

# Heterocycles in Organic and Combinatorial Chemistry



## Proceedings of the Second Eurasian Meeting on Heterocyclic Chemistry



**Novgorod the Great, Russia.**  
September 14 - 17, 2002

## “Heterocycles in Organic and Combinatorial Chemistry“

Novgorod the Great, Russia. September 14 - 17, 2002

### Welcome from the chairman

It is a great pleasure for me to welcome all the participants in this small pearl of Eurasian continent – in the ancient town Novgorod the Great.

The name of our meeting “Heterocycles in Organic and Combinatorial Chemistry” emphasizes the modern challenge to synthetic chemists from the industry. Nowadays heterocyclic chemistry is not only the art of synthesis; it is more and more moved into the area of new technologies, such as, e.g. high throughput synthesis of the large libraries of heterocyclic compounds.

We have called our meeting “Eurasian” (*EuroAsian*) to underline that we live at the same continent, which - only due to historical tradition - is artificially separated to Europe and Asia. Because of the absence of physical border between the Asian and the European parts of Eurasia, it would be correct - in geographical sense - to call ourselves Eurasian scientists. In spite of cultural, economical, and political difference and diversity, we all are the neighbors living at the same peace of land.

It is our second meeting. The previous one, held in Suzdal (Russia) in 2000 was our first and (we hope) successful initiative to establish such intra-continental links. That time most participants voted to organize next meeting in Russia, which geographically is pure Eurasian state, the place where the West and the East of the continent really meet one another.

Our choice of place for new meeting is Novgorod, which Russians of the past called *His Majesty Lord Novgorod The Great*. The town is strongly linked to Russian history with its Eurasian flavor. Those were Novgorodians, who invited Scandinavian prince Rurik to keep law and order, thus giving birth to famous Rurik dynasty that ruled over all Russian lands throughout more than 750 years. Those were Novgorodians, who in the early 10th century moved to Constantinopol to secure equal trade with Bizantine giving rise to the integration of East Slavic tribes into the ancient Kievan Russian state. And also those were Novgorodians, who developed and used (for about 600 years) the “veche” – ancient parliament of all citizens that took all vital decisions on the life and foreign policy of the city.

Welcome to Novgorod, the cradle of Russian republican and democratic traditions! The ancient republic's special political structure, spiritual freedom and territorial independence were highly favorable to evolve culture and art. Famous Novgorod Kremlin, ensembles of monasters and churches always attract a lot of tourists from abroad. This town is considered as one of the world cultural heritage sites by UNESCO comission.

I wish you fruitful work, enjoyable contacts, and GREAT staying in Novgorod the GREAT.



Eugene V. Babaev

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# **ABSTRACTS**

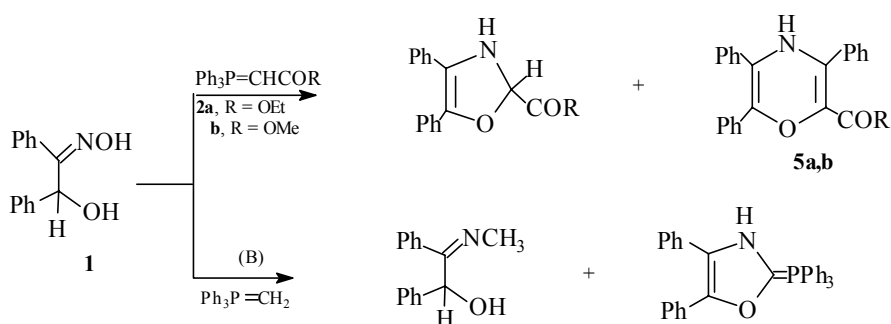
of Lectures  
and  
Poster Presentations

ALKYLIDENE PHOSPHORANES IN HETEROCYCLIC SYNTHESIS.  
APPLICATION OF WITTIG REAGENTS ON  $\alpha$ -IMINO KETONES

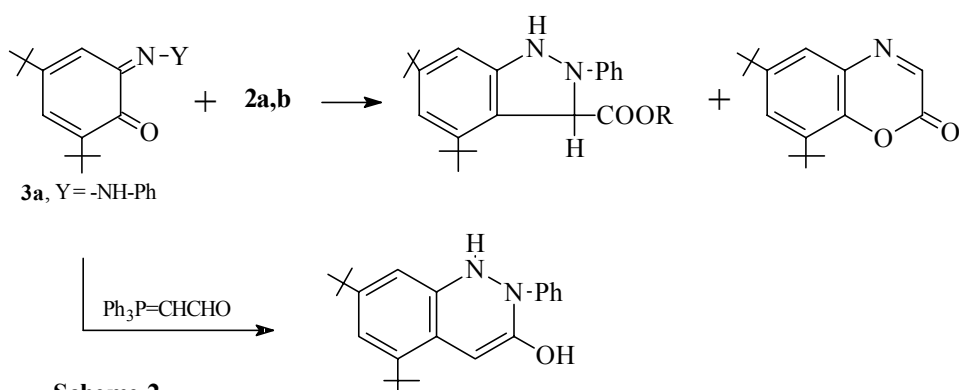
**Wafaa M. Abdou, Azza A. Kamel and Ashraf A. Sediek**

*Department of Pesticide Chemistry, National Research Centre, Dokki, Cairo, Egypt*

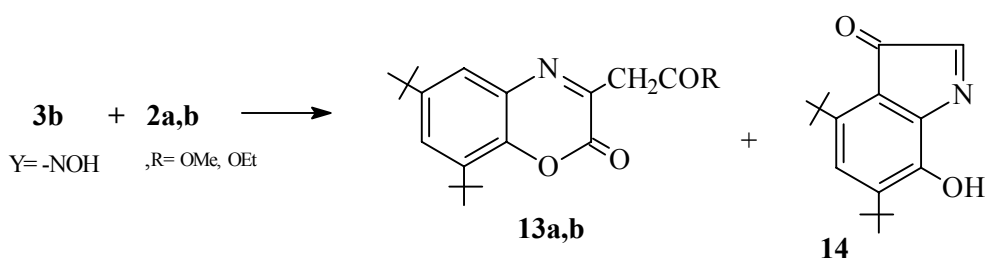
Our interest was directed to study the qualitative structure relationship (QSR). With this aim, we herein report the construction of several different nitrogen-containing heterocycles such as oxazolines, oxazines, quinolines and pyrroles for pharmacological evaluations. Synthesis of the desired compounds was achieved by treatment of oxoimines with stabilized, moderate and active phosphorus ylides (e. g. Schemes 1-3).



**Scheme 1**



**Scheme 2**



**Scheme 3**

## CHEMICAL CONSTITUENTS OF *PHRAGMITES AUSTRALIS*

**Amal F. Al-Aboudi, Musa H. Abu-Zarga and Manar K. Fayyad**

*Chemistry Department, Jordan University, Amman, Jordan*

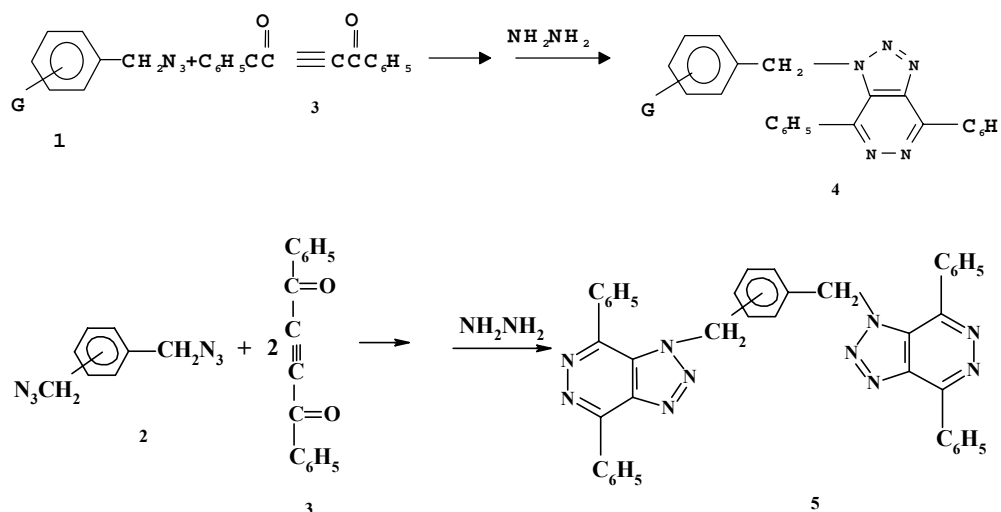
*Phragmites australis* (cav.) trin.ex steudel (syn. *Phragmites communis*), known as common reed, is one of the most widely distributed species in the world, it belongs to the Gramineae family, and has been commonly used in constructed wetlands for the treatment wastewater. Keeping in view the ability of the plant to uptake heavy metals from wastewater, isolation and structural elucidation studies have been carried out on the butanolic extract of the plant. Seventeen compounds were separated; seven flavonoid glycosides; one flavone, seven simple phenolic compounds, and two simple nitrogen heterocyclic compounds were also isolated. The structures were elucidated by different spectroscopic and chemical methods ( $^1\text{H}$  and  $^{13}\text{C}$ -NMR, MS, UV.. etc). It is worth mentioning that, with the exception of tricetin, tricetin glucoside and quercetin glucoside, all the compounds are isolated for the first time from *Phragmites australis*.

# APPLICATION OF 1,3-DIPOLAR CYCLOADDITION REACTIONS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

Sultan T. Abu-Orabi

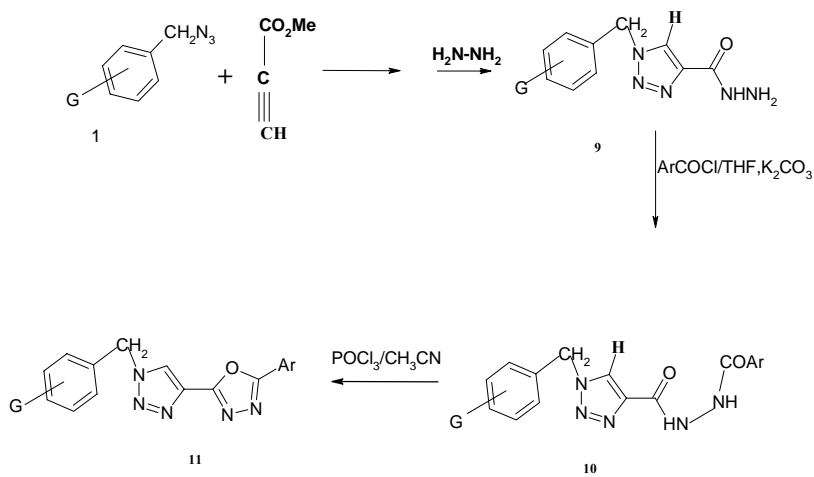
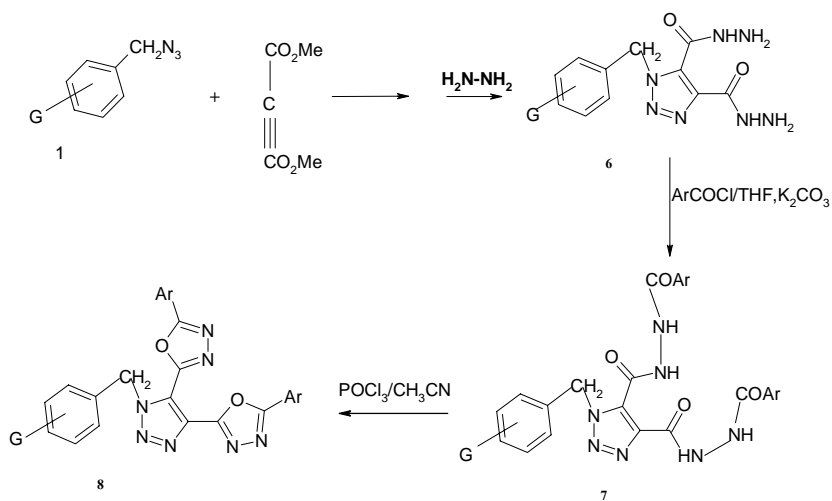
Chemistry Department, Yarmouk University, Irbid, Jordan  
E-mail: [abuorabi@excite.com](mailto:abuorabi@excite.com)

1,3- Dipolar Cycloaddition reactions of organic azides with different acetylenic and ethylenic compounds considered to be the most important method for the synthesis of 1,2,3- triazole and triazoline derivatives respectively. We have found that when substituted benzyl azides **1** and bis (azidomethyl) benzenes **2** were reacted with dibenzoylacetylene **3** followed by the reaction of hydrazine formed the corresponding triazolopyridazine and bis (triazolopyridazine) derivatives **4** and **5** respectively.



Moreover, a series of 4,5- bis [5- aryl- 1,3,4-oxadiazol-2-yl]-1- substituted benzyl- 1,2,3-triazoles **8** was prepared via the dehydration of the corresponding 4,5- bis [N- aroyl- N-hydrazinocarbonyl] -1-substituted benzyl -1,2,3- triazoles **6** which were prepared from substituted benzyl azides with dimethyl acetylenedicarboxylate followed by hydrazine.

In a similar procedure, a series of 2-[1-benzyl-1,2,3-triazolo-4] -5-aryl-1,3,4-oxadiazoles **11** were prepared via phosphorous oxychloride promoted dehydration of the corresponding carbohydrazides **10**.



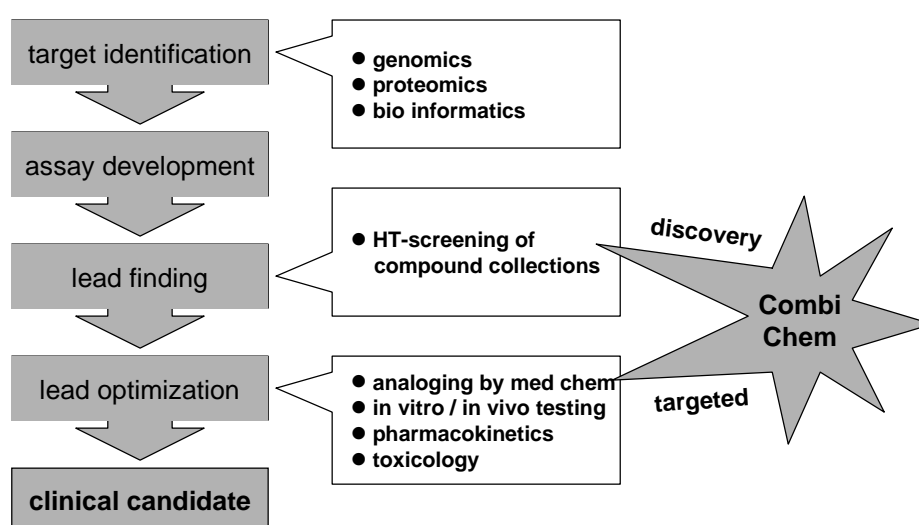


# HIGH THROUGHPUT SYNTHESIS OF HETEROCYCLES FOR LEAD DISCOVERY AND LEAD OPTIMIZATION

**M. Bauser**

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Besides HTS and Genomics, Combinatorial Chemistry is one of the major contributors to BAYER's outstanding Pharma Research Platform. It allows the "production" of thousands of new drug like compounds needed for discovery and also refinement of biological activity.



Unique "building blocks" or "Synthons" are in general the starting point and a prerequisite for unique druglike libraries. Subsequent high throughput derivatization in parallel in solution and on a solid support transform them into compound libraries. The quality of these libraries in terms of purity are as high as for classically "hand made" derivatives. Therefore purification in high throughput is necessary to deliver these libraries to screening facilities in a timely fashion. Compound logistics, storage and data handling are also crucial in this process.

## BIOACTIVE HETEROCYCLIC COMPOUNDS FROM NATURAL SOURCES

**M. Iqbal Choudhary and Atta-Ur-Rahman**

*H. E. J. Research Institute of Chemistry, International Centre for Chemical Sciences, University of Karachi, Karachi-75270, Pakistan  
Fax: 92-21-9243190*

New techniques and approaches in natural product chemistry based on ethnomedicinal approaches, rapid dereplication, high-throughput screening and advanced sophisticated spectroscopic techniques almost changed the natural product chemistry into natural product sciences.

The medicinal plants of Pakistan and other developing countries have traditionally served the local population in the fight against various diseases since centuries; many of them have provided the basis for development of medicinally important drugs.

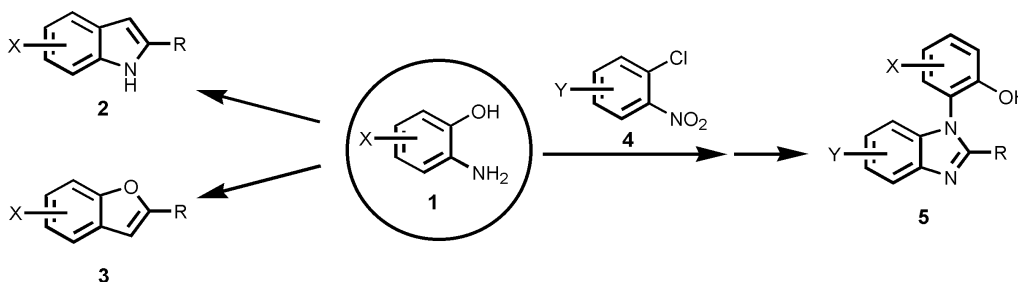
Based on their ethnomedicinal information, we selected several plants for their bioassay-directed phytochemical investigations. These investigations have resulted in the identification of a large number of bioactive heterocyclic constituents with antioxidants, anticholinesterase,  $\alpha$ -glucosidase inhibitors, anti-leishmanial and anti-epileptic activities. This includes a large number of withanolides flavonoids and alkaloids. The chemical structures of these heterocycles were determined through modern spectroscopic techniques.

Wei-Min Dai

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Bicyclic heterocyclic compounds, such as indoles **2**, benzofurans **3**, and benzimidazoles **5**, are the common scaffolds of biologically active molecules and are the focus of research in drug discovery and development. Structural diversity of these heterocycles can be achieved by engineering substituents at different positions of the skeletons. Moreover, the functionalized substituents, such as nitrogen-based group, enables further incorporation of diversity by using different building blocks in subsequent transformations. In order to realize these possibilities, one needs to assure (a) maximum tolerance of the chosen chemical transformations toward the substrate structures and (b) availability of the starting materials from commercial sources preferred at low cost. For developing our diversity-oriented syntheses, we focused on use of the inexpensive 2-aminophenols **1** as illustrated in Scheme 1.

We report on the synthesis of substituted indoles **2** and benzofurans **3** from the common starting materials **1** by selective conversion of OH or NH<sub>2</sub> into a better leaving group (OH → OTf; NH<sub>2</sub> → I) suitable for Pd(0)-Cu(I)-catalyzed cross-coupling with 1-alkynes. It was followed by KO<sup>t</sup>Bu-mediated ring closure of the 2-alkynyl-substituted anilides and phenol acetates [1-3]. We have developed the chemistry to synthesize nitrogen-substituted derivatives of **2** and **3** (X = NO<sub>2</sub>, NH<sub>2</sub>, ArSO<sub>2</sub>NH), respectively, from nitro 2-aminophenols **1** (X = NO<sub>2</sub>). On the other hand, 2-aminophenols **1** underwent a Pd(0)-catalyzed selective amination with 2-chloronitrobenzenes **4** to furnish 2-nitroanilines, which were reduced and condensed with acyl chlorides to form benzimidazoles **5** [4]. We found a simple class of amide-derived P,O-ligands could be used for the above amination of **1** with **4**. A chiral version of the P,O-ligands was used by us in asymmetric allylic alkylation in high enantioselectivity [5]. Preliminary results on synthesis of indoles using microreactors will be discussed as well.



**Scheme 1.** General synthesis of bicyclic heterocycles from 2-aminophenols

*Acknowledgment.* This work is supported by the Innovation and Technology Fund (ITS/119/00), the Area of Excellence Schemes (AoE/B-15/01 and AoE/P-10/01), the HKUST Post-Doctoral Fellowship Matching Fund, and the Department of Chemistry, HKUST.

- [1] Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275.  
 [2] Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* submitted.  
 [3] Dai, W.-M.; Lai, K. W. unpublished results.  
 [4] Dai, W.-M.; Wang, X.; Liu, J.-T.; Zhang, Y. unpublished results.  
 [5] Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y. Williams, I. D. *Org. Lett.* **2002**, *4*, 1615.

STUDIES IN THE SYNTHESIS OF BENZO[*b*]THIOPHENE DERIVATIVES  
AND  
POLYCONDENSED SYSTEMS INCORPORATING FUSED THIOPHENE RING

**Asish De**

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Our group is involved in the synthesis of sulfurheterocycles over the last two decades. In the present lecture some of our recent works will be presented. We have developed several expedient routes to substituted benzo[*b*]thiophene derivatives using the methodology of directed metalation. Tricyclic and tetracyclic compounds incorporating a fused thiophene ring were also synthesized through annelation reactions on a preformed benzo[*b*]thiophene core. Many of the target molecules are analogues of bioactive natural products. Access to these molecules, involved in most of the cases extensive use was made of the methodology of directed metalation.

## SYNTHESIS OF CYCLIC AND ACYCLIC OLIGOPYRROLES

**Wim Dehaen**

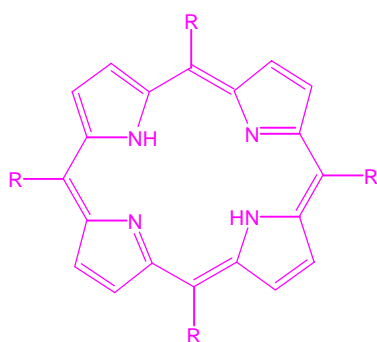
*Laboratory of Organic Synthesis, Department of Chemistry, K.U. Leuven,  
Celestijnenlaan 200F, 3001 Leuven  
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Firstly, we will describe the synthesis of several porphyrin derivatives, including (i) acetylene porphyrins from 1,2,3-thiadiazoles, (ii) pyrimidine derivatives, (iii) porphyrin dendrimers, (iv) porphyrins with NLO possible properties and (v) corroles.

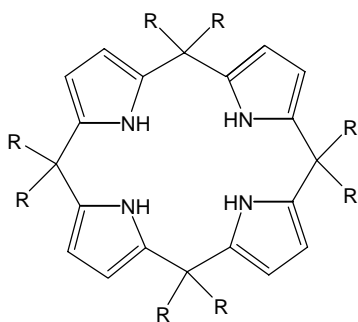
Then, we will report our results on calix[4]pyrroles including their synthesis, and that of their N-confused isomers, functionalisation at the periphery, and synthesis of related porphotetramethenes.

Dipyrrromethanes are easily prepared and can be mono- or difunctionalized by electrophilic substitution as an alternative to the synthesis of calixpyrroles.

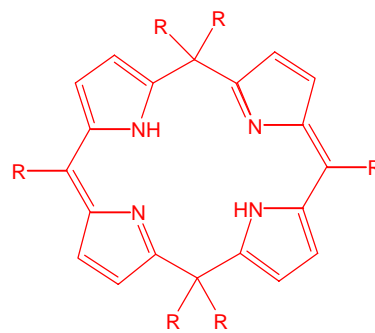
Finally we will give some comments on our most recent work on the synthesis of calix[4]phyrins and dipyrrromethenes.



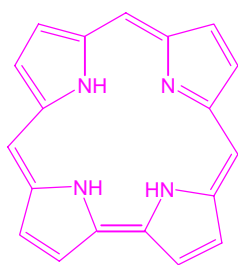
**porphyrins**



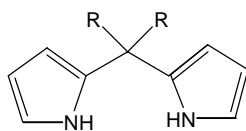
**calix[4]pyrrole**



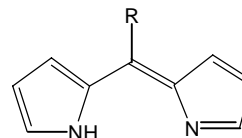
**calix[4]phyrin**



**corrole**



**dipyrrromethane**



**dipyrrromethene**

# NOVEL HETEROCYCLES FROM THE REACTIONS OF TERTIARY AMINES AND AMIDINES WITH DICYANOMETHYLENE COMPOUNDS

**Dietrich Döpp, A. A. Hassan, S. Jüschke, M. A. M. Gómaa and J. Leven**

*Institut für Chemie, Gerhard-Mercator-Universität Duisburg, D-47048 Duisburg, Germany*

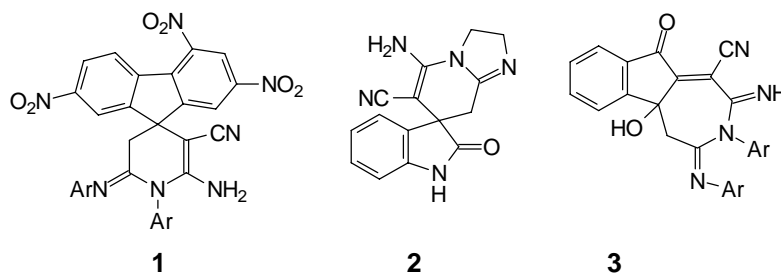
Interactions of electron rich compounds with typical electron poor  $\pi$ -systems (tetracyanoethylene and some of its analogues) go far beyond forming just charge transfer complexes. Recently we have investigated some deep-seated chemical transformations giving new heterocyclic structures in appreciable yields.

1. N-Arylisindolines are didehydrogenated by tetracyanoethylene (TCNE) to N-arylisindoles, which in turn undergo dicyanomethylenation and an oxidative coupling to novel 1,1'-bi-(3-dicyanomethyleneisindolyl-idene)s which have a strained *Z*-geometry and resemble hetero-cyclic analogues of the tetracyanoquinodimethane type of  $\pi$ -acceptors.

2. On the other hand, the same 1-arylisindolines, after dehydrogenation by 2-(dicyanomethylene)-1,3-indanedione (DCID), form N-arylisindoles bearing the 3-cyano-1,4-dioxo-1,4-dihydro-naphth-2-yl substituent at carbon atoms 1 and 3. The latter residues result from an electron transfer mediated isomerization of DCID into 2,3-dicyano-1,4-naphthoquinone [1].

3. Higher ring homologues of the aforementioned isindolines, namely 2-aryl-2,3-dihydro-1*H*-benz[d,e]isoquinolines and 6-aryl-6,7-dihydro-5*H*-dibenz[c,e]azepines, featuring benzylic activation of the hydrogen atoms  $\alpha$  to nitrogen as do the isindolines mentioned above, are not dehydrogenated by TCNE and DCID but just form the corresponding cyclic iminium ions by transfer of a hydride ion to the acceptors generating e.g. tetracyanoethanide or an analogous anion from DCID. These anions in turn deliver a cyanide ion to the iminium ions, thus the overall reaction is an  $\alpha$ -cyanation of an activated amine [2].

4. Nucleophilic attack by  $N^2$  of  $N^1, N^2$ -diarylacetamidines and heterocyclic amidines, as 2-methyl 4,5-dihydroimidazole or 2-methylbenzimidazole, on one cyano carbon of the acceptors 3-(dicyanomethylene)-2-indolinone and 9-(dicyanomethylene)-2,4,7-trinitrofluorene eventually results in the formation of novel spiroheterocycles (for example, **1** and **2**), whereas DCID with the same amidines gives rise to highly functionalized indeno[2,3-*d*]azepines (**3**).



[1] G. J. Ashwell, M. R. Bryce, S. R. Davies and M. Hasan, *J. Org. Chem.* **1988**, *53*, 4585.

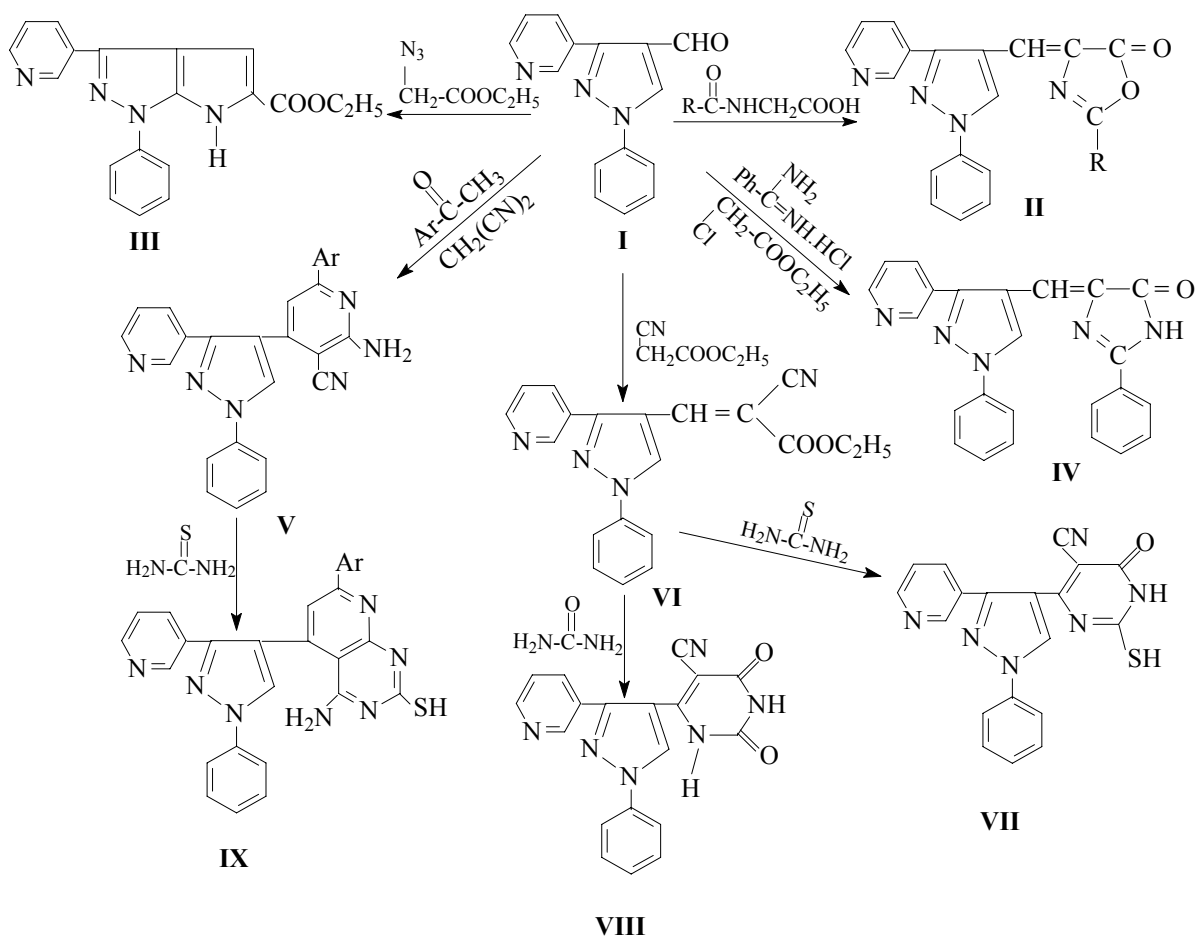
[2] D. Döpp, S. Jüschke and G. Henkel, *Z. Naturforsch.* **2002**, *57b*, 460.

# SYNTHESIS AND REACTIVITY OF SOME PYRIDILPYRAZOLE DERIVATIVES

**M. A. El-Borai, Y. H. Hafiz and M. R. Sadek**

*Chemistry Department, Faculty of Science, Tanta University, Tanta, Egypt*

In continuation of our systematic work on the synthesis and study of the reactivity of pyrazole derivatives, we report here some novel synthesized compounds starting from 1-phenyl-3'-pyridylpyrazole-4-carboxaldehyde **I**.



Details of the synthesis and the structure of the obtained compounds were confirmed by IR, NMR, and mass data, will be presented at the conference.

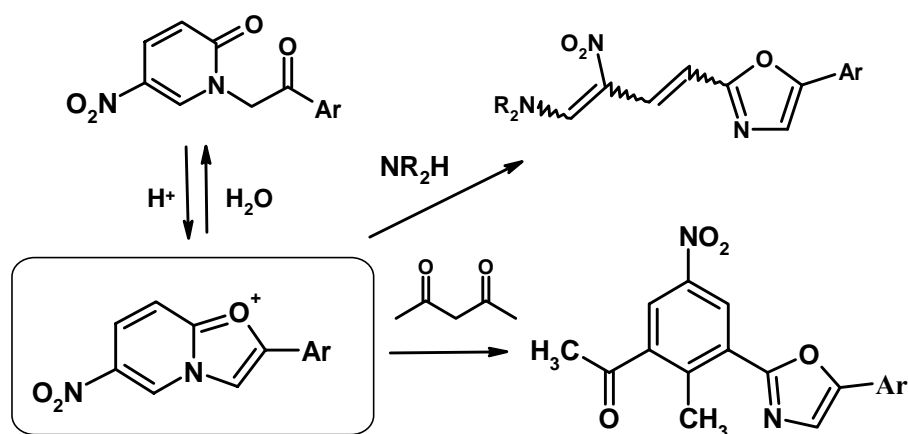
# REACTIVITY OF 6-NITROOXAZOLO[3,2-A]PYRIDINES

**Alexander A. Bush and Eugene V. Babaev**

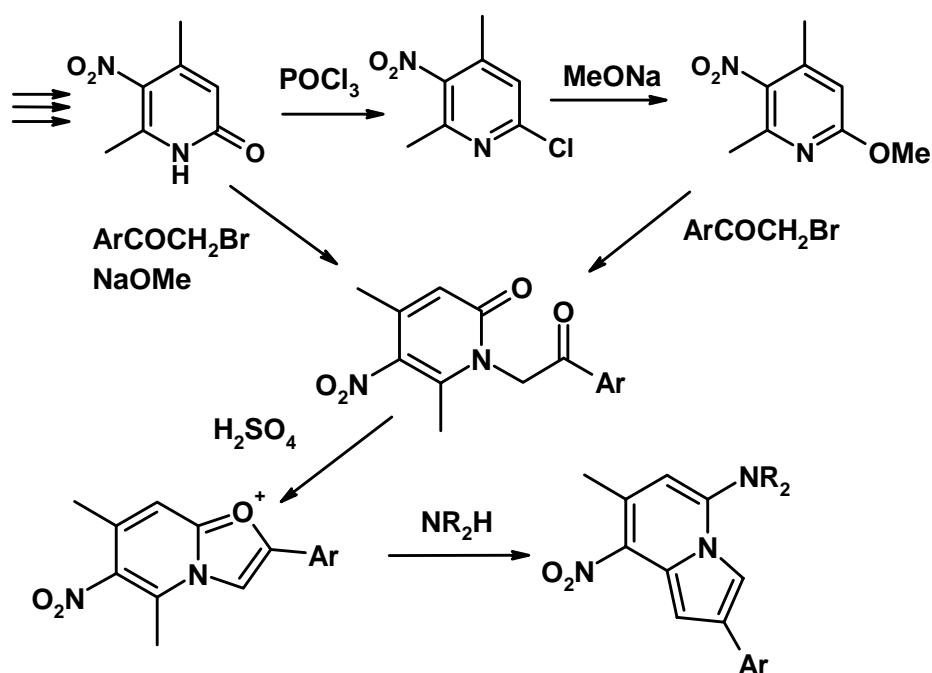
*Chemistry Department, Moscow State University, Moscow 119899, Russia*

*E-mail: a\_bush@mail.ru*

Oxazolo[3,2-a]pyridines may undergo ring opening and transformation of 5- or 6-membered rings and serve as precursors of different heterocycles (see review [1]). We found several unusual ring transformations for 6-nitroderivatives of this bicyclic cation:



In most cases pyridine fragment is opened / transformed in reactions with C- and N-nucleophiles. On the contrast, 5-methyl-6-nitroderivative under the action of secondary amines could be converted to 5-amino-8-nitroindolizines:



[1] E. V. Babaev, *J. Heterocycl. Chem.* (Lectures in Heterocyclic Chemistry), **2000**, 37, 519-526.



# SYNTHESIS OF CERTAIN NOVEL 1,2,4-TRIAZOLES AS POTENTIAL INSECTICIDAL AGENTS

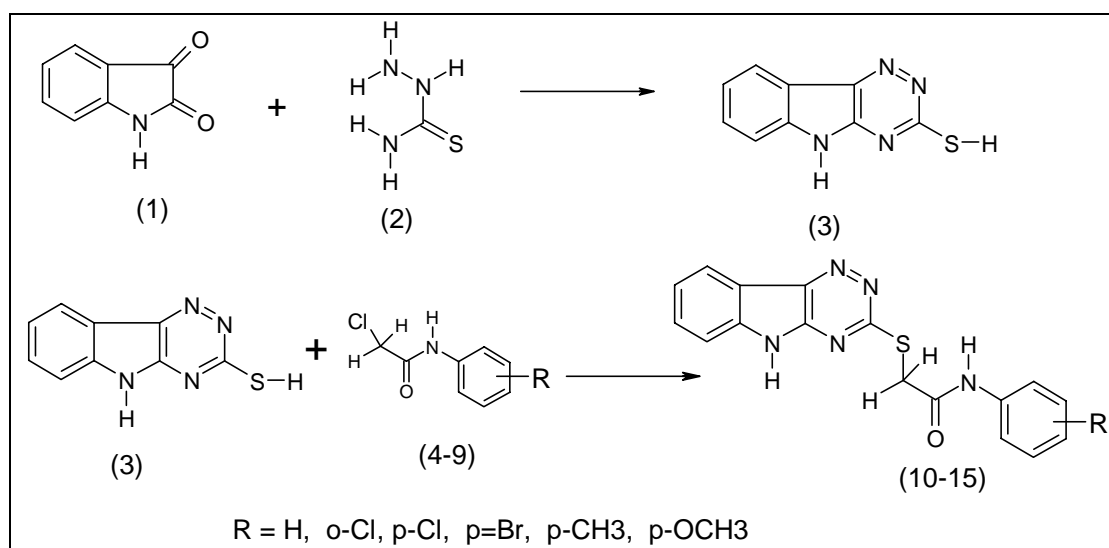
**Esam Ahmed El-Malt**

*Department of Chemistry, Faculty of Agriculture, Minia University, Minia, Egypt*

Six of novel 1,2,4-triazoles derivatives namely, *N*-(4-methoxyphenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (10), *N*-(4-chlorophenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (11), *N*-(2-chlorophenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (12), *N*-(4-methylphenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (13), *N*-(phenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (14) and *N*-(4-bromophenyl)-2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylthio)-acetamide (15), were synthesized by the reaction of 5*H*-[1,2,4]triazino[5,6-*b*]indole-3-thiol (3) with 2-chloro-*N*-(substituted-phenyl)-acetamide derivatives (4-9). Their infrared, nuclear magnetic resonance and mass spectra spectroscopy were in full agreement with their assign chemical structures.

The potentialities of the synthesized compounds (10-15) as insecticides were performed against both of the two worms, Cotton leafworm, *Spodoptera littoralis* (Boisd.) and Black cut worm, *Agrotis ipsilon* (Hufn.). All of the tested compounds were showed an excellent insecticidal activity against the two worms. The most active compound is the compound 11 followed by compound 15. According to their biological activities, it could be sort the rest of the compounds as follows: 12>10>13>14. It could be recommended to use these compounds as potential insecticides agents.

The possible chemical structure-insecticidal activity relationships were discussed.



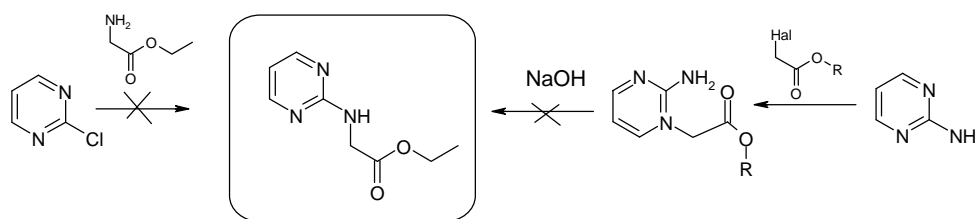
# SOLID PHASE APPROACH TO THE SYNTHESIS OF METHYL N-(PYRIMIDYL-2)GLYCINATE

**Denis S. Ermolat'ev and Eugene V. Babaev**

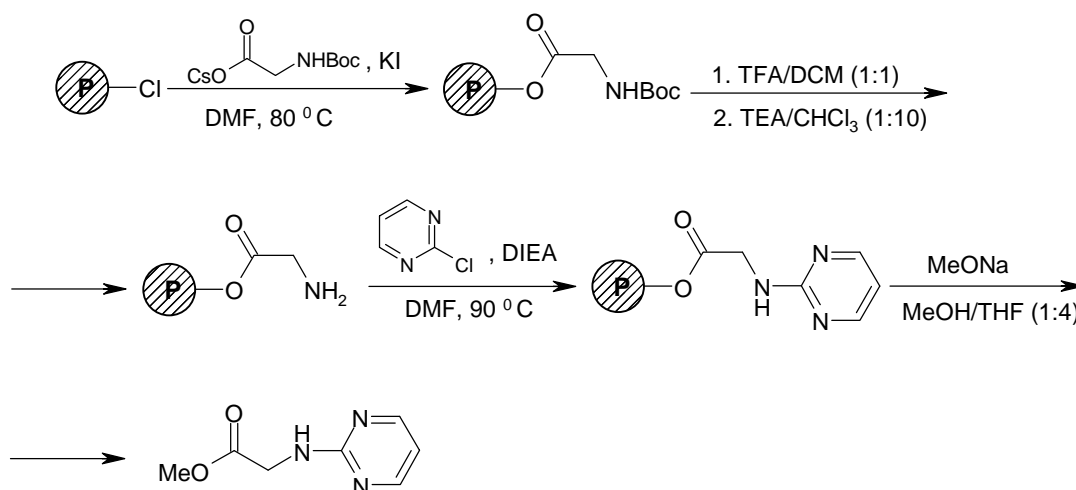
*Chemistry Department, Moscow State University, Moscow 119899, Russia*

*E-mail: [chemistry@hotbox.ru](mailto:chemistry@hotbox.ru)*

Aminoacids derivatives, in particular N-substituted  $\alpha$ -aminoacids are important synthetical precursors. It is sometimes difficult to obtain such N-substituted acids, especially for the cases when the substituent attached to the aminogroup is a heterocycle. Attempting to prepare ethyl N-(pyrimidyl-2)-glycinate via reaction of 2-chloropyrimidine and ethyl glycinate we observed predominant formation of diketopiperazine. Alternative strategy – alkylation of endocyclic nitrogen atom in 2-aminopyrimidine with chloroacetic acid (or its esters) followed by Dimroth rearrangement (which usually provides safe route to 2-alkylaminopyridines) – also failed due to intramolecular self-condensation between 2-aminogroup and acetic acid fragment.



We have found an advantage of the solid phase synthetic strategy over usual liquid phase processes for synthesis of the target compound. Glycine was immobilized onto Merrifield resin (loading capacity 1.0-1.1 mmol/g). Hetarylation of the obtained resin with 2-chloropyrimidine occurred selectively, and the cleavage of the linker was performed with MeONa solution.



The overall yield was 76%, and the purity of the product – 95-97%. The structure was proved by NMR. The suggested strategy could be recommended for preparation of other N-(hetaryl)glycinates.

# TAUTOMERIC INTERCONVERSIONS OF $\Delta^2$ -ISOXAZOLINE DERIVATIVES

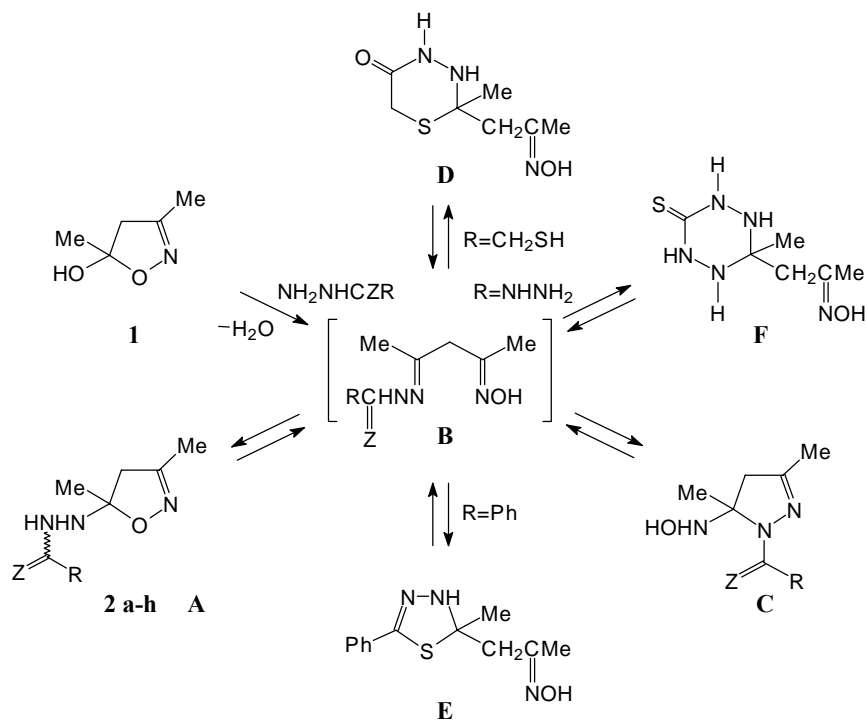
Andrei Yu. Ershov

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The study of the 5-functionally substituted  $\Delta^2$ -isoxazolines is of interest in the field of recyclization in the heterocyclic series because the presence of a cyclic hemiacetal fragment in their molecules indicates the high tendency to the breaking of the C<sub>(5)</sub>-O bond. This bond breaking leads to the formation of complex variants of ring-chain and ring-ring isomeric (tautomeric) transformations.

The reaction of 5-hydroxy- $\Delta^2$ -isoxazoline **1** with a series of acylhydrazides, thiobenzhydrazide, thiosemicarbazide, and thiocarbonohydrazine leads to the formation of 5-hydrazino(thiosemicarbazido)- $\Delta^2$ -isoxazolines **2a-h**. New types were found of ring-ring (**A**  $\rightleftharpoons$  **C**, **A**  $\rightleftharpoons$  **E**, **A**  $\rightleftharpoons$  **F**) tautomeric equilibria in solutions with the participation of not only  $\Delta^2$ -isoxazoline **A** cycle but also of additional  $\Delta^2$ -pyrazoline **C**, 1,3,4- $\Delta^2$ -thiadiazoline **E**, and tetrahydro-1,2,4,5-tetrazine-3-thione **F** rings. On the example of compound **2d** a new type of tautomeric transformations involving three different rings: three-ring tautomerism of the  $\Delta^2$ -isoxazoline **A**  $\rightleftharpoons$   $\Delta^2$ -pyrazoline **C**  $\rightleftharpoons$  tetrahydro-1,3,4-thiadiazin-5(6*H*)-one **D** system was found.



**2a-h**: Z=O, R=Me (**a**); R=Et (**b**); R=*i*-Pr (**c**); R=CH<sub>2</sub>SH (**d**); R=Ph (**e**);  
Z=S, R=Ph (**f**); R=NH<sub>2</sub> (**g**); R=NHNH<sub>2</sub> (**h**)

*Acknowledgments.* Russian Foundation for Basic Research (grant No 02-03-33110) has supported this work.

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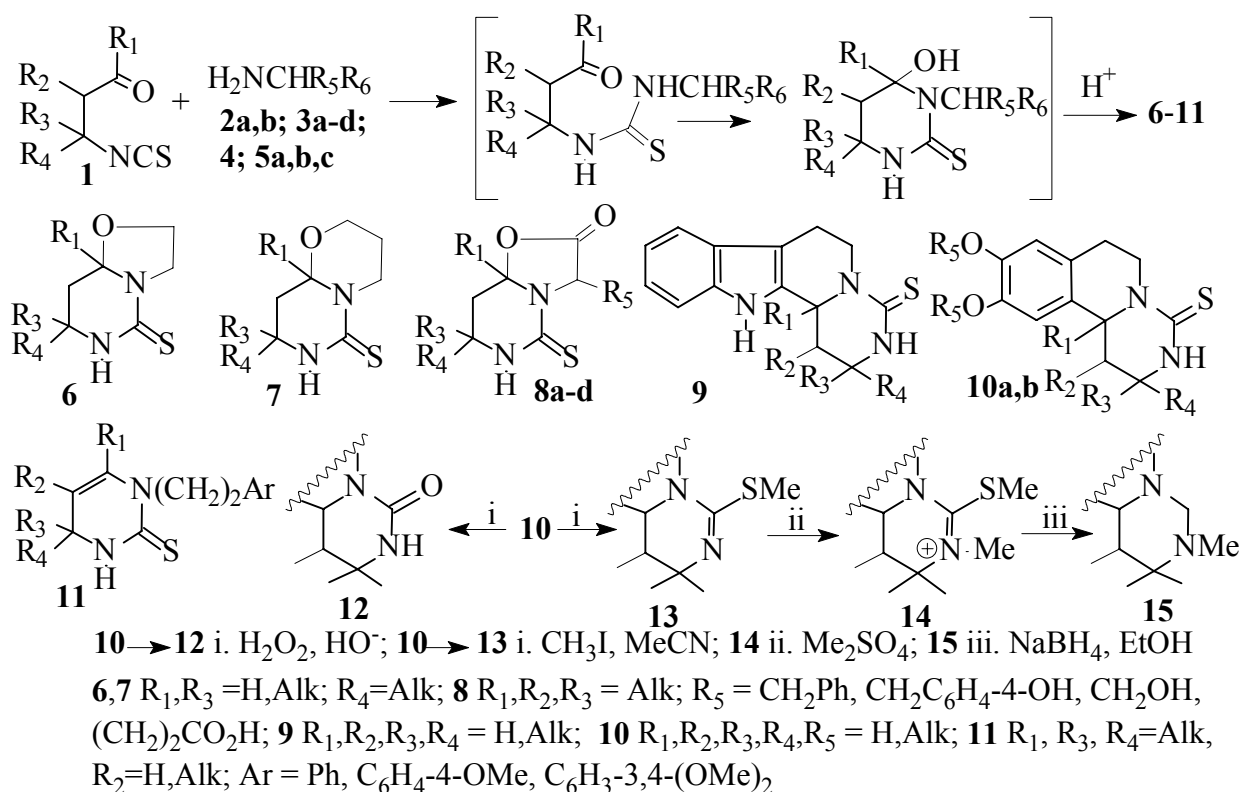
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THE REACTIONS OF 1,3-ISOTHIOCYANATOCARBONYL COMPOUNDS WITH  
NITROGEN CONTAINING BINUCLEOPHILES

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It has been shown that acid catalyzed reaction of 1,3-isothiocyanatocarbonyl compounds with nitrogen containing binucleophiles: aminoalcohols **2a** ( $R_5=H$ ,  $R_6=CH_2OH$ ), **2b** ( $R_5=H$ ,  $R_6=CH_2CH_2OH$ ),  $\alpha$ -aminoacids **3a** ( $R_5=CH_2Ph$ ,  $R_6=CO_2H$ ), **3b** ( $R_5=CH_2C_6H_4-4-OH$ ,  $R_6=CO_2H$ ), **3c** ( $R_5=CH_2OH$ ,  $R_6=CO_2H$ ), **3d** ( $R_5=CH_2CH_2CO_2H$ ,  $R_6=CO_2H$ ), tryptamine **4** ( $R_5=H$ ,  $R_6=CH_2-3-Ind$ ) leads to heterocycles **6-11**.



The compounds **10** and **11** were obtained by interaction of phenylethylamines **5a** ( $R_5=H$ ,  $R_6=CH_2C_6H_3-3,4(OMe)_2$ ), **5b** ( $R_5=H$ ,  $R_6=CH_2C_6H_3-3,4(OH)_2$ ), **5c** ( $R_5=H$ ,  $R_6=CH_2C_6H_3-4-OMe$ ) with **1**. The regiodirection of this reaction depends on size of the substituents  $R_1$  and  $R_2$ , electronwithdrawing properties of the aryl substituent of **5** and reaction conditions. Decreasing of  $R_1$  and  $R_2$  size and increasing of electron-donating properties of the aryl substituent promotes formation of a pyrimidoisoquinolines **10** under milder conditions. The pyrimidoisoquinolines **10** have been converted to compounds **12-15**.

We thank Bayer AG and Russian Foundation for Basic Research (Grant No 01-03-32167) for financial support.

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW 4,5-DISUBSTITUTED-THIAZOLYL AMIDES, DERIVATIVES OF 4-HYDROXY-PIPERIDINE OR OF 4-N-METHYL PIPERAZINE.

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Several thiazolyl derivatives [1] have been reported to affect inflammation, to inhibit inflammation mediators and enzymes contributing to arachidonic acid cascade. Based on these findings and on results from our investigations a series of some new thiazolyl amides possessing a 4-hydroxy piperidinyl or a 4-N-methyl piperaziny ring have been synthesized.

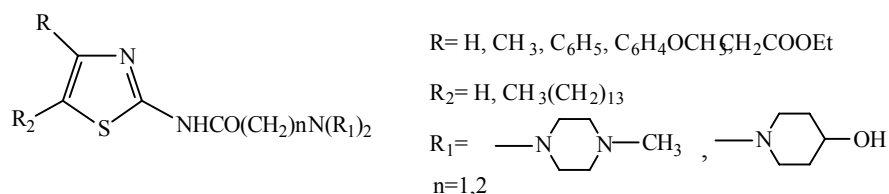


Figure 1. Structure of synthesized compounds.

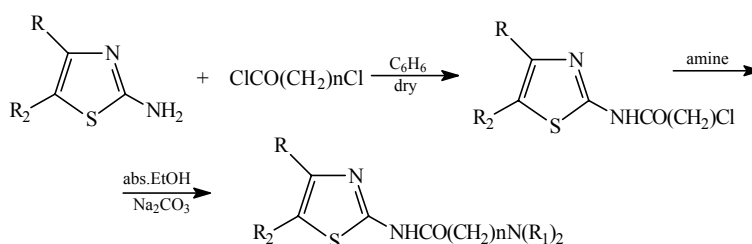


Figure 2. Synthetic procedure.

Physicochemical parameters e.g. log P have been calculated theoretically, as an expression of lipophilicity. The in vivo antiinflammatory activity of the synthesized compound determined using carrageenin included mice paw edema (32.2-64.3 %) In vitro the compounds have been screened for their reducing activity of the free stable radical DPPH and for their hydroxy free radical scavenging activity. For some representatives the inhibition on the soybean lox has been performed. The preliminary results reveal that the tested compounds exhibit in generally good biological activity. The results are discussed in terms of structural characteristics. The presence of a R1 = phenyl group seems to be crucial for high activity in vivo. The length of the chain also plays an important role. The derivatives with n = 1 are stronger inhibitors. The nature of the alicyclic amine is an important feature, since the 4-N-methyl piperaziny derivatives possess higher in vivo results.

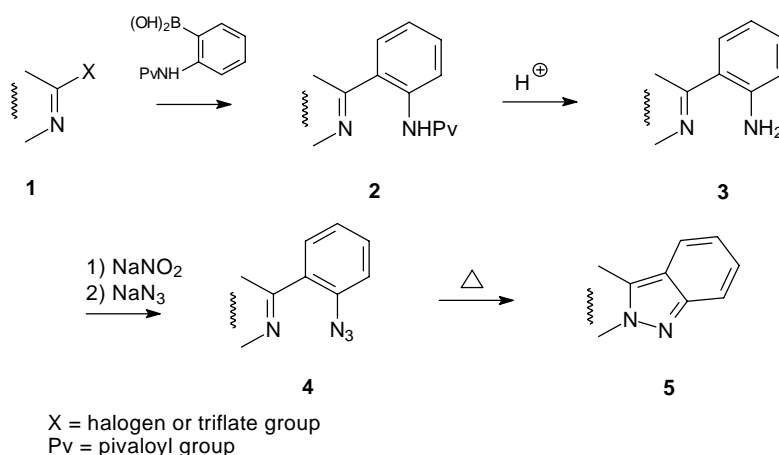
[1] A. Geronikaki and D. Hadjipavlou-Litina, *Arzneim. Forsch./Drug Res.* **1996**, 46, 1134.

# SYNTHESIS OF NEW POLYFUSED HETEROCYCLES OF BIOLOGICAL IMPORTANCE BY MEANS OF Pd(0) CATALYSIS

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Recently we have found that a large number of polyazaheterocycles behave valuable biological (antiviral, intercalating, reverse transcriptase inhibitory, etc.) properties. For this reason, a growing interest arose for synthetic methods leading to new fused heterocyclic rings.



In the course of our activity in this area, a general protocol to polyfused pyrazoles and related compounds has been elaborated<sup>1</sup>. The key step of this pathway is the Suzuki cross-coupling reaction of a properly substituted azine (**1**) with a protected anilino boronic acid to give a biaryl compound (**2**). After deprotection to an amine (**3**), an azidophenyl derivative (**4**) can be obtained *via* diazotation and aza transfer reaction. Finally, heat treatment of the azide (**4**) – *i.e.* generation of a nitrene – gives rise to the fused target compound **5**.

By the application of this methodology, numerous new polycyclic rings have been synthesized during the recent years<sup>2-5</sup>. The lecture discusses the problems of the particular reaction paths and their solutions. Furthermore, some outstanding biological properties of the new derivatives will also be presented.

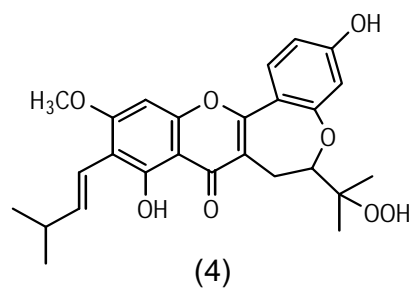
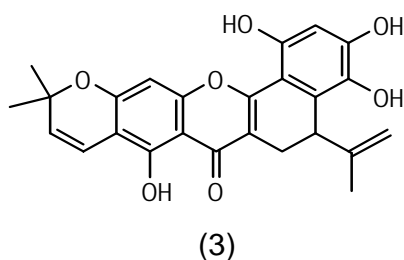
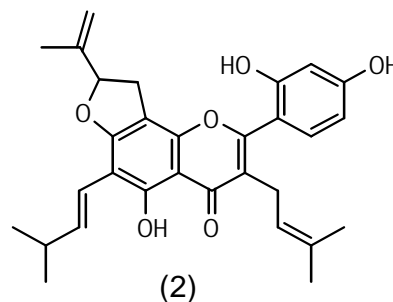
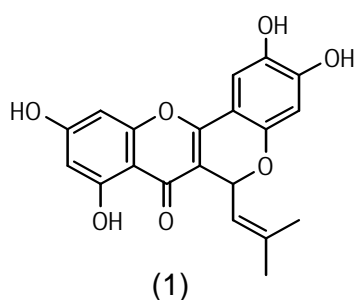
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- [2] Gy. Hajós, Zs. Riedl, J. Molnár, and D. Szabó, *Drugs of the Future*, **2000**, 25, 1, 47-62.
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# BIOACTIVE HETEROCYCLIC NATURAL PRODUCTS FROM INDONESIAN MORACEAE

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Lia Dewi Juliawaty**

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Moraceae consists of 60 genera and about 1400 species, and distributed mostly in temperate and tropical Asia. Plants belonging to this family are known to be a good source of prenylated flavones in addition to stilbene and aryl benzofuran derivatives. The existence of isoprenyl groups attached to the flavone skeleton at C-3,6, and 8 positions or at B ring, enable it to form a variety of heterocyclic rings fused to the mother skeleton, including furano, pyrano, oxepineno and oxocino flavones. In our search for bioactive compounds from Indonesian tropical plants, a phytochemical investigation of several species of *Morus* and *Artocarpus* (Moraceae) has been undertaken. In this paper we report the isolation of a number of prenylated flavones including artoindonesianin (1), artoindonesianin H (2), artoindonesianin V (3), and artoindonesianin B (4), most of which showed very strong toxicity against P388 murine leukemia cell.



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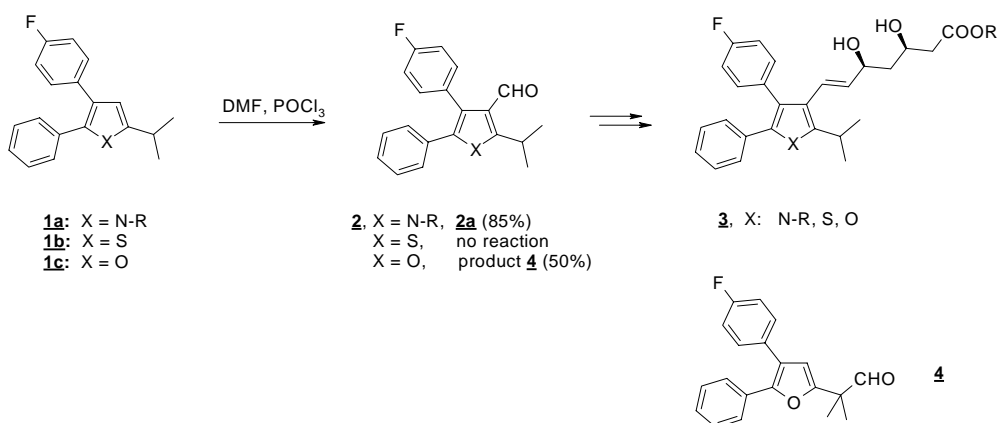
# HETEROCYCLIC CHEMISTRY IN PHARMACEUTICAL RESEARCH

Walter Hübsch

Bayer Pharma, Chemical Research, D-42096 Wuppertal, Germany

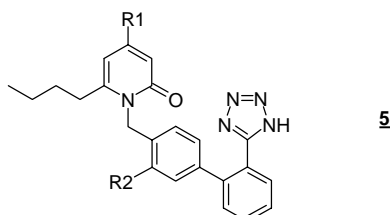
E-mail: [walter.huebsch.wh@bayer-ag.de](mailto:walter.huebsch.wh@bayer-ag.de)

Heterocycles very often play an important role in medicinal chemistry. During our research on HMG CoA reductase inhibitors several substituted pyrrols [1], thiophenes and furans (**3**) were identified as inhibitors of this important enzyme of cholesterol biosynthesis.



In a first synthetic approach towards the prototypes **3** a formylation of the heterocyclic intermediates **1** with Vilsmeier reagents was planned to yield the aldehydes **2**.

However, a surprisingly different reactivity of these identically substituted and chemically related  $\pi$ -excessive heterocycles was observed. Only the pyrrol **1a** was formylated in the free 4-position, whereas thiophene **1b** was recovered unchanged and furan **1c** reacted in a very unusual way at the isopropyl group to form product **4**.



In a second case study, medicinal chemistry research and investigations on the chemical process of substituted pyridones (**5**) [2] as angiotensin II receptor antagonists are described.

- [1] a) Hübsch, W.; Angerbauer, R.; Fey, P.; Bischoff, H. Petzinna, D.; Schmidt, D.; Thomas, G.; EP 287890 (Bayer AG).  
 b) Hübsch, W.; Angerbauer, R.; Fey, P.; Bischoff, H. Petzinna, D.; Schmidt, D.; Thomas, G.; EP 300278 (Bayer AG).
- [2] Hübsch, W.; Dressel, J.; Fey, P.; Hanko, R.; Krämer, T.; Müller, U.; Müller-Gliemann, M.; Beuck, M.; Kazda, S.; Stasch, J.; Knorr, A.; Wohlfeil, S.; Zaiss, S.; EP 542059 (Bayer AG).



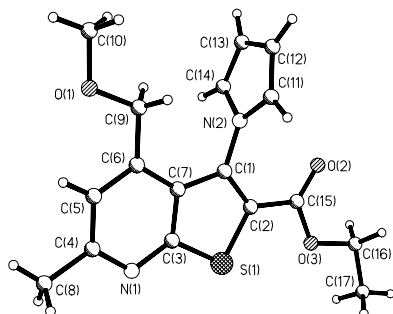
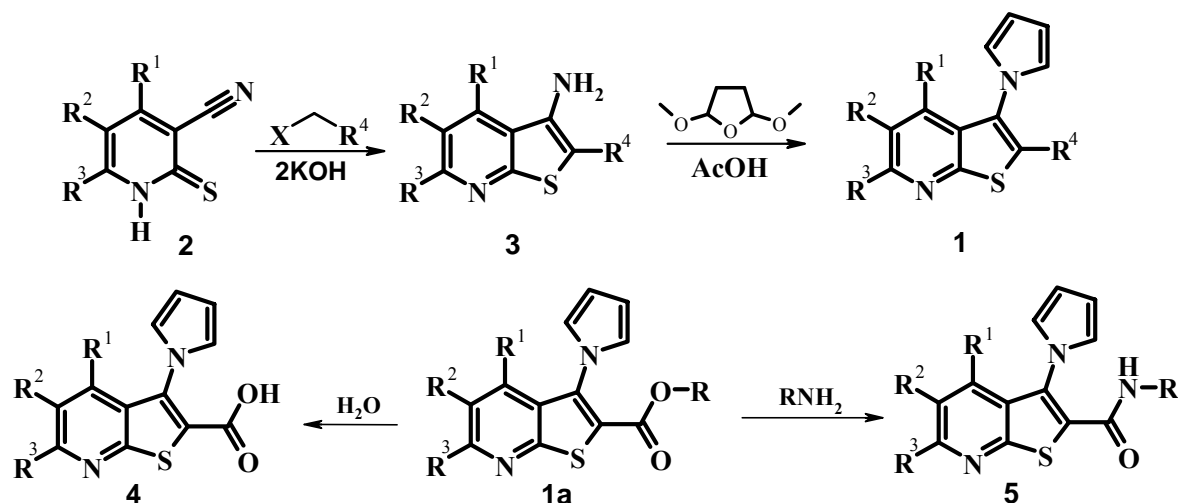
INTERMOLECULAR OVERCROWDING 3-(PYRROL-1-YL)-THIENO[2,3-b]PYRIDINES:  
MOLECULAR STRUCTURE OF 2-ETHOXYCARBONYL-4-METHOXYMETHYL-6-METHYL-  
3-(PYRROL-1-YL)THIENO[2,3-b]PYRIDINE

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A. V. Butin and G. D. Krapivin

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A series substituted 3-(pyrrol-1-yl)thieno[2,3-b]pyridines **1** were prepared in two steps: 1) alkylation of 3-cyano-2(1H)-thiopyridones **2** by N,N-diarylchloroacetamides, alkyl(aryl)chloroacetates and nitrobenzyl-bromides and Torp-Cygler cyclization in the presence of KOH; 2) reaction 3-aminothieno[2,3-b]pyridines **3** with 2,5-dimethoxytetrahydrofuran in acetic acid.

Acids **4** were obtained by basic hydrolysis of ethers **1a**. Aminolysis of ethers **1a** by primary amines results in amides **5**.



3-(Pyrrol-1-yl)thieno[2,3-b]pyridines **1,4,5** are typical intermolecular overcrowding compounds. X-Ray analysis of 2-ethoxy-carbonyl -4- methoxymethyl -6- methyl -3- (pyrrol-1-yl)-thieno[2,3-b]pyridine shows that pyrrol ring is placed perpendicularly by thienopyridine plane : the angle between pyrrol and thienopyridin planes is about 90°.

NOVEL SYNTHESIS FOR AZAXANTHONES OF EXPECTED  
BIOLOGICAL ACTIVITY

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This work is the continuation of program with the aim to synthesis a new substituted heterocycles which can achieve activity in both pharmacological and pesticidal areas.

In the present work, the synthesis of azaxanthone derivatives is reported using 3-chloro-4-(o-methoxy or 2,4,6-trimethoxybenzoyl)-6-aryl pyridazines as starting materials which are easily cyclized by Royer's method to give the azaxanthone derivatives. These derivatives are allowed to react with different reagents such as amines, hydrazines, N-aminophthalimide and chlorosulphonic acid.

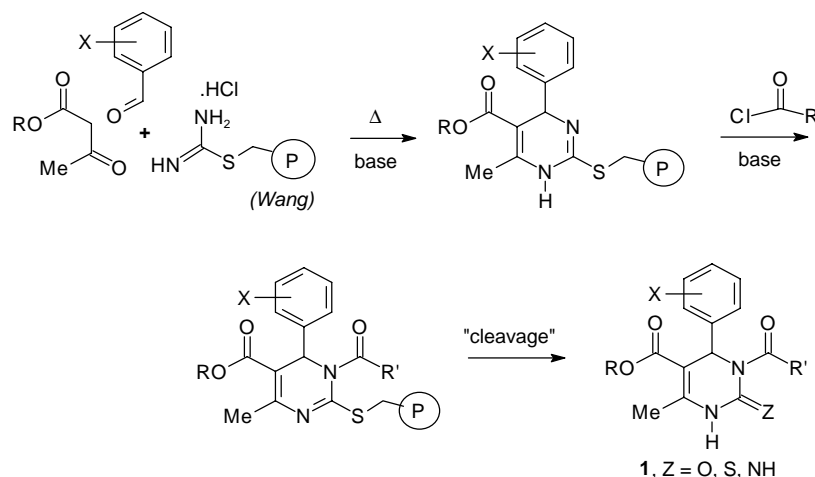
The structures of the products are inferred from elemental and spectroscopic data . Also the biological activity of these products is under investigation.

# BUILDING COMBINATORIAL LIBRARIES OF DIHYDROPYRIMIDINES USING MULTICOMPONENT CHEMISTRY. SOLUTION PHASE AND SOLID-PHASE PROTOCOLS

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4-Aryl-3,4-dihydro-2(1*H*)-pyrimidone esters of type **1** (DHPMs) represent a heterocyclic system of remarkable pharmacological efficiency [1]. In recent years, appropriately functionalized derivatives have emerged as *e.g.* calcium channel modulators,  $\alpha_{1a}$ -adrenoceptor-selective antagonists, mitotic kinesin Eg5 inhibitors, and neuropeptide Y (NPY) antagonists. Close structural analogs derived from **1** have been reported as effective antiviral (Hepatitis B) agents, and as group 2 metabotropic glutamate receptor antagonists [2]. We have recently developed new synthetic methodology towards DHPMs of type **1**, including a high-speed microwave-promoted variations of the classical Biginelli dihydropyrimidine synthesis that is amenable to parallel or automated sequential synthesis [3]. Furthermore, a solid-phase protocol for the synthesis of structurally highly diverse DHPM derivatives has been established (see below) [4]. In the key step, a polymer bound thiouronium salt is condensed with unsaturated enones (derived from  $\beta$ -ketoesters and aromatic aldehydes). The resulting polymer bound 1,4-dihydropyrimidines are cleaved from the resin employing multidirectional resin cleavage strategies.



In this lecture, recent advances regarding the combinatorial synthesis of dihydropyrimidines and related scaffolds will be highlighted, using both solution-phase and solid-phase chemistry. Special attention will be given to microwave-assisted reactions.

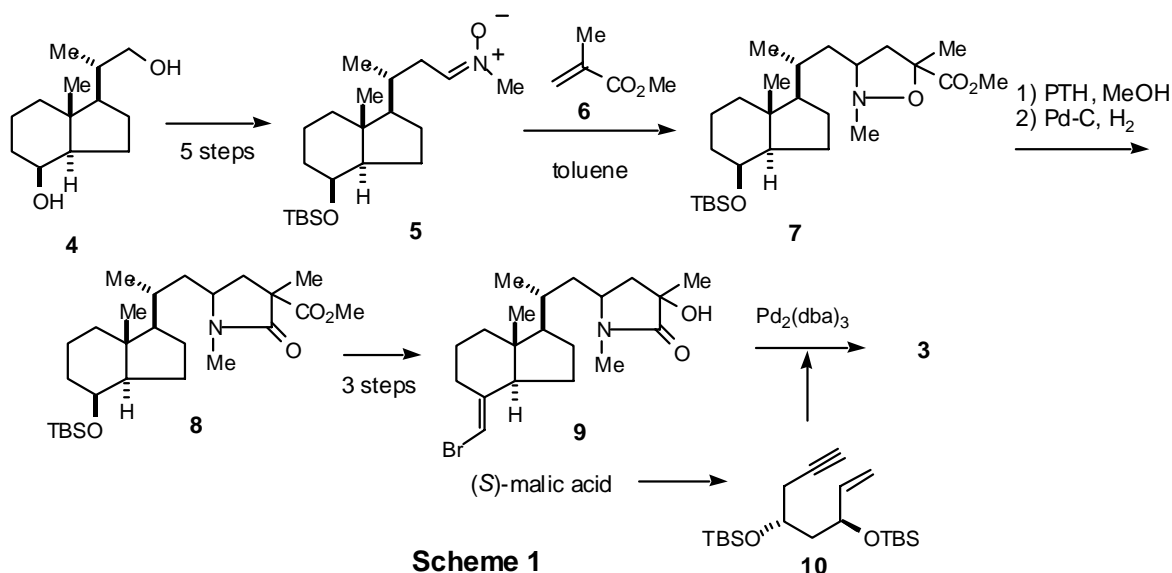
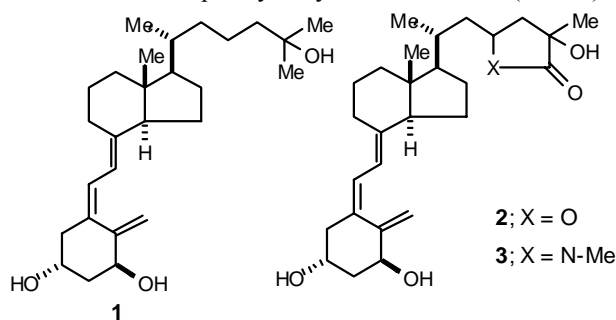
- [1] For a review on DHPMs, see: Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
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NOVEL HETEROATOM-CONTAINING VITAMIN D<sub>3</sub> ANALOGS:  
EFFICIENT SYNTHESIS OF 1 $\alpha$ ,25-DIHYDROXYVITAMIN D<sub>3</sub>-26,23-LACTAM

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1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> (1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub>) (**1**), the hormonally active form of vitamin D<sub>3</sub>, has a wide variety of biological activities including the regulation of calcium homeostasis and the control of cellular growth, differentiation, and apoptosis. Although about 2000 analogs of 1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub> (**1**) have been developed, only a few analogs which contain nitrogen in their structures were reported. In the course of our recent studies towards the development of novel vitamin D<sub>3</sub> analogs, we focused on one of the major metabolite of **1**, so-called 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>-26,23-lactone (**2**) which induces differentiation of human promyelocytic leukemia cell (HL-60) and inhibits bone resorption induced by **1**, while, it has very weak binding affinity against vitamin D nuclear receptor. On the basis of **2**, we have designed the 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>-26,23-lactam (**3**) as a novel vitamin D<sub>3</sub> analog. In this paper, we describe the efficient synthesis of novel vitamin D<sub>3</sub> analogs **3**. Our synthesis of **3** are outlined in scheme 1. Inhoffen-Lythgoe diol **4**, derived from vitamin D<sub>2</sub>, was converted into nitron **5** in five steps using the methods developed by Uskokovic et.al.<sup>1</sup> The 1,3-dipolar cycloaddition reaction of **5** with methyl metacrylate (**6**) generated isoxazoline **7** with separable 4 isomers in 70% yield. After deprotection of silyl ether of **7** with PTS, obtaining isoxazoline-alcohol was reduced with hydrogen over Pd-C to give lactam **8** in 90% yield. Protection of the tertiary alcohol of **8** as TMS ether, successive oxidation of the secondary alcohol followed by the Wittig reaction gave **9**. Finally, vinyl bromide **9** was coupled with **10**, which was derived from (*S*)-malic acid, by the way of palladium catalyst conditions developed by Trost<sup>2</sup>, and subsequent deprotection of silyl ether with TBAF and Dowex-50W gave the 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>-26,23-lactam (**3**) in 50-60% yield. The biological activities of the novel vitamin D<sub>3</sub> analogs **3** are under investigation in our laboratories.



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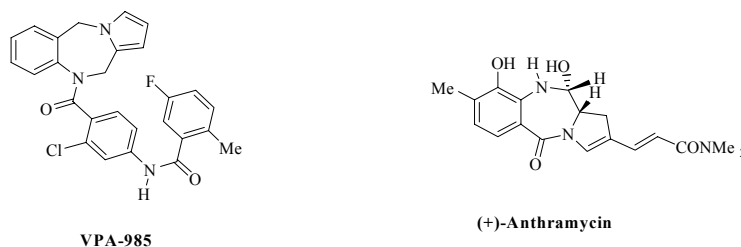
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THE SYNTHESIS OF 6,11-DIHYDRO-5H-PYRROLO[1,2-*c*][1,3]BENZODIAZEPINES,  
 PYRROLO[2,1-*c*][1,4]BENZODIAZOCIN-6(5H)-ONES AND 1,5,10,11-TETRAHYDRO-4H-  
 PYRROLO[2,3-*c*][1,6]BENZODIAZOCIN-4-ONES WITH POTENTIAL  
 BIOLOGICAL INTEREST

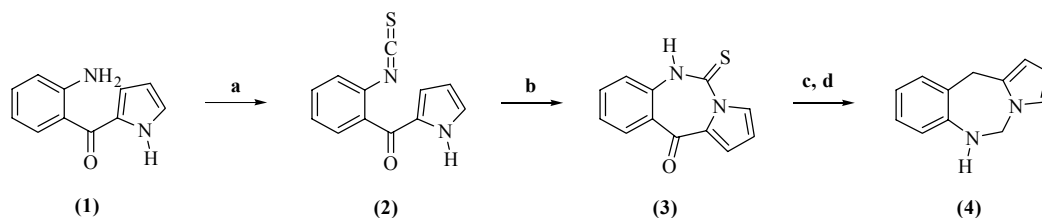
**Nikolaos Karousis, Athanasios Kimbaris, Konstantina Koriatopoulou, Georgios Rotas,  
 Georgios Tsakonas and George Varvounis**

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Arginine vasopressin (AVP) is a hormone that regulates solute free water clearance of body fluids. The hormone exerts its actions through three well-defined receptor subtypes: vascular V<sub>1a</sub>, hormone-releasing V<sub>1b</sub>, and renal V<sub>2</sub> receptors. The blockade of V<sub>2</sub> receptors by non-peptide antagonists may be useful in treating diseases characterised by excess renal reabsorption of free water. VPA-985 is a clinical AVP antagonist. On the other hand, anthramycin is the lead member of the naturally occurring family of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) antitumour antibiotics produced naturally by *Streptomyces refuineus*. The cytostatic and antitumour effects of anthramycin are believed to be due to their selective interaction with DNA, which causes inhibition of nucleic acid synthesis, and production of excision-dependent single- and double-strand breaks in cellular DNA. There is strong evidence that C11 of anthramycin forms a covalent linkage with the N-2 of guanine in duplex DNA to form the anthramycin-(N2-guanine) DNA adduct.



Practicable syntheses of analogues of these biologically active compounds will be presented. For example, the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system in VPA-985 has been replaced by pyrrolo[1,2-*c*][1,3]benzodiazepine **4** synthesised from (2-aminophenyl)(1*H*-pyrrol-2-yl)methanone **1** in four steps.

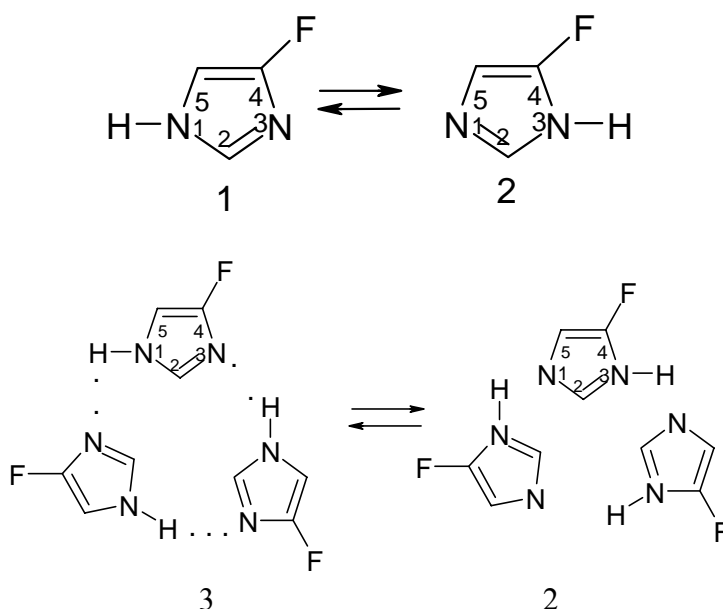


Reagents: (a) CCl<sub>4</sub>, (b) DMF, K<sub>2</sub>CO<sub>3</sub>, (c) Raney Nickel, EtOH, reflux (d) HO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>3</sub>H, H<sub>2</sub>NNH<sub>2</sub>.H<sub>2</sub>O, reflux

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Imidazole can exist in many tautomeric forms, among which frequently can be found the product of 1H-3H tautomeric conversion (1) → (2) [1]. Geometrically and energetically the 1H-3H proton transfer in imidazole by of intramolecular mechanism can't be realise. Intermolecular dimeric mechanism consist of two stages. The first stage is 1H-2H proton transfer and the second – 2H-3H proton transfer and consequently it is a complicated process.



We suggest an intermolecular trimeric mechanism of the 1H-3H proton transfer in imidazole (3), as the same mechanism of the proton transfer in pyrazoles is shown by X-ray structure analysis [2]. The enthalpy of the proton transfer in trimeric structure of imidazole (1) by means of quantum-chemical semiempirical AM1 method in regime of reaction coordinate ( $R_{NH}$ ) was calculated. The values of activation enthalpy and heat of reaction  $\Delta\Delta H^\ddagger$  and  $\Delta\Delta H$  are 454.4 and 3.8 kJ/mol. Such an excessive high value of  $\Delta\Delta H^\ddagger$  and low value of  $\Delta\Delta H$  indicate the tunnel mechanism of the 1H-3H proton transfer in trimeric structure of 4-F-imidazole.

- [1] B.Shickman, M.Mascal, J.J.Titman and I.G.Wood, *J.Am.Chem.Soc.*, **1999**, 121, 11486.  
[2] A.L.Llamas-Saiz, C.Foces-Foces, I.Sobrados and J.Elguero and W.Mautermans, *Acta Cryst.* **1993**, C49, 724.

## PHARMACOLOGICALLY DRIVEN SYNTHESIS OF HETEROCYCLES

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The importance of 1,3,4-oxadiazole-2(3*H*)-thione lies in many biological activities associated with them. They have significant bactericidal, fungicidal, herbicidal activities and as well as some of them are strong enzyme inhibitor such as monoamine oxidase, cyclooxygenase, lipoxygenase, succinate dehydrogenase etc. These syntheses and multidimensional biological activities of various analogues of this class and results associated with other classes of heterocycles will be discussed.

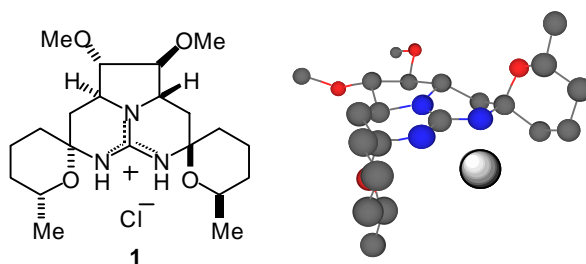
# C<sub>2</sub>-SYMMETRIC CHIRAL PENTACYCLIC GUANIDINE: A NOVEL PHASE-TRANSFER CATALYST FOR THE ASYMMETRIC ALKYLATION AND EPOXIDATION

**Tetsuya Kita<sup>1</sup>, Angelina Georgieva<sup>2</sup>, Yuichi Hashimoto<sup>1</sup>, Tadashi Nakata<sup>2</sup> and Kazuo Nagasawa<sup>1</sup>**

<sup>1</sup>*Institute of Molecular and Cellular Biosciences, University of Tokyo*

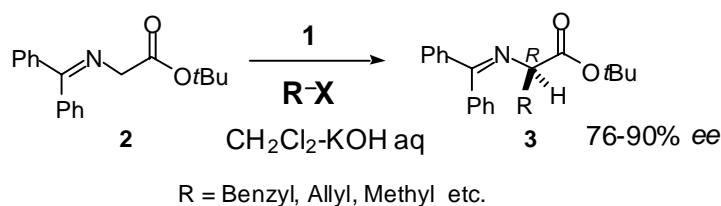
<sup>2</sup>*RIKEN (The Institute of Physical and Chemical Research)*

The guanidine group, which contributes to the stabilization of three-dimensional structures in proteins, is a superbases that forms stabilized complex salts with anionic compounds through parallel interactions including hydrogen bonding. Thus, the guanidine-containing molecules suggest to us their use as a new “reaction vessel”. In the course of our studies aimed at the development of new organocatalysts, we have designed **1** based on the mother skeleton of the marine natural product ptilomycalin A and related compounds. This compound was rationally designed to have a C<sub>2</sub>-symmetrical chiral reaction cavity around the substrate recognition/activation site (guanidine function). Thus, this catalyst is expected to show some asymmetric induction through steric hindrance at this cavity, if the reaction proceeds at the substrate activation site, i.e., the guanidine moiety.



The pentacyclic guanidine was prepared as described before using 1,3-dipolar cycloaddition protocol.<sup>[1]</sup>

Firstly, we examined the alkylation of glycinate Schiff base **2** with various alkyl halides in the presence of a catalytic amount of **1** in a 1 M aqueous KOH/dichloromethane, and we found that the alkylation products **3** were obtained mainly as the (*R*)-form and with high enantio-excess of 76-90% *ee*.



We will also discuss the asymmetric epoxidation of chalcone and its derivatives in the presence of **1** as a phase-transfer catalyst.

[1] K. Nagasawa, A. Georgieva, H. Takahashi, T. Nakata, *Tetrahedron* **2001**, 57, 8959-8964.

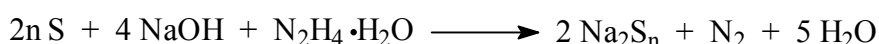


SYNTHESIS OF HETEROCYCLIC COMPOUNDS IN THE REACTION OF  
BENZOTRICHLORIDE WITH THE SYSTEM SULFUR - ALKALI- HYDRAZINE HYDRATE

**N. A. Korchevin, N. V. Russavskaya, V. A. Grabelnykh and E. N. Deryagina**

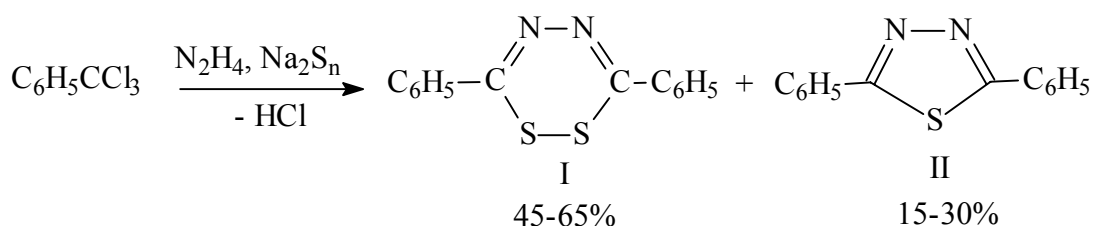
*A.E. Favorsky Irkutsk Institute of chemistry, Siberian Branch, Russian Academy of Sciences,  
664033, Irkutsk, Russia  
E-mail: [vlad@irioch.irk.ru](mailto:vlad@irioch.irk.ru)*

Sulfur is readily dissolved in aqueous-alkaline solutions of hydrazine hydrate to give polysulfides:



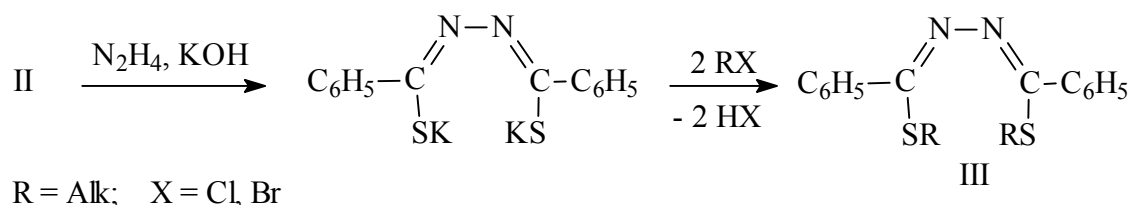
The reactions of such solutions with mono-, di or trialkyl halides result in the corresponding products of thiilation (dialkyl polysulfides or poly(alkylene polysulfides)).

Benzotrichloride reacts with sulfur solution in aqueous-alkali hydrazine hydrate distinctly different. The reaction results basically in two sulfur-nitrogen-containing heterocyclic compounds - 2,5-diphenyl-1,3,4-triazole (I) and 3,6-diphenyl-1,2,4,5-dithiadiazine (II):



The yield of the compounds I and II depends upon polysulfidicity value of sulfur solution. When the value n is increased, the yield of the compound (II) is also increased, and the yield of the compound (I) is decreased. Elemental sulfur is a by-product of the reaction. Elemental sulfur is formed from polysulfanes, which are the products of the reaction of sodium polysulfides with hydrogen chloride.

Bisalkylthioaldazines (III) are formed by the reductive cleavage of dithiadiazine (II) disulfide bond followed by alkylation:



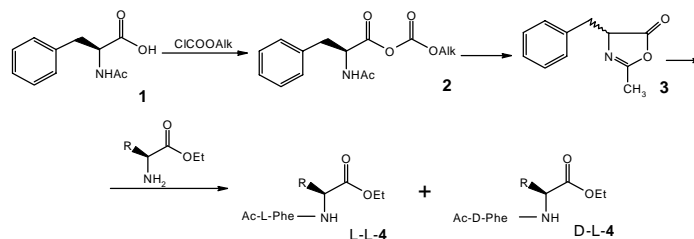
*The work has been done under financial support of Russian Foundation of Basic Research (Grant 00-03-32810).*

# DIASTEREOSELECTIVITY IN THE SYNTHESIS OF DIPEPTIDES OF N-ACETYLPHENILALANINE (THEORETICAL INVESTIGATION)

V. P. Krasnov<sup>1</sup>, V. A. Potemkin<sup>2</sup>, E. A. Zhdanova<sup>1</sup>, N. Z. Solieva<sup>1</sup> and O. N. Chupakhin<sup>1</sup>

<sup>1</sup>*Institute of Organic Synthesis of Ural Branch of RAS, <sup>2</sup>Chelyabinsk State University, Russia*

The peptide synthesis using the ‘mixed anhydrides’ method is usually accompanied by racemization. This process proceeds through the 5(4*H*)-oxazolone formation that is catalyzed by bases.



It has been demonstrated that the interaction of 5(4*H*)-oxazolone (3) with the amino esters is stereoselective in the contrast to the interaction of mixed anhydride (2). The reaction has been carried out with 20% excess of triethylamine at  $-13^{\circ}\text{C}$  for 25 h. The content of L-L diastereoisomer in the reaction mixture was 39.1, 34.3, 25.8 and 10.3 % in the following order Ala, Phe, Val, Glu(OEt) (by the HPLC and <sup>1</sup>H NMR data). Thus the stereoselectivity is increased depending on the volume of the amino acids side chain.

It has been provided a theoretical investigation of the processes using the global energy minimization by the movement along Hessian eigen vectors in the MM3 forcefield. The account of solvation effects has been fulfilled within MERA model. It has been found that the reason of the stereoselectivity is the difference between the complexes “substrate - reactant” formation for various stereoisomers. So, the movement of reactant to R-isomer of oxazolone leads to H-bond formation between amino group of reactant and carbonyl group of oxazolone. Another hydrogen of the amino group interacts with  $\pi$ -electronic system of phenyl radical. Both molecules in complex have no steric strain. The analogous movement of reactant to S-isomer is impossible due to steric strain provided by etoxy-radical. Therefore, more convenient reactant position is at another side of oxazolone ring (at the side of phenyl radical). The complex formation is also accompanied by hydrogen bonding of amino group with carbonyl and by its interaction with  $\pi$ -electronic system of phenyl radical. This complex has a little steric strain that leads to preferred formation of D-L isomer. The difference between energies of complexes “S-isomer – Ala-derivative” and “R-isomer – Ala-derivative” is 2.9 kJ/mole. The difference increases in the sequence Ala, Phe, Val, Glu(OEt) and achieves 7.5 kJ/mole for complexes with Glu(OEt)-derivative. It is in a good agreement with the experimental data. The quantitative relationships between yields of diastereomers and energies of complexes formation are obtained.

*The work is financially supported by the Russian Foundation for Basic Research (grants 00-15-97390 and 01-03-96424).*

# SOME APPLICATIONS OF COMBICHEM ON THE DISCOVERY AND PROCESS STUDY OF AGROCHEMICALS

**Li Bin**

*Shenyang Research Institute of Chemical Industry, Shenyang 11002, PR China*

The following works done in our group will be introduced briefly:

1 Combinatorial synthesis of biological pyrimidinyl ureas

A four member of library of pyrimidinylureas were prepared in mixture and characterized by IR, HNMR, HPLC and GC/Mass for biological screening.

2 Solution-Phase Synthesis of Combinatorial Urea Library

A 25 member library of ureas including the commercial herbicides Monuron and Diuron was generated by the “indexed” combinatorial strategy. This library was characterized by LC/Mass. The herbicides Monuron and Diuron are successfully “rediscovered”.

3 A eighty-member library was generated by solution phase parallel synthesis in two weeks. This library was characterized by LC/Mass and HNMR.

4 Combinatorial synthesis of herbicidal imidazolinetrione cluster library.

A 16 member library of imidazolinetrione was generated by the “clustered” combinatorial strategy developed by our group. This library was characterized by GC/Mass and NMR. Some compounds possess good herbicidal activity.

5 Process Study of Ethyl ( $\alpha$ -p-tosylate) lactate with Combinatorial Strategy

15 reactions were run at the same time with parallel combinatorial strategy for the process study of ethyl ( $\alpha$ -p-tosylate) lactate which is a key intermediate in the manufacturing aryloxyphenoxy herbicides such as quizalofop-ethyl.

6 Process Study of herbicide Sulcotrione with Combinatorial Strategy

The process study of herbicide Sulcotrione was carried out with parallel combinatorial strategy through 30 reactions.

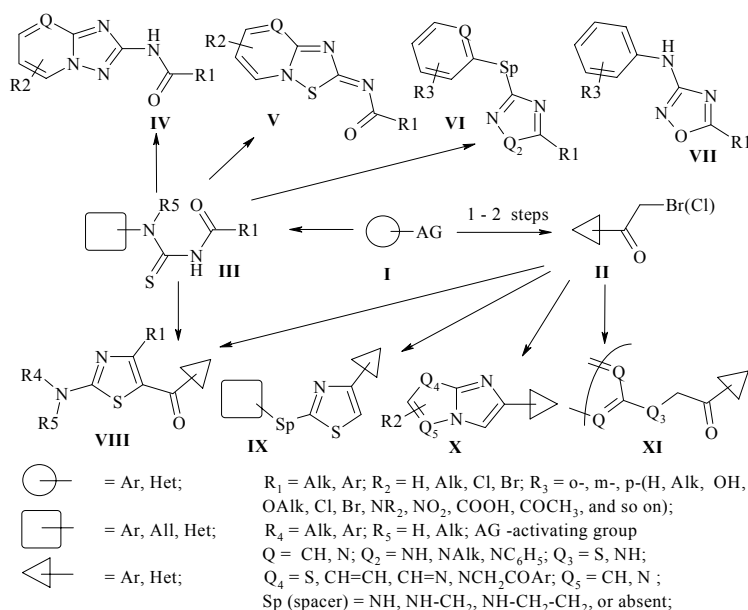
# NEW CHEMICAL ENTITIES FROM TWO-COMPONENT CONDENSATIONS: EFFECTIVE ALTERNATIVE FOR MULTICOMPONENT REACTIONS

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Multi-component reactions (MCRs) have been considered sometimes [1] as a most efficient way to the large, highly diverse libraries. Unfortunately, usually MCRs are sensitive to reaction conditions, and rarely could be realized as protocols. Some examples of highly reproducible and robust enough two-component condensations have been elaborated, starting from commercially available aliphatic and aromatic (heteroaromatic) amines and some other activated compounds **I**. In one or two steps they could be easily transformed into a powerful building blocks **II** and **III**, and then into a number of five- and six-membered heterocycles **IV** – **XI**.



Core structures **IV** – **XI** represent large set of pure drug-like compounds, with mild basicity/acidity, variable ability to H-bonding,  $\pi$ - $\pi$ -stacking, and van der Waals interactions, including rigid (ortho-substituents, fused rings) and flexible molecules, with advanced functionality (OH, NH<sub>2</sub>, COOH, and so on) in at least one ring for follow-up chemistry. Structures of previously unknown types (**IV**–**VII**) have been revealed by X-ray investigation, others confirmed by NMR- and mass-spectroscopy.

[1] L.Weber. *Drug Discovery Today*, **2002**, 7, 2, 143 – 14.

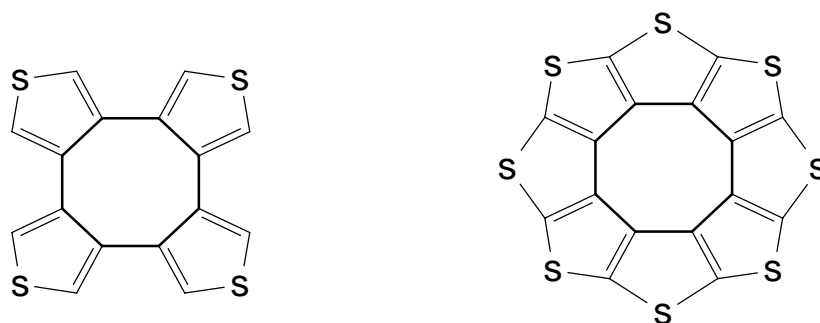
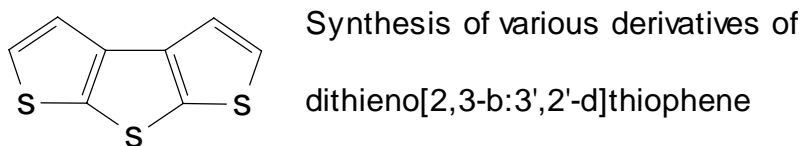
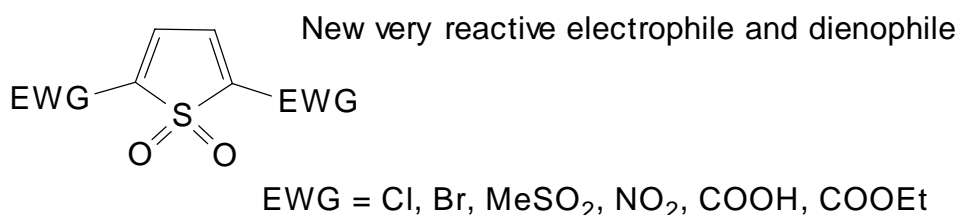
## NEW ADVENTURES IN THIOPHENE CHEMISTRY

**Valentine G. Nenajdenko, Andrej M. Moiseev, Victor V. Sumerin,  
Konstantin Yu. Chernichenko and Elizabeth S. Balenkova**

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Thiophene is one of the most important heterocyclic systems. Their derivatives are very important for medicinal and material chemistry, for example as thiophene oligomers and polymers have found potential use as new organic conductors, semiconductors, photosensitive materials and light emitting devices. In spite of the thiophene chemistry is well studied new synthetic approaches to the thiophene ring functionalisation as well as synthesis of new molecules having thiophene core is very attractive.

Quite recently we started new project devoted synthesis of new unusual thiophene and its condensed analogues derivatives which are important both from fundamental organic chemistry point of view and for organic synthesis as very reactive electrophiles and dienophiles. Very new results of this study will be presented in the report.



## THE RING TRANSFORMATION OF 3-METHYL-5-NITROPYRIMIDIN-4(3H)-ONE

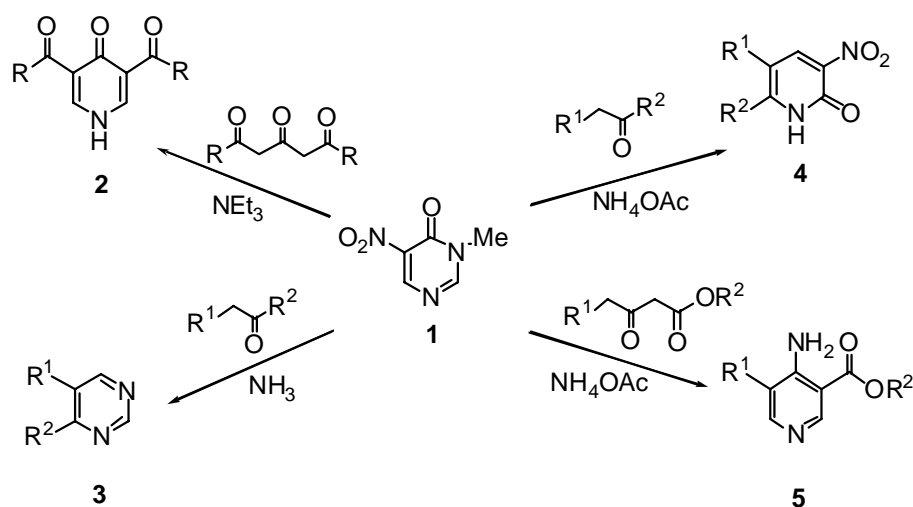
**Nagatoshi Nishiwaki, Mina Tamura, Kazushige Hori, Yasuo Tohda and Masahiro Ariga\***

*Department of Chemistry, Osaka Kyoiku University,  
Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan*

The ring transformation is one of powerful methods for preparation of polyfunctionalized systems. 3-Methyl-5-nitropyrimidin-4(3H)-one (**1**) has a suitable structure for the present purpose, and it leads to various kinds of azaheterocyclic compounds.

The highly electrophilic 2- and 6-positions of **1** readily react with bidentate nucleophiles to afford a ring transformed product via bicyclic intermediate. The reaction of pyrimidinone **1** with active methylene compounds leads to 3,5-difunctionalized 4-pyridones **2** in high yields.<sup>[1]</sup> When pyrimidinone **1** is treated with ketones in the presence of ammonia, 4,5-disubstituted pyrimidines **3** are similarly afforded.<sup>[2]</sup> In these reactions, pyrimidinone **1** behaves as the synthetic equivalent of activated diformylamine.

On the other hand, the use of ammonium acetate realizes the different reactivity. In the reaction of **1** with ketones in the presence of ammonium acetate as the nitrogen source, the carbonyl group at the 4-position is activated to cause the ring transformation at the 4- and the 6-positions, and 5,6-disubstituted 3-nitro-2-pyridones **4** are obtained in addition to pyrimidine derivatives **3**.<sup>[2]</sup> In this case, pyrimidinone **1** behaves as the synthetic equivalent of  $\alpha$ -nitroformylacetic acid. The ratio of these products **3** and **4** is considerably influenced with electron density and steric hindrance of ketone. In the reaction of **1** with active methylene compounds in the presence of ammonium acetate, the ring transformation proceeds at the 2- and 6-positions, and the carbonyl group of the substrate is additionally converted to the amino group affording functionalized 4-aminopyridines **5**.



[1] M. Ariga *et al.*, *Synthesis*, **1997**, 1277.

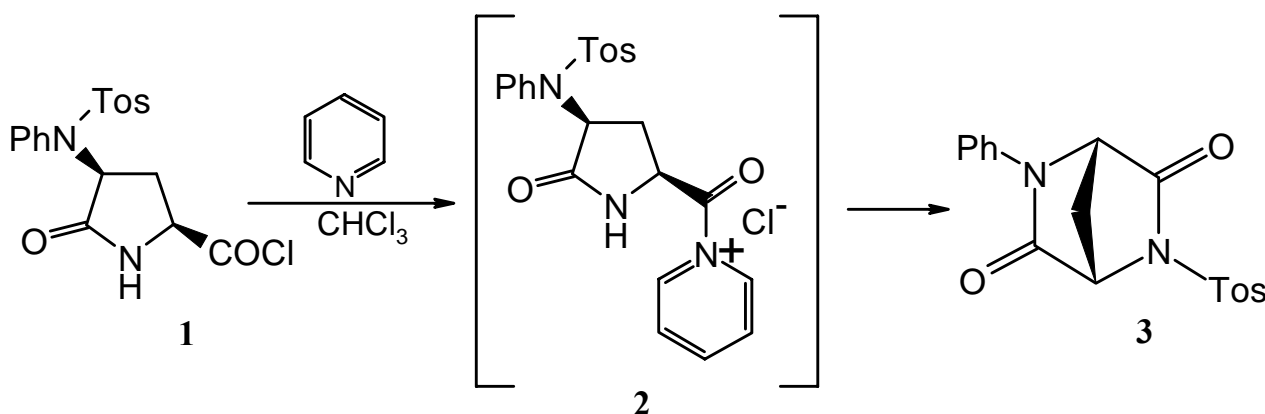
[2] M. Ariga *et al.*, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 27.

# REARRANGEMENT OF THE STERICALLY CONSTRAINED 5-OXOPROLINE DERIVATIVE

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We have shown that *cis*-4-phenylamino-5 oxoproline derivatives are useful for synthesis of amides and natural peptides analogues [1]. However, in the course of studying the possibility to use (2*S*,4*S*)-4-(*N*-tosyl)phenylamino-5-oxoprolinyl chloride (**1**) as a chiral resolving agent for resolution of heterocyclic amines we have revealed that this acyl chloride undergoes rearrangement to 3-(4'-methylphenylsulfonyl)-6-phenyl-3,6-diazabicyclo[2.2.1.]heptane-2,5-dione (**3**) in chloroform in the presence of tertiary amines. The structure of compound **2** has been confirmed by <sup>1</sup>H NMR spectroscopic data and X-ray crystallographic analysis.



The possibility of this rearrangement is likely to be due to the spatial structure of the intermediate acylammonium salt **2** that was formed between acyl chloride **1** and tertiary amine (e.g., pyridine). In such intermediate a migration of Tos-group from 4-phenylamino to N<sup>2</sup> of 5-oxoproline cycle concurrently with intramolecular acylation takes place since the reaction centers are brought close together. The acylammonium salt formation was confirmed by <sup>1</sup>H NMR and IR spectroscopic studies.

*The work was financially supported by the Russian Foundation for Basic Research (grants 00-03-32776, 00-15-97390).*

[1] Nizova I.A., Krasnov V.P., Levit G.L., Kodess M.I. *Amino Acids*, **2002**, 22, 179.

## FINDING OF BIOLOGICAL ACTIVITIES IN DRUG-LIKE COMPOUNDS BY COMPUTER PREDICTION

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*V.N. Orekhovich Institute of Biomedical Chemistry of RAMS,  
119992, Moscow, Russia*

Millions of organic chemical compounds are synthesised, hundreds of thousands of which have been tested to find new prospective leads for different pharmacotherapeutic areas. A huge amount of diverse chemical and biological data is already obtained in numerous pharmaceutical R & D. This rich knowledge should be used to reduce the time & financial expenses at the key stages of drug R & D, decrease the risk of negative results in the whole R & D process and increase the probability of finding the prospective NCEs.

Computer program PASS [1] estimates the probabilities for more than 780 kinds of biological activities on the basis of structural formulae of compounds with average accuracy ~85%. PASS predictions are based on the analysis of structure-activity relationships (SAR) for the training set consisting of more than 43,000 biologically active compounds. Despite the incompleteness of the training set, PASS algorithm is robust enough to obtain the reliable SAR [2] or even predict such raw characteristic of compound as "drug-likeness" [3]. Even among Top200 drugs new biological actions are suggested on the basis of PASS predictions [4].

Keeping in mind that (1) calculation of biological activity spectra for 10,000 compounds on an ordinary PC takes several minutes and (2) only structural formula is necessary to obtain the prediction, PASS can be effectively used to find new prospective hits among the compounds already synthesised or just planned for the synthesis.

The program is open for adding new compounds and biological activities to the training set when such novel data will be found in pharmaceutical R & D. To provide scientific community with PASS services, the Association of PASS users is organized. Work of the Association will assist: (1) many researchers to obtain the program without payment of the License fee, and (2) PASS developers to keep in up-to-date state of the PASS training set.

- [1] PASS: Prediction of Activity Spectra for Substances. Available from: URL: <http://www.ibmh.msk.su/PASS>.
- [2] Poroikov V, Filimonov D, Borodina Yu, Lagunin A, Kos A. Robustness of biological activity spectra predicting by computer program PASS for non-congeneric sets of chemical compounds. *J Chem Inform Comput Sci.* **2000**, 40, 1349-1355.
- [3] Anzali S, Barnickel G, Cezanne B, Krug M, Filimonov D, Poroikov V. Discriminating between drugs and nondrugs by Prediction of Activity Spectra for Substances (PASS), *J. Med. Chem.* **2001**, 44, 2432-2437.
- [4] Poroikov V, Akimov D, Shabelnikova E, Filimonov D. Top 200 medicines: can new actions be discovered through computer-aided prediction? *SAR and QSAR in Environm Res.* **2001**, 12, 327-344.

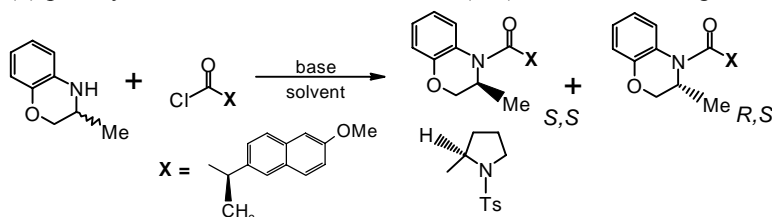


(±)-1,2-DIHYDRO-3-METHYL-4H-1,4-BENZOXAZINE INTERACTIONS WITH (S)-NAPROXEN AND N-TOSYL-(S)-PROLINYL CHLORIDES. THEORETICAL INVESTIGATION

V. A. Potemkin<sup>1</sup>, E. V. Bartashevich<sup>1</sup>, G. L. Levit<sup>2</sup>, V. P. Krasnov<sup>2</sup>, I. N. Andreeva<sup>2</sup>, V. N. Charushin<sup>2</sup> and O. N. Chupakhin<sup>2</sup>

<sup>1</sup> Chelyabinsk State University, <sup>2</sup> Institute of Organic Synthesis of Ural Branch of RAS, Russia

It has been shown that the interaction of (±)-1,2-dihydro-3-methyl-4H-1,4-benzoxazine with (S)-naproxen chloride is accompanied by kinetic resolution with the predominant formation of (S,S)-diastereoisomer [1], whereas the interaction with N-tosyl-(S)-prolinyl chloride leads to formation of (R,S)-diastereoisomer preferably.



For interpretation of these kinetic phenomena the theoretical investigation have been provided. The general features determining these kinetic resolution processes are defined. (R,S)- and (S,S)-diastereoisomers formed in the reaction have considerably different conformational states. The enthalpy of formation of (S,S)-product with (S)-naproxen chloride is less, than that of (R,S) product (PM3 computation:  $\Delta H_{SS} = -217.4$  kJ/mole;  $\Delta H_{RS} = -207.7$  kJ/mole). This explains the advantage of a (S,S)-diastereoisomer yield in the presence of weak polar solvents. On the contrary, in the reaction with N-tosyl-(S)-prolinyl chloride the enthalpy of formation of (R,S) product is lower, which agrees with advantage of a yield of this diastereoisomer. The modeling of complexes "substrate - reactant", "substrate - solvent", "substrate - catalyst" has been carried out by means of combination of MultiGen [2], PM3 and *ab initio* methods. It has been found the non-equivalent opportunity of the (S)-naproxen chloride and N-tosyl-(S)-prolinyl chloride disposition at the asymmetric substrate. The movement of (S)-naproxen chloride to (S)-isomer is characterized by  $\pi$ - $\pi$ -electronic interaction, and hydrogen bond. The energy of formation of this complex is  $\Delta E_{SS} = -41.1$  kJ/mole. The similar approach to (R)-isomer is impossible due to the steric barrier provided by methyl group. In this case, the hydrogen bond cannot be formed. Instead of it, more weak electrostatic interaction Cl...H is formed. Energy of complex formation is  $\Delta E_{RS} = -37.0$  kJ/mole. It results in higher probability of reaction of (S)-isomer. The movement of N-tosyl-(S)-prolinyl chloride to (R)-isomer leads to lower energy complex formation, than its movement to (S)-isomer ( $\Delta E_{RS} = -40.9$  kJ/mole;  $\Delta E_{SS} = -32.2$  kJ/mole), which is in agreement with experimental yields. The elucidation of solvate complexes geometry results in conclusion about the asymmetry of substrate solvation and the competition between solvent and reactant. So the reactant should supersede a molecule of solvent since the solvation of substrate is carried out mainly at the side of the reactant approach. The kinetic resolution in the reactions with (S)-naproxen chloride depends on molecular volume of solvent and LUMO of catalyst. The reactions with more polar N-tosyl-(S)-prolinyl chloride depend on dipole moment of solvent and LUMO of catalyst (the exclusion is 4-(dimethylamino)pyridine (DMAP)). The elucidation of the geometry of "substrate - catalyst" complex shows that the catalysts such as triethylamine, 4-methylmorpholine, N,N-diisopropylethylamine, don't interact with hydrogen of substrate at the limiting stage due to steric effect. Pyridine also doesn't interact with hydrogen of substrate at the limiting stage due to low basicity. Another process is observed in the reactions with DMAP as a catalyst. The base center of this molecule is in planar pyridine moiety. It has no steric barrier for movement to substrate and possesses high basicity (pKa = 9.7). Thus, interaction with DMAP leads to equalization of diastereoisomers yields.

The work is financially supported by the Russian Foundation for Basic Research (grants 00-03-32776 and 00-15-97390)

- [1] Charushin V.N., Krasnov V.P., Levit G.L. et al. *Tetrahedron: Asymmetry*, **1999**, 2691.  
[2] Grishina M.A., Potemkin V.A., Arslambekov R.M., *IVTN-2002*, Book of Abstr., Moscow, **2002**, 22.

## SYNTHESIS OF OXATHIACROWN ETHERS WITH FLUORESCENT SUBSTITUENTS

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and A. A. Abramov**

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Moscow 119899, Russia*

Thiacrown ethers are capable to selectively bind to the ions transition and heavy metals, that makes them useful agents in radioactive waste processing, making ion-selective electrodes and to use as chemical sensors. Chemical sensors might be created by attaching functional groups capable of changing its property, for instance, ability to fluoresce, during interaction of macrocycle with guest ion.

We have synthesized potential chemical sensors- 12- and 15-membered oxathiacrown ethers that contain benzyl and naphthylmethyl substituents. Starting compounds for these syntheses were allylbenzene, 2-allylanisole and 1-allyl-2-methoxynaphthalene. Cyclisation of corresponding diols and dibromides was carried out in high dilution conditions in the presence of lithium and cesium carbonate, 1,8-dimercapto-3,6-dioxaoctane and 1,11-dimercapto-3,6,9-trioxaundecane having been used as nucleophiles.

The presented compounds were characterized by mass-, <sup>1</sup>H and <sup>13</sup>C NMR spectra and GC-MS. The extraction ability was studied for the above mentioned compounds with Sr and Pb cations in nitrate and picrate solutions.

# NEW REACTION OF TERMINAL ACETYLENES WITH NITRATES AS A METHOD FOR SYNTHESIS OF 3-ACYL-5-ARYL(ALKYL) ISOXAZOLE DERIVATIVES

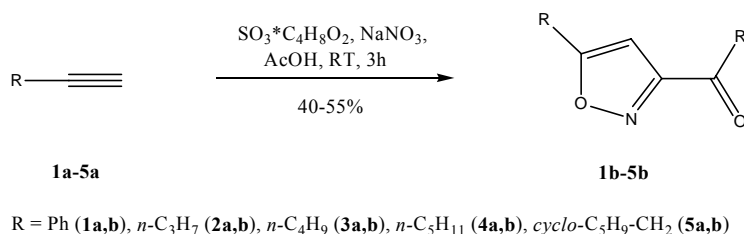
V. O. Rogatchov<sup>1</sup>, V. D. Filimonov<sup>1</sup>, M. S. Yusubov<sup>2</sup> and W. Bender<sup>3</sup>

<sup>1</sup>Tomsk Polytechnic University, 634034, Tomsk, Russia

<sup>2</sup>Siberian State Medical University, Tomsk, Russia

<sup>3</sup>Bayer Pharma, Chemical Research, D-42096 Wuppertal, Germany

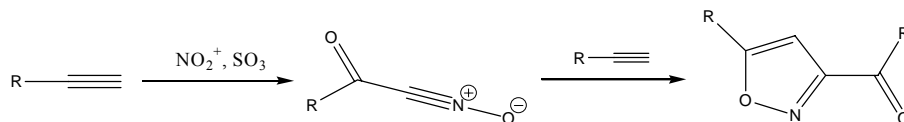
Earlier we have shown, that acetylenes in ice acetic acid at the presence of nitrates and KI give 1-iodo-2-nitroalkenes<sup>1</sup>, and reaction of phenylacetylene with sulfuric acid or sulphuric anhydride results to 4,6-diphenyl-1,2-oxathiin-2,2-dioxide as a new type of unsaturated  $\beta$ -sultones<sup>2,3</sup>. However at action of SO<sub>3</sub> and NaNO<sub>3</sub> on phenylacetylene unexpectedly was obtained 3-benzoyl-5-phenylisoxazol<sup>4</sup>. Further we have shown, that this reaction with nitrates of s-metals or ammonium and SO<sub>3</sub>-dioxane complex is general for terminal aryl- and alkylacetylenes and gives isoxazoles with 40-55 % yields:



Reactivity of alkynes **1a-5a** in this reaction is very similar.

It is known, that one of the general methods of synthesis of isoxazoles is the condensation of acetylenes with nitrile oxides, which one often are generated *in situ*<sup>5</sup>. The compounds **1b**, **2b**, **3b** were obtained earlier from corresponding alkynes **1a**, **2a**, **3a** and NaNO<sub>2</sub>/HNO<sub>3</sub> in nitromethane in the presence of the Bu<sub>4</sub>N<sup>+</sup>AuCl<sub>4</sub><sup>-</sup> in 40, 35, and 38 % yields<sup>6</sup>.

We suppose, that the mechanism of formation of isoxazoles **1b-5b** from terminal acetylene and NO<sub>3</sub><sup>-</sup>/SO<sub>3</sub> system includes of nitrile oxides formation, which one reacts with following molecule of alkyne in the 1,3-cycloaddition mode giving of the isoxazol cycle. In accordance of this assumption we have shown by GC-MS method that nitrile oxide is formed in the reaction mixture of acetylene and NO<sub>3</sub><sup>-</sup>/SO<sub>3</sub>:



- [1] Yusubov M.S., Perederina I.A., Kulmanakova Y.Y., Filimonov V.D., Ki Van Chi // *J. Org. Chem. (Russia)*. **1999**, 35, 1296.
- [2] Yusubov M.S., Filimonov V.D., Rogatchov V.O., *J. Org. Chem. (Russia)*, **1996**, 32, 1272.
- [3] Rogatchov V.O., Yusubov M.S., Filimonov V.D., *J. Org. Chem. (Russia)*, **1999**, 35, 439.
- [4] Rogatchov V.O., Yusubov M.S., Filimonov V.D., *J. Org. Chem. (Russia)*, **2001**, 37, 1250.
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- [6] Gasparrini F., Giovannoli M., Misiti D., Natile G., Palmieri G., Maresca L., *J. Amer. Chem. Soc.* **1993**, 115, 4401.

Financial support of this work by the Russian Foundation of Basic Research (grants N 00-03-32812 and N 02-03-06577) and Bayer AG, Germany, is gratefully acknowledged

# INVESTIGATION OF REACTIVITY OF DIAZOIMIDAZOLES AND THEIR DIAZONIUM SALTS IN C-AZO COUPLING REACTIONS

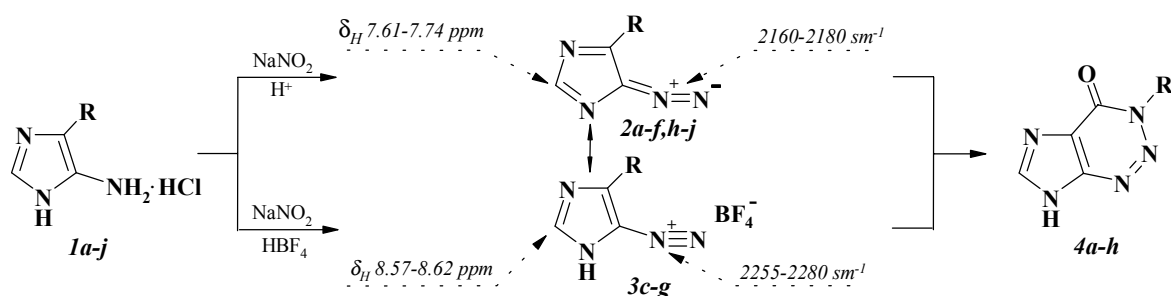
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*The Urals State Technical University, 620002, Ekaterinburg, Russia*

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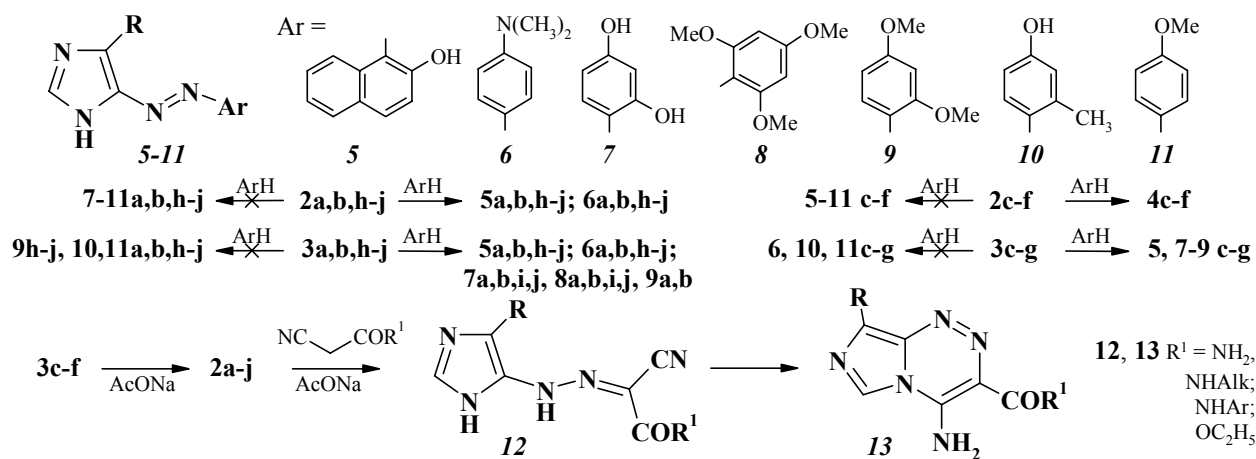
The diazo function confers interesting properties; both chemical and biological to the compound to which is bound. The most important class of these derivatives is represented by the diazoazoles. In fact, depending on the structure of diazo function and experimental conditions, these heterocyclic derivatives can participate in conversions, which are characteristic for aromatic diazonium salts as well as for aliphatic diazo compounds.

In this poster we would like to present comparative study of reactivity of diazo compounds and diazonium salts of imidazole series. In order to obtain an appropriate object needed for the investigation, we have conducted systematic research of diazotization reaction of 5-aminoimidazole-4-*N*-alkyl(aryl)carboxamides (1a-j) and have developed a very mild procedures for the synthesis of 5-diazoimidazoles (2a-j) and imidazolyl-5-diazonium salts (3c-g) in high yields.



**1-3, 5-11** a R = CONH<sub>2</sub>, b R = CONHCH<sub>3</sub>, c R = CONHC<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*p*, d R = CONHC<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*o*, e R = CONHC<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>-*p*, f R = CONHC<sub>6</sub>H<sub>4</sub>-Cl-*p*, g R = CONHC<sub>6</sub>H<sub>4</sub>-COOC<sub>2</sub>H<sub>5</sub>-*p*, h R = CONHC<sub>6</sub>H<sub>11</sub>, i R = COMorpholinyl, j R = COPiperidinyl;  
**4 a** R<sup>1</sup> = H, b R<sup>1</sup> = CH<sub>3</sub>, c R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*p*, d R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*o*, e R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>-*p*, f R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>-Cl-*p*, j R<sup>1</sup> = C<sub>6</sub>H<sub>4</sub>-COOC<sub>2</sub>H<sub>5</sub>-*p*, h R<sup>1</sup> = C<sub>6</sub>H<sub>11</sub>

Further we have studied interactions of the compounds 2 and 3 with aromatic coupling components and active methylene reagents. It was determined that diazonium salts 3 are much more reactive than corresponding diazo compounds 2 in these reactions.



Reactivity of diazonium salts of imidazole 3 is lower than that of diazonium salts of benzimidazole and 1,2,4-triazole, and reactivity of imidazole, pyrazole and 1,2,3-triazole, possessing in structure diazo function, is similar. As was expected, diazo compounds react slowly only with the most active aromatic azo components (*N,N*-dimethylaniline and  $\beta$ -naphthol), but interact easily with ethyl ester cyanoacetic acid and its amides.

Therefore, results obtained have great importance for prediction of diazo compound reactivity towards other substrates. The experimental results are explained by use of semi-empirical methods of calculation. Elemental analysis, mass spectrometry, IR and  $^1\text{H}$  NMR spectroscopy provide evidence for the structure of the compounds synthesized.

*This work was supported by the Russian Foundation for Basic Research (grant no. 01-03-96433a) and the US Civilian Research and Development Foundation (project no. RCI-2393-EK-02 and REC 005).*

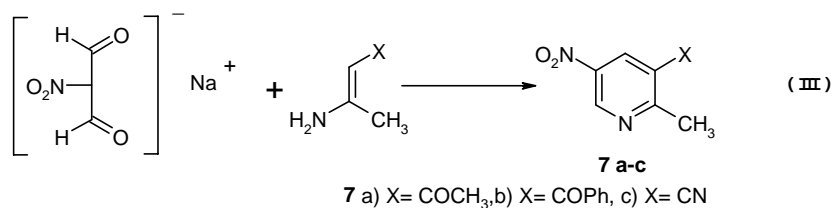
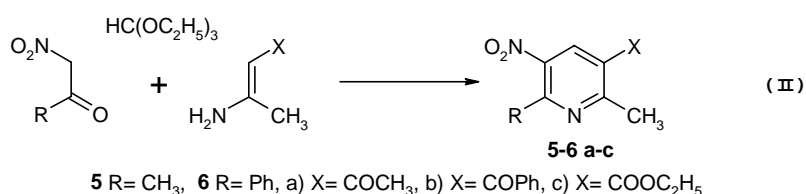
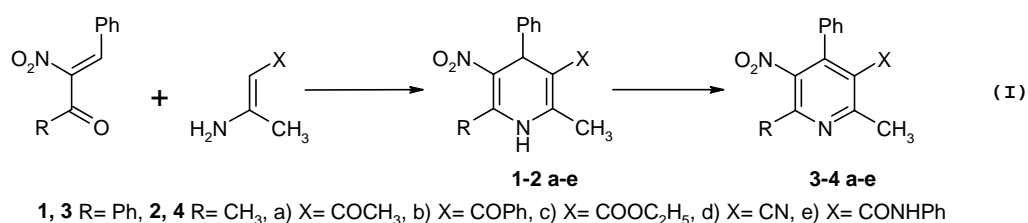
# SYNTHESIS OF NITROPYRIDINES FROM NITROCARBONYL COMPOUNDS

**G. P. Sagitullina, L. V. Glyzdinskaya, G. V. Sitnikov,  
E. O. Silina and R. S. Sagitullin**

*Department of Organic Chemistry, Omsk State University,  
644077 Omsk, Russia.*

*E-mail: [shkil@univer.omsk.su](mailto:shkil@univer.omsk.su)*

Synthesis of some new nitropyridines from nitrocarbonyl compounds has been carried out. Formation of nitropyridine ring with needful substituents has been realized by diverse variants of Hantzsch synthesis (Scheme I-III).



*Financial support from RFBR through project no. 00-03-32832 and Ministry of Education through project no. E 00-5.0-11 is gratefully acknowledged.*

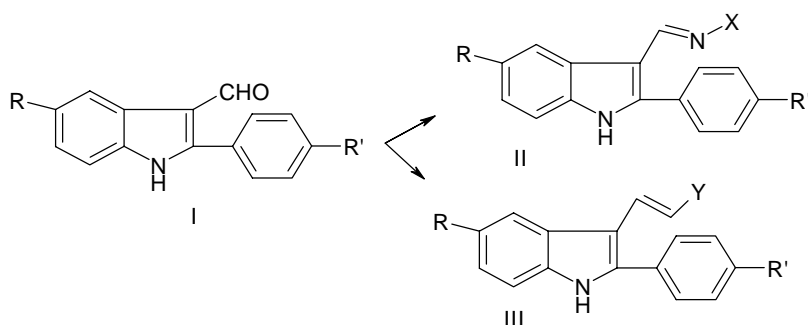
# SYNTHESIS AND TRANSFORMATIONS OF SOME ARYL-INDOLES AND BIS-INDOLE-ALDEHIDES

**N. Targamadze, N. Narimanidze, N. Samsonia, N. Tsetsadze and J. Chikvaidze**

*Iv. Javakhishvili Tbilisi State University, Georgia*

We had studied the condensations of some new 2-aryl-indole-3-carbaldehydes (I) and bis-indole-aldehydes(IV) with hydroxyl-amines, also with the derivatives of hydrazine and some CH-acids in definite conditions. The correspondence products are obtained.

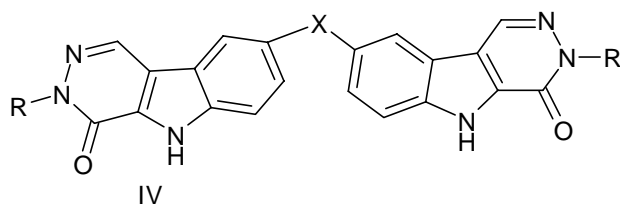
Deformation of arylindole-aldehydes proceeds in poliatomic alcohols under the high temperature. Simultaneously bis-indolodiazides (V,V',VI,VI') were isolated under heating of bis-aril-hydrazones in ice acid. The originalities of these reactions and influence of substituted groups had been analyzed in our report.



R = CH<sub>3</sub>, Cl  
R' = OCH<sub>3</sub>; H

X = OH, , , ,

Y = COOH, NO<sub>2</sub>.



V    X = O,    R = C<sub>6</sub>H<sub>5</sub>,                      VI    X = O,    R = C<sub>6</sub>H<sub>4</sub>(NO<sub>2</sub>)-p  
V'    X = CH<sub>2</sub>, R = C<sub>6</sub>H<sub>5</sub>,                      VI'    X = CH<sub>2</sub>, R = C<sub>6</sub>H<sub>4</sub>(NO<sub>2</sub>)-p

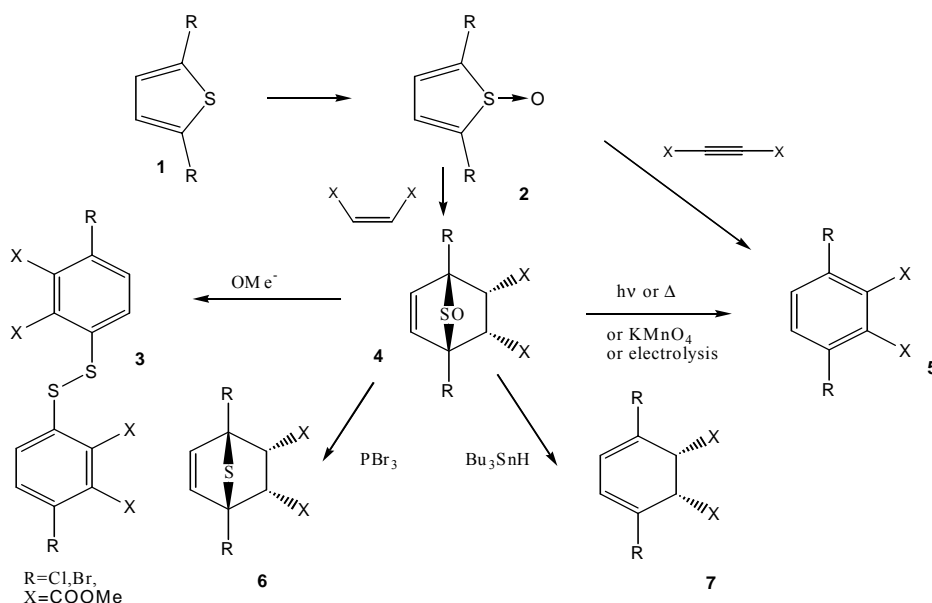
## THIOPHENE S-OXIDES - PREPARATION AND REACTIONS

**Thies Thiemann**

*Institute of Advanced Material Study, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi  
Fukuoka 816-8580, Japan*

Substituted thiophene *S*-oxides **2** can be prepared either by oxidation of thiophenes with peracids in the presence of a Lewis acid<sup>[1]</sup> or by the reaction of zirconacyclopentadienes with thionyl chloride.<sup>[2]</sup> Thiophene *S*-oxides act as dienes in Diels Alder type reactions. With alkynes they give functionalized aromatic compounds, with alkenes they give 7-thiabicyclo[2.2.1]heptene *S*-oxides, which themselves can be transformed to arenes, cyclohexadienes, or diaryl disulfides.

Thiophene *S*-oxides show cytotoxicity. This may be due to the generation of reactive oxygen. When thiophene *S*-oxides are photoirradiated in the presence of oxidizable substances, they lose oxygen quickly and revert to the corresponding thiophenes. The nature of the photoextruded oxygen is still a matter of debate. In absence of oxidizable additives, photoirradiation of thiophene *S*-oxides may lead to hydroxylated thiophenes, furans or thiophenes, depending on the substituent(s) of **2**.



Electrochemical studies on thiophene *S*-oxides have shown that in the presence of proton donors the molecules can be reduced cleanly to the thiophenes. In absence of a proton donor a more complex reductive behavior is observed. Electro-oxidatively, 2,3,4,5-tetraphenylthiophene *S*-oxide has been transformed electro-oxidatively to *Z*-dibenzoylstilbene.

- [1] T. Thiemann, Y. Q. Li, C. Thiemann, T. Sawada, D. Ohira, M. Tashiro, S. Mataka, *Heterocycles* **2000**, *52*, 1215 and ref. cited.  
 [2] B. T. Jiang, T. D. Tilley, *J. Am. Chem. Soc.* **1999**, *121*, 9744.

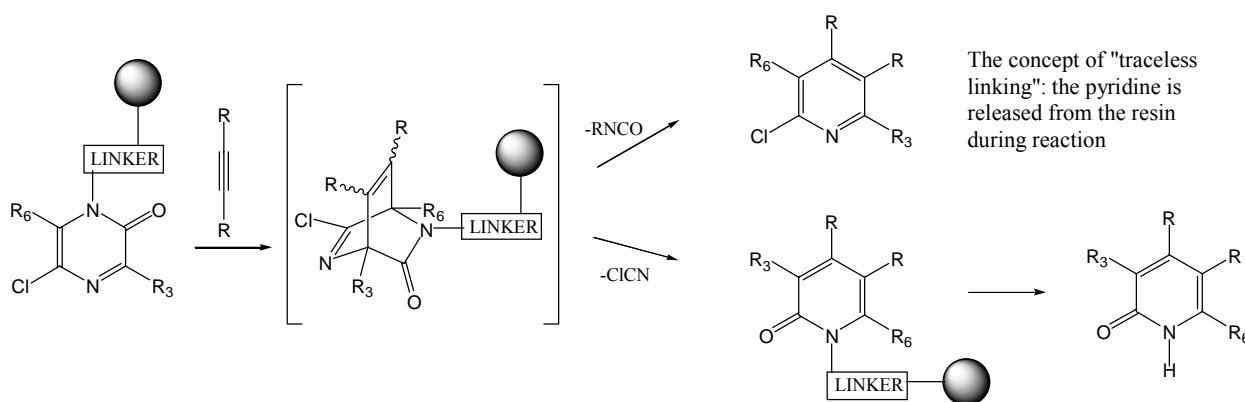


# AN EXPLORATORY STUDY OF THE SOLID PHASE CHEMISTRY OF 2(1H)-PYRAZINONES

**Erik Van der Eycken and Nadzeya Kaval**

*Katholieke Universiteit Leuven, Department of Chemistry, Laboratory for Organic Synthesis,  
Celestijnenlaan 200F, B-3001 Leuven, Belgium  
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We will describe our research on the inter- and intramolecular Diels-Alder reactions with the 2-azadiene system of 2(1H)-pyrazinones. The easily accessible and multifunctionalized 2-azadiene system of these compounds will be shown to offer unique opportunities for cycloaddition reactions with electron-rich and electron-poor dienophiles. Subsequent retro-cycloaddition reactions yielding 2(1H)-pyridines and/or 2(1H)-pyridinones from the adducts of alkynes are discussed. Application of an intramolecular version of this cycloaddition-retro-cycloaddition process is shown to yield c-anellated 2(1H)-pyridin(on)es. In contrast, cycloaddition with alkenes provides stable adducts with interesting functionalities for further elaboration. These properties render these compounds useful synthons for the elaboration to alkaloid compounds and analogues of (phyto)pharmaca. In the course of an exploratory study we investigated the chemistry of 2(1H)-pyrazinones on a solid support. A suitable linker had to be determined. In case of Diels-Alder reactions with alkynes, a concept of "traceless linking" has been worked out, allowing easy separation of the 2(1H)-pyridines and 2(1H)-pyridinones formed during reaction.



See for example References:

- Synthesis of  $\alpha$ -carbolines and  $\beta$ -carbolinones via Intramolecular Diels-Alder Reactions of 2(1H)-Pyrazinones, A. Tahri, K. J. Buysens, E. V. Van der Eycken, D. M. Vandenberghe, G. J. Hoornaert, *Tetrahedron*, **1998**, 54, 13211 – 13226.
- Lewis acid catalyzed Diels-Alder reactions of olefinic and acetylenic compounds with 6-methyl-3,5-dichloro-2H-1,4-oxazin-2-one, W. De Borggraeve, F. Rombouts, E. Van der Eycken, G. Hoornaert, *Synlett*, **2000**, 713 – 715.
- Synthesis of a conformationally restricted dipeptide analogue and its evaluation as a  $\beta$ -turn mimic, W. M. De Borggraeve, F. J. R. Rombouts, E. V. Van der Eycken, S. M. Toppet, G. J. Hoornaert, *Tetrahedron Letters*, **2001**, 42, 5693-5695.
- Stereoselective intramolecular Diels-Alder reactions of 3-alkenyl(oxy)-2(1H)-pyrazinones, W. M. De Borggraeve, F. J. R. Rombouts, B. M. P. Verbist, E. Van der Eycken, G. J. Hoornaert, *Tetrahedron Letters*, **2002**, 43, 447-449.  
and references cited herein.

# COMPARATIVE INVESTIGATION OF HETEROCYCLIZATION OF FUNCTIONAL VICINAL FUNCTIONALLY SUBSTITUTED ACETYLENYLARENES AND -HETARENES

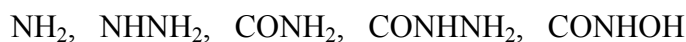
**Sergei F. Vasilevsky**

*Institute of Chemical Kinetics and Combustion, Siberian Branch of RAS,  
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The synthesis and study of the heterocyclization of vicinally substituted functional acetylenylarenes and –hetarenes are an actual and rapidly developing field of organic chemistry. Indeed, cyclization of vicinally functionalized aromatic and heteroaromatic acetylenic compounds has recently become very important as a method for the synthesis of condensed polynuclear heterocycles by the search for biologically active compounds, which are difficult to obtain by other methods .

Besides, the study of the cyclization rules would help to solve a fundamental problem, *i.e.* the studying of structure-property correlations, their systematization that allow to carry out synthesis of almost inaccessible heterocycles.

We have carried out systematic investigation of heterocyclization of aryl and hetaryl acetylenic derivatives with *vic*-functional groups :



The existence of two nucleophilic centers of different-character in the binucleophilic groups had made it possible to selectively use one of them to attack carbon atoms of the triple bond.

We have showed that cyclization in benzene and pyrazole series occurred by different way depending on structure of substitute at C-atom of the triple bond, position of interaction groups, nature of condensing means.

Our synthetic studies have allowed us to prepare various condensed benzo- and pyrazolo-pyrrolidinones, -pyridinones, -pyridazinones, -pyrroles and -pyrazoles.

As follows from our data, the cycloisomerization of vicinally substituted functional acetylenylarenes and –hetarenes exhibits a tendency to cyclize the system affording 5- and 6-membered fused cycles.

Reasons of community, differences and peculiarities of the ring-closure reactions will be discussed.

*This work was supported by RFBR grants (02-03-32265), CRDF REC-008, "Integration" program grant of SB RAS, ACCU SB RAS No. 33-03-40135.*

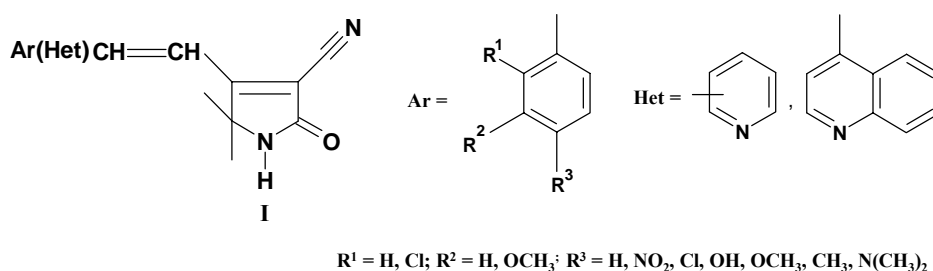
COMPUTER ANALYSIS OF THE BIOLOGICAL ACTIVITY OF  
2-OXO-2,5-DIHYDRO-1H-PYRROLE-3-CARBONITRILE DERIVATIVES

N. Veretennikova<sup>1</sup>, A. Skorova<sup>1</sup>, D. Jansone<sup>1</sup>, E. Lukevics<sup>1</sup>, L. Leite<sup>1</sup> and G. Melikyan<sup>2</sup>

<sup>1</sup>*Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia,  
7821038; E-mail: [hgs@osi.lv](mailto:hgs@osi.lv)*

<sup>2</sup>*Department of Organic Chemistry, Yerevan State University, Yerevan 375049, Armenia  
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The OREX expert system was used for the study of structure-activity relationships of the set of unsaturated aryl(hetaryl)  $\delta$ -lactams:



OREX is a system of tools to analyze structure-activity relationships of chemical compounds, that was elaborated in the Latvian Institute of Organic Synthesis. OREX implements the logico-structural approach (LSA). LSA algorithms are based on the selection of the reliable biological activity features, i.e., structural characteristics defining the type of compound activity. This approach includes the special language for chemical structures description and procedures for activity prediction and SAR analysis. The standart model database contains about 9000 structures, which are described with the aid of this language and treated statistically. In the result the knowledge base was created, that contains the descriptor set for every activity with statistical characteristics.

In the course of the computer analysis of the compounds **I** we got the list of possible pharmacological and therapeutical activities, which includes basically cardiovascular activities such as cardiostimular phosphodiesterase inhibitors, anti-arrythmic potassium channel agonists, and vasodilators. The possibility of possessing these activities is controlled by lactam and phenyl rings in the structures of the studied compounds. Introduction of the substituents into phenyl ring or substitution of aryl by heteryl ring results in anticipation of other activities, for example, anticancer or antiviral.

Compounds **I** were synthesized by treatment of 4,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carbonitrile with aryl- and hetarylcarbaldehydes in the presence of basic catalyts.

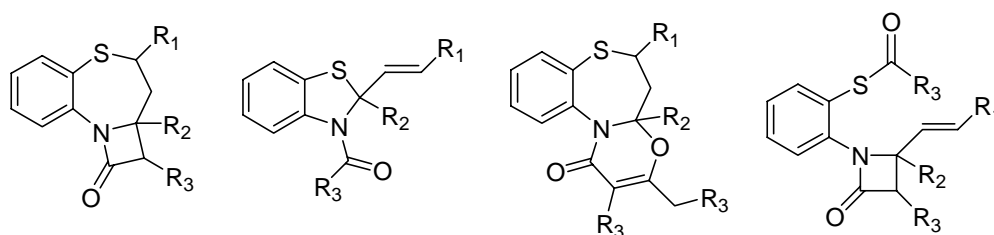
Their chemical and biological properties will be discussed.

# A STRUCTURE DIVERSE HETEROCYCLIC LIBRARY DERIVED FROM REACTION OF 2,3-DIHYDRO-1,5-BENZOTHIAZEPINES AND ACYL CHLORIDES

Jiayi Xu

*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, PR China*

Benzodiazepine and benzothiazepine derivatives are very important pharmaceutical agents. The  $\beta$ -lactam skeleton is the key structural element of the most widely employed family of antimicrobial agents. Most of the important antibiotics possess the representative structure of a  $\beta$ -lactam fused to a five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms. The effective antibiotics, penicillin, penam and penem, have fused thiazolidine- $\beta$ -lactam structures, and cephalosporin and cephem are fused dihydrothiazine- $\beta$ -lactams. The synthesis of bicyclic  $\beta$ -lactams became a desirable goal based on the discovery of penicillin and cephalosporin. Though most of them have been obtained by biosynthesis, by chemical modification of intermediates that are produced *via* biosynthesis, or by chemical synthesis, it seemed to be necessary to synthesize some novel compounds with a fused  $\beta$ -lactam-heterocyclic ring for bioassay of antibacterial activity because of the growing resistance of bacteria against penicillin and cephalosporin-like compounds and the need for medicines with a more specific antibacterial activity. Up to now, some  $\beta$ -lactam derivatives of thiazoline and dihydrothiazine have been synthesized by various methods. The synthesis of a few examples of  $\beta$ -lactam derivatives of benzothiazepines has been published. During last decade, our working group has paid much attention to the cycloaddition reactions of benzoheteroazepines, and stereochemistry and spectral properties of their cycloadducts. Herein we report the preparation of a structure-diverse heterocyclic library derived from reaction of 1,5-benzothiazepines and acyl chlorides *via* parallel solution phase combinatorial synthesis. In the syntheses, it has been found that the structures of the products depend on acyl chlorides. An acyl chloride with a more acidic  $\alpha$ -hydrogen gives mainly a  $\beta$ -lactam derivative. An acyl chloride with a less acidic  $\alpha$ -hydrogen or without an  $\alpha$ -hydrogen produces a thiazepine ring-contracted product. An acyl chloride with a moderate acidic  $\alpha$ -hydrogen gives rise to a thiazepine ring-contracted product and oxazinone fused products besides a  $\beta$ -lactam derivative. While a good nucleophilic acyl chloride with a more acidic  $\alpha$ -hydrogen yields both a  $\beta$ -lactam derivative and a thiazepine ring-opening  $\beta$ -lactam derivative. The reaction mechanism was also discussed.



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- [2] Xu, J.X.; Zuo, G.; Lai, W. L. *Heteroat. Chem.*, **2001**, 12, 636.
- [3] Xu, J.X.; Zhang, Q. H.; Zuo, G.; Lai, W. L. *Heteroat. Chem.*, **2002**, 13, 276 and cited there.
- [4] Xing, Q. Y.; Wang, H. Z.; Zhou, X.; *et. al. J. Heterocycl. Chem.*, **2001**, 38, 561.
- [5] Toth, G.; Levai, A.; Balazs, B.; Simon, A. *Liebigs Ann.*, **1997**, 995.

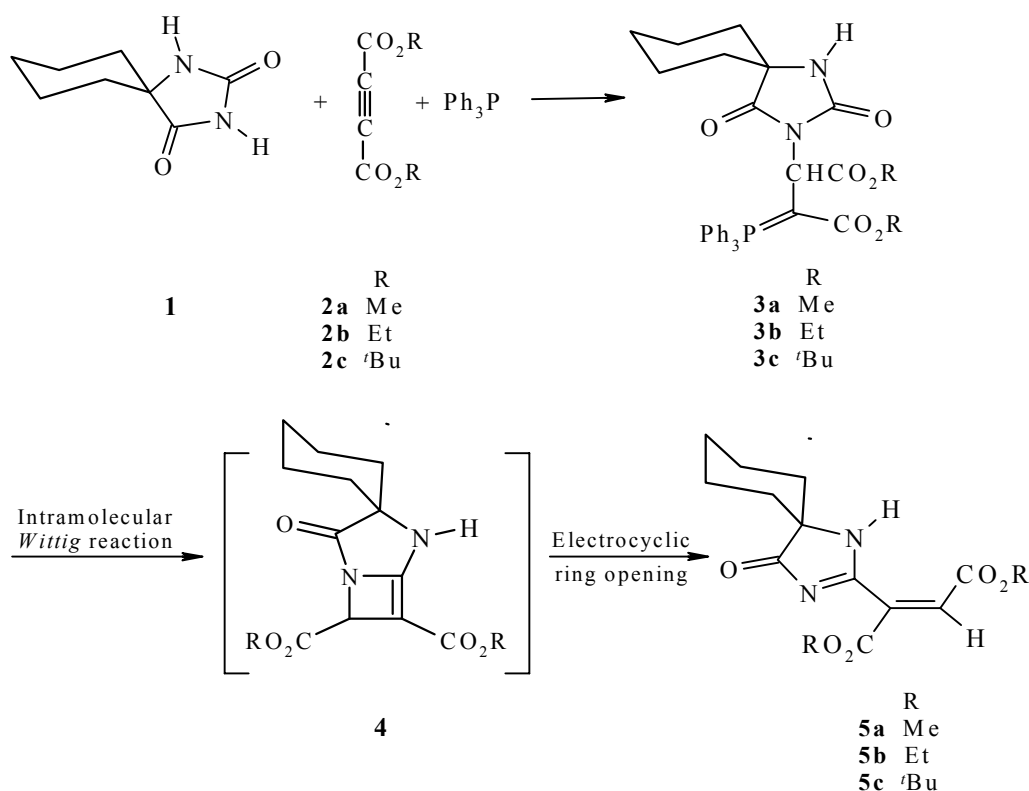
# EFFICIENT SYNTHESIS OF 2-VINYLATED SPIRO-IMIDAZOL-4-ONES

**Issa Yavari and Nader Zabarjad-Shiraz**

*Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14115-175, Tehran, Iran*

Stable crystalline phosphorus ylides **3** are obtained in excellent yields from the 1:1:1 addition reaction between spiro-hydantoin **1** and dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine. These ylides exist in solution as a mixture of two geometric isomers. This is due to the restricted rotation around the carbon-carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group.

Ylides **3** undergo intramolecular *Wittig* reaction[1] to produce the fused bicyclic intermediates **4**, which apparently isomerise under the reaction conditions employed to produce the final products **5** in excellent yields.



Phosphorus ylides **3** can be considered as potentially useful synthetic intermediates. The procedure described here provides an acceptable method for the preparation of phosphoranes bearing a hydantoin residue, which can be employed for the synthesis of 2-vinylated spiro-imidazol-4-ones.

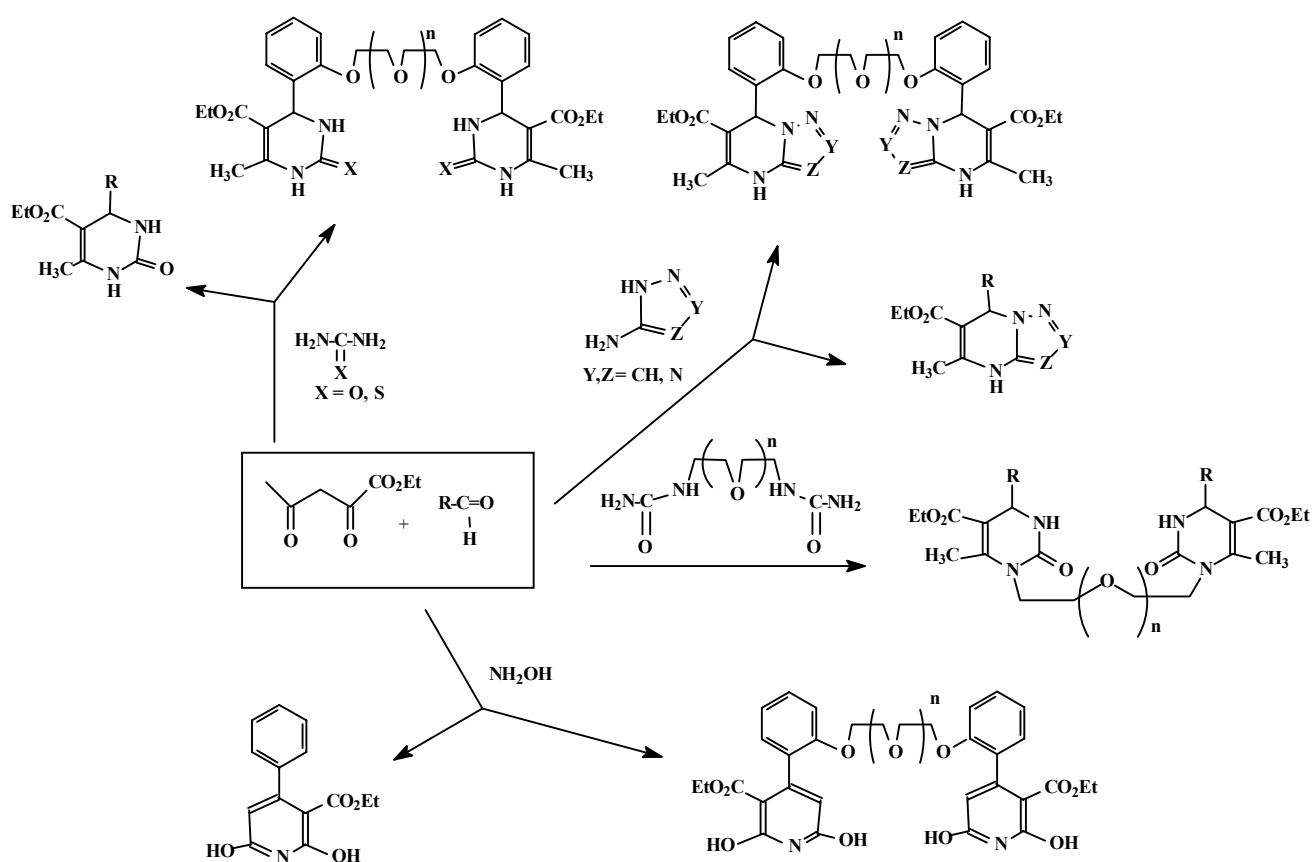
[1] Nicolaou, K. C., Harter, M. W., Gunzner, J. L., and Nadin, A., *Liebigs Ann.*, **1997**, 1283.

THREE – COMPONENT REACTIONS IN THE COMBINATORIAL SYNTHESIS OF AZINES

**M. S. Zhidovina, I. G. Ovchinnikova, O. V. Fedorova, M. S. Valova,  
G. L. Rusinov and O. N. Chupakhin**

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Ekaterinburg, Russia  
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This report deals with the target synthesis of new derivatives of dihydropyrimidines and pyridines, being nifedipine analogues.



*This work was possible due to financial support from Russian Foundation of Basic Researches (Grant No 02-03-32332).*