3a** is determined by the x-ray analysis. In order to determine the structures of compounds **3,4,6,7** complete assignment of signals of the NMR ^{1}H and ^{13}C spectra was performed on the basis of characteristic values of chemical shifts and cross-peak analysis in the two-dimensional spectra of ^{1}H-^{1}H COSY and NOESY correlations, as well as ^{1}H-^{13}C HSQC and HMBC and ^{1}H-^{15}N HMBC correlations.

The work was supported by the program number 8 of the Presidium of RAS “Development of methods of synthesis of chemicals and creation of new materials”, RFBR (project № 14-03-00672), and the grant for support of leading scientific schools SS – 274.2014.3.

Convenient synthesis of 3-furylphthalides

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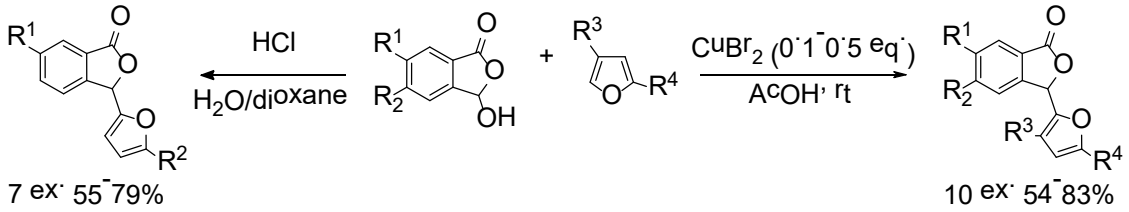
The phthalide moiety is the structural subunit of a variety of natural compounds [1] and a building block for the synthesis of various carbo- and heterocyclic compounds. Our research group has previously developed a synthetic procedure towards furylphthalides *via* an acid catalyzed condensation of phthalaldehydic acid with a set of furans. However, this method suffered from poor yields of the target phthalides as bis(2-furyl)(2-carboxyphenyl)methanes, the bis-addition side products, were also formed in these conditions. Hence, we carried out optimization of the previously employed reaction conditions which allowed to improve the furylphthalides yields up to 55-79% [2] (Scheme 1).



Scheme 1. Synthesis of 3-(fur-2-yl)-*3H*-isobenzo-1-ones

Nevertheless, this method appeared to be effective only with water-soluble substrates. We managed to solve this problem by developing an alternative approach for water-insoluble substrates based on the dehydrative coupling reaction in an organic solvent employing $CuBr_2$ as catalyst [3]. The dehydrative coupling strategy has recently found wide application and has been employed on a variety of alcohols that easily form stable carbocations [4], which react with various nucleophiles. The cost-effectiveness, mild reaction conditions, simple isolation procedures and high product yields make it a method of choice for the preparation of the title 3-(fur-2-yl)phthalides.

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This work was supported by Ministry of Science and Education of the Russian Federation within the Targeted Federal Program “Research and development on priority directions of development of scientific and technological complex of Russia for 2014-2020” (contract № 14.577.21.0046) and RFBR (16-33-00229).

$Bi(OTf)_3$ catalyzed synthesis of 3-(fur-2-yl)isoindolin-1-ones

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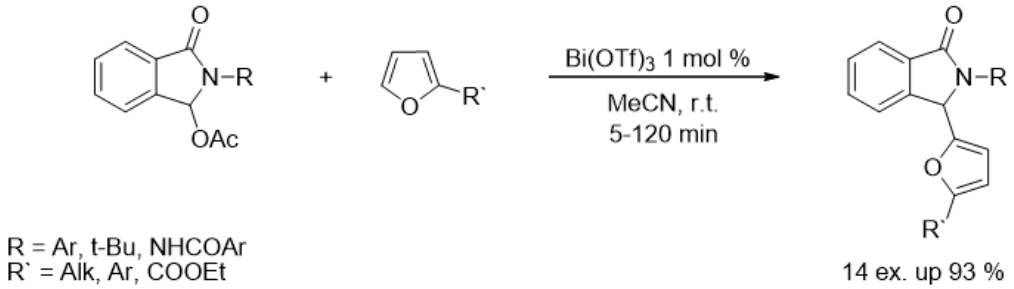
Isoindolinone subunits are found in many natural and bioactive synthetic compounds (nuevamine, pazinaclone, pagoclone, lennoxamine). Acetoxylactams are available building-blocks for organic synthesis, of which N-acyliminium cations are easily generated in the catalysis of Bronsted or Lewis acids. Reaction acetoxylactams with various nucleophiles - allyltrimethylsilan, siloxyalkenes, 1-alkynes, 1,3-dicarbonyls, aromatic and heteroaromatic rings - have been studied sufficiently detail [1-3].

In our group α-amidoalkylation reaction was adapted to series furans containing alkyl, aryl and carbethoxy group. Preparative high yields 3-furylisoindolin-1-ones (up 93%) were obtained when bismuth triflate catalysis in acetonitrile at room temperature (Scheme 1). Complete conversion of the reactants is observed for furans with electron-donating substituents in a few minutes. For furans with electron-withdrawing substituents – the reaction mixture must be stirred for 2 hours.



Scheme 1. $Bi(OTf)_3$ catalyzed synthesis of 3-(fur-2-yl)isoindolin-1-ones

The cost-effectiveness, mild reaction conditions, simple isolation procedures and high product yields make it a method of choice for the preparation of the title 3-(fur-2-yl)isoindolin-ones.

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The study was performed using the equipment of the Center for Joint Use "Ecological and Analytical Center". This work was also supported by Russian Foundation for Basic Research (13-33-00229).

Synthesis of enantiomerically enriched metallocenes and their using in the reactions [3+2] cycloaddition

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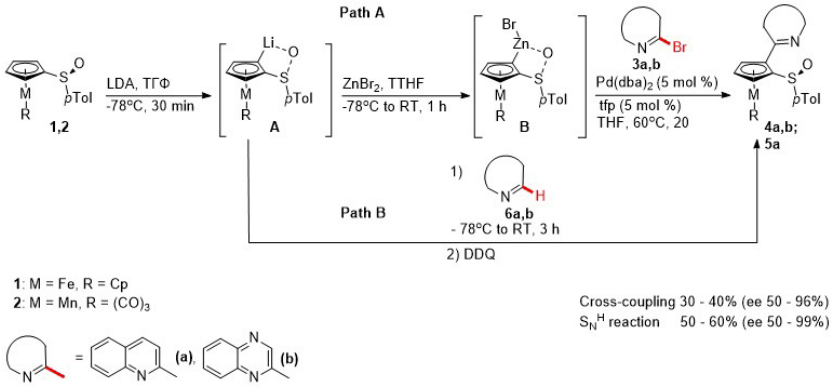
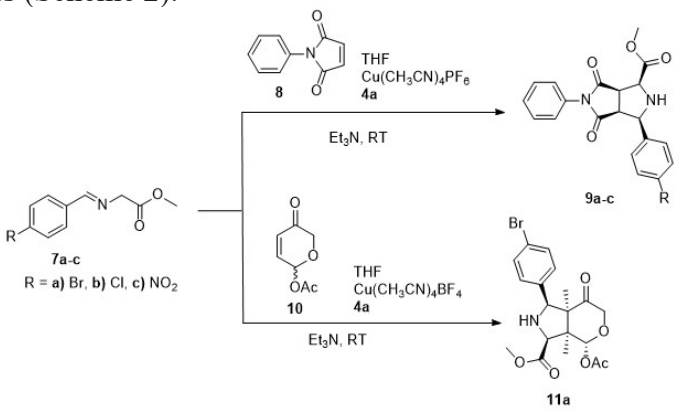
Previously it has been described synthesis of the enantiomerically enriched ferrocenes (**4a,b**) based on the C-C couplings (S_N^H methodology and Negishi cross-coupling) of azines and the derivatives of (*S*)-ferrocenyl-*p*-tolylsulfoxide **1** (Scheme 1) [1],[2]. Further S_N^H methodology (Scheme 1, Path B) and Negishi cross-coupling reaction (Scheme 1, Path A) have been applied to the synthesis of (hetaryl) cymantrene **5a**. All compounds were obtained with good yields and selectivity.



Scheme 1. Synthesis of planar chiral metallocenes

(S_{Fc},*S*)-[2-(Quinolin-2-yl)-ferrocen-1-yl]-*p*-tolylsulfoxide **4a** was applied to Cu-catalyzed cycloaddition reactions in excellent yields (Scheme 2).



Scheme 2. Asymmetric cycloaddition reactions

The optical purity of all chiral compounds was determined by HPLC on an analytical column (Chiralcel OD-H).

References

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This work was supported by the Russian Science Foundation (Project № 14-13-01177), the Russian Foundation for Basic Research (Project No. 16-33-00554 мол_а)

Diastereoselectivity of Phenoxazines Reactions

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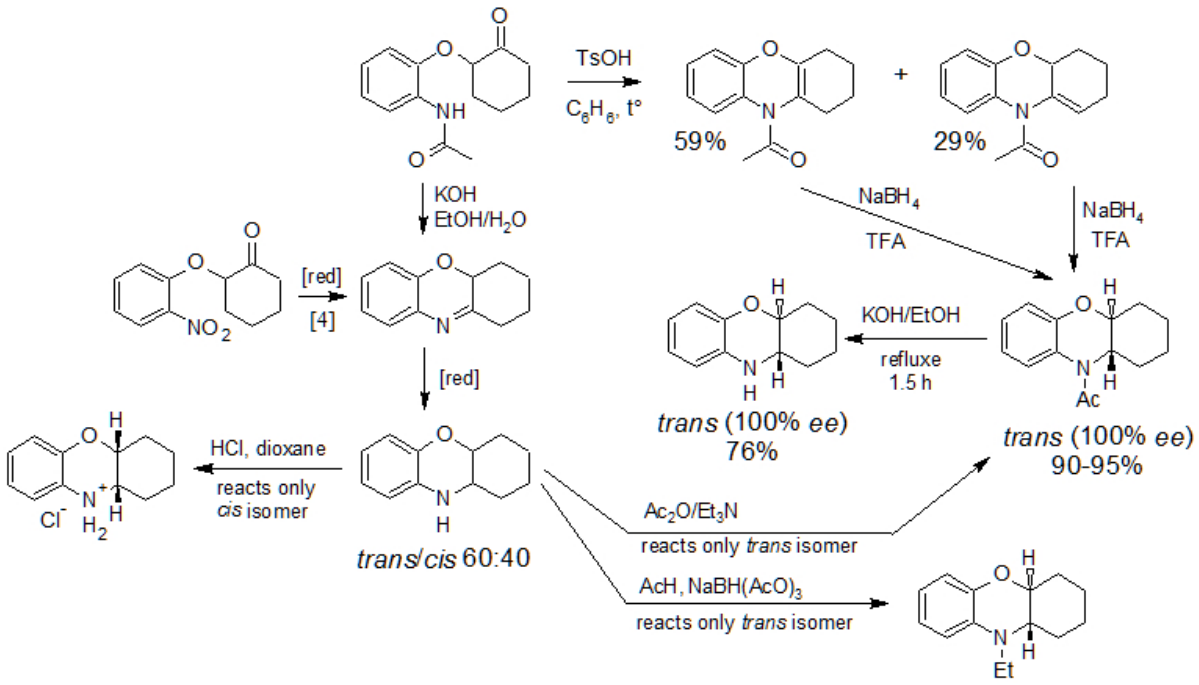
Recently, organic compounds containing phenoxazine moieties have attracted chemists due to their biological activities. For example, N-substituted phenoxazines exhibit antiproliferative activity [1], have been identified as modulators of MDR [2] and as potent specific inhibitors of Akt signaling [3]. Our attention was drawn to the synthesis and stereoselective reactions of tetrahydro- and hexahydrophenoxazines, because there is little information about this subject in the literature. And our results shed light on some aspects of this problem. We carried out the transformations shown in Scheme.



References:
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Development of new semi-synthetic approaches to heterocyclic allocolchicinoids

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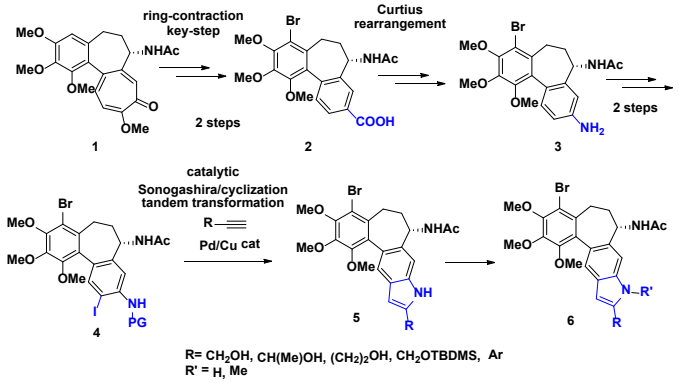
Our research is concentrated on elaboration of synthetic methodologies for asymmetric synthesis of furano- and pyrroloallocolchicinoids – a new generation of colchicine-site tubuling binding antitumor agents.

Recently it has been shown, that heterocycle analogues of combretastatine A-4, 4-heterylcoumarin, and allocolchicinoids, bearing heterocycle moiety, demonstrate high *in vitro* and *in vivo* antitumor activity.

The search for novel colchicinoids remains a highly demanding challenge because besides acting as mitosis inhibitors, recent studies have shown that microtubule-targeting agents may also exhibit effects in the areas of (i) mitosis-independent cell death and metastasis, (ii) tumor angiogenesis, and (iii) vascular-disrupting activity. Moreover, the development of drugs overcoming Pgp/β-III-tubulin-mediated drug resistance is a key task in cancer research.

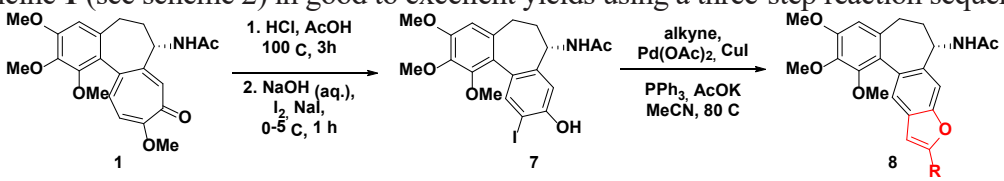
Pyrroloallocolchicinoids type **6** were synthesized starting from commercially available colchicine in 8 steps (see scheme 1).



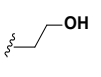
Scheme 1. A semi-synthetic route to pyrolloallocolchicines via Curtius rearrangement.

At the first step the "protecting" halogenation of colchicine into A-cycle was carried out. The ring-contraction reaction with the following Curtius rearrangement lead to colchamine **3**. It's selective ortho-halogenation and protective group or/and leaving group installation (for example Ac or $CF_3C(O)$) to afford intermediate **4**. The last is implied in tandeme Sonogashira/Larock-type cyclization reaction sequence to yield colchicinoid **5**. It undergoes alkylation to afford the target indoloallocolcinoid **6** in ten steps from naturally occurring colchicine with retention of configuration at C-7 center.

A series of conformationally flexible furanoallocolchicinoids **8a-j** were synthesized starting from commercially available colchicine **1** (see scheme 2) in good to excellent yields using a three-step reaction sequence.



Scheme 2. Synthesis of furanoallocolchicinoids

	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j
R										
Yield, %	86	83	84	93	86	74	41	49	72	41

Some of presented molecules (**8c, 8d**) demonstrate significant *in vitro* activity against different tumor cell lines (**AsPC-1**, **HEK293**, **Jurkat**) appearing in nanomolar concentration range (table 1).

Reactivity of 1,4-Dichlorophenazine in Oxidation and Nucleophilic Substitution Reactions

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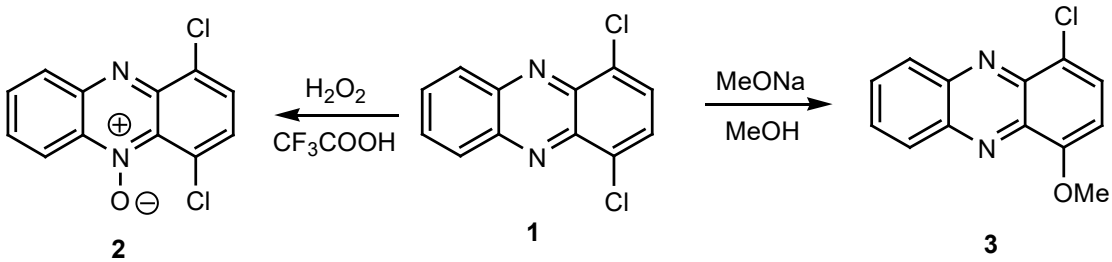
The phenazine system is a pharmacophoric fragment presented in the several antibiotics and signalling metabolites isolated from *Streptomyces* and *Pseudomonads sp.* and marine organisms. Antimicrobial, antitumor, antimalarial and antiparasitic properties of some phenazines are reported in the literature [1-3]. The biological activity of phenazines is based on their ability to intercalate in DNA as well by the inhibition of topoisomerases and electron transfer pathways and methanogenesis, initiation of radical oxidation processes. We have investigated the possibility of an application of 1,4-dichlorophenazine (**1**) as scaffold for preparation of novel bioactive derivatives of phenazine. Synthesis of 1,4-dichlorophenazine (**1**) has been described previously, but it chemical properties still being unknown [4].

An important class of bioactive derivatives of phenazines is their *N*-oxides. So, as the initial step, possibilities of the oxidation of 1,4-dichlorophenazine (1) have been investigated. We have founded that by the treatment with hydrogen peroxide in refluxing trifluoroacetic acid phenazine (**1**) can be efficiently converted into N-monooxide derivative of 1,4-dichlorophenazine (**2**) in 78% yield (Scheme). It should be noted, that all attempts for oxidation of phenazine (**1**) in another reaction conditions or by other oxidizers were failed.



Scheme. Reaction of 1,4-dichlorophenazine (**1**).

Another promising way for transformation of 1,4-dichlorophenazine (**1**) is reactions of nucleophilic substitution of halogen atoms. The study of interaction of phenazine (**1**) with sodium methoxide in boiling methanol showed that reaction leads to the substitution of one halogen atom and 1-methoxy-4-chlorophenazine formed in 72% yield (**3**).

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Investigation of a reaction of 1*H*-pyrimidine with 5-bromopyrimidine in various reaction media

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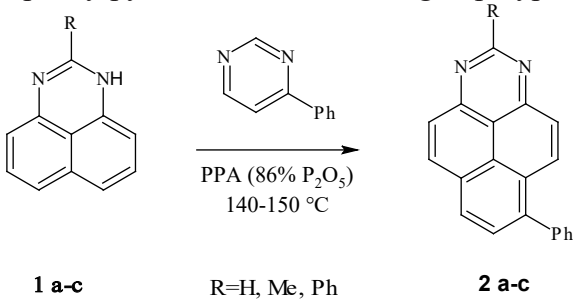
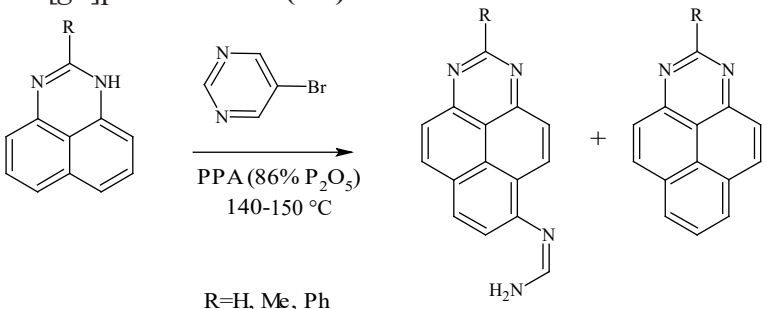
Previously we reported an effective method of 6-phenyl[*gh*]benzoperimidines synthesis based upon the reaction of 1*H*-perimidines with 4-phenylpyrimidine under heating in polyphosphoric acid (PPA):



1 a-c R=H, Me, Ph **2 a-c**

Scheme 1.

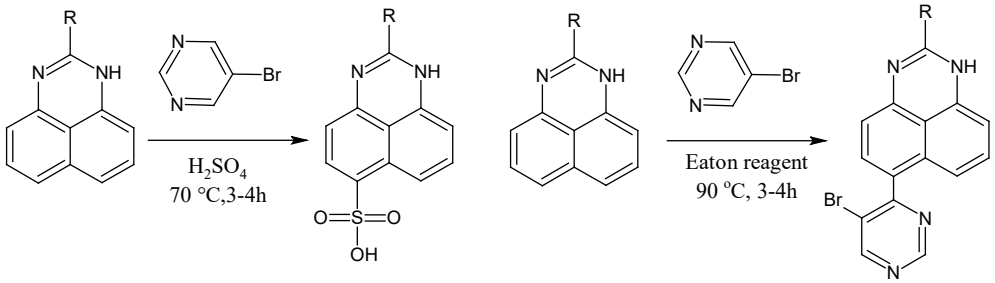
To extend the series of benzo[*gh*]perimidines derivatives we tried to used the reaction of 1*H*-perimidines with 5-bromopyrimidine which contrary to the expected result led to the formation of earlier unknown compounds **3(a-c)** and benzo[*gh*]perimidines **4 (a-c)**:



1 a-c R=H, Me, Ph **3 a-c** **4 a-c**

Scheme 2.

During our attempts to synthesize compounds similar to **2** containing bromine in position 7 this reaction underwent different reaction media:



1 a-c R=H, Me, Ph **5 a-c** **1 a-c** R=H, Me, Ph **6 a-c**

Scheme 3.

The results of the reaction fulfilled in sulfuric acid were products of 1*H*-perimidines **5 (a-c)** sulfonation with yields 60-70%. Conducting of a reaction in Eaton's reagent resulted in the alkylated derivative of substrate **1** with a quantitative yield (Scheme 3).

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Catalytic system «O_2 – $Cu(OAc)_2$» in the synthesis of substituted 5-aminotetrazoles

[1]Shchipalkin A. , [1]Chelusnova J. , and [1]Kuznetsov V.

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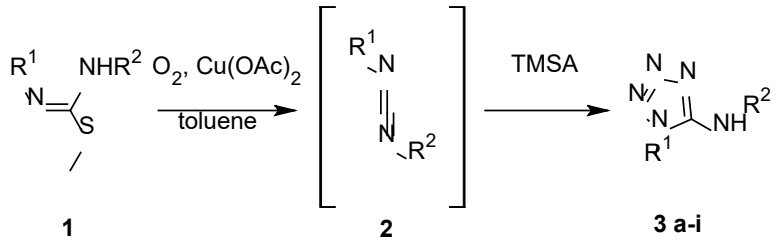
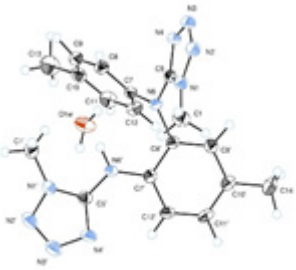
Nowadays, tetrazole derivatives are intensively-studied heterocycle compounds in medical chemistry. These compounds have been developed, certified, and successfully used in medicine and agriculture. Importance of this research is highlighted by a growing number of publications in this field of study. One of the methods for the synthesis of 5-methyltetrazoles is 1,3-cycloaddition which undergoes between commercially available carbodiimides and silylazide derivatives [1]. We have developed a convenient catalytic method of the synthesis *in situ* of symmetrical and asymmetrical carbodiimides. The system copper (II) acetate – oxygen allows to obtain a wide range of labile intermediates. Thus, the reaction of 1,3-cycloaddition leads to 5-aminotetrazoles in the presence of trimethylsilylazide.



3a: R^1=Ph, R^2=Ph
3b: R^1=4-Cl-phenyl, R^2=4-Cl-phenyl
3c: R^1=4-CH_3-phenyl, R^2=4-CH_3-phenyl
3d: R^1=2-CH_3-phenyl, R^2=2-CH_3-phenyl
3e: R^1=3-CH_3-phenyl, R^2=2-CH_3-phenyl
3f: R^1=Ph, R^2=CH_3
3g: R^1=4-CH_3-phenyl, R^2=CH_3
3h: R^1=CH_3, R^2=Ph
3i: R^1=CH_3 , R^2=CH_3-4-CH_3-phenyl



Asymmetric isothioureas when used as starting materials led to formation of isomeric 5-aminotetrazoles in equal amounts, which were separated by flash chromatography. These data prove the absence of selectivity of cycloaddition. Furthermore, it was established that increase of reaction duration led to the side reaction undergoing through "C-H" activation. The formation of side products, dimers, trimers and tetramers of 5-aminotetrazoles, was proved by X-ray analysis.

The structures of the obtained compounds were confirmed by physico-chemical methods.

[1] J. Org. Chem. 1980, V.45, p. 5130 – 5136.

Photochromism of novel pyrryl(coumarinyl)thiazoles

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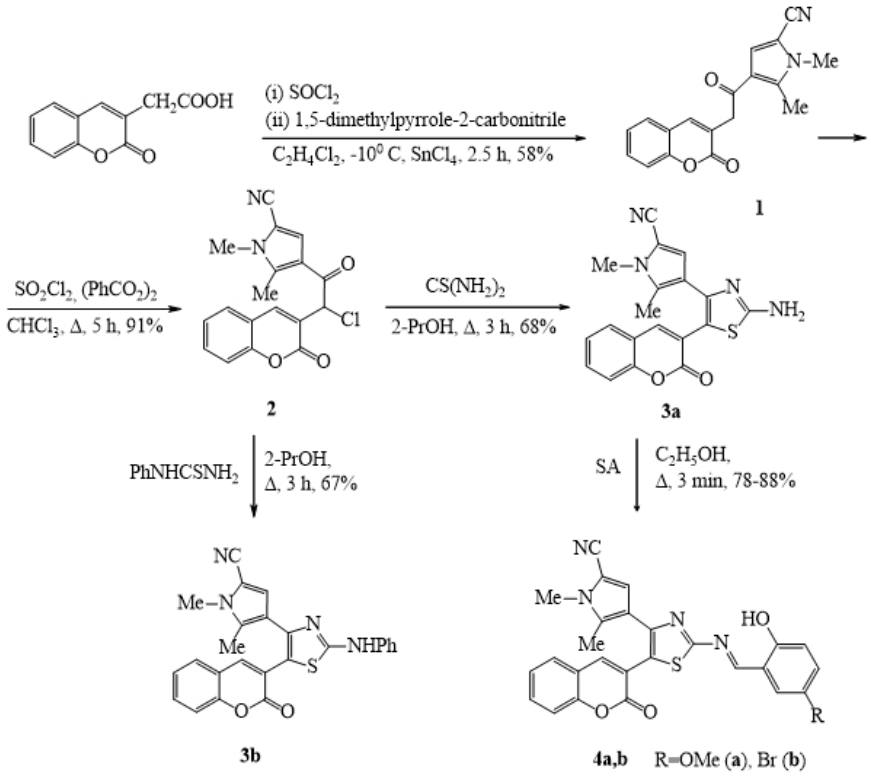
Fluorescent and photochromic dihetarylethenes are widely used as the optical information recording media and the efficient molecular switches with high thermal stability of the initial and cyclic isomers [1,2]. We have synthesized 1,3-thiazole-bridged dihetarylethenes containing pyrrole and coumarin substituents and investigated their photochromic and spectral fluorescent properties.



Depending on the nature of the substituent in the bridging fragment diarylethenes **3a,b** are capable of fotomodulation of fluorescent properties while thiazoles **4a,b** exhibit ASS-emission due to the ESIPT-effect.

References
[1] Irie, M. *Chem. Rev.* **2000**, 100, 1685.
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This study was supported in the framework of the State Order for 2016 No. 007-01114-16 PR 0256-2014-0009.

Synthesis of benzo[*f*]quinazolines via TfOH mediated intramolecular cyclization of 4-alkynyl-5-arylpyrimidines

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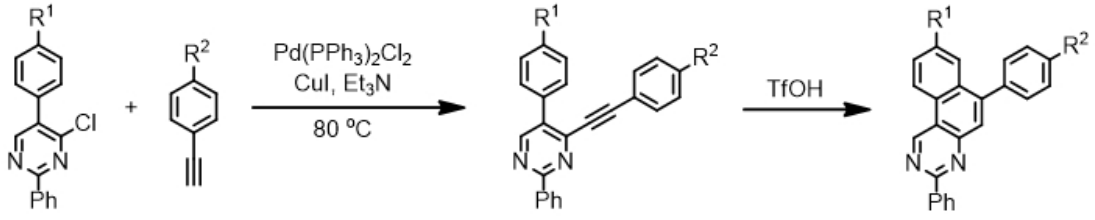
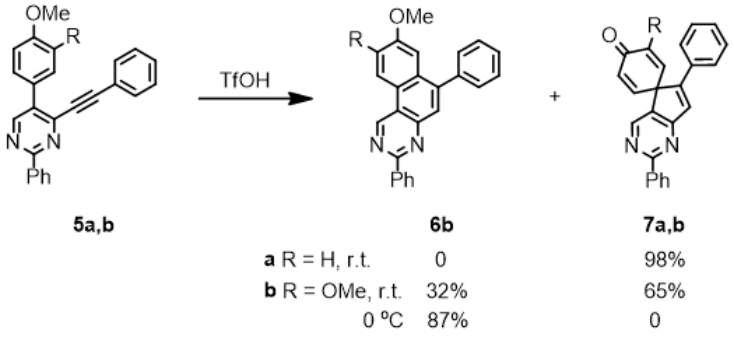
Intramolecular cyclization of *o*-alkynylated biaryl derivatives is a powerful and atom economical process for the preparation of condensed conjugated systems. To the best of our knowledge, the vast majority of published work considers alkynylcarbocycles and few examples with *o*-alkynyl(aryl)heteroarenes have been described until now. We are pleased to present intramolecular cyclization of readily available 5-aryl-4-ethynylpyrimidines as an efficient approach to benzo[*f*] quinazolines, which is enabled by catalysis with superacid.



Alkynylpyrimidines **3** can be easily obtained by Sonogashira cross-coupling of 5-aryl-4-chloropyrimidines **1** with arylacetylenes **2**. Treatment of pyrimidines **3** with TfOH at r.t. readily affords cyclization products in excellent yields. Even substrate with electron-withdrawing nitro group is able to cyclize at higher temperature, though in low yield.



Under the same conditions pyrimidines **5** with electron-rich aryl substituent can give attractive spirocompounds **7** - products of *ipso*-cyclization with formation of five- instead of six-membered ring condensed to the pyrimidine core. Pyrimidine **5a** provides ketone **7a** exclusively, whereas for compound **5b** with inconsistent influence of two methoxy groups both reaction pathways are possible. In this case the reaction selectivity could be controlled by adjusting the temperature.

This work was supported by Russian Foundation for Basic Research (grant №16-33-00171).

Synthesis of (Z)-3-(2-phenylhydrazono)benzofuran-2(3H)-one on the base of catalytic olefination reaction of phenyl hydrazone of salicylic aldehyde

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[a] - Baku State University
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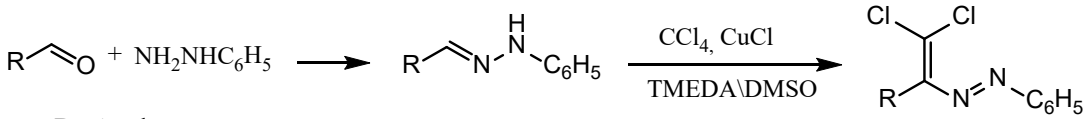
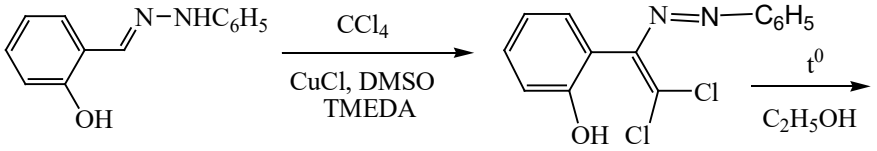
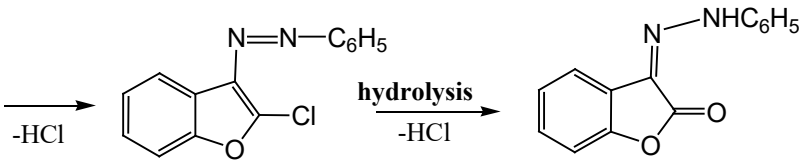
In previous studies on the base of catalytic olefination reaction of N-unsubstituted hydrazones of carbonyl compounds with different polyalkylhalides we elaborated synthesys of various functional substituted alkenes. Continuing the synthetic capabilities of catalytic olefination reaction we carried out catalytic olefination reaction of phenylhydrazones of carbonyl compounds to open access to dichlorodiazabutadienes.

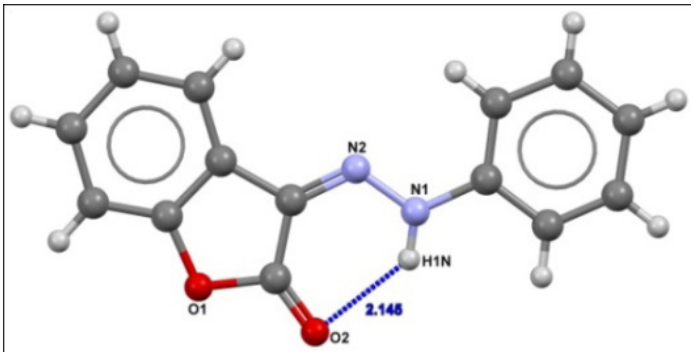


R=Aryl

This reaction with salicylic aaldehyde was investigated in the same conditions. We found that intramoleculear nucleophilic substitution takes place to form after hydrolisis (Z)-3-(2-phenylhydrazono) benzofuran-2(3H)-one**.** The structure of synthesized compound was proved by X-ray method and the presence of intramolecular hydrogen bond in the crystal was found.







A new approach to recyclization of 2,4-diphenylpyrano[3,2-c] chromen-5(4h)-one by redox activation of hydrogen sulfide

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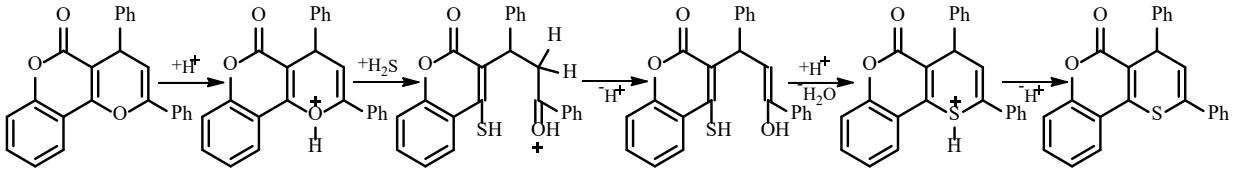
Oxygen- and sulfurcontaining heterocyclic compounds belonging to chromenone are widely distributed in nature, they are part of the vegetable raw material and many food products. These compounds are of great practical interest, they are anticoagulants and possess fluorescent properties and are used in medicine as important drugs. Previously, we have conducted the reactions of furan and 2,5-dimethilfuran with oxidized form of hydrogen sulfide at room temperature in the absence of strong acids [1]. This was possible due to the redox activation of hydrogen sulfide to unstable radical cation using chemical and electrochemical methods in organic solvents.

In this work we propose a new method for recyclization of 2,4-diphenylpyrano[3,2-c]chromen-5(4H)-one at the presence of H_2S. The inreaction of substrate with hydrogen sulfide was investigated in CH_3CN, CH_2Cl_2 and solvent mixture CH_3CN:CH_2Cl_2 (1:1). The radical cation of H_2S is able to be fragmented with the formation of a proton and a thiyl radical in organic media. 2,4-diphenylthiopyrano[3,2-c]chromen-5(4H)-one was obtained as a result of the electrochemical reaction of 2,4-diphenylpyrano[3,2-c]chromen-5(4H)-one with H_2S (fig.1), which was conducted at oxidation potential of hydrogen sulfide on a platinum electrode according to the scheme:



Scheme 1.

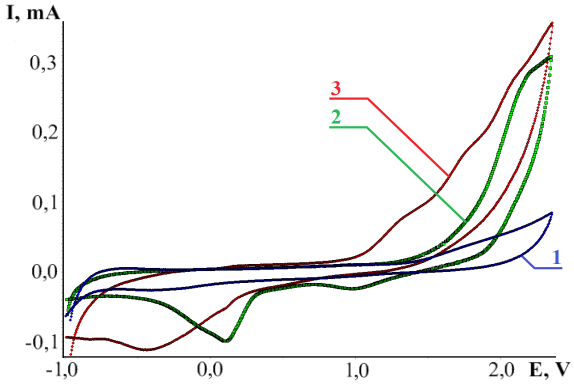


Fig. 1. CVA of the oxidation: 1 – *n*-Bu_4NClO_4, 2 – 2,4-diphenylpyrano[3,2-c]chromen-5(4H)-one, 3 – reaction products of H_2S with substrate (CH_3CN:CH_2Cl_2 (1:1), Pt-anode, Ag/AgCl, 0,1 *n*-Bu_4NClO_4, C = $5 \cdot 10^{-3}$ M)

The potential of the electrolysis depends on the nature of organic solvent. The oxidation potential of H_2S is comparable with the data for the oxidation thiopyran. Therefore, the substrate is also exposed to electrochemical oxidation during the electrolysis. The conversion of 2,4-diphenylpyrano[3,2-c]chromen-5(4H)-one varies from 68 to 92% and it depends on the nature of organic solvent. Consequently, the redox activation of hydrogen sulfide contributes to obtaining of 2,4-diphenylthiopyrano[3,2-c] chromen-5(4H)-one (29-44%) and thiopyrilium salt (13-37%) without the use of mineral or organic acids that are required in conventional synthetic methods.

References

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This work was supported by RFBR (grant № 16-03-00730)

Synthesis of a new functionalized pyridazines from methyl 4-(2-oxoacetyl)phenylcarbamate

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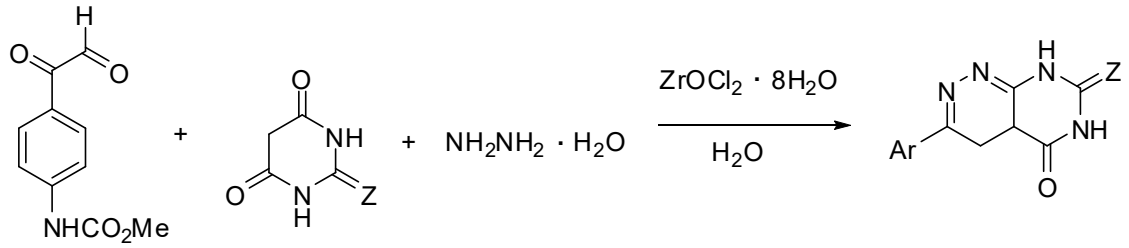
Aryl(hetaryl)glyoxals [1,2] are widely used in the synthesis of a variety of heterocyclic compounds having significant potential biological activity. In this connection, the synthesis of a new functionally substituted arylglyoxals and their subsequent involvement in heterocyclization reaction is of considerable interest. Oxidation of methyl N-(4-acetylphenyl)carbamate (**1**) with selenium dioxide in dioxane - water mixture (30: 1, by volume) at 80-90 °C C for 4 h was obtained methyl 4-(2-oxoacetyl)phenylcarbamate (**2**) in 87% yield.

1 **2**

By ternary condensation of compound (**2**) with barbituric and thiobarbituric acids, and hydrazine hydrate in the presence of $ZrOCl_2$ x $8H_2O$ [3] at room temperature obtained methyl 4-(5,7-dioxo-4,4a,5,6,7,8-hexahydropyrazino[3,4-*d*]pyrimidine-3-yl)phenylcarbamate (**3**) and methyl 4-(5-oxo-7-thioxo-4,4a,5,6,7,8-hexahydropyrimido[4,5-*c*]pyridazine-3-yl)phenylcarbamate (**4**) in 74 and 76% yields, respectively.



2 **3, 4**

Ar=4-$MeO_2CHNC_6H_4$, Z=O (**3**), Z=S (**4**)

The structure of the novel compounds (**2-4**) was confirmed by IR, ^{1}H NMR spectroscopy, mass spectrometry, and the composition was determined by elemental analysis.

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This work was supported by Foundation of Ministry of Education and Science of the Russian Federation, № 115021010181.

Synthesis and reactivity of condensed triazolo[4,3-*c*]pyrimidines and tetrazolo[1,5-*c*]pyrimidines

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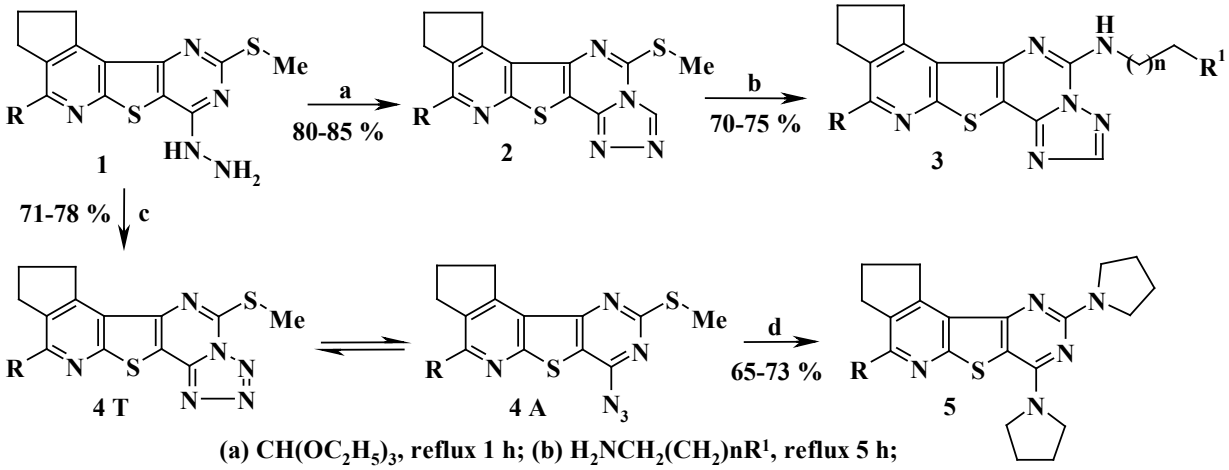
[c]Aristotle University of Thessaloniki, School of Pharmacy, Thessaloniki 54124, Greece; e-mail: geronik@pharm.auth.gr

As a continuation of our previous works on annelated triazoles [1,2] and tetrazoles [2–4] herein we report the synthesis and reactivity of 10-alkyl-5-(methylthio)-8,9-dihydro-7*H*-cyclopenta[4',5'] pyrido[3',2':4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **2** and 10-alkyl-5-(methylthio)-8,9-dihydro-7*H*-cyclopenta[4',5']pyrido[3',2':4,5]thieno[2,3-*e*]tetrazolo[1,5-*c*]pyrimidines **4** starting from the relevant 7-hydrazino derivatives **1**. In fact, compounds **1** gave cyclization under the action of triethyl orthoformate or of nitrous acid, respectively. As a result of the reactions the corresponding fused triazolo[4,3-*c*]pyrimidines **2** and tetrazolo[1,5-*c*]pyrimidines **4** were formed. Further we have examined the Dimroth rearrangement of triazolo[4,3-*c*]pyrimidines **2** under basic conditions by heating them with primary amines. As a result not only the Dimroth rearrangement occurred but also the substitution of SMe group took place with formation of 10-alkyl-8,9-dihydro-7*H*-cyclopenta[4',5']pyrido[3',2':4,5] thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amines **3**. The azide-tetrazole equilibrium was observed in compounds **4**. The ^{1}H NMR spectra of compounds **4** in solution of DMSO-d_6/CCl_4 1/3 show the expected double set of signals: the ratio of tautomers **2T**:**2A** was found to be approximately 2:3. Further, we have examined the reactivity of compounds **4** with pyrrolidine. Thus, by refluxing compound **4T/4A** (4 h) in an excess of pyrrolidine the nucleophilic substitution not only of SMe group, but also of the an azide group with formation of the relevant 7,9-dipyrrolidinthieno[3,2-*d*]pyrimidines **5** occurred.



(a) $CH(OC_2H_5)_3$, reflux 1 h; (b) $H_2NCH_2(CH_2)nR^1$, reflux 5 h;
(c) AcOH, $NaNO_2$, 0-5 °, then r.t. 12 h; (d) pyrrolidine, reflux 4 h

R = alkyl; n = 1, 2; R^1 = OH, $CH(Me)_2$.

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Sirakanyan, S.N.; Spinelli, D.; Geronikaki, A.; et al. *Tetrahedron* **2014**, 70 *(45)*, 8648.
Sirakanyan, S.N.; Spinelli, D.; Geronikaki, A.; et al. *Tetrahedron* **2016**, *accepted*.

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Tryptamine – new reactive matrix for MALDI mass spectrometry of steroids

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MALDI mass spectrometry currently is one of the most popular instrument for analysis of different organic compounds. Its main advantages when compared to other "soft ionization" method are following: high resolution, wide mass range, and rapidity. However, in the case of aldehydes and ketones this method is hardly applicable due to their low desorption/ionization efficiences. The solution of these problems can be found in the use of chemical modification of organic molecules. The most popular methods involve the introduction of ionizable groups or the residues of derivatizing agents which makes the determination of the analyte structures more easily. One of the promising approaches in this case are based on the use of compounds, which simultaneously may act as a derivatizing agent and a matrix. Such derivatization method reduces time for sample preparation, increases the ion yields and resolution in mass spectra. In this work, similar methodology has been applied to the analysis of carbonyl-containing compounds by MALDI mass spectrometry. The proposed method is based on the ability of the analytes to yield Schiff bases.

Various aromatic amines (substituted arylamines, tryptamine) were tested as potential reactive matrix compounds for analysis of aliphatic and alicyclic carbonyl-containing compounds. The solutions of analytes in toluene were treated by the excess of derivatization agent and the reaction mixtures were shaken at 50°C for 30 min. Without further purification, 1 μl of the resulting solution was dropped on the stainless steel target for MALDI measurements and dried under ambient conditions. MALDI mass spectra were recorded using Bruker autoflex speed time-of-flight (TOF) mass spectrometer (Bruker Daltonics Inc., Germany) equipped with a solid-state ultraviolet (UV) laser of 355 nm (1 kHz repetition rate, 1000 shots for each spectrum) and operated in positive reflectron mode.

MALDI mass spectra of the initial carbonyl compounds did not reveal peaks of analyte ions. Mass spectra of derivatives depended on applied reactive matrix: in case of aryl amines only weak peaks of derivatization products were observed, but the intensities of corresponding ions were rather high when tryptamine was used. Further optimization of reaction and MALDI conditions allowed us to record MALDI mass spectra of derivatives of all tested compounds, including biologically important steroids.

Hypervalent Iodine Reagents for Green Synthesis

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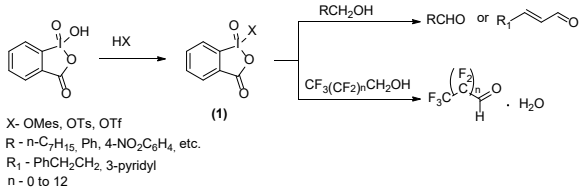
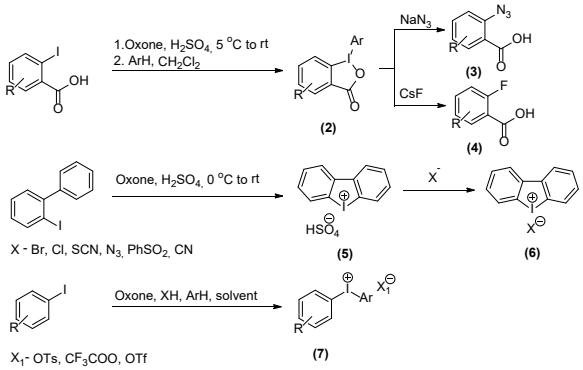
In recent years, hypervalent iodine reagents have emerged as environmentally friendly and efficient oxidizing reagents for various synthetically useful oxidative transformations [1]. Organosulfonate derivatives of 2-iodoxybenzoic acid **(1)** are convenient, environmentally friendly oxidation reagents, which are particularly useful for poorly oxidizable substrates [2].



Moreover, various iodine (III) reagents can be conveniently prepared from iodoarene using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an inexpensive and environmentally safe oxidant. Obtained arylbenziodoxolones **(2)** can be transformed into corresponding azides **(3)** or fluorides **(4)** via nucleophilic substitution [3]. Dibenziodolium hydrogen sulfate **(5)** can be readily converted to various other dibenziodolium salts **(6)** by anion exchange [4]. The use of Oxone allows to prepare different diaryliodonium salts **(7)**.



Acknowledgment. This work was supported by a research grant from the Ministry of Education and Science of Russian Federation (project "Science" No. 4.2569.2014/K).

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Silver metal-organic frameworks (MOFs) based on thiacalix[4]arenes tectones

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The strategy of molecular tectonics is based on self-assembly in the solid phase of the molecular building blocks - tectones having in their structure binding sites capable of recognition by various weak intermolecular interactions. By controlling the self-assembly into organized structures (layers, membranes, crystals, etc.) one can create various functional materials having desired properties (conductors and semiconductors, sensors, nonlinear optical, magnetic materials, etc.) [1]. From this point of view thiacalix[4]arene platform having conformational rigidity necessary to achieve the desired orientation in space of several binding sites, seems to be a promising «building block» for the design and synthesis of spatially predorganized structures - metal - organic structures (MOFs). Of the four stereoisomers of thiacalix[4]arenes: *cone*, *1,3-alternate*, *partial cone* and *1,2 alternate*, the first is the most interesting for design of discrete systems and clusters, while others - for infinite 1D - 3D structures.

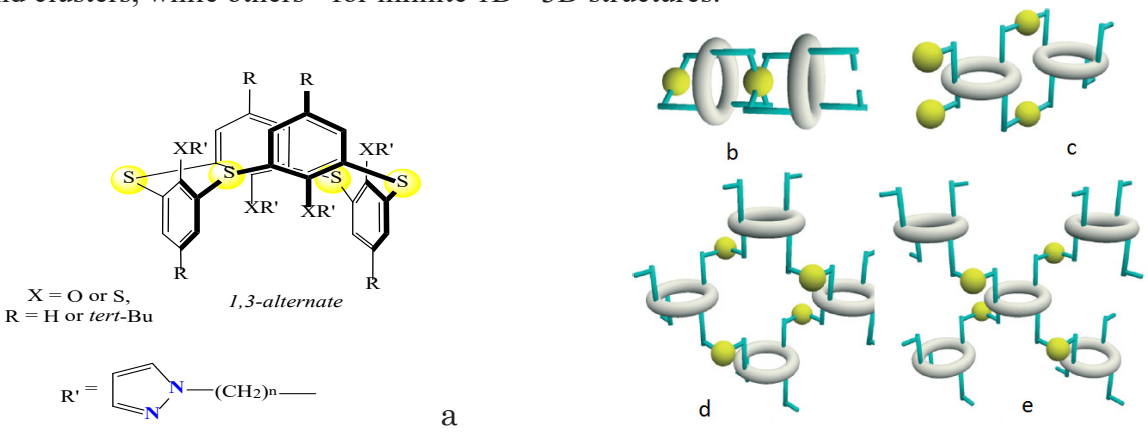

Fig. 1.

In this report synthesis of tectones on the basis of thia- and mercaptothiacalix[4]arenes derivatives with pyrazolyl moieties in *1,3- alternate* conformation will be discussed. A large variety of networks with different dimensionality (Fig.1a,b) with silver cations (AgX, X = NO_3, BF_4, XF_6 when X is P, As or Sb) [2] will be presented: from 1D to extended 2D and to a series of three isostructural porous diamond-like 3D architectures.

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Domino transformations of dinitriles under basic conditions

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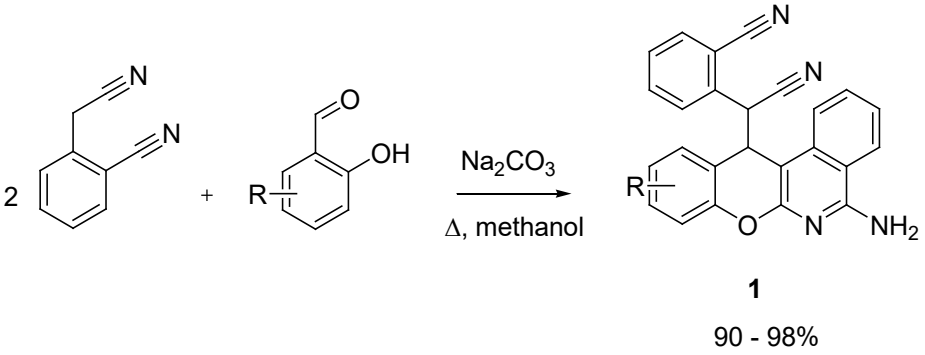
The nitrile group has a great synthetic potential. The nitrile derivatives, including compounds with two nitrile groups, are commonly used in domino processes. For example, multicomponent reactions with malonic dinitrile, which are extensively covered in the literature, lead to the formation of 2-aminochromenes, which are one of the privileged scaffolds in medicinal chemistry. Current study describes transformations of the dinitriles that have two nitrile groups divided by three carbons with different salicylic aldehydes under action of base.

It was discovered, that the interaction of homophtalonitrile with salicylic aldehyde in methanol in the presence of sodium or potassium carbonate proceeded as a three-component reaction with the formation of diastereomeric chromenoisoquinolines **1** (Scheme 1).



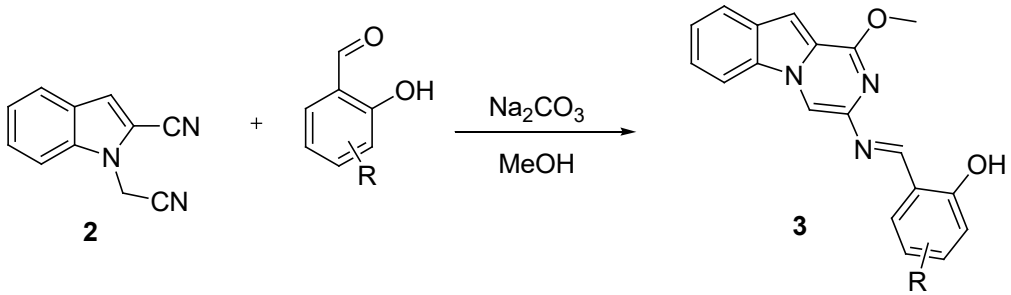
1

90 - 98%

Scheme 1.

The use of *L*-proline as a catalyst in this reaction improved the diastereomeric ratio.

The 1-(*N*-cyanomethyl)-2-cyanoindole **2** was used as a heteroaromatic substrate in this reaction. It reacted with salicylic aldehyde in methanol under the action of sodium carbonate in another way with the formation of pyrazinoindole derivative **3** (Scheme 2). Compound **3** became a result of the reaction between initially formed aminopyrazinoindole that gave the Schiff base with the aldehyde. Corresponding transformation can be performed in ethanol, trifluoroethanol and with the use of benzaldehyde.



2 **3**

Scheme 2.

The reflux of **2** in methanol and ethanol gives the alkoxyaminopyrazinoindoles with methoxy and ethoxy substituents respectively with high yields.

This work was supported by RFBR and Moscow government (grant *#15-33-70034 mol_a_mos)* and by the President of Russian Federation grant *(MK-5319.2016.3)*.

Formal total synthesis of marine secondary metabolite dragmacidin A

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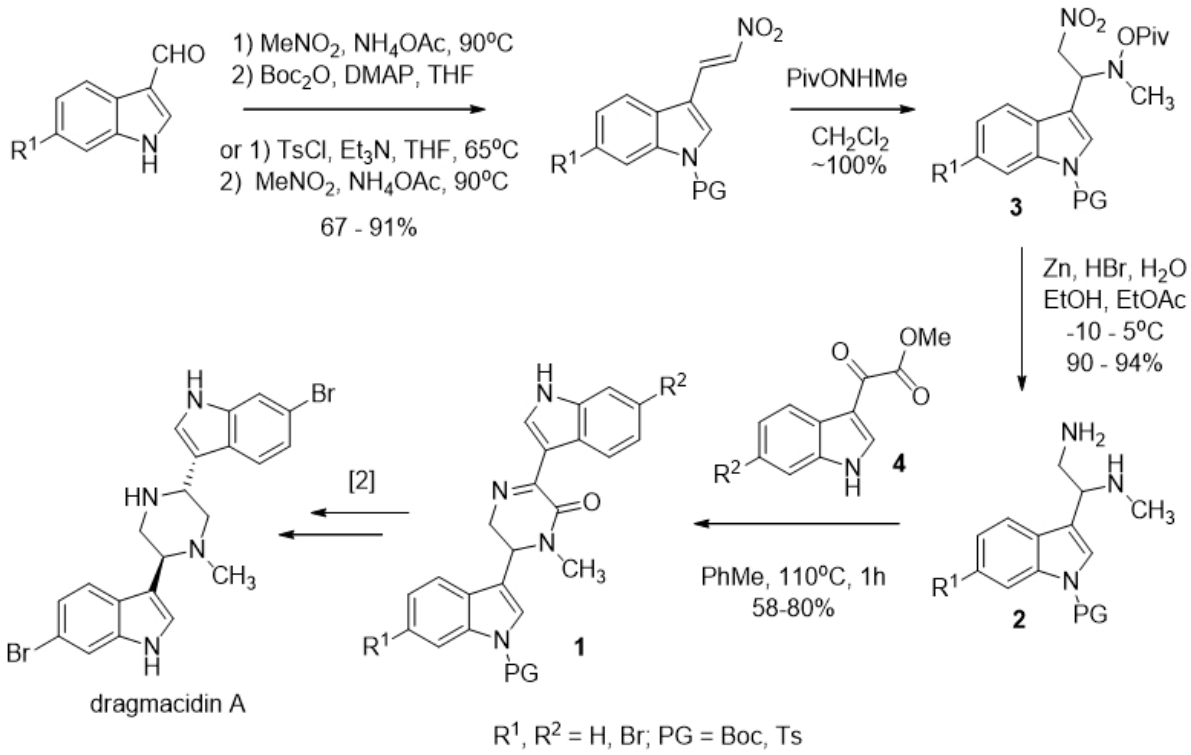
An 1-(indol-3-yl)ethane-1,2-diamine motif occurs in the structures of different marine secondary metabolites, such as discodermindoles, dragmacidins, hamacanthines, spongotines, topsentins and trachycladindoles [1]. Several of them have one or two methylated nitrogen atoms. Many of these alkaloids exhibit useful biological activity [1]. Here we propose a practical synthetic approach to bis(indolyl)dihydropirazinones **1** (Scheme 1), which (R^1=R^2=Br, PG=Ts, Boc) can be easily transformed to (+/-)-dragmacidin A, a secondary metabolite from *Hexadella* sponges, according to the known procedure [2].



Scheme 1.

Our approach included the use of *N*^{1}-methyl-1-(indol-3-yl)ethane-1,2-diamines **2** as the key synthetic intermediates. They were prepared by reduction of adduct **3**, obtained from corresponding 3-(2-nitrovinyl) indoles and *N*-methyl-*O*-pivaloylhydroxylamine. The cyclization of diamines **2** with indol-3-glyoxylic esters **4** in boiling toluene gave desired dihydropirazinones **1** selectively.

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Development of methods of synthesis of dual action antibiotics on the bases of antimicrobial agents of different classes

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A promising strategy aimed at the manufacture of drugs active against resistant microorganisms, having a broad spectrum of action compared with the initial antibiotics and retarding the development of antibiotic resistance is preparation of dual action antibiotics, i.e. heterodimers formed by drugs of different classes [1]. We developed methods of synthesis and obtained series of dual action antibiotics on the basis of antifungal agents amphothericin B and benzoxaboroles (Fig. 1) and on the basis of antibacterial antibiotics azithromycin and glycopeptides (Fig. 2) [2]. The structures of the obtained hybrid antibiotics were confirmed using NMR spectroscopy and HR mass spectrometry methods, including MS/MS data. Investigation of the antimicrobial activity of the obtained compounds revealed derivatives that are perspective for the further investigations.

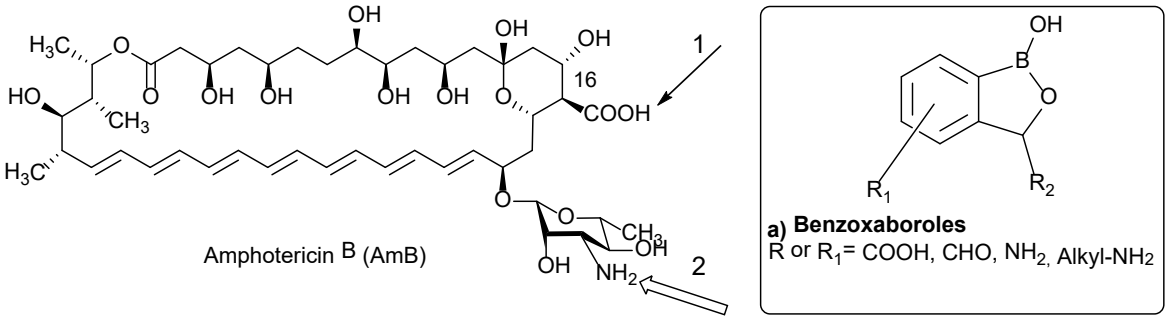

Fig. 1. Dual action antibiotics on the basis of amphothericin B and benzoxaboroles.

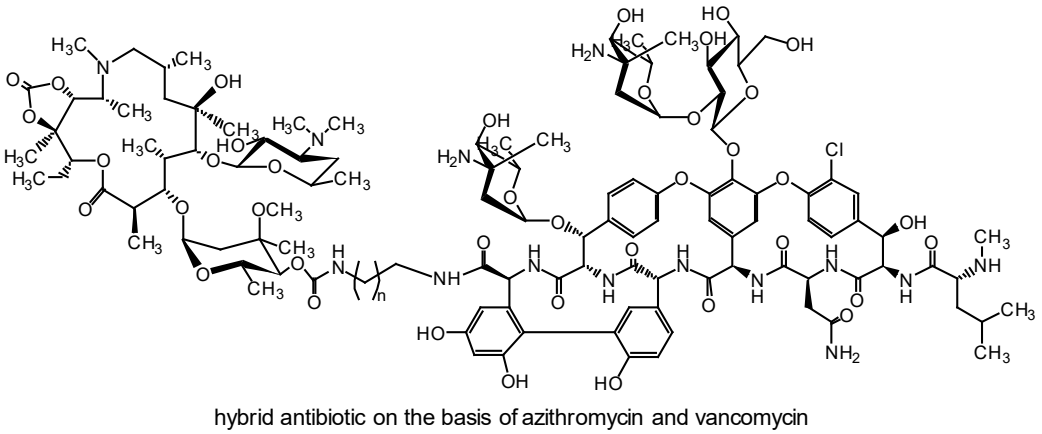

Fig. 2. Dual acition antibiotics on the basis of azithromycin and glycopeptide antibiotics (on the example of vancomycin).

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The reported study was funded by the Russian Foundation for Basic Research according to the research project № 16-34-60110.

Semi-synthetic derivatives of olivomycin SA: synthesis and antitumor properties

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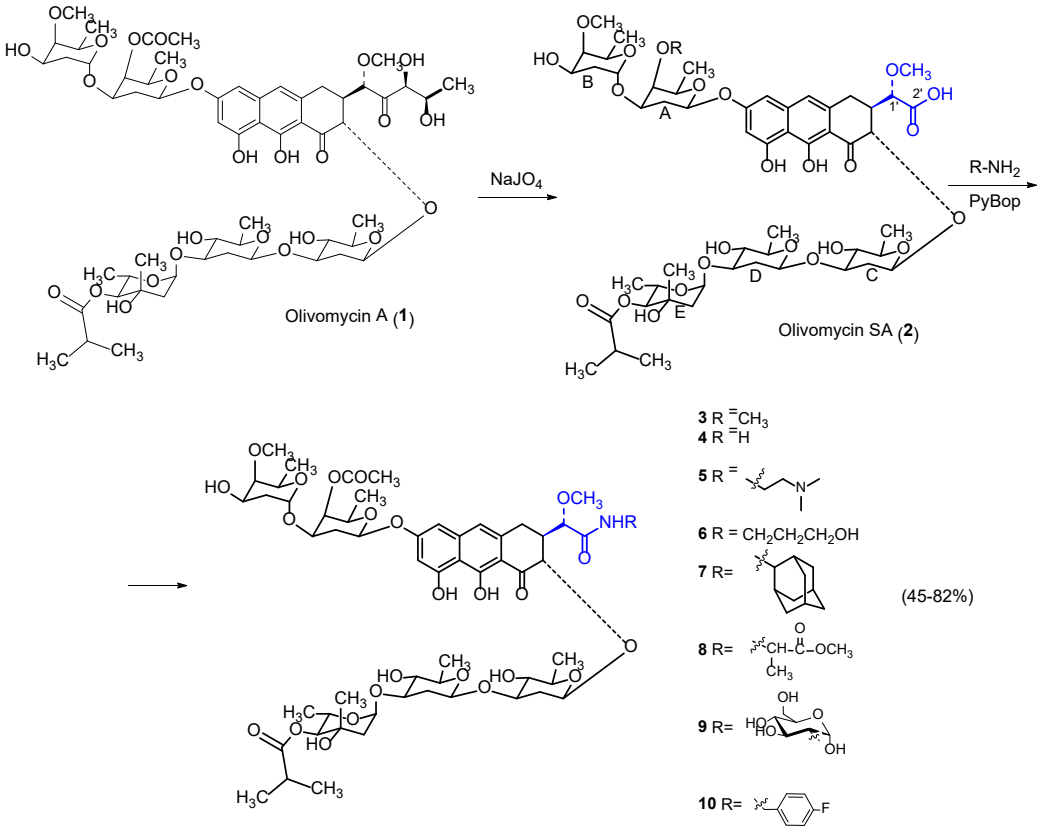
Interest to antitumor antibiotics of the aureolic acid group significantly increased after new perspective targets for these compounds have been discovered. Chemical modifications of this chemical class are scarce, although some derivatives have been obtained biosynthetically. Since olivomycin A (**1**) is the most promising scaffold with the best therapeutic index, we developed a new method of its modification which includes periodate oxidation of the aglycon's side chain and amidation of the obtained olivomycin SA intermediate (**2**) by different amines (Scheme 1).



Scheme. 1. Synthesis of olivomycin SA amides.

Investigation of the antitumor potency of newly synthesized amides of **2** revealed that N,N-dimethylaminoethylamide of olivomycin SA (**5**) (N,N-dimethylaminoethylamide of 1'-de-(2,3-dihydroxy-n-butyroyl)-1'-carboxy olivomycin A), demonstrated the most promising properties and is therefore perspective for the further preclinical testing. Studies of the mechanism of action of **5** in comparison with the starting olivomycin A (**1**) and *in vivo* experiments are under way.

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This study was partly funded by the Ministry of Education and Science of Russia, contract №14.N08.12.0058.

Synthesis of 6-tetrazolyl substituted azocino[5,4-*b*]indoles

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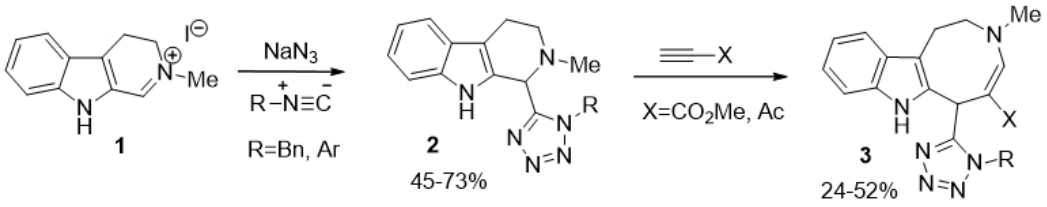
The development of effective methods for the synthesis of original bioactive compounds on the basis of domino- and multi-component processes is a challenging task of synthetic and pharmaceutical chemistry.

A number of multi-component reactions, for example azido-variant Ugi reaction, proceeds via formation iminium intermediates. The stable cyclic iminium salts could be successfully used to develop new domino-processes.

Such a process was previously implemented for dihydroisoquinolinium salt generated from cotarnine chloride. Tetrazolyl substituted isoquinolines were obtained in high yields [1]. However this reaction was studied only in the case of isoquinoline salt without any substituents attached to the position 1. Salts of 3,4-dihydro-*β*-carbolines **1** were not considered.

3,4-Dihydro-*β*-carbolinium salts are attractive compounds for the three-component Ugi azido-reaction. From these reactions we isolated 1-tetrazolyl substituted *β*-carbolines **2** in good yields (45-73%), under the action of alkynes with electron-withdrawing groups the obtained compounds **2** formed azocino[5,4-*b*] indoles **3** – the products of enlargement of tetrahydropyridine ring to tetrahydroazocine one.



Scheme 1.

It was shown that azocines possess high AChE and BchE inhibitory activities [2] and may be of interest as potential drugs for the treatment of Alzheimer's disease. In the near future we are planning to measure AChE and BChE inhibitory activities for the all 6-tetrazolyl substituted azocino[5,4-*b*]indoles **3** synthesized in the framework of this study.

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Synthesis of New Amino Derivatives of Colchicine

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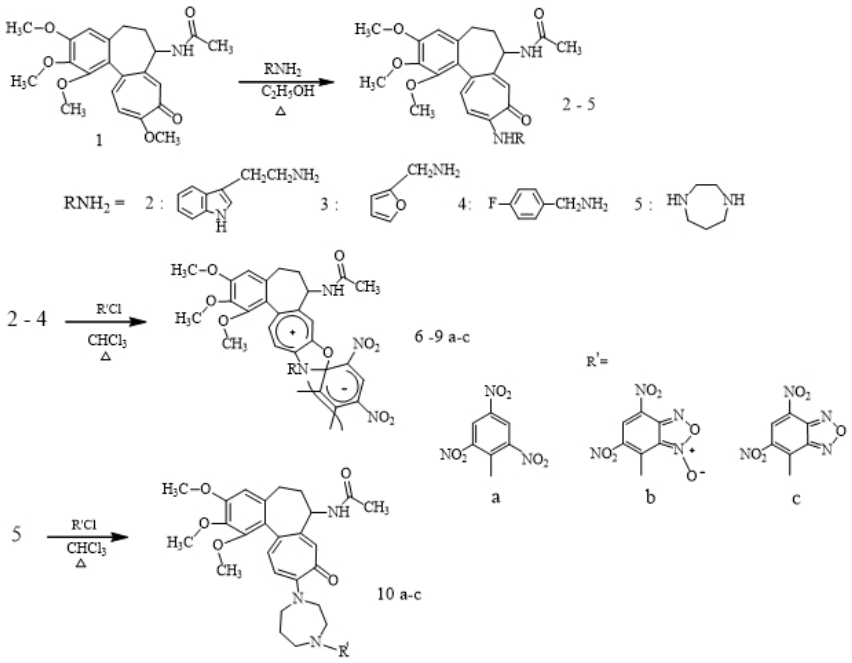
Colchicine **1**, one of the most known alkaloids tropolone group, has a broad spectrum of the biological activity and used as a medicine for gout, amyloidosis and the number of tumor diseases. Although colchicine is a potent antimitotic agent, its medicinal uses are limited due to its high toxicity. Therefore, the synthesis of colchicine analogues with a high antitumor activity and low toxicity is important. Amino derivatives of colchicine are very promising compounds for this goal.

In the present work, we report on the synthesis of nove amino derivatives of colchicine **2-5**. We also obtained the products of their reaction with super-electrophiles - amino derivatives **10a-c** and bipolar spirocyclic systems **6(a-c) - 9(a-c)**. Synthesis and structures of obtained compounds are shown in the scheme below.



Amino derivatives of colchicine **6(b-c) -10(b-c)** are promising targets for biological testing, e.g., they may be potential exogenous sources of nitric oxide (II), which is a multimodal regulator of many physiological processes [1]. The use of colchicine derivatives with a picryl fragment **6a -10a** enables new approaches to the study of stereodynamics in molecules with flexible structure and variable stereo configuration [2].

The structures of the isolated compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy using the homo- and heteronuclear correlation techniques.

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This work was performed within the framework of Project part of the State Assignment for scientific activity No. 4.129.2014/K from Ministry of Education and Science of the Russian Federation.

Biological Evaluation of Both Mirror Images of Thalidomide and Fluorothalidomide

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Thalomide®, a brand name of thalidomide, is one of the effective drugs on the market for treatment of multiple myeloma and of a complication of leprosy. The drug is available from Celgene Corporation and the sale is $221MM (2014), its derivatives Revlimid® ($4980MM) and Pomalyst® ($679MM). On the other hand, thalidomide is also the notorious drug in the medicinal history. In the late 1950s, thalidomide was used as a sleeping-pill tranquilizer and was popular among pregnant women. However, thalidomide was banned after it was found to cause malformation in children delivered from women who took it during pregnancy. In 1979, Blaschke and co-workers reported that only (*S*)-thalidomide was teratogenic based on animal study. Since then it had been believed the thalidomide disaster could have been avoided if only the (*R*)-isomer of thalidomide had been marketed. In the 21st century, Thalomide® is again on the market, but it still used as a racemate, due to its rapid epimerization under physiological conditions. In this context, we developed a non-racemizable thalidomide analogue, 3'-fluorothalidomide.[1] In this presentation, we report the biological evaluation of enantiomers of thalidomide and 3'-fluorothalidomide (Fig. 1). The antitumor activities of racemate and enantiomers of thalidomide and 3'-fluorothalidomide were evaluated against H929 cell from multiple myeloma (MM) in vitro using an Annexin V assay. While the racemate and enantiomers of thalidomide have very weak antitumor activities, the 3'-fluorothalidomide markedly inhibited the growth of H929. Especially, racemate and (*S*)-3'-fluorothalidomide have the stronger inhibitory activity than the other compounds.

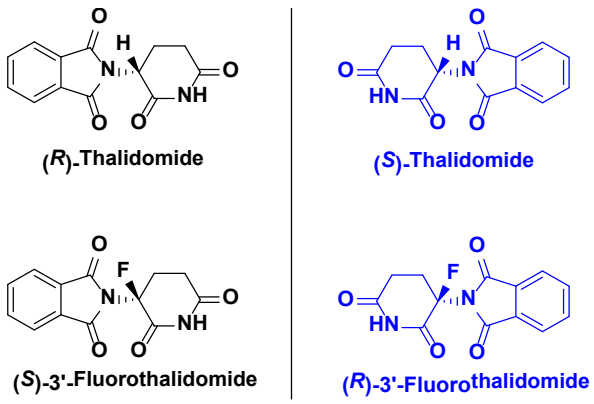

Fig. 1.

References

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"Green" method for the synthesis of indolyl- and pyrrolyl(hetero)arenes

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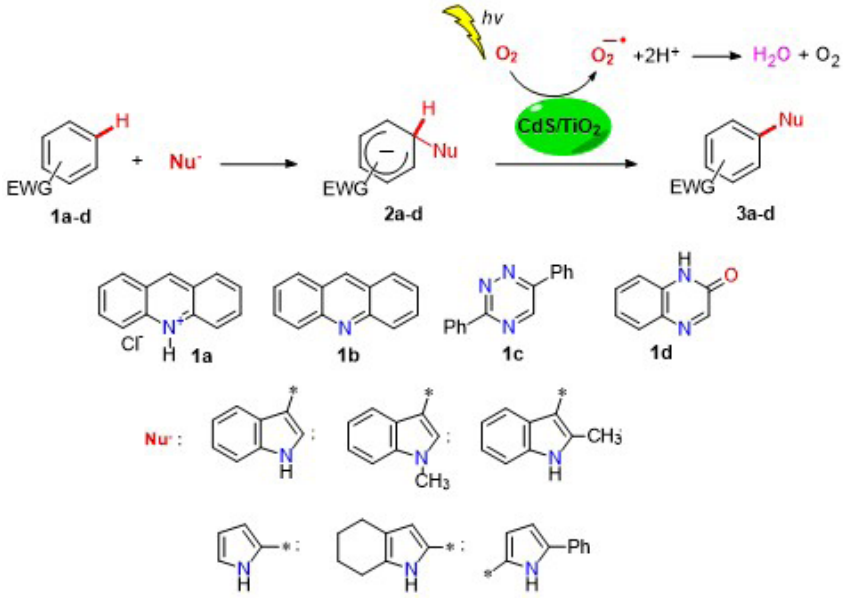
For the last time the functionalization of C-H bonds is one of great important trends in the development of modern organic synthesis. One type of C(sp^2)-H bond functionalization is the reactions of nucleophilic aromatic substitution of hydrogen (S_N^HAr). It is cross-coupling reactions which do not require any transition metal catalysis and prior functionalization of azines.

For S_N^H reactions the effective photocatalytic oxidative system working in heterogeneous phase has been found: air oxygen/TiO_2 photocatalyst. We have established that azaaromatic compounds and their activated forms are able to undergo the double C–H/C–H coupling reaction with indoles and pyrrole under aerobic conditions in the presence of nanosized particles of TiO_2 under irradiation with UV light [1]. Using of CdS/TiO_2 allows carry out the oxidative "azine - (hetero)aromatic nucleophile" couplings under irradiation with visible light. The method is quite general, it allows under mild conditions (usually at room temperature) to obtain bi(hetero)arenes in high yields, which are of interest to pharmaceutical industry and materials science.

The presented method has the features of a "green" process: the absence of reagents homocoupling, oxidizer - air oxygen, a by-product – water and easily separate heterogeneous catalyst.



Scheme 1. C-H/C-H couplings of azaaromatics with indoles and pyrroles

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This work was supported by the Russian Science Foundation (Project No. 14-13-01177), the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools, Grant NSh-3656.2014.3), the Russian Foundation for Basic Research (Project No. 16-03-00958).

OFET-based memory devices operating *via* optically and electrically modulated charge separation between the semiconductor and 1,2-bishetarylethene dielectric layers

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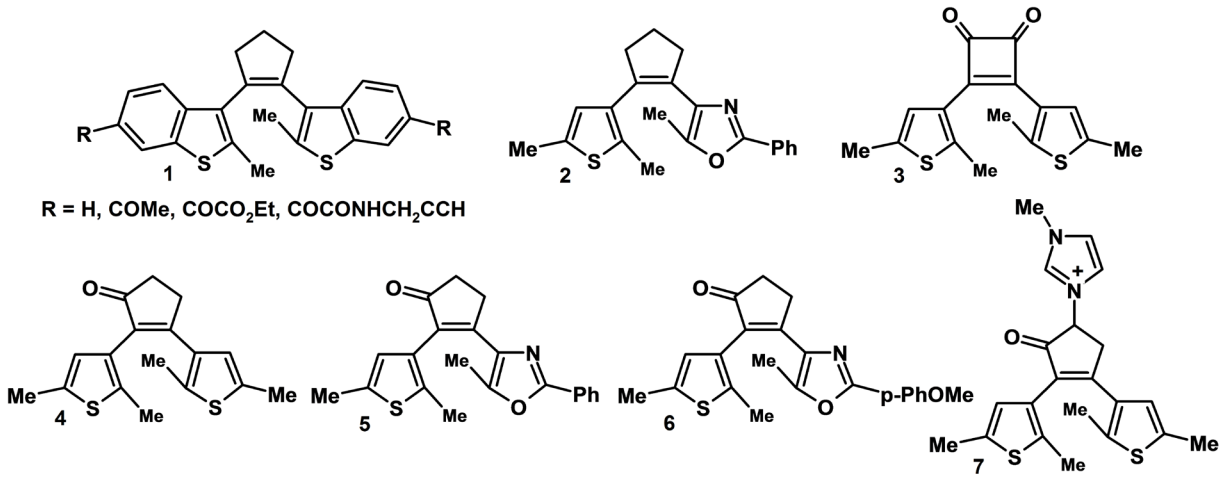
Organic field-effect transistors modified with photochromic molecules were extensively investigated in order to construct memory elements with enhanced optical switching characteristics [1]. Here we present a concept of the memory elements operating *via* optically and electrically triggered charge separation between the organic semiconductor ([60]fullerene) and the photochromic dielectric (specially designed substances **1**-**7** [2], scheme 1) layers. The proposed approach allowed us to decrease the device programming time by 3 orders of magnitude down to few milliseconds with a high potential to reach practically interesting microsecond operation regime [3]. Additionally, the designed devices showed exceptionally wide memory windows reflected by the switching coefficients of ~10^5 at reasonably low operation voltages (3-10 V).

Scheme 1



We have proposed a promising concept of designing OFET-based organic memory elements operating via optically and electrically triggered charge separation between the semiconductor and the photochromic dielectric layers. The first fabricated devices demonstrated highly promising electrical characteristics, good stability, and reliability. Further exploration of this concept and using different combinations of photochromic and semiconductor materials might lead to the development of industrially interesting technologies of novel types of memory devices and light sensors based on organic materials.

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Novel Bio-Based Copolymers from Waste Streams

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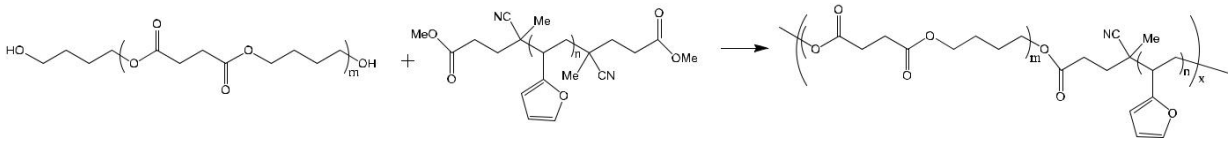
Polybutylene succinate (PBS) and its copolymers are valuable biodegradable plastics with a growing area of industrial applications. Main building block of PBS, succinic acid can be obtained from waste-derived sugar feedstock via fermentation. A new route has been suggested for a synthesis of block copolymers of PBS and poly(2-vinylfuran) (PVF), which can also be derived from renewable sources. A small incorporation of vinylfuran aromatic moieties can improve thermal and fire resistant properties of the resulting materials.

Lipase-catalysed process may contribute to development of metal-free strategy in the production of PBS and its copolymers [1]. First step, a synthesis of cyclic oligomeric esters was investigated in details. The reaction's conditions were optimized and its kinetics was studied. Step two is subsequent ring-opening polymerisation of the oligomers. While in literature purified dimers were used in this step, polymerisation of crude mixture of cyclic oligomers was carried out successfully. 2-Vinylfuran, a precursor of PVF was synthesised from furfural by Wittig reaction [2]. Polymerisation of 2-vinylfuran was performed using 4,4'-azobis(4-cyanopentanoic acid) (ACPA) as an initiator. A series of block-copolymers was prepared from PBS oligomers with Mw of 4.4 kDa and telechelic poly(2-vinylfuran) with Mw of 2.3 kDa (Scheme 1). It was found that at the same reaction's conditions, a higher proportion of PVF led to block copolymers with lower average molecular weights.

Nextek predicted through their cost model that the minimum plant size would be 10,000 tonnes output of plastic per year for the effective use of fixed costs (Figure 1). The plants in Europe are based on the same capacity, which confirms the estimations regarding scale up.



Scheme 1. Preparation of block copolymers.

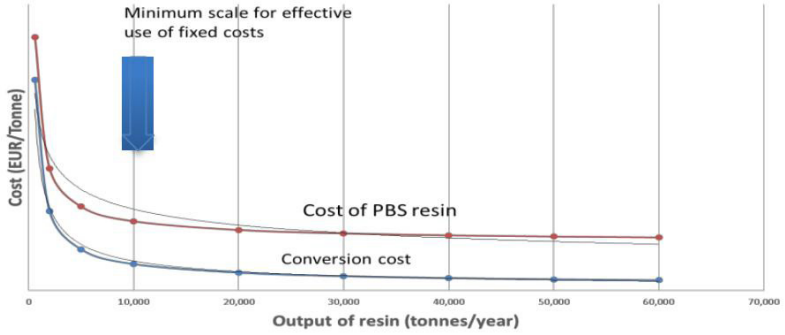


Figure 1. Impact of scale on cost of PBS.

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This work was supported by the European Union's FP7 research project entitled "*New tailor-made biopolymers produced from lignocellulosic sugars waste for highly demanding fire-resistant applications*" (Acronym: BRIGIT, Grant agreement no: 311935).

The Interaction of Derivatives of 1,2-Diazaphenalene with Bifunctional Electrophilic Reagents

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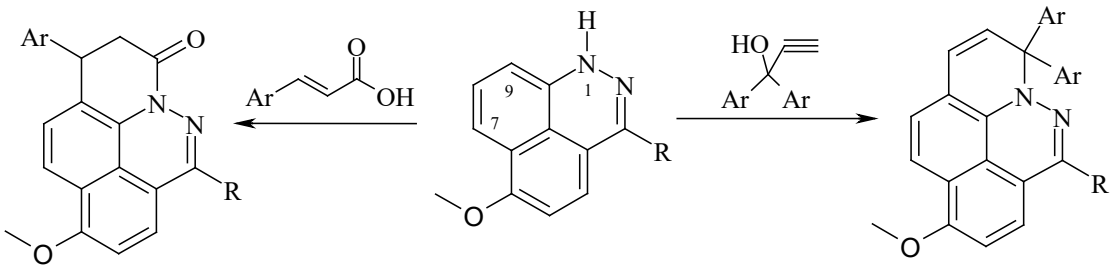
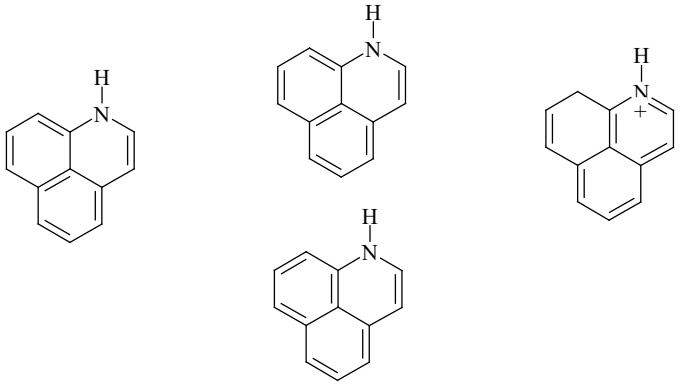
Derivatives of 1,2-diazaphenalene are convenient objects for study electrophilic substitution reactions. Previously it was shown that the most suitable places for formylation are the first and ninth positions [1], wich are located in peri-positions of the heteroring and implied the possibility of heterocyclization.

Our present study describes the interaction derivatives of 1,2-diazaphenalene with cinnamic acids and 1,1-diaryl-2-propyn-1-ols under acid catalysis.



The formation of the pyran ring by the reaction of α-naphthols with cinnamic acids occurs in *ortho*-position to hydroxy group. 1,2-Diazaphenalene is the heterocyclic structural analogue of α-naphthol. Its pyrrole nitrogen is located in the place of the hydroxyl group, however, activating effect can be achieved in two alternative ways: by analogy with α-naphthol (**A**), and also due to conjugation of pyrrole nitrogen with *peri*-position via the π-system of the external contour of 1H-1,2-diazaphenalene (**B**).



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The Reaction of 4,8-Dihydroxynaphthalene-1,5-Dicarbaldehyde and Fisher Base

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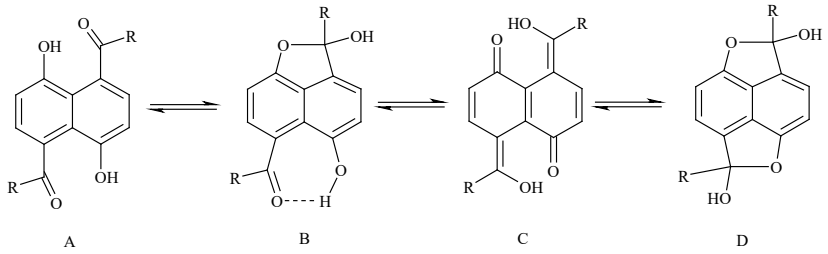
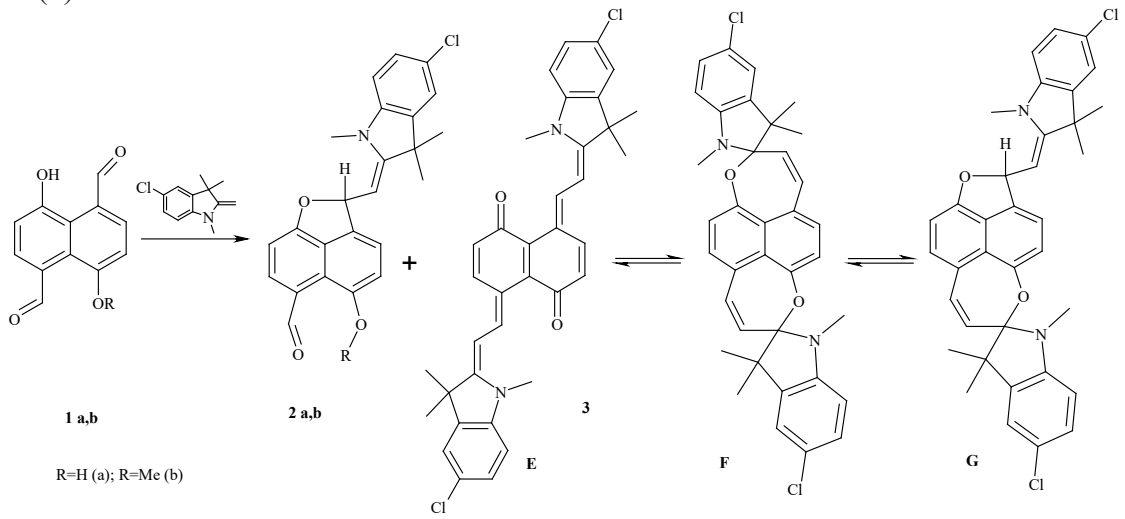
1,5-Naphthalene-diols with symmetric carbonyl function in the *peri*-positions are be able to be observed as molecules with benzoid-quinoid and with ring-chain tautomerism.

Previously it was shown that these diols exist in two forms in the solution: symmetric dialdehyde **A** and cyclic hemiacetal **B** [1].



At the same time the condensation of these compounds with Fischer bases similarly to ortho-hydroxynaphthaldehydes may lead to the formation of tautomeric systems with photochromic activity.

In the present work it is shown that 4,8-dihydroxynaphthalene-1,5-dicarbaldehyde 1a or its monomethyl ether 1b to be cured with Fisher base were formed products containing one equivalent (2a,b) and two equivalents (3) of the Fischer base.



Identification of these products based on data of mass spectrometry and NMR spectroscopy includes the signals correlation of the protons for the compounds **2** and aldehydes **1**. The main form of compound **3** is a deep colored open-chain form **E**. Symmetrical structure **3E** also confirmed by NMR^{1}H.

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This work was supported by the internal grant of the Southern Federal University (project No 213.01-2014/005ВГ).

Electrophilic fluorination of quinolones with NF-reagents

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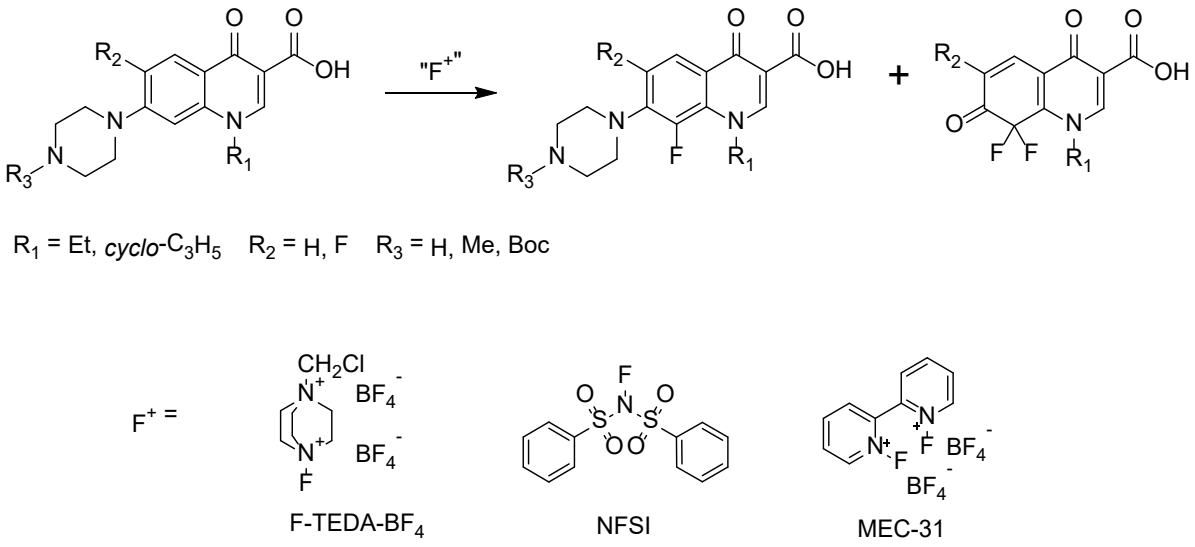
In recent years, many publications were devoted to the use of NF-reagents for electrophilic fluorination of aromatic and heterocyclic compounds [1].

The objective of the present research was the investigation of the selectivity of fluorination of fluoroquinolones norfloxacin, pefloxacin and ciprofloxacin and its non-fluorinated congeners with NF-reagents. Fluoroquinolones represents an important class of broad-spectrum antibiotics and the development of new methods of synthesis of fluoroquinolones is on the agenda [2].

We have shown that fluorination of 1-R_1-7-(4-R_3-piperazin-1-yl)-4-oxo-6-R_2-1,4-dihydroquinoline-3-carboxylic acids with NF-reagents NFSI, F-TEDA-BF_4 and MEC-31 proceeds predominantly at the 8 position of quinoline fragment in acetonitrile, water and under solvent-free conditions. The main products of fluorination are shown on the Scheme 1.



Scheme 1. Fluorination of quinolones

The structures of the products obtained were determined by ^{1}H, ^{13}C, ^{19}F NMR and HRMS.

The influence of the reaction conditions and NF-reagent structure on the selectivity of fluorination and the mechanistic insights into fluorination process will be discussed.

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This work was supported by the Russian Foundation for Basic Research (project No. 16-33-00944)

Synthesis of amphiphilic *p-tert*-butyl(ThIA)Calix[4]arene derivatives with 1,3-BUTADIyne FRAGMENTS

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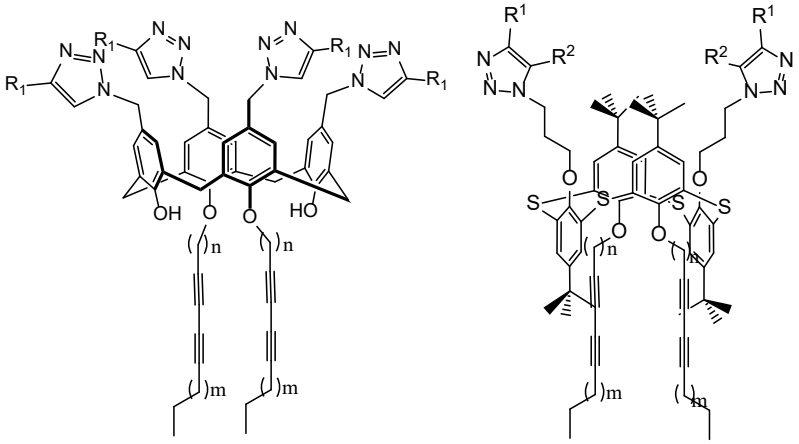
(Thia)calix[4]arene derivatives are well-known objects of supramolecular chemistry with unique properties. Calixarenes are widely used in recognition and binding of various substrates. The ability of selective functionalization of the lower and upper rim as well as a variety of stereoisomeric configurations gives the possibility to obtain receptors with various structures. Covalent binding of (thia)calix[4]arenes with 1,3-butadiyne fragments will provide selective colorimetric sensors by polymerization of diacetylene moieties.

In this work, new synthetic strategy for the wide series of (thia)calix[4]arene – based bifunctional receptors in *1,3-alternate* stereoisomeric form bearing polymerizable 1,3-butadiyne fragments on the one side and azide fragments for the CuAAC reaction on another.



Scheme 1.

(Thia)calixarene derivatives with 1,3-butadiyne fragments were used in copolymerization with 10,12-pentacosadiynoic acid to give functional PDA nanoparticles. In this work, experimental physical-chemical studies of obtained nanoparticles have been conducted.

This work was supported by RFBR (grant № 16-33-00337)

Novel ligands of NMDA-receptor based on isoxazole scaffold

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Recent findings in NMDA receptor pharmacology showed their involvement in the depression pathogenesis. Moreover, the application of ketamine which is well-known NMDA-receptor blocker can improve patients' condition with treatment-resistant depression. Unfortunately, wide use of this drug is limited for its serious side effects and the lack of selectivity. Here we propose the novel potential ligands of the NMDA-receptor ifenprodil binding site, based on isoxazole scaffold, which can provide necessary selectivity (Fig.1).

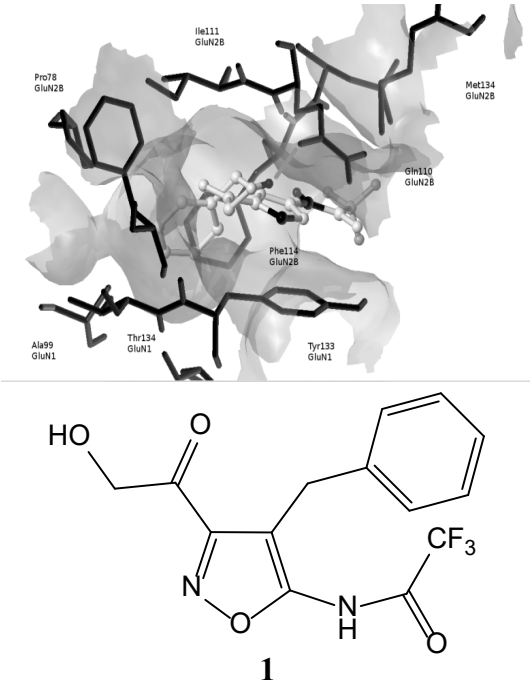

Fig. 1. The binding mode of the proposed antagonist **1** and it aminoacid environment

In our group we have developed the general synthetic approach to polyfunctionalized isoxazoles based on heterocyclization of electrophilic alkenes under the treatment of tetranitromethane-triethylamine complex [1]. Using this methodology we elaborated convinient synthetic routes to a series of isoxazole derivatives, which are efficient ligands of NMDA-receptor according to computational studies.

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This work was supported by RFBR (Project 14-03-00469-a) and Presidium RAS (program No. 8P)

3,7-diazabicyclo[3.3.1]nonanes in supramolecular and medicinal chemistry

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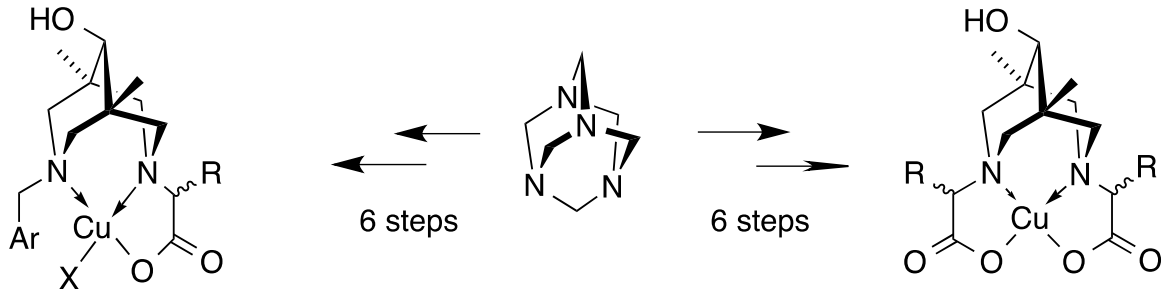
This report explains the results of our long time work in the field of 3,7-diazabicyclo[3.3.1]nonane's (bispidine) chemistry [1] and points out novel directions of research for the future [2-5].

The current achievements and known features of this type of ligands are discussed including the possibility of bispidines to form supramolecular polymers both in crystals and in gel-phase. The comprehensive knowledge about structure and methodology of investigation of supramolecular gels and metallogels will be presented. Then we discuss the ways of the possible application of bispidines and their complexes as bioactive compounds.

The radiation therapy is one of the modern and useful methods for the treatment of the oncological diseases, particularly, for the brain, head and neck tumors as well as for the tumors of some other localization. The problem of short decay time can be solved by use of new radiopharmaceuticals containing long-lived isotopes, particularly, ^{64}Cu. To do this, the elaboration of easily modified ligand systems with high affinity to the metal cation and with wide possibilities of chemical modifications including the conjugation to the biological vectors is proposed.



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Strecker reaction with cyclic imines

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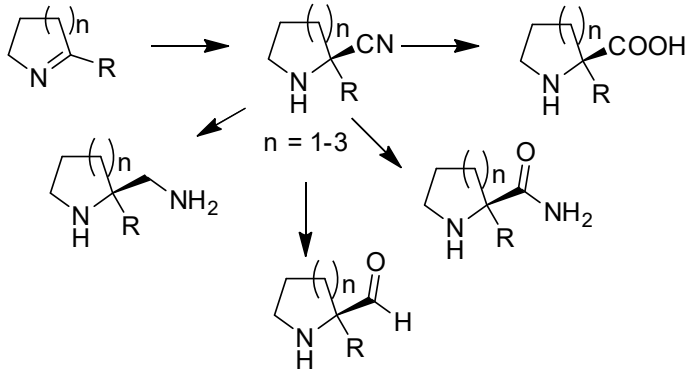
Amino acids are important class of organic compound in different fields of chemistry, industry and medicine. Various biological active natural compounds contain amino acids. Residue cyclic amino acids (e.g. proline) have been attracting much attention due to their structure peculiarities, which give a conformation rigidity of proteins compared with other amino acids. Moreover last decades proline, pipecolic acid and their derivatives bearing substituents in α-position have been playing an important role as catalyst in different reactions. On the other hand, there are no any common methods of synthesis of α-substitute derivative. So we decided to develop a new method of synthesis of different derivatives of proline, pipecolic acid and their homologue with α-substituents.

For this purpose we decided to use hydrocyanation with cyclic imines. This method allows to obtain α-amino nitriles. It was found that stability of cyclic amino nitriles depends on ring size and nature of substituents in α-position.

Amino nitriles are versatile intermediates for the synthesis of several classes of organic compound such as amino acids, diamines, alkanolamines, amides. Also this reaction could be carried out in asymmetric form[1].



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This work was supported by the Russian Science Foundation (RSCF) (grant number 16-33-60012 mol_a_dk).

Efficient Synthesis of Vinyl Ether Functionalized Carbohydrates with Calcium Carbide as an Acetylene Source

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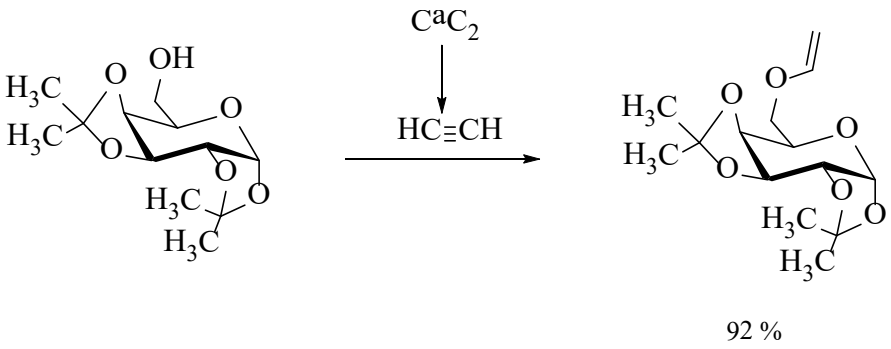
Carbohydrates represent the most abundant and common class of biomolecules in nature. Their structural diversity, multiple functionalities and biological innocuousness make carbohydrates attractive in the field of asymmetric synthesis,[1] biomass-based polymers,[2] supramolecular chemistry,[3] biosensors,[4] etc.

Sugar-based ethenyl ethers are valuable chiral synthons due to the versatile reactivity of the vinyloxy function.[5] Among different methods, the direct vinylation of carbohydrates with acetylene in the presence of bases seems to be a simple and an efficient route to this class of compounds.[6]

We have developed an efficient and a simple method for the direct vinylation of carbohydrates in high yields employing calcium carbide as an acetylene source (Scheme 1). The applied reaction conditions allow for use of standard glass equipment in a scientific laboratory.



Scheme 1. A representative example of the vinylation of 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose

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This work is supported by RFBR (grants № 15-33-20536 and № 14-03-01005). G. Werner acknowledges Saint Petersburg State University for a postdoctoral fellowship (№ 0.50.1186.2014). The authors also express their gratitude to the Centre for Magnetic Resonance, the Centre for Chemical Analysis and Materials Research and Interdisciplinary Center for Nanotechnology (Saint Petersburg State University) for physicochemical measurements.

Efficient Pathway to Vinyl Phenyl Ethers with Calcium Carbide as an Acetylene Source

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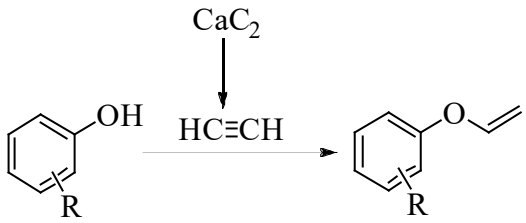
Vinyl ethers represent a highly valuable class of compounds that have been used for the polymer synthesis as well as organic synthesis including Claisen-rearrangement, cycloaddition, cyclopropanation, hydroformylation, metathesis, and Heck reaction.

The synthesis of vinyl ethers in the industrial graduation mostly occurs through conversion of the suitable alcohols and phenols with acetylene in a present of basic catalysts. Such reactions involving high-pressure are not easily to perform with the standard laboratory equipment.[1]

We have successfully developed a new process for the synthesis of vinyl ethers using the calcium carbide as source of acetylene. Under the applied reaction conditions the synthesis of the vinyl ethers in high yields in a laboratory with the standard glass equipment was achieved (Scheme 1).



Scheme 1. Vinylation of phenols with calcium carbide

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This work is supported by RFBR (grants № 15-33-20536 and № 14-03-01005). G. Werner acknowledges Saint Petersburg State University for a postdoctoral fellowship (№ 0.50.1186.2014). The authors also express their gratitude to the Centre for Magnetic Resonance, the Centre for Chemical Analysis and Materials Research and Interdisciplinary Center for Nanotechnology (Saint Petersburg State University) for physicochemical measurements.

Natural herbicides from a renewable feedstock.

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Contemporary herbicides are mired by problems with resistance and ecological impact, leading to restrictions and bans. Sorgoleone (1) is a naturally occurring and incredibly potent herbicide [1]. Sorgoleone is the major active constituent of the root exudate of *Sorghum bicolor,* but is only produced in very small amounts. To make this viable for use in agriculture, a method for large scale production is needed. A synthetic route for Sorgoleone was first published in 1990 by Sargent *et al* [2] but consisted of 17 steps.

Work at the BioComposites Centre [3] has led to the synthesis of the saturated congener of Sorgoleone in 5 steps from a by-product of the cashew nut industry, Cardol (2). The synthesis starts with hydrogenation as to stop side reactions, then is followed by a methylation before oxidising to the quinone form. The next step is a Thiele acetylation, which is followed by deacetylation and further oxidation to form the product (1).

Currently, work is building upon this foundation and attempting to retain the unsaturation present in the aliphatic side chain, using a biosynthetic pathway and Cardol derivatives as starting material.

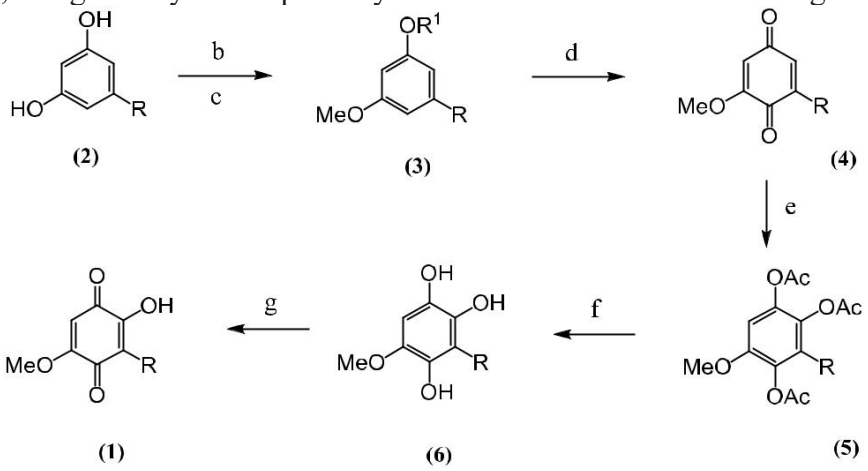

Fig.1 R=$C_{15}H_{31-2n}$ where n=0 to 3, R^1=H or Me

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This work was supported by UK Knowledge Transfer Partnership Program (project KTP07459) and UK Biotechnology and Biological Sciences Research Council (BBSRC project BB/M012867/1).

One-pot Synthesis of GABA Amides via the Nucleophilic Addition of Amines to 3,3-Disubstituted Cyclopropenes

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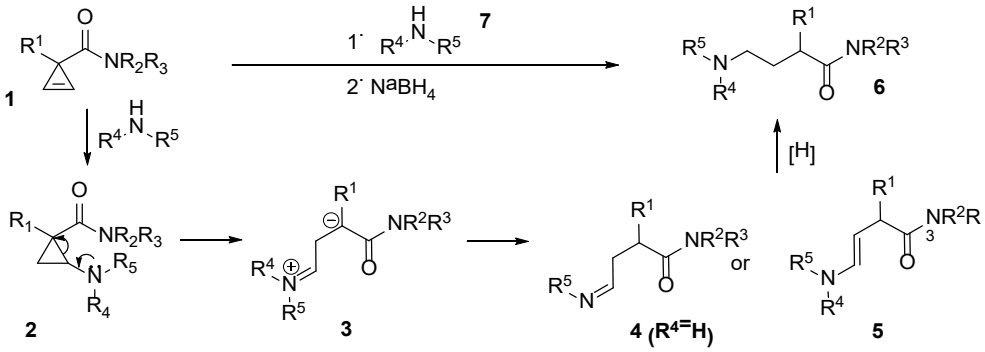
γ-Aminobutyric acid (GABA) is the prominent inhibitory neurotransmitter in the mammalian central nervous system, playing a principal role in reducing neuronal excitability making it of immense importance for modern bioorganic and medicinal chemistry.

In our studies [1] of donor-acceptor cyclopropanes (DAC), we investigated the possibility to access substituted GABA derivatives **5** via the ring opening of DAC **2**. In this work we demonstrated [2] one-pot synthesis of various GABA amides. Nucleophilic addition of primary and secondary amines across the double bond of cyclopropene-3-carboxamides is followed by ring-opening of the resulting donor-acceptor cyclopropanes. Subsequent in situ reduction of enamine (imine) intermediates allow access to substituted GABA derivatives.

The propensity of DACs toward ring cleavage corresponds to the polarization of the C–C bond between electron-donating (EDG) and electron-withdrawing (EWG) groups. Addition of an electron-rich amino group triggers the desired bond cleavage in intermediate **2** affording zwitterionic intermediate **3**. Then, in the presence of a proton source, this intermediate stabilizes in a form of imine **4** (if derived from primary amine **7**) or enamine **5** (secondary amine **7**). Species **4** or **5** can then subsequently be reduced in situ to give GABA amide **6**, or be employed as electrophilic or nucleophilic moiety in diverse imine or enamine chemistry.



Scheme 1.

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Cyclization of triaryl divinyl ketones catalyzed by acid

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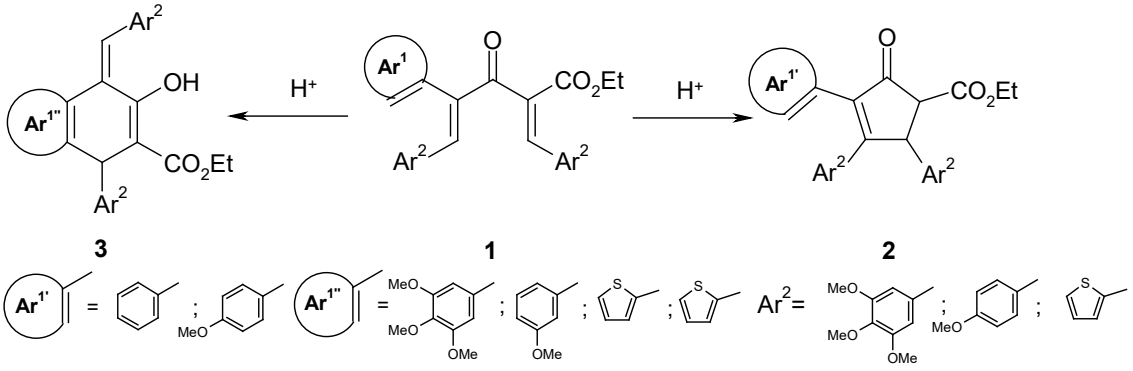
The Nazarov reaction is widely used in organic synthesis for the preparation of diversely substituted cyclopentenones by the cyclization of divinyl ketones. The classical version of this reaction requires a Lewis acid as catalyst, but the latter various acidic catalysts including Bronsted acids were also used.

The aim of this work is study of the cyclization of triaryl-substituted divinyl ketones in the presence of Lewis and Bronsted acids. It was found that in depend on aryl substituents the reaction can precede in two alternative ways. The first way is a classical Nazarov reaction resulting in the formation of triarylcyclopentenones **2**. The alternative reaction involves the electrophilic substitution in an aromatic system with vinyl ketone group that leading to product **3**. Various catalysts have been investigated and it was found that the reaction direction does not depend on the nature of catalyst, and the best results were obtained using dry hydrogen chloride as catalyst in absolute methylene chloride as solvent.



Scheme 1. Cyclization of triaryl divinyl ketones.

The structures of reaction products were proved by different spectroscopic methods (NMR, MS and IR), including X-ray analysis. In this contribution we will also discuss the some mechanistic aspects of these transformations.

This work was financial supported by the Russian Foundation for Basic Research (RFBR Grant № 15-53-05049).

Membranes for fuel cells based on polyimides with the inclusion of polysiloxanes and crown-ethers

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The basic part of any fuel cell (FC) is a membrane-electrode assembly (MEA). “The heart” of solid polymer MEA is proton exchange membrane. Typically, proton exchange membrane (PEM) is a film of polymer with hydrophobic main chain and acid groups on the side chains. [1]. There is a number of demands for PEM such as a combination of high proton conductivity and high mechanical durability, chemical resistance and low production cost.

The major breakthrough in the technology of PEM was the appearance of perfluorosulfonic acid (PFSA) Nafion - DuPont company’s product obtained in 1962 [2]. Despite the fact that PFSAs are still excellent membrane materials for fuel cells, they have several significant disadvantages that limit their widespread use [3]. The technological need for innovative high-performance and cost-effective soft materials as well as the drive for new knowledge and fundamental understanding has led to significant reseach efforts in the field of PEM.

Polyimides (PIs) with excellent characteristics such as thermal stability, electrical properties and chemical resistance as well as their high strength and high modulus are particularly attractive for researchers, due to the large variety of possible chemical structures. However, the polyimides themselves may not satisfy all the requirements for PEM. Thus block copolymers where each repeating unit performs a specific function should be developed for high-efficient PEM. The main idea of our development is a combination of polyimides with polysiloxanes and crown-ethers for producing materials with enhanced proton conductivity, thermal stability and resistance to aggressive environment (Fig. 1.):

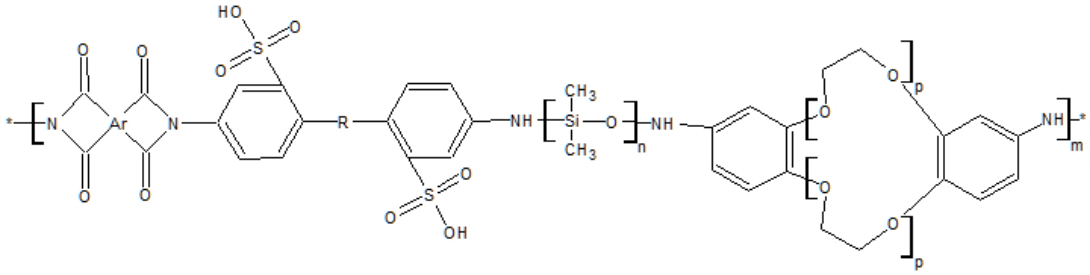

Fig. 1. The structure of the block co-polymer for PEM

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Photocyclization of the 1,2-oxazolylphenylethens: a new method for synthesis of substituted naphthalene

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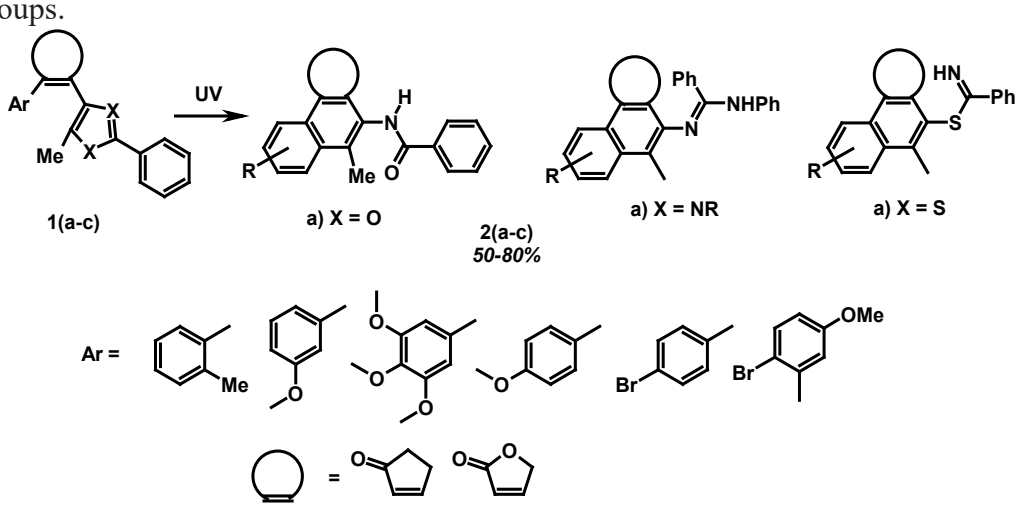
Photochemical reactions of diarylthenes are widely used in organic synthesis for the preparation of polyaromatic compounds. Recently we have found a new rearrangement of diarylethenes **1**, comprising benzene and five-membered heterocyclic rings as aryl moieties [1,2]. It was shown that UV-irradiation of methylene chloride solution of such diarylethenes leads to the formation of naphthalene derivatives.

The aim of this work is to study the influence of substitutes in benzene moiety on the reaction product yields and to develop a preparative method for the synthesis naphthalene derivatives with different functional groups.



Photocyclization reaction of a wide range of unsymmetrical diarylethenes with various substituents in benzene ring has been studied. In addition the effect of different heteroatoms on the ring-opening process has been also investigated.

In this contribution we will also discuss the some mechanistic aspects of this phototransformation and the effect of solvent and oxygen on this process.

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Reactions of 2,5-diformylfuran with arenes under superelectrophilic activation

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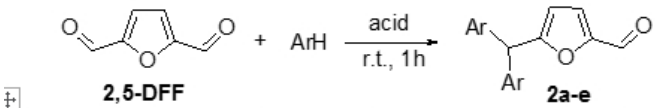
Because of the problems associated with the depletion of natural resources and pollution of the environment, more and more attention is paid to the chemical processing of plant raw material, which are renewable natural resources. The obtained from renewable raw material furfural and its derivatives are considered as promising compounds in laboratory and industrial organic synthesis. The furfural derivatives may find their application not only as a nutritional supplements and as a fuel, but also as drugs, additives and materials for synthesis of polymers.

This work includes superelectrophilic activation of 2,5-diformylfuran (2,5-DFF) with Bronsted (TfOH) and Lewis ($AlBr_3$, $AlCl_3$) acids in presence of arenes (see **Table** and **Figure**).

2,5-DFF in reactions with benzene under the action of TfOH or AlX_3 (X = Cl, Br) at r.t. for 1 h gives product of Friedel-Crafts process, 5-(diphenylmethyl)furan-2-carbaldehyde **2a** in quantitative yield (entries 1-3). For isomeric *ortho*- and *meta*-xylenes better results were obtained with Lewis acid $AlBr_3$ (entries 4, 6, 8). Reactions in TfOH led to oligomeric material (entries 5, 7), although *para*-xylene gave in both TfOH (entry 9) and $AlBr_3$ (entry 8) the target compound **2e**. Unger the action of $AlBr_3$ 2,5-DFF with *ortho*- xylene afforded regioselectively **2b**. In case of *meta*-xylene two regioisomers **2c** and **2d** are formed (entry 6), due to electrophilic substitution in different positions of aromatic ring.

It should be noted that under this superacidic conditions only one formyl group of 2,5-DFF is activated, the second one is remained unreacted.



2,5-DFF **2a-e**

Entry	ArH	Acid	Reaction product		Yield, %
			no.	Ar	
1	Benzene	$AlBr_3$	**2a**	Ph	98
2	Benzene	$AlCl_3$	**2a**	Ph	98
3	Benzene	TfOH	**2a**	Ph	98
4	*o*-Xylene	$AlBr_3$	**2b**	3,4-$Me_2C_6H_3$	72
5	*o*-Xylene	TfOH	Oligomers		
6	*m*-Xylene	$AlBr_3$	**2c** **2d**	2,4-$Me_2C_6H_3$ 3,5-$Me_2C_6H_3$	36 15
7	*m*-Xylene	TfOH	Oligomers		
8	*p*-Xylene	$AlBr_3$	**2e**	2,5-$Me_2C_6H_3$	78
9	*p*-Xylene	TfOH	**2e**	2,5-$Me_2C_6H_3$	87

Table. Reactions of 2,5-DFF with arenes under superelectrophilic activation.

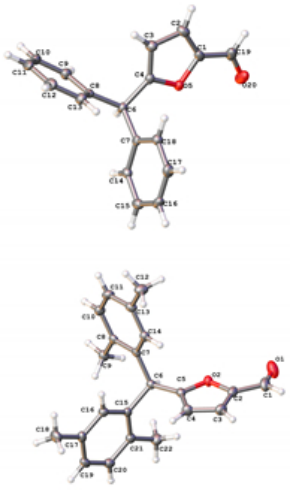


Fig. X-ray structures of **2a** (top) and **2e** (bottom).

This work was supported by the Russian Science Foundation, grant no. 14-13-00448

Synthesis of Aryl and Hetaryl-substituted 1,2,4-Triazolo[1,5-*a*]-1,3,5-triazinones

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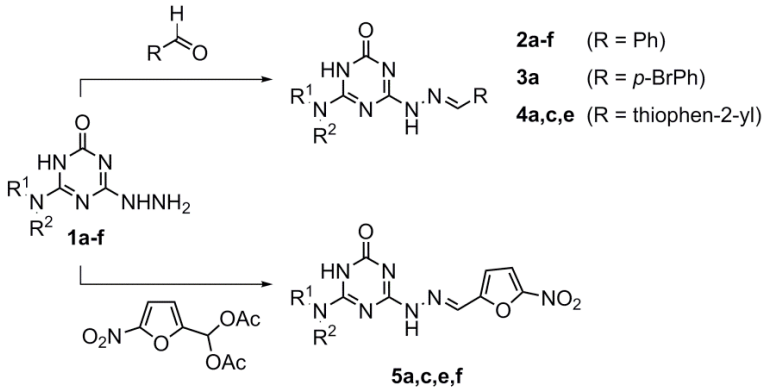
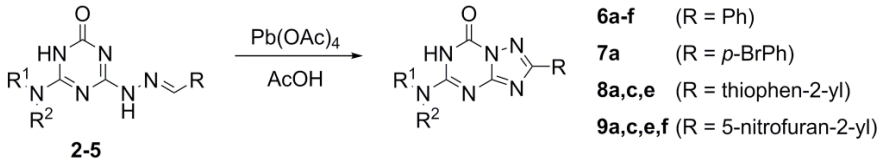
The 1,2,4-triazolo-1,3,5-triazine heterocyclic system is an aza-analogue of purine, and is of interest as a promising basic structure to design new bioactive compounds. 1,2,4-Triazolo[1,5-*a*]-1,3,5-triazine derivatives, containing aryl or hetaryl substituents at position 2, and their cyclic and acyclic nucleosides are of interest as antiviral and antitumor compounds. To synthesize new aza-analogues of guanine, 4-amino-substited 6-hydrazinyl-1,3,5-triazin-2-ones **1** were used as starting materials. Benzylidene derivatives **2** and **3** were obtained by the reaction of **1** with the corresponding benzaldehyde in ethanol. The reaction with benzaldehyde proceeded smoothly at room temperature, whereas in the case of p-bromobenzaldehyde, the reaction required a higher reaction temperature (75°C). To obtain thiophenylmethylidene and 5-nitrofurylidene derivatives **4** and **5**, reflux of the starting material **1** with 2-thiophenecarboxaldehyde or 5-nitrofurfural diacetate in ethanol and longer reaction times were required.



NR^1R^2 = $N(CH_3)_2$ (a); NHPr-n (b); NHPr-i (c); $N(CH_2)_4$ (d); $N(CH_2)_5$ (e); $N(CH_2)_2O$ (f)

The desired 5-aminosubstituted 2-aryl(hetaryl)-1,2,4-triazolo[1,5-*a*]-1,3,5-triazin-7-ones **6-9** were obtained via oxidative cyclization of the corresponding compounds 2-5 with lead(IV) tetraacetate in acetic acid. The completion of the reaction was achieved after maintaining the reaction mixture at 80-85°C for 10-14 h. IR, NMR, and X-ray studies showed that the only products of the reaction were the [1,5-*a*]-isomers [1].



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New chiral isonitriles for multicomponent reactions

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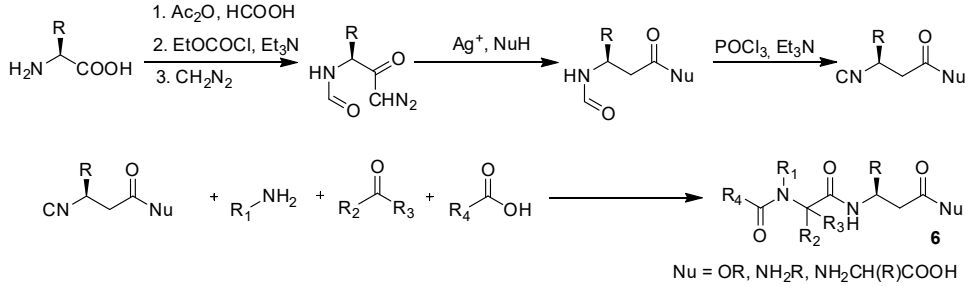
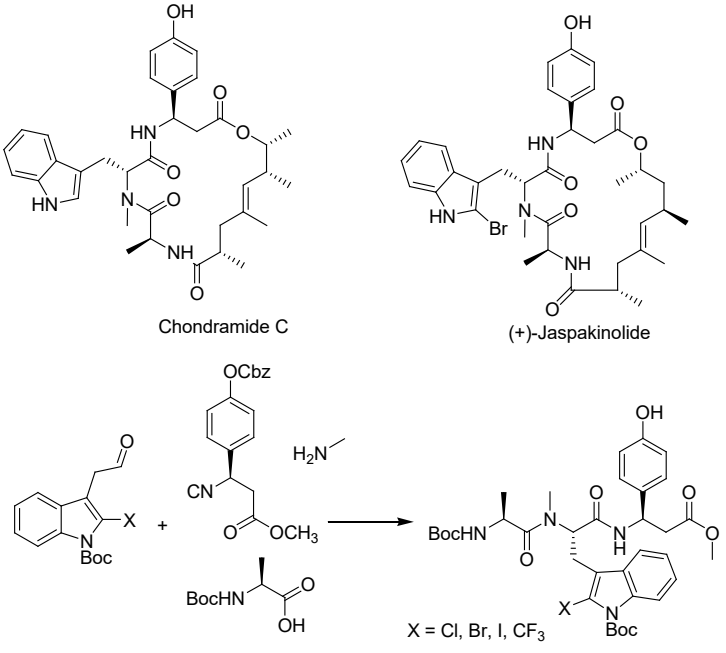
Optically pure β_3-amino acids are the building block for synthesis of biologically active substances and drugs. Many natural compounds containing fragments β_3-amino acids in their structure possess diverse biological activities, such as antiviral, antimicrobial, antitumor, antiinflammatory, etc... For example, peptides containing fragments of β-amino acids have a great potential for modern medicine. As is known, the introduction of β-amino acids in the peptide chain structure greatly improves its metabolic stability. However, the synthesis of peptides such raids number of disadvantages, such as multistage, high cost.

So we decided to develop an efficient method for the synthesis of new chiral β_3-isonitriles. Such isonitriles can be effectively used in the Ugi multicomponent reactions for preparing peptides containing a fragment of β-amino acids (Scheme 1).



Scheme 1. Synthesis and synthetic potential of chiral β_3-isonitriles

β_3-Amino acids are important structural fragments of natural peptides and depsipeptides. Natural depsipeptides jaspamide and chondramide contain the β_3-amino moiety. These compounds have shown great therapeutic potential as anti-cancer and antibiotics. So we decided to offer the shortest way for synthesis of the peptide part of jaspamide and chondramide starting from commercially available 3-indolylacetic acid using Ugi reaction. Also we are going to obtain a series of derivatives with different substituents in 2-nd position of indole ring (Scheme 1).



Scheme 2. Synthesis of the peptide part of jaspamide and chondramide

The Chemoselectivity of the IMDA Reaction *N*-Furfuryl-3-(2-furyl/2-thienyl)allylamines with Maleic Anhydride

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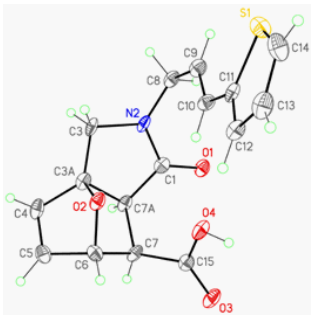
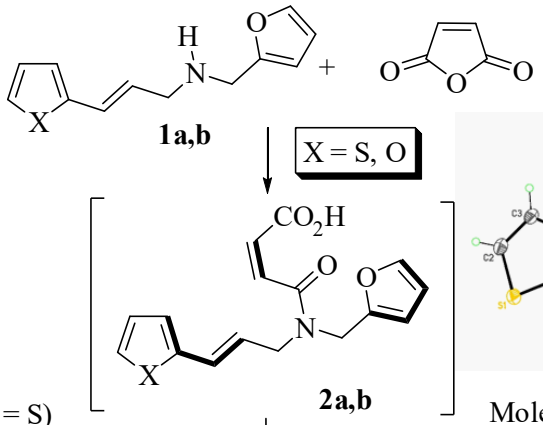
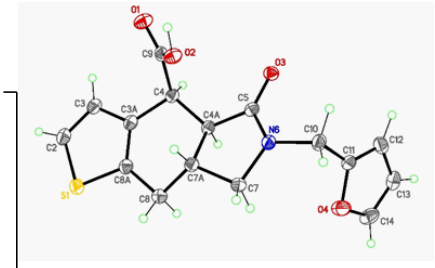
Previously we have developed a new domino reaction based on the interaction of 3-(2-furyl)allylamines with α,β-unsaturated acid anhydrides, which leads to the formation of various hexahydro-4*H*-furo[2,3-*f*] isoindoles and their carboxyl derivatives [1, 2]. This study describes a rather rare example of the complete chemoselectivity in the intramolecular Diels–Alder furan (IMDAF) reaction in the presence of two competing diene centers. The initial *N*-furfuryl-3-(2-furyl/2-thienyl)allylamines **1a**,**b**, easily available in two steps from furyl- or thienylacroleins, were studied in a tandem N-acylation / intramolecular [4+2]-cycloaddition with maleic anhydride.



Molecular structure of **3a** (X = S)





Molecular structure of **4a** (X = S)

Acylation of the nitrogen atom in these compounds leads to the intermediate amide **2**, which could not be isolated (the cyclization has been occurred at room temperature). The latter, possessing two diene moieties, furan and vinylfuran or vinylthiophene, may undergo IMDAF or IMDAV (the intramolecular Diels–Alder vinylarene) competitive reactions.

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[1] Horak, U. I.; Lytvyn, R. Z.; Homza, Y. V.; Zaytsev, et al. *Tetrahedron Lett*. 2015, *56*, 4499-4501.
[2] Zubkov, F. I.; Zaytsev, V. P.; Mertsalov, et al. *Tetrahedron* 2016, *72*, doi:10.1016/j.tet.2016.03.023.

This work was supported by the Russian Foundation for Basic Research (RFBR) according to the research projects № 16-33-00389, 16-03-00125 and by the Ukrainian State Fund for Fundamental Research (grant F53.3/013).

Enantioselective Synthesis of Troponoids by Rhodium(II) Catalysis

Zhi-Jun Jia, Sandip M., Merten C., Daniliuc C., Antonchick A.* and Waldmann H.*

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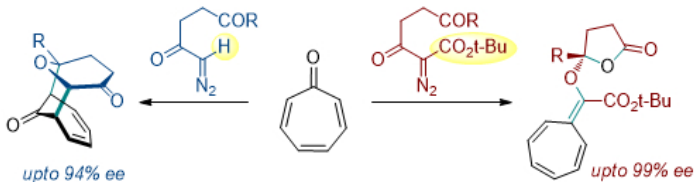
The dirhodium(II)-catalyzed 1,3-dipolar cycloaddition reactions of diazocarbonyl compounds is a powerful domino process for the construction of complex oxapolycyclic systems,[1] and catalytic asymmetric version of this sequence employing chiral Rh(II)-carboxylates have been realized for selected intra- and intermolecular reactions.[2] In contrast to achiral transformations enantioselective 1,3-dipolar cycloadditions of carbonyl ylides with heterodipolarophiles have rarely been explored.[3] Only in two cases were catalytic enantioselective 1,3-dipolar cycloadditions of carbonyl ylides with aldehydes as dipolarophile reported,[3] and the corresponding cycloadditions with ketones are unprecedented. Thus, to the best of our knowledge, enantioselective cycloadditions of tropone with carbonyl ylides have not yet been explored. In this context, we reported the first Rh(II)-catalyzed highly enantioselective 1,3-dipolar cycloaddition reaction between the carbonyl moiety of tropone and carbonyl ylides derived from diazodiketoesters to afford troponoids in good to high yields and with excellent enantioselectivities.[4] We further showed that α-diazoketone-derived carbonyl ylides in contrast to carbonyl ylides derived from diazodiketoesters undergo (6+3) cycloadditions with tropone to yield the corresponding bridged heterocycles with excellent stereocontrol.[4] The observed substrate controlled chemoselective switch of reactivity is a highly interesting example of a programmable synthesis.



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[1] D. M. Hodgson, A. H. Labande, S. Muthusamy, *Org. React.* **2013**, *80*, 133-496. [2] a) D. M. Hodgson, T. Brückl, R. Glen, A. H. Labande, D. A. Selden, A. G. Dossetter, A. J. Redgrave, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5450-5454; b) D. M. Hodgson, R. Glen, A. J. Redgrave, *Tetrahedron: Asymmetry* **2009**, *20*, 754-757; c) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417-1418; d) N. Shimada, M. Anada, S. Nakamura, H. Nambu, H. Tsutsui, S. Hashimoto, *Org. Lett.* **2008**, *10*, 3603-3606; e) N. Shimada, T. Oohara, J. Krishnamurthi, H. Nambu, S. Hashimoto, *Org. Lett.* **2011**, *13*, 6284-6287. [3] a) H. Suga, K. Inoue, S. Inoue, A. Kakehi, *J. Am. Chem. Soc.* **2002**, *124*, 14836-14837; b) H. Tsutsui, N. Shimada, T. Abe, M. Anada, M. Nakajima, S. Nakamura, H. Nambu, S. Hashimoto, *Adv. Synth. Catal.* **2007**, *349*, 521-526. [4] S. Murarka, Z-J. Jia, C. Merten, C-G. Daniliuc, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 7653-7656.

Unusual Interaction of 3-(Phenyl)allylamines with Maleic Anhydride

Zubkov F.[a], Voronov A.[a], Ukhanova M.[a], Alekseeva K.[a], Nikitina E. [a], Zaytsev V.[a], Khrustalev V.[a], Tilve S. [b].

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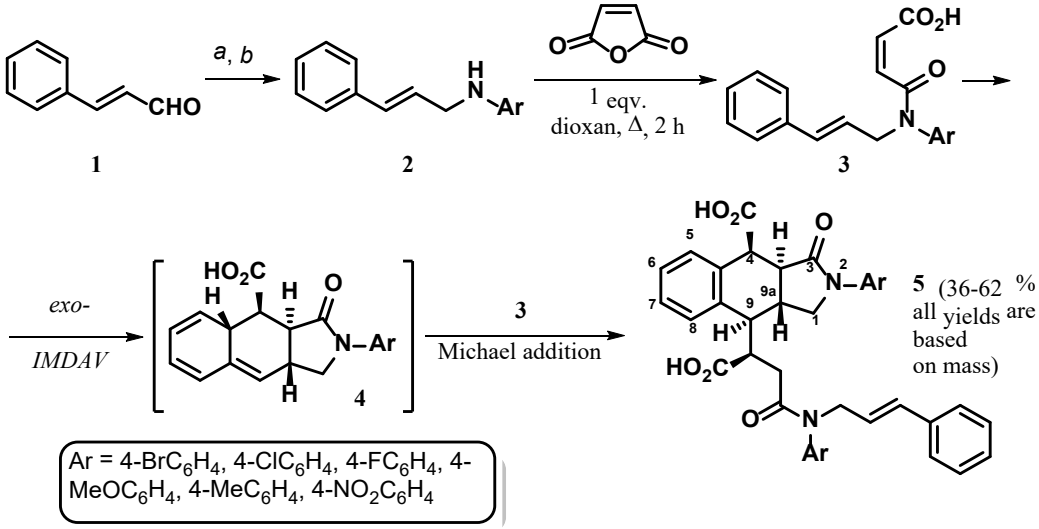
Recently, we have proposed several powerful approaches [1-3] to the synthesis of heterocyclic compounds containing lactone and lactam moieties. The main leitmotif of the described transformations is the IMDAV reaction (intramolecular Diels–Alder vinyarenes reaction), basing on the interaction between 3-aryl(hetaryl)allylamines and α,β-unsaturated acid anhydrides.

The present study is an extension of this methodology.

3-(Phenyl)allylamines (**2**) react readily with maleic anhydride at room temperature giving amides **3**. When this reaction was carred out at 100 °C, the intramolecular [4+2]-cycloaddition in amides **3** was observed. However, neither adducts **4**, north products of their aromatization were isolated. Instead of this the products of the Michael addition **5** were formed.



Scheme 1. Reagents and conditions: (a) $ArNH_2$, $MgSO_4$/ CH_2Cl_2, rt; (b) $NaBH_4$/ MeOH, rt.

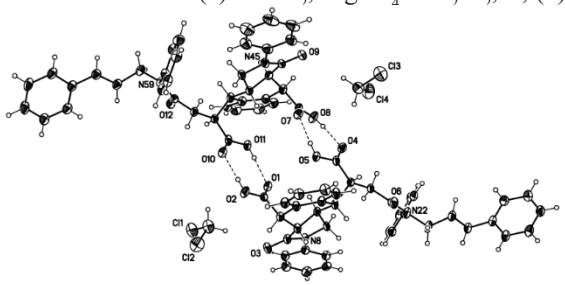


Figure 1. Molecular structure of compound **5** (Ar = Ph)

References

[1] Horak, U. I.; Lytvyn, R. Z.; Homza, Y. V.; Zaytsev, V. P *et al. Tetrahedron Lett*. 2015, *56*, 4499-4501.
[2] Zubkov, F. I.; Zaytsev, V. P.; Mertsalov, D. F. *et al. Tetrahedron* 2016, *72*, doi: 10.1016/j.tet.2016.03.023
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This work was supported by the Russian Science Foundation (project № 16-43-02009) and by the Indian DST Foundation project № DST/RSF/15/P-61

An Easy Construction of Furo[2,3-*f*]isoindole Core by the IMDAV Reaction

Zubkov F.[a], Sizykh A.[a], Zaytsev V.[a], Mertsalov D.[a], Homza Yu.[b], Horak Yu.[b], Lytvyn R.[b], Obushak M.[b]

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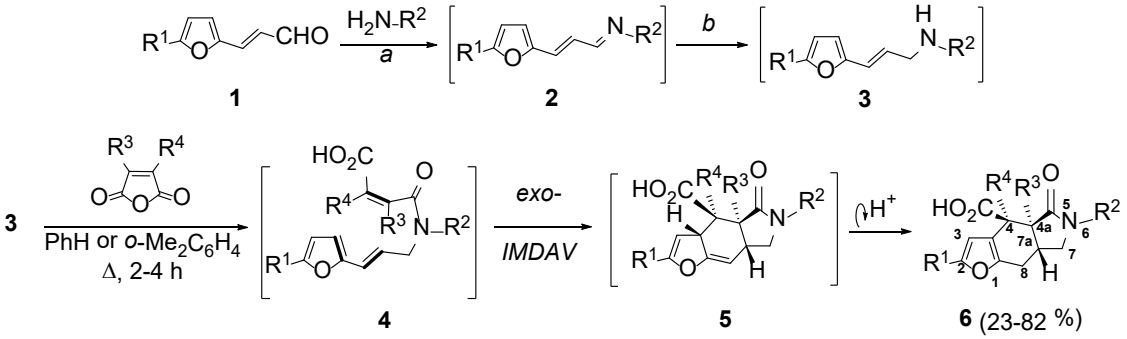
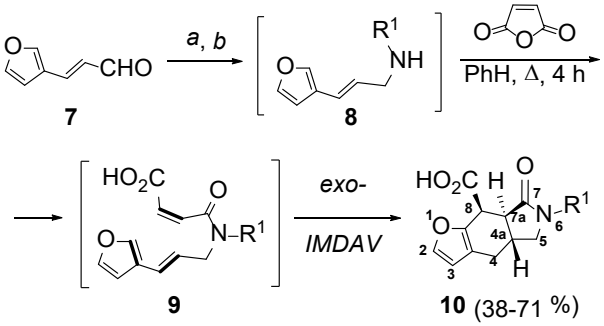
The vinylogues of furfurylamines - 3-(furyl)allylamines (**3**), easily available in two steps from furylacroleins (**1**), were studied in the tandem N-acylation / intramolecular [4+2]-cycloaddition reaction with maleic, pyrocinchonic, and citraconic anhydrides [1, 2]. By using a domino reaction of 3-(furyl) allylamines (**3**) and α,β-unsaturated acid anhydrides under mild conditions, various hexahydro-4*H*-furo[2,3-*f*]isoindole-4-carboxylic acids (**6**) were synthesized efficiently. The domino sequence includes three steps: an acylation of the nitrogen atom in 3-(furyl)allylamines (**3**), the intramolecular Diels–Alder cycloaddition in the resulting N-acyl vinylfurans (**4**) (IMDAV reaction), and a prototropic shift in the adducts **5** followed by recovery of aromaticity of the furan nucleus.



Scheme 1. R^1 = H, Alkyl, Ar; R^2 = Alkyl, Ar, Hetaryl; R^3 and R^4 = H, Me (45 examples). Reagents and conditions: (a) $MgSO_4$/ CH_2Cl_2/ rt or AcONa/ EtOH/ Δ; (b) $NaBH_4$/ MeOH or THF/ rt.

3-Furylacrolein (**7**) can be easily involved into the IMDAV reaction similar to that described above.



Scheme 2. R^1 = Alkyl, Ar (6 examples). Reagents and conditions: (a) R^1-NH_2/ $MgSO_4$/ CH_2Cl_2, rt, 4 h; (b) $NaBH_4$/ MeOH, rt, 4 h.

References

[1] Horak, U. I.; Lytvyn, R. Z.; Homza, Y. V.; Zaytsev, *et al*. *Tetrahedron Lett*. 2015, *56*, 4499-4501.

[2] Zubkov, F. I.; Zaytsev, V. P.; Mertsalov, *et al*. *Tetrahedron* 2016, *72*, doi:10.1016/j.tet.2016.03.023.

This work was supported by Ukrainian State Fund for Fundamental Research (grant F53.3/013) and by the Russian Foundation for Basic Research (RFBR) according to the research projects № 16-03-00125, 16-33-00389.

1-acetyl-3-(pyridyl-2)-5-phenil-4,5-dihydropyrazole copper complexes

Korablina D.D.[a], Vorozhtsov N.I.[b], Beloglazkina E.K.[b], Sviridova L.A.[b], Kalenikova E.I.[a]

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[b] *M. V. Lomonosov Moscow State University, Faculty of Chemistry*
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In recent years, complexes of transition metals with organic ligands have been the object of attention of researchers engaged in the search of new pharmacologically active compounds. One promising direction in this area is obtaining of small molecule analogs of superoxide dismutases. Based on the structure of these enzymes their counterparts should be stable coordination compounds of copper, nickel, or manganese that mimic the activity of the native enzyme.

We have studied the interaction of 1-acetyl-3-(2-pyridyl)-5-phenyl-4,5-dihydropyrazol with copper (II) chloride. Besides intended product **1**, after prolonged storage or heating of the reaction mixture, compound **2** was formed and a minor amount of the product **3** was also detected (see Fig.1). Structures of all obtained complexes were confirmed by the X-ray diffraction data.

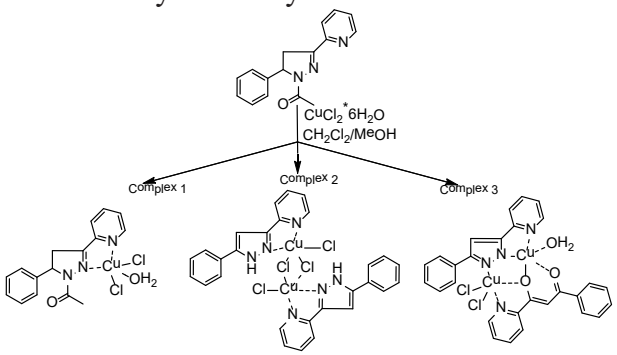

Fig 1.

Electrochemical studies were also carried out for the dihydropyrazole ligand and its copper complex **1** using cyclic voltammetry (CV) technique on a glassy carbon electrode in DMF solution.

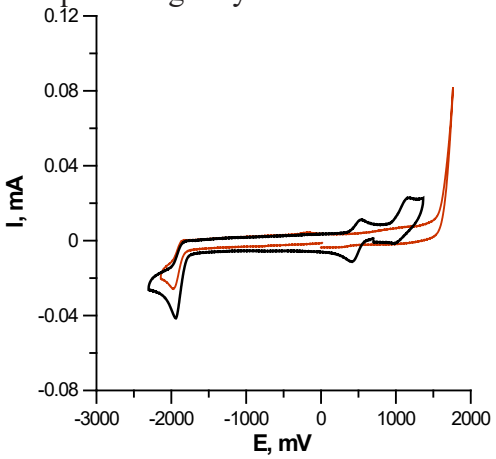

Fig. 2. CVA for ligand (red) and complex 1 (black), DMF solution

Reversible cyclic voltammograms demonstrate two peaks of Cu(II) → Cu(I) and Cu(I) → Cu(0) transitions compared to the original ligand. The first reduction potential of the copper ion in the complex **1** is 0.4 V. That makes its further investigation promising, since first reduction potential of SOD mimics is considered to be in the potential range of 200-400 mV while structural matching of low-molecular analogs and native metalloenzymes.

This work was supported by Russian Foundation for Basic Research (Grant № 16-03-00921).

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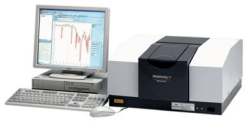

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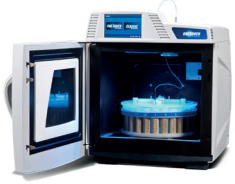

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North-Caucasus Federal University is one of ten federal universities in Russia, unique academic institutions created as a new category of higher educational establishment in the framework of the national Education project implementation. University is located on Stavropol Territory, one of Russia's most picturesque regions. Gold-yellow wheat, fruit gardens, the incredible local cuisine are characteristic of the Stavropol Territory that is called the Gate to the Caucasus. Numerous cultures and confessions have coexisted here for centuries, and today the city is home to over 100 ethnic groups, each of them maintaining the essence of its traditions and customs.

NCFU provides training for qualified staff in areas designated as priorities within the socio-economic development of the District and acts as the leading expert platform for intercultural dialogue in the ethnically diverse region, as well as neighboring countries. It is committed to the principle of integration of scientific, educational, economic and social processes and is working to strengthen the Russian state and society. It is one of the country's leading universities.

Today the large, integrated scientific and educational staff represents a combination of youth and experience. It remains true to its traditions in training future specialists and is open to innovation and exploring new scientific contacts. It is a center for scientific activity and innovation playing a key role in the life of the North-Caucasus Federal District. The North-Caucasus Federal University comprises 13 institutes:

- Research Institute of Chemistry and Chemical Technology;
- Institute of Humanities;
- Institute of Mathematics and Natural Sciences;
- Institute of Life Sciences;
- Institute of Law;
- Institute of Economics and Management;
- Institute of Education and Social Sciences;
- Institute of Oil and Gas;
- Institute of Information Technologies and Telecommunications;
- Institute of Construction, Transport and Engineering;

- Institute of Electric Power Engineering, Electronics and Nanotechnologies;
- Institute of service, tourism and design (Pyatigorsk branch);
- Nevinnomysk Institute of technology

Today the NCFU employs 2000 highly competent teachers most of them holding high scientific degrees (Doctors of Science –358; 1484 Candidates of Science of the entire teaching staff body). The University can boast of 26 scientific schools and 24 areas of research. Besides, the University offers training within 286 subject areas for undergraduate, master, postgraduate courses and medical residency studies and 14 bilingual programs. The student body counts 25 000 youngsters of 86 nationalities, 1100 of them are overseas students from 51 countries. North-Caucasus Federal University benefits from the history of successful international cooperation under the auspices of 80 bilateral agreements with universities and centers of science and education in 32 countries. The university regularly hosts international conferences, seminars and masterclasses with participation from experts from leading overseas scientific and educational organizations.

The university has an advanced chemistry establishments that allows both students and stuff to have the opportunity to work in the modern laboratories on the state-of-art equipment. This research activity is mostly hold in cooperation with European and North-American institutions and its results regularly published in well-known peer-reviewed chemistry journals. Chemistry department is a hosting party and organizer for Russian and International conferences on regularly basis.

Today North-Caucasus Federal University is unique center of science and professional training for competitive employees with high standards of personal culture and creative thinking, the university has great potential for development and offers wide-ranging opportunities for intellectual and professional growth, laying the foundation for success in an ever-changing world.