Plenary Lectures
(PL)

BDSHC
Blue Danube Symposium
on Heterocyclic Chemistry

CRAFTING CHIRAL SPACE FOR MOLECULAR RECOGNITION IN A CATALYTIC SYNTHETIC REACTION

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Introducing asymmetry into organic structures represents a continuing contemporary challenge of particular importance for biologically important molecular targets. Rationally devising catalytic systems to achieve such a result is a most significant goal. Asymmetric reactions involving transition metal catalysis have focused exclusively on reactions 1) in which the enantiodiscriminating event of forming or breaking a bond occurs within the coordination sphere of the metal and, thereby, proximal to the asymmetric inducing groups and 2) in which only one type of bond is formed, i.e., C-H, C-O, or C-C. Catalytic allylic alkylations differ in both respects. Bond breakage or formation occurs outside the coordination sphere of the metal and, therefore, distal to any enantiodiscriminating groups. In addition, many different types of bonds can be formed—C-C, C-N, C-S, C-O, C-H etc. Efforts to define the requirements for asymmetric transition metal complexes that can effect such reactions generally, the types of catalytic processes in which asymmetry can be introduced, and the applicability of these catalytic processes will be outlined. The utility of this methodology for developing synthetic strategy to biologically significant heterocycles will be highlighted.

SYNTHESIS OF HETEROCYCLIC NATURAL PRODUCTS

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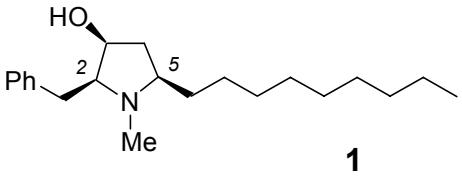
In recent years, a major research topic in our group has been the synthesis of heterocyclic natural products. We have developed photochemical methods for the synthesis of new saturated heterocyclic skeletons both in diastereoselective[1] and enantioselective[2] fashion. Based on transition metal catalysis and lithiation strategies we have explored methods for the regioselective substitution of polybrominated five-membered heterocycles (furans, thiazoles, benzofurans).[3] Examples for successfully completed syntheses of heterocyclic natural products include the total syntheses of (+)-preussin (**1**),[4] (+)-cystothiazole E (**2**),[5] and (+)-wailupemycin B (**3**).[6]



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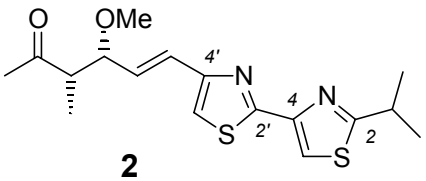

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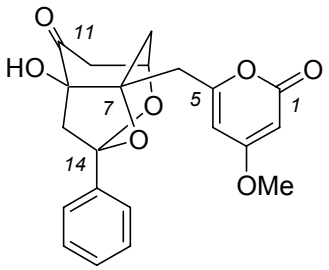

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In the talk, the basic ideas behind the above-mentioned concepts will be outlined and the results of more recent studies will be presented. Current synthetic target compounds include terpenes and alkaloids as well as biologically active thiazoles and furans.

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FROM AMINO ACIDS TO FUNCTIONAL HETEROCYCLES

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Nature's ubiquitous biosynthetic pathways are reflected in the structures of the multitude of metabolites it produces. Many of these have intriguing chemical structures that belong to families of biogenetically-related classes of compounds. The various arrays of functional and stereochemical motifs present in such compounds have presented synthesis chemists with exciting challenges in the design and implementation of asymmetric processes. Indeed, some of the more innovative advances in organic chemistry have been instigated by the desire to achieve stereochemical control in conjunction with the synthesis of natural products.

We shall highlight results from a number of on-going projects in which natural and unnatural amino acids were used as starting materials in the synthesis of heterocyclic molecules possessing diverse biological activities.

STITCHING WITH NITROGEN

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Molecules produced by the living systems have always inspired synthetic organic chemists and, as a consequence, today's favorite targets, both in academic and industrial pharmaceutical chemistry laboratories, are some of the most complex natural substances ever discovered. Due to their inherent complexity, the time required for structure-activity studies and then synthesis of sufficient quantities of the chosen leads is staggering. This is particularly true when extensive carbon-carbon bond frameworks need to be constructed.

Lacking Nature's enzymatic control, synthetic organic chemists have learned to rely on such highly reactive agents as organolithiums and enolates. Thus, modern organic synthesis depends heavily on inert atmospheres and dry solvents to support the use of these extremely basic and/or acidic species, requiring that most heteroatom functionality in turn be protected and protic solvents are avoided. A heavy price is therefore exacted when the goal is to synthesize the extensive carbon-carbon bond frameworks found in many natural products.

Fortunately, the universe of possible small molecule drug candidates remains virtually unexplored: the ratio of synthesized to reasonably possible structures is roughly the same as the mass of a proton is to the mass of the sun. With this kind of structure space available, we propose a synthetic strategy which relies upon *heteroatom*-carbon bond connections and the use of at least one relatively high-energy, "spring-loaded" component, making the bond-forming processes pre-programmed and exergonic. New molecules of dazzling complexity can arise from very short reaction sequences between spring-loaded blocks which become permanently united together via heteroatoms. We begin with nitrogen, which is second only to carbon in its connectivity potential in organic chemistry.

SYNTHESIS OF POLYHETEROCYCLIC NITROGEN-CONTAINING MARINE NATURAL PRODUCTS

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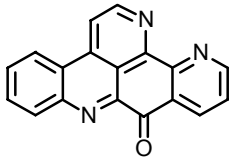
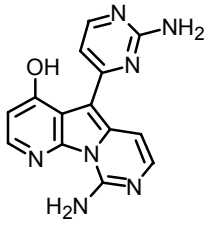
The synthetic routes used for the preparation of marine alkaloids such as ascididemin, variolin B and lamellarins will be described.

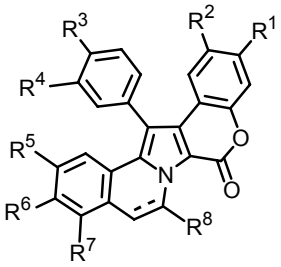
Marine natural products constitute an important source of bioactive substances with a wide range of potentially valuable activities and constitute a unique platform from which to obtain chemical diversity. An important set of alkaloids with structures without precedent in the terrestrial natural products have been isolated from sponges, tunicates and molluscs. Around 10 % of the extracts of these marine invertebrates exhibit cytotoxicity against different tumour cell lines. Because only small quantities can be produced by isolation procedures, there is a need for the development of efficient methods for the synthesis of these interesting natural products, to facilitate their biological evaluation. We will describe new synthetic procedures for the preparation of ascididemin and variolin B and the application of known synthetic routes to the preparation of compound libraries related to the lamellarins.



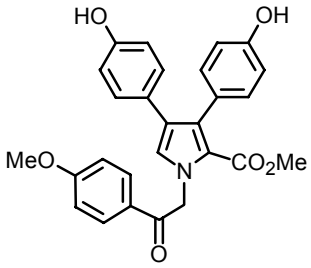
Ascididemin



Variolin B



Lamellarins A-N



Lamellarin O

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TOTAL ENANTIOSELECTIVE SYNTHESIS AND IN VIVO BIOLOGICAL EVALUATION OF A FLUORESCENT BODIPY ALPHA-GALACTOSYLCERAMIDE

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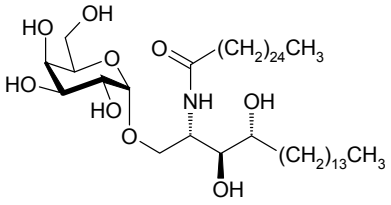
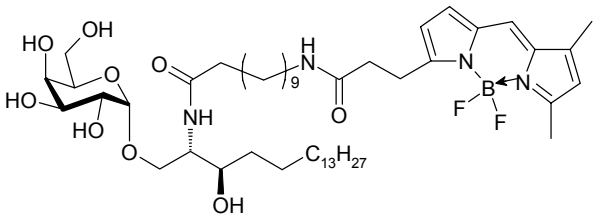
Natural Killer T (NKT) cells are a distinct subset of mature lymphocytes that coexpress markers of both natural killer (NK) and T cells, and use a semi-invariant αβ−T-cell receptor (TCR). It has been established that KRN 7000 **1**, an α-Galactosylceramide (α-GalCer) derived from a marine sponge[1], specifically activate NKT cells through a CD1d/α-GalCer/TCR interaction. It then induces rapid release of large amounts of cytokines characteristic of both type 1 (IFN−γ) and type 2 (IL-4) immune response[2]. In a variety of models of autoimmune pathologies (multiple sclerosis[3] and autoimmune diabete[4]), as well as in tumor rejection[5], activation of NKT cells by α-GalCer initiate immune responses by modulating Th_1/Th_2 balance.



KRN7000 1



BODIPY α-GalCer 2

In an attempt to bring some new insights into the cells and the factors involved in *in vivo* NKT cells activation, the original fluorescent α−GalCer derivative **2** has been prepared following a convergent synthetic scheme[6]. This biological probe **2** has shown to be as active as KRN7000 **1** in typical apoptosis test. We also demonstrated that its behaviour depends on the way of administration. After intraperitoneal injection the BODIPY molecule **2** was dominantly trapped by peritoneal macrophages. After intravenous injection fluorescent material has been found both in spleen and liver antigen presenting cells (APCs). This novel chemical reagent is thus likely to become a highly promising tool for *in* and *ex vivo* studies on its trafficking in APCs.
Full results obtained using these methodologies will be disclosed.

Keywords
Natural Killer T-cells, α−galactosylceramide, convergent synthesis, fluorescence, Bodipy.

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CYCLIC AMIDINES AND SIDEROPHORES, DIPOLES AND THE NICHOLAS REACTION

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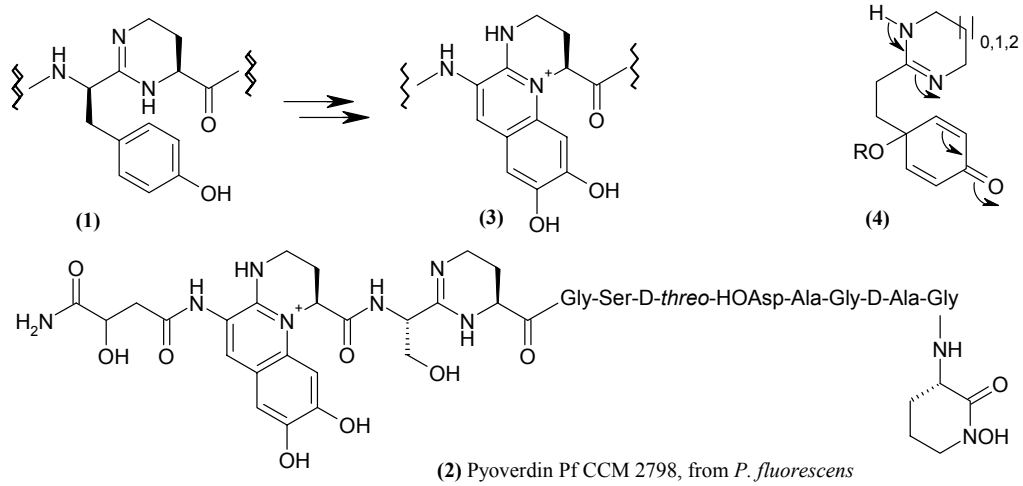
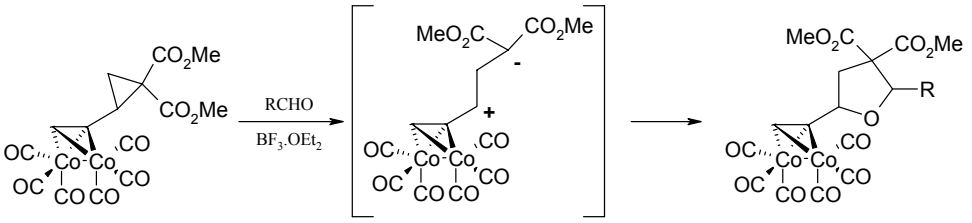
We have developed cyclic amidine amino acids of the imidazoline and tetrahydropyrimidine (THP), e.g. **1**, families [1]. The pyoverdins, e.g. **2**, siderophores (iron-binding molecules) produced by, e.g. *Pseudomonas fluorescens* often contain THP derivatives; the fluorescent pyrimidoquinoline chromophore **3** derives from *oxidative cyclization* of **1**, a tyrosine-derived THP [2]. Siderophores are essential growth factors for their parent organisms and several strains of *Pseudomonas* are severe human pathogens. In connection with biomimetic approaches to **3**, we report synthesis of chromophore models by oxidative cyclization of 5-, 6- & 7-membered cyclic amidines via dienones **4** [3].



(2) Pyoverdin Pf CCM 2798, from *P. fluorescens*

From a different project we report the first generation of a 'Nicholas' carbocation (i.e. stabilised by an adjacent alkyne bis(cobalt) complex) [4] from a C–C bond cleavage in an activated cyclopropane, and its application in novel dipolar cycloadditions with aldehydes to form furans and an extension to pyrrolidines using electron-deficient imines [5].



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MICROWAVE-ASSISTED PROTOCOLS FOR THE GENERATION OF PRIVILEGED HETEROCYCLIC SCAFFOLDS

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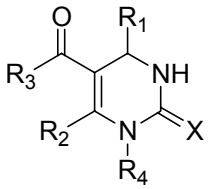
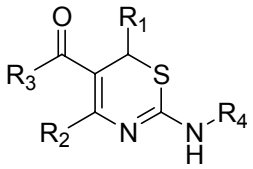
The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. In the last decade a considerable amount of attention has focused on multicomponent condensation reactions (MCRs) of the Biginelli type [1]. The heterocyclic pyrimidine derivatives **1** (DHPMs) derived from the acid-catalyzed condensation of a ß-ketoester, aldehyde and (thio)urea building block (Biginelli condensation) represent privileged scaffolds with remarkable pharmacological properties [2].



1; X = O, S



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Several solution- and solid phase strategies for the assembly of dihydropyrimidine (DHPM) libaries of type **1** will be presented. A key technology for both the solution and the solid phase approach is the utilization of high-speed microwave-assisted chemistry, which reduces reaction times from many hours to several minutes, and often produces better yields [3,4]. Libraries of DHPMs were initially constructed employing multicomponent Biginelli chemistry in solution, and on solid phase with one of the components attached to a polymer support. Several different protocols were elaborated employing multidirectional- and cyclative cleavage strategies [5]. In the solution phase procedures, polymer-supported reagents and scavengers were used in order to make these protocols amenable to a high-throughput format [6]. Scaffold decoration focused on the introduction/elaboration of substituents R^1, R^3, and R^4 around the DHPM core. The high-throughput generation of related 1,3-thiazine scaffolds of type **2** that can be considered as isomers of the classical Biginelli dihydropyrimidines **1** (X = S) will also be described.

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EX-CHIRAL POOL DERIVED ENAMINONES IN THE SYNTHESIS OF FUNCTIONALISED HETEROCYCLES

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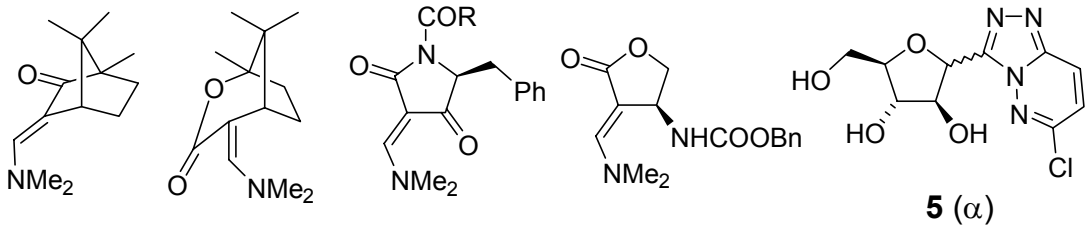
Chiral enaminones and related hydrazones, such as 5-substituted (*S*)-3-[(*E*)-(dimethylamino)methylidene]-2-pyrrolidinones and tetrahydrofuran-2-ones, are easily available and versatile reagents for the preparation of various functionalised heterocyclic compounds. They were employed as key-intermediates in the synthesis of 3-heteroaryl substituted derivatives of amino and hydroxy acids, amino alcohols, polyols, and their (cyclic) analogs [1]. In continuation of our research in this field, we have recenly extended these studies also on preparation and transformations of *N*,*N*-dimethylenaminones **1**–**4**, derived from D-(+)-camphor, L-phenylalanine, and L-aspartic acid. The following topics will be presented:

a) Stereoselective syntheses from D-(+)-camphor derived enaminones **1**,**2**: dimethylamine substitutions, cyclocondensations, synthesis of [1,2,4]-triazolo[4,3–*x*]azin-3-yl substituted bicyclo[2.2.1]heptan-2-ones [2], 2-oxabicyclo[3.2.1]octan-3-ones, and 4-(substituted amino)-2-oxabicyclo[3.2.1]octan-3-ones.
b) Synthesis of (2*S*,4*E*)-1-acyl-2-benzyl-4-[(dimethylamino)methylidene]-3,5-dioxopyrrolidines **3** and (4*S*,3*E*)-4-benzyloxycarbonylamino-3-[(dimethylamino)-methylidene]tetrahydrofuran-2-one **4** and their reactions with *N*- and *C*-nucleophiles.
c) Synthesis of 1-(6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)-*α*-*D*-*arabino*-furanoside **5** and its *β*-anomer **6** form D-glucose and D-mannose *N*-(6-chloropyridazin-3-yl)hydrazones.



1 **2** **3** **4** **5** (α) **6** (β)

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REARRANGEMENT OF SOME NITROGEN CONTAINING HETEROCYCLES STUDIED BY ^{1}H-^{15}N NMR SPECTROSCOPY

Antonín Lyčka[a], Antonín Klásek[b] , Kamil Kořistek [b], Michal.Holčapek[c]

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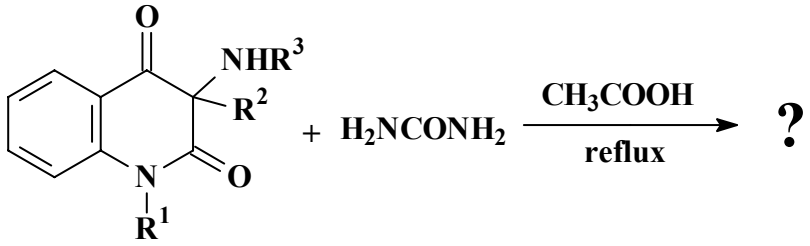
1-Substituted 3-alkyl/aryl-3-amino-1*H*,3*H*-quinoline-2,4-diones (**1**) react with urea in boiling acetic acid in several completely different manners in dependence on the type of substitution in positions R^1, R^2 and R^3, respectively:



1

All compounds were characterized by their ^{1}H, ^{13}C, IR and atmospheric pressure chemical ionisation mass spectra, however, the measurements and analysis of ^{1}H - ^{15}N correlated NMR spectra were of key importance in structure elucidation. Substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones react with urea in acetic acid to give novel 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones [1].. Starting compounds bearing primary amino group in position 3 give 3-acylaminocarbonylamino-2,3-dihydro-21*H*-indol-2-ones. Starting compounds bearing secondary amino group in the position 3 react accordingly to the character of the further substituent in position 3. If hydrogen atom in α-position of the substituent in position 3 is present, 4-alkylidene-1´*H*-spiro[imidazolidine-5,3´-indole]-2,2´-diones arise. If a hydrogen atom is not present in this position, the reaction leads to 3,3*a*-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones. The reaction mechanisms of these transformations were proposed [2].

Acknowledgment:
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STEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITIONS OF CHIRAL NITRONES

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The present lecture is devoted to regio and stereoselectivity of the chiral nitrone cycloaddition with model alkenes. 1,3-Dipolar cycloadditions between the D-erythrose and D-threose derived nitrones and styrene/methyl acrylate/acrylamide/chiral sugar dipolarophiles derived from D-erythrose and D-threose proceed in regioselective manner to afford the corresponding diastereomeric isoxazolidines in good yields [1]. The chiral nitrones, suitable for the synthesis of N/O-modified nucleosides and modified azanucleosides, were easily prepared from D-xylose by the multistep synthetic routes [2]. New chiral nitrones undergo regioselective 1,3-dipolar cycloadditions with *N*-vinylated bases (uracil, adenine) giving isoxazolidinyl nucleosides in good yields. The chiral nitrones derived from amino acids, prepared from the corresponding aminoaldehydes, starting from L-phenylalanine and L-valine, react with methyl acrylate to give the corresponding diastereomeric isoxazolidines [3]. The effect of the addition of Lewis acid on the induced stereoselectivity of chiral nitrones have been investigated. The cycloadducts thus obtained were used in the synthesis of polyhydroxylated pyrrolizidines, indolizidines and chiral diamino diol derivatives.

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NEW ROUTES TO DIAZINO-FUSED RING SYSTEMS

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We recently described several pyridazinones with remarkable pharmacological activities. Among these compounds, GYKI 16084, a 2-substituted 3(2*H*)-pyridazinone is currently being investigated in Phase II clinical trials as a new drug candidate for treatment of benign prostatic hyperplasia [1], and E 7229, an antiarrhythmic 3(2*H*)-pyridazinone has been selected for clinical studies [2]. Some fused pyridazinones were found to display interesting CNS activity [3].

As a part of these studies, syntheses of pyridazino[4,5]-fused systems starting from pyridazine precursors have been accomplished. Annelation of pyridazines through two heteroatoms; two carbon atoms; or one carbon and one heteroatom have been conveniently achieved by nucleophilic substitution reactions [4], Diels-Alder reactions [5] or intra/ and intermolecular 1,3-dipolar cycloaddition reactions [6,7], respectively.

More recently, we have also elaborated new efficient synthetic routes with wide scope to polycyclic pyridazines and their diazine analogues by utilization of the Suzuki cross-coupling reaction with a subsequent ring closure reaction or by application of the *tert*.-amino effect. In these approaches, halodiazines, and diazinecarbaldehydes with an *ortho*-(*tert*.-amino) group, respectively, have been used as easily available starting materials.

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SUBSTITUTED 3-HYDROXYQUINOLIN-4(1H)-ONES – THEIR SYNTHESIS AND BIOLOGICAL ACTIVITY

Pavel Hradil , Jan Hlaváč

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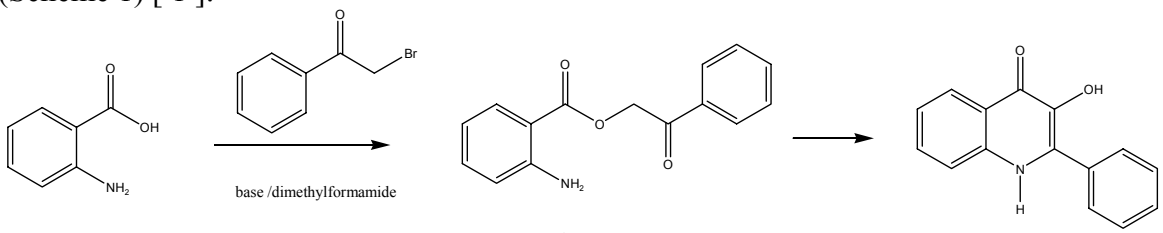
We have been dealing with synthesis of various derivatives of 3-hydroxyquinolin-4(1H)-ones for last years. Synthesis of these compounds was discovered incidentally, when we were trying to prepare 2-aryl-3H-benz[e][1,4]oxazepin-5-one by cyclization of phenacyl anthranilates via method described in literature. But the reaction was running through a different way and the formation of title compounds was noticed. Since this reaction was headed to little studied group of compounds isosteric with naturally occurring compounds – flavones, which exhibit a lot of biological activities, we started studying this reaction. The style of the reaction is simple. First anthranilic acid is converted with high yield to phenacyl anthranilate by reaction of its salt and 2-phenacyl halogenide. Thus prepared phenacyl anthranilate is cyclized to 2-substituted-3-hydroxyquinolin-4(1H)-ones (Scheme 1) [1].



Scheme 1

We studied connection of substitution of benzene part of quinolinone ring with various group – for example methoxyroup or halogens [2] with biological activity.
We also studied influence of the substitution on the nitrogen and the substitution of the ketone part as well on cyclization[3]. Besides polyphosphoric acid, the cyclization proceeds also in phosphoric acid, acetic acid, trifluoroacetic acid or N-methylpyrrolidone. Generally, for esters of substituted anthranilic acid and 2-hydroxyketones, the cyclization is running smoothly and the title compounds are isolated in very high yield. The structure of the 3-hydroxyquinolin-4(1H)- ones was proved by NMR, independent synthesis and roentgen-structure analysis. Cytostatic, tuberculostatic and antiprotozoal properties of these compounds were tested. Moderate activity was mostly observed, but some compounds exhibit very good cytostatic activity.

This work was financially supported by the Grant Agency of the Czech Republic. (Grant No. 203/01/1360)

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NEW ROUTES TO OXINDOLE DERIVATIVES

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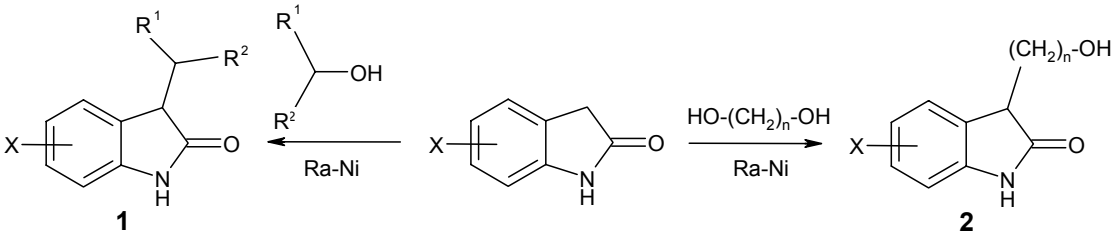
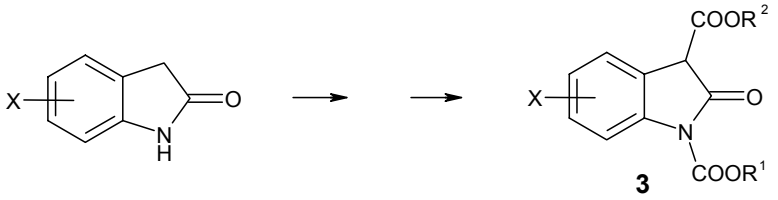
P.O. Box 100, H-1475 Budapest, Hungary

Oxindole derivatives are important targets in medicinal chemistry. The direct alkylation and acylation of deprotonated oxindoles have limited synthetic significance because of the lack of regioselectivity. In our laboratory, new reaction conditions were elaborated for the synthesis of 3-alkyloxindoles (**1**) by Raney nickel-induced alkylation of oxindoles with alcohols, turning this method into a highly efficient synthetic tool. The method was also extended to the preparation of 3-(ω-hydroxyalkyl)oxindoles (**2**) [1].



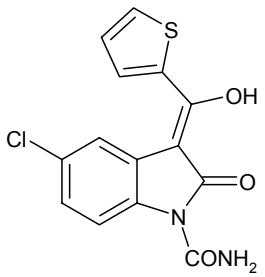
1 **2**

The *N*-, *O*- and *C*(3)-acylation reactions of oxindoles have also been studied. Two protocols have been developed for the synthesis of 1,3-di[alkoxy(aryloxy)carbonyl]-oxindoles (**3**) with identical or different acyl groups in the two positions, starting from oxindoles [2].



3

A new, practical synthesis of the antirheumatic oxindole derivative **tenidap** will also be presented [3].



tenidap

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α-EPIMERAZIBLE NON-RACEMIC KETONES AND ALDEHYDES CAN BE EASILY ACCESSED BY CRYSTALLIZATION-INDUCED DYNAMIC RESOLUTION OF IMINES

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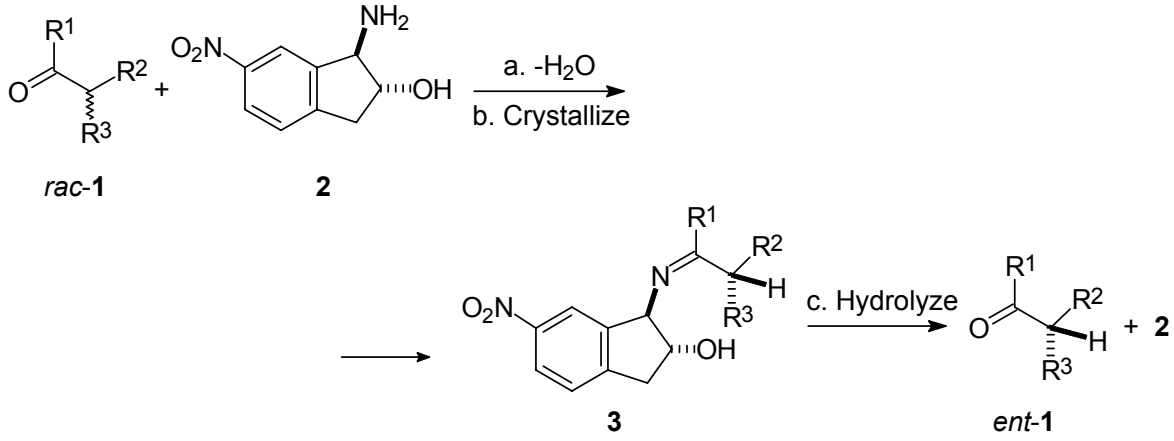
We will describe an operationally simple deracemization process of aldehydes and ketones. This new crystallization-induced dynamic resolution (CIDR) protocol allows for nearly complete conversion of the racemic mixture into one enantiomer. Crystallization of imines derived from racemic ketones or aldehydes **1** and *trans*-(1*R*,2*R*)-1-amino-6-nitroindan-2-ol (**2**) afforded diastereomerically pure, crystalline imines **3**. Biphasic hydrolysis of **3** then affords recovered **2** and enantiomerically enriched **1** in high yield and enantiomeric ratio (substrate, yield/ee: 2-methylcyclohexanone, 97%/92; 2-ethylhexanal, 94%/98; 2-methylcyclopentanone, 94%/98; 2-cyclohexylcyclohexanone, ND/98; 3-methyl-2-pentanone, ND/76). This highly effective CIDR process is likely due to π-stacking of **2** and a hydrogen-bonding of the imine with the free hydroxyl of **2** in the solid state.[1,2] The scope, limitations, and industrial perspective of this process will be discussed.



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APPLICATION OF BRASSININ AND ITS ANALOGS IN THE SYNTHESIS OF INDOLE PHYTOALEXINS

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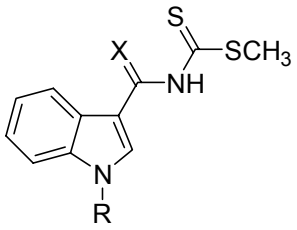
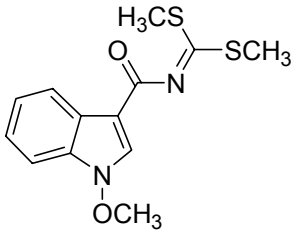
[b]Division of Biological Sciences, Graduate School of Science, Hokkaido University, Kita 10, Nishi 8, Sapporo 060-0810, Japan

Readily available indole phytoalexin brassinin (**1**) was proved to be the biosynthetic intermediate of further sulfur containing indole phytoalexins from crucifers [1,2]. This finding prompted us to investigate its oxidation and cyclization reactions as well as the synthesis and reactions of its analogs (for example **2** and **3**) with the aim to develop new syntheses of cruciferous phytoalexins.



1, R=H, X=H,H
2, R=Boc, X=H,H
3, R=CH_3O, X=O

Retrosynthetic analysis of target compounds resulted in the elaboration of the first synthesis of 1-methoxybrassenin B (**4**), new syntheses of cyclobrassinin (**5**) or spirobrassinin (**6**) and other phytoalexins using brassinin (**1**) and its analogs as starting compounds [3,4].



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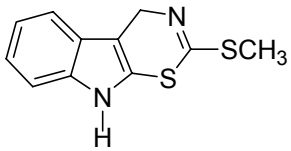

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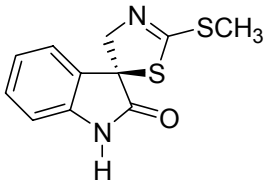

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ON DIETER BINDER, LORNOXICAM AND THE TREATMENT OF PAIN

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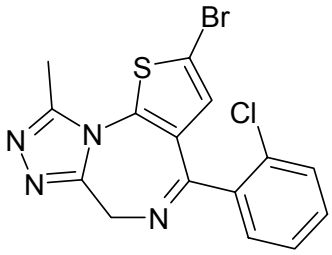
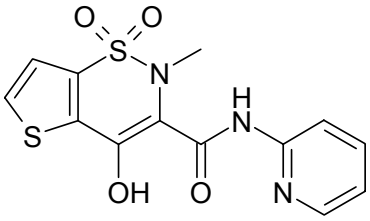
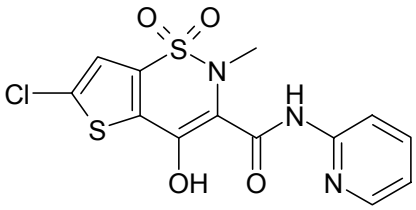
The unexpected death of Professor Dieter Binder provides the opportunity to commemorate the work of a great and successful Austrian drug researcher. Some of the pioneering work on the concept of "benzene-thiophene bioisosterism" will be presented, above all the three marketed drugs Brotizolam, Tenoxicam and Lornoxicam.



Brotizolam



Tenoxicam



Lornoxicam

The latter compound has been in the focus of Dieter Binders work during the last years due to its broad application potential. The lecture will include some information on the state of the "COX-debate" and an outlook to major lines in development of drugs for the treatment of pain.

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"CUT & PASTE CHEMISTRY" FOR THE DIVERSIFICATION OF THE CYCLOPEPTIDIC NATURAL PRODUCT HUN-7293

Erwin P. Schreiner

Novartis Forschungsinstitut, Brunner Strasse 59, A-1235 Wien, Austria

One of the success-critical factors for the identification of high quality hits in high-throughput screens and, therefore, for the whole drug discovery process, is the chemical diversity of the compound collections available. In addition to production of chemical libraries by combinatorial synthesis the collections are still fed with natural products isolated from various sources. A natural product in which we became interested was the fermentation product HUN-7293, a cyclic depsipeptide identified as a potent inhibitor of the expression of the adhesion molecules ICAM-1 and VCAM-1. Initial activities focused on classical structural modifications delivering derivatives with a significantly better biological profile. However, to further expand the diversity around HUN-7293 a platform of degradation protocols as part of a "Cut & Paste Chemistry" approach was developed, allowing broad modifications ranging from distinct chemical point mutations to the preparation of natural product-like molecules with quite artificial backbones. Development of the new methodologies and synthesis of several prototype molecules will be discussed.

CHEMICAL CROP PROTECTION – IN SEARCH OF NOVEL FUNGICIDES

Urs Müller

Syngenta Crop Protection AG, Schwarzwaldallee 215, CH-4002 Basel, Switzerland

Chemical crop protection is a well-established technology that helps to sustain the production of sufficient food, feed and fiber to meet the world's needs. It will continue to play an important role in the agribusiness, although novel biotechnological methods may partly achieve the same goal [1]. The protection of crops against diseases in the period from seeding to harvest is crucial not only to secure crop yield but also in many cases to guarantee the production of healthy food and feed free of naturally occurring toxins. This paper aims to give an overview of the approaches used in chemistry and biology, illustrated by recent projects, to discover novel fungicides.

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MODERN DRUG DISCOVERY IN ONCOLOGICAL RESEARCH

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S. Steurer and S. K. Zahn

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Boehringer Ingelheim Austria GmbH, Vienna

Boehringer Ingelheim Austria GmbH in Vienna is the center of Oncology within Boehringer Ingelheim.
The presentation gives a medicinal chemist's view of the processes involved in modern drug development in oncological research. The ever increasing complexity of drug discovery demands an effective coordination between biology, pharmacology, medicinal chemistry and structural research.
Following cancer relevant target discovery (e. g. enzymes involved in cell cycle and cell proliferation) and biological assay development, medicinal chemistry comes into play and can be regarded as the central discipline within drug development. The process of drug discovery generally begins with the high throughput screening of large compound libraries on a new target. The 'hits' discovered from the screening serve as a starting point for the medicinal chemist. Through systematic molecular changes structure activity relationships (SAR) are established and the potency of the molecules increased. However, in addition to activity medicinal chemistry must synthesize molecules which embody suitable drug-like properties related to physicochemical and pharmacological criteria.
The medicinal chemist faces the need of creating and synthesizing a large number of compounds to approach the desired drug-like profile of a new drug candidate often accompanied with time constraints. This requires innovative strategies and tools both in chemical synthesis and compound purification as well as in logistics and analytics. This presentation therefore will focus on the still growing process of automation within medicinal chemistry applying parallel synthesis, automation based synthesis and purification and last but not least computer based data management.
Many lead-structures are based on scaffolds containing heterocycles. Although heterocyclic chemistry may be seen as a classical part of synthetic organic chemistry the medicinal chemist faces the challenge to apply new synthetic methods e.g. transition metal catalyzed reactions. New reactions often reveal ways to structural variations that would hardly be possible by "classical" methods. So the syntheses performed are still challenging and strongly influenced by academic research on new synthetic methods.
Thus this presentation covers the "adventure" of drug discovery through the eyes of a medicinal chemist faced with the challenge of turning small molecules into new and innovative drugs.

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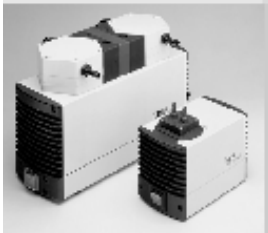

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Oral Presentations (OP)

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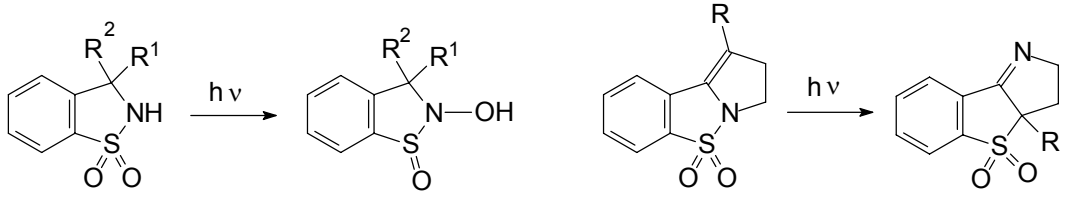
NOVEL EFFICIENT PHOTOTRANSFORMATIONS OF 1,2-BENZISOTHIAZOLE 1,1-DIOXIDES

D. Döpp, I. Elghamry, P. Lauterfeld, D. Schneider, M. Schneider, G. Henkel, U. Seidel

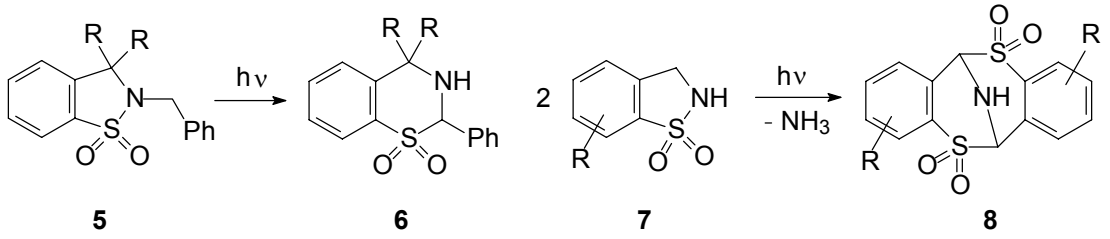
Institut für Chemie, Universität Duisburg-Essen, D-47048 Duisburg, Germany

Four hitherto unexplored phototransformations of the title compounds, depending on their substitution pattern, have been investigated in detail in solution using 254 nm excitation:

1) A novel oxgen shift in **1** from sulfur to nitrogen generating 2-hydroxy-2,3-dihydro-[1,2]benzisothiazole 1-oxides **2** (R^1 = H, Me, Ph, R^2 = Me, Ph) which constitute the first available derivatives of a novel class of cyclic sulfine hydroxamic acids [1]. When $R^1 \neq R^2$, the reaction is of moderate diastereoselectivity (both the S and N atoms in **2** become new stereogenic centers).
2) A facile allylic skeletal rearrangement of dihydropyrrolo[1,2-*b*][1,2]benzisothiazole 5,5-dioxides **3** to the isomeric 2,3-dihydro[1]benzothieno[3,2-*b*]pyrrole 4,4-dioxides **4** [2].



3) A new ring expansion of *N*-substituted title compounds, e.g. **5**, to 2*H*-1,3-benzothiazine 1,1- dioxides as **6** [3].
4) A condensating dimerization of 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (**7**, R = H) generating a new cleft molecule **8** [4]. The utility of this reaction, starting from properly substituted derivatives of **7**, to generate acceptor molecules capable of complexing small guest molecules is being explored.



Details and rationales for all conversions will be presented. Special emphasis will be laid on structure proof by single crystal X-ray structural analysis.

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FUSED NITROGEN HETEROCYCLIC COMPOUNDS VIA ALLENYLAZINES

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The reaction of a symmetrical azine (**1**) with two molecules phenylisocyanate (**2**) is well known as an intermolecular criss-cross cycloaddition [1,2]. Products are fused heterocycles (**3**) containing two five-membered rings.

An intramolecular variation has been developed [3] at our Department few years ago. The symmetrical allenylazine (**4,** R = Bn) underwent thermally initiated intramolecular cycloaddition leading to heterocycle (**5**) composed of four five-membered rings. We have found that the reaction does not proceed when the substitution R = H, Et. But substituents such as R = -CH_2-morfolino, -CH_2-(N-methylpiperazino), -CH_2-piperidino, -CH_2-pyrrolidino, -Ph etc. were found suitable for formation of products (**5**).

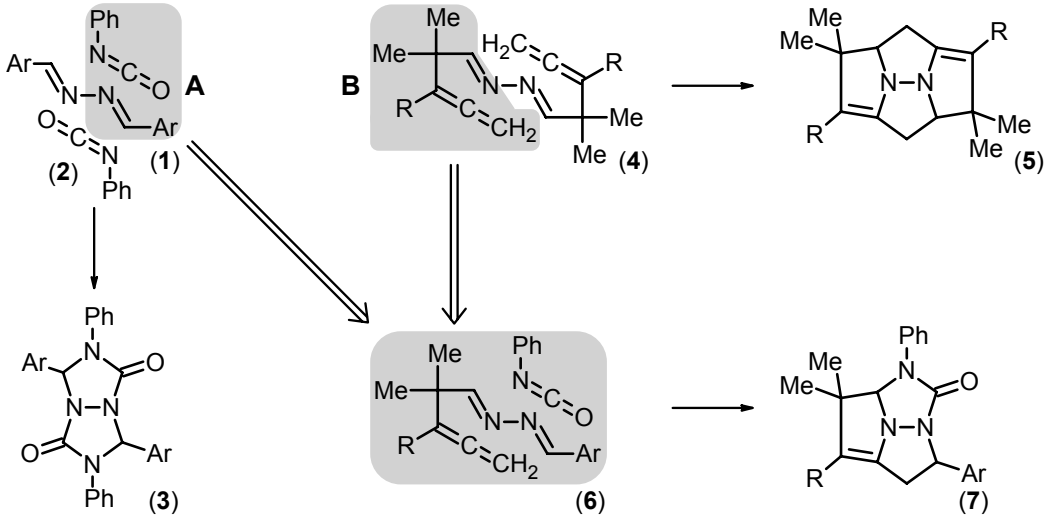
In last period a new type of criss-cross cycloaddition was studied. The new method combined both intermolecular **A** and intramolecular **B** approaches.

Non-symmetrical allenylazines (**6**) react with dipolarophile (**2**) affording in „one pot“ arrangement novel type of heterocycles (**7**) containing three fused five-membered rings.

Also some other dipolarophiles gave similar corresponding products.

Because we succeeded to trap an intermediate suggesting that the initiation step is an intramolecular attack we gave to the reaction a name *intra-intermolecular criss-cross cycloaddition*.

Heterocycles (**5**) and (**7**) were searched for transformations and the products obtained were analysed and identified.



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ENANTIOSELECTIVE α-OXYFUNCTIONALIZATION OF BENZOHETERACYCLANONES

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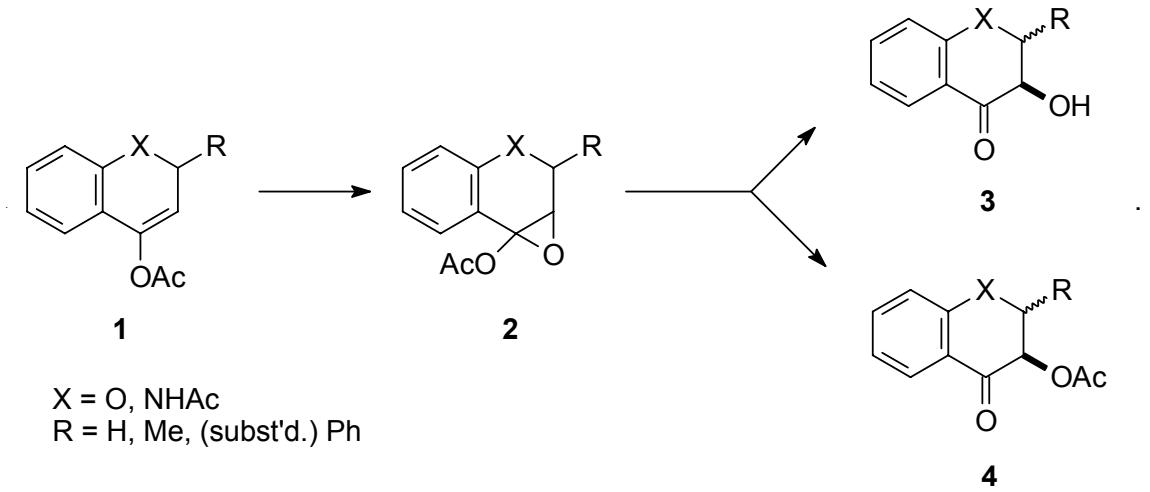
In continuation of our previous work on the epoxidation of enolacetates **1** of cylic ketones by dimethyldioxirane and the transformations of the intermediate epoxide **2** into α-hydroxy ketones **3** and α-acetoxy derivatives **4** we have performed comparative oxidation experiments in the chromanone and dihydroquinolone series.



This methodology offers an easy and highly diastereoselective entry to the field of α-oxygenated benzoheteracyclanones. Both the stability of the epoxide **2** and the relative (2,3-*cis* or *trans*) configuration of products **2**,**3** were found to be strongly dependent on the heteroatom X.

Enantioselective oxidation has been achieved by using dimethyldioxirane as oxygen source in combination with chiral, non-racemic Mn(III)salen complexes, the enantiomeric excesses could be improved by addition of various nitrogen or oxygen co-ligands.

Mechanistic aspects as well as factors governing stereoselectivity will be discussed in our presentation.

A NOVEL AND RAPID APPROACH TO AZETIDIN-2-ONE DERIVATIVES

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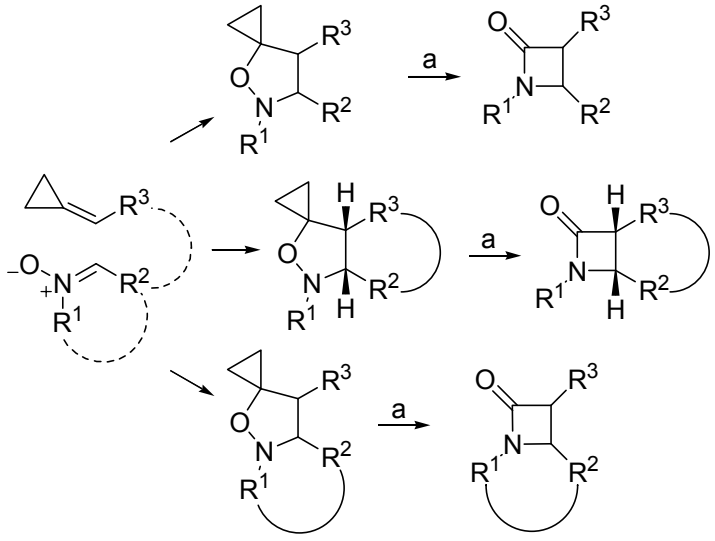
b) Laboratoire des Carbocycles (CNRS), Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bât. 420, Université de Paris-Sud, 91405 Orsay, France

5-Spirocyclopropane isoxazolidines, easily obtained by intra- and intermolecular 1,3-dipolar cycloaddition of nitrones with methylenecyclopropane derivatives [1], are smoothly converted in β-lactam derivatives in the presence of a protic acid at 70-110 °C [2-4]. The formation of the β-lactam ring occurs with concomitant extrusion of a molecule of ethylene. The two step process cycloaddition / acidic thermal rearrangement was applied to the synthesis of several monobactams, carbopenams and 3,4-*cis* ring-fused azetidin-2-ones.



a) Δ, H^+, – CH_2=CH_2

Some synthetic and mechanistic aspects of this new general approach to β-lactams will be discussed in this communication.

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CATALYSIS BASED TOTAL SYNTHESIS OF LATRUNCULIN B

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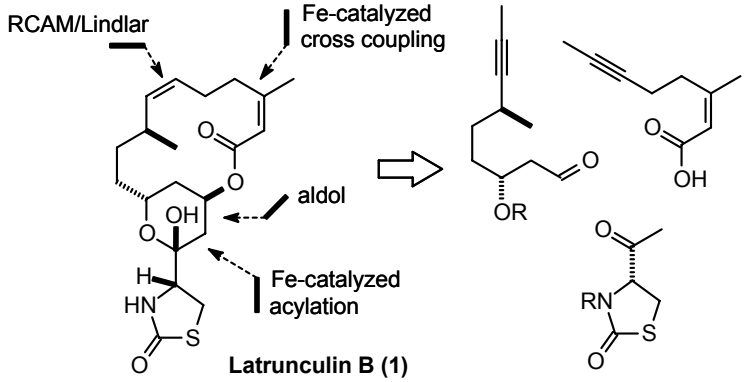
The Red Sea sponge *Latrunculia magnifica* (Keller) is conspicuously immune to predation in its natural habitat, apparently relying on its reddish-colored exudates. From this fluid latrunculins A and B were isolated as the ichthyotoxic principles.[1] Later these and related compounds have also been found in taxonomically unrelated organisms from different marine habitats.[2] Latrunculins A and B appear to be the first macrolides isolated from a marine species and the first natural products to embody the heterocyclic 2-thiazolidinone moiety.

The latrunculins gained particular importance because of their striking selectivity and the surprisingly rapid onset of action.[3]



The presented total synthesis of latrunculin B is highly convergent, flexible and elaborates on novel catalytic transformations recently developed our laboratory (see scheme). In the key step the macrolide is formed using ring closing alkyne metathesis (RCAM) [4] followed by *Lindlar* – hydrogenation. A cross coupling reaction using cheap and environmentally benign iron catalysis was applied to the synthesis of the *Z*-configured unsaturated acid.[5] Furthermore, the synthesis of the heterocyclic ketone was also accomplished using an iron catalyzed acylation procedure.

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SYNTHESIS, STEREOCHEMISTRY, AND CHEMISTRY OF INDENO[1,2-B]PYRIDINE-2,5-DIONE SYSTEM

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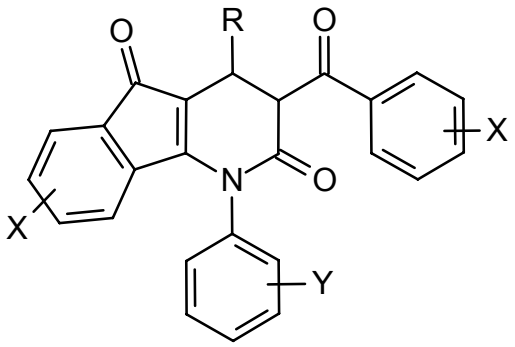
Faculty of Chemistry, Jagiellonian University, Kraków, Poland

Summing up some years of an experience in this field [1-8] the following aspects of indeno[1,2-*b*]pyridine-2,5-dione chemistry and properties will be presented:



1. An original efficient two-step synthesis of this system starting from open chain molecules containing aromatic rings only as well as its scope and limitations
2. Attempts to elucidate the mechanism of this cascade formation of the fused heterocyclic system
3. Stereochemistry of the latter that leads to its interesting spectral properties
4. Stability of the system and results of its hydrolytic transformations due to enaminone and β-keto anilide fragments built into its tetrahydropyridine-2-one ring
5. Applications of the synthetical method presented for the preparation of selectively fluorinated derivatives, indan-2,3-dione derivatives and natural products.

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[4] A. Kolasa: 5th BDSHC, Častá Papiernička, Slovak Republic, 1995: PO 36
[5] A. Kolasa, T. Jasiński: 6th BDSHC, Brno, Czech Republic, 1996: PO 67
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HETEROCYCLIC CARBON RADICAL ADDITIONS FOR THE SYNTHESIS OF α-AMINO ACIDS

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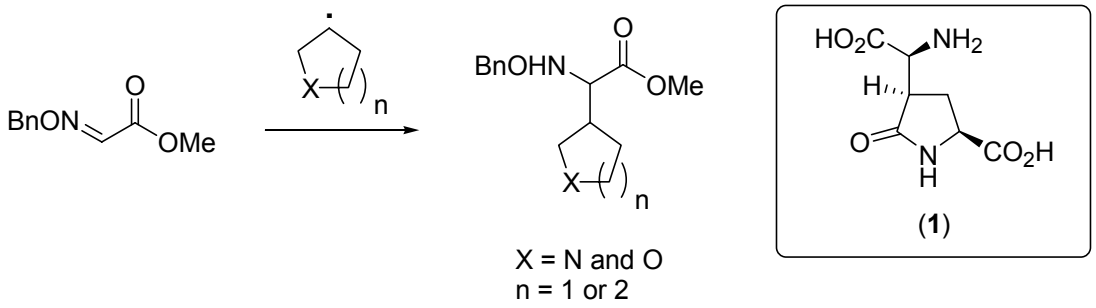
Among the different types of radical acceptors containing a carbon-nitrogen double bond, the oxime ethers are known to be excellent radical acceptors. We have already developed the use of glyoxylic oxime ethers for the synthesis of α-amino acid derivatives [1]. In continuation of this work we carried out preliminary studies on the addition of carbon radicals derived from heterocycles to oxime ethers. Additions of this type could be used for the synthesis of novel α-amino acid such as Penmacric acid (**1**) [2] and initial results for the synthesis of are presented.



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NEW CYCLIZATION REACTION AFFORDING DINITROGEN HETEROCYCLES: EXTENSION AND DIASTEREOSELECTIVITY

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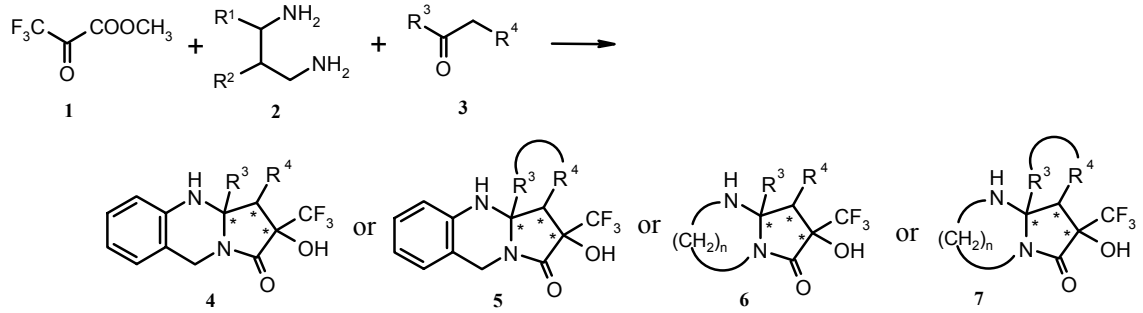
16628 Prague 6, Czechia

The three-component cyclization has been extended to a series of diamines and oxo compounds affording products with high diastereoselectivity in particular cases. Some of the products were transformed to *Deoxyvasicinone* alkaloid analogues.

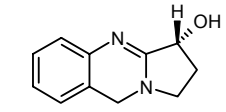
Recently, a new three-component cyclization reaction, involving methyl 3,3,3-trifluoropyruvate (**1**), 1,3-diamine (**2**) and oxo-compound (**3**) that afforded di-, tri- or tetracyclic dinitrogen heterocycles (**4-5**) possessing the structure close to that of alkaloid *Peganine*, has been uncovered at our Department [1,2]:



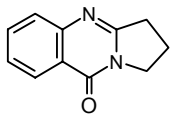
The cyclization has been extended for the synthesis of non-aromatic di- and tricyclic heterocycles **6-7**. The pyruvate **1** in the original procedure was substituted with trifluoroacetaldehyde, ethyl mesoxalate or hexafluoroacetone, which substantially broadened synthetic possibilities of the cyclization.

Stereogenic centers in the products **4-7** give a possibility of the existence of the corresponding diastereoisomers. We have found that the diastereoselectivity can be influenced both by the starting diamine (**2**) and the oxo compound (**3**) up to 95%.

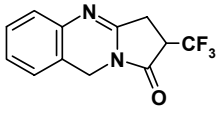
Some of the cyclization products were transformed to unsaturated structures, which are close to that of the alkaloid *Deoxyvasicinone*:

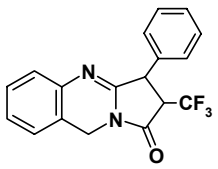


Peganine (*Vasicine*)



Deoxyvasicinone





The research has been supported by the Grant Agency of the Czech Republic (Project No. 203/02/0306).

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STEREOSELECTIVE SYNTHESIS OF ENANTIOMERICALLY PURE 2-ISO-OXACEPHEMS

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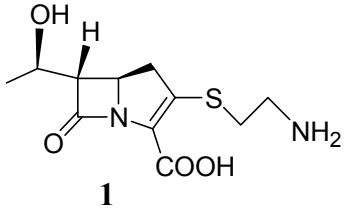
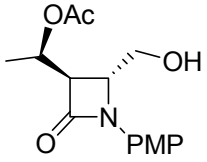
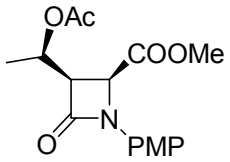
Our aim has been to synthetize *Thienamycin* (**1**) analogues in the 2-iso-oxacephem series. *Thienamycin* has broad antibacterial activity and β-lactamase stability due to its 1-hydroxyethyl side chain [1]. Among the previously synthetized 2-iso-oxacephems some compounds showed antibacterial or β-lactamase inhibitory activity [2].
Recently we published the stereoselective synthesis of monocyclic β-lactams (**2a**,**b** and **3a**,**b** enantiomers, only series **a** are shown here) starting from L- and D-threonines as chiral building blocks [3]. These β-lactams are suitable intermediates for 2-iso-oxacephems.



1

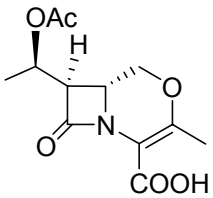


2a

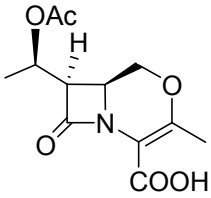


3a

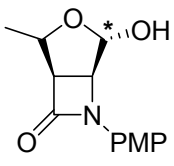
Now, we report the total synthesis of compounds **4a** and **4b**, which are formed from the corresponding *trans*-3,4-disubstituted monocycles **2a** and **2b**. The inversion at α-carbon atom in compound **4b** should furnish the completely identical stereocenters in positions α*R,*6*S,*7*S* of the 2-iso-oxacephem with the *Thienamycin* α*R,*5*S,*6*S* carbapenem skeleton. We have promising results by using *Mitsunobu* type inversion [4] in α-position after successful selective deacetylation of the corresponding α-acetoxybenzyl ester.
Meanwhile, the reduction of *cis*- esters (**3**) have also been performed. These intermediates can lead to the preparation of **5a**,**b**. The reduction of ester **3a** provided a new stereochemically pure bicyclic compound (**6**), which contains a new stereocenter (labeled by *). The configuration of this new chiral center was determined by X-ray crystallography using its *p*-bromobenzoyl derivative. Currently, we are studying the route for formation of the second ring to give **5a**, **5b**.



4a



5a



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A THREE STEP SYNTHESIS OF THE BENZOCARBOLINE ISOCRYPTOLEPINE VIA TWO CONSECUTIVE Pd-CATALYZED REACTIONS [1]

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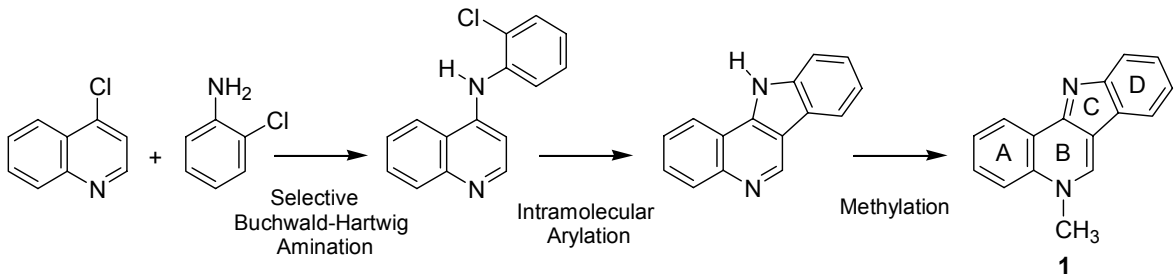
E-mail: bert.maes@ua.ac.be

In traditional folk medicine, a decoction of the root of the West African *Cryptolepis sanguinolenta* is used to treat fevers (including fever caused by malaria, a parasitic disease caused by *Plasmodium* sp.), intestinal disorders and rheuma. Isocryptolepine (**1**) (cryptosanguinolentine) is one of the characterized alkaloids from the root of this plant which possesses an interesting antiplasmodial activity. The synthesis of substituted analogues of this natural product is primordial to establish a structure-activity relationship (SAR). Therefore we developed a new approach for the synthesis of the 11*H*-indolo[3,2-*c*] quinoline skeleton. The new method is based on two consecutive palladium-catalyzed reactions; a selective Buchwald-Hartwig amination of 2-chloroaniline with 4-chloroquinoline followed by an intramolecular arylation reaction of the resulting 4-(2-chlorophenylamino)quinoline. Theoretically, the new method is based on the different reactivity of an activated (4-chloroquinoline) and non-activated C-Cl bond (2-chloroaniline) towards oxidative addition [2]. Intramolecular arylations with non-activated C-Cl bonds such as in 4-(2-chlorophenylamino)quinoline are not straightforward and have never been used to construct carboline containing skeletons.



1

In comparison with literature procedures 5-methyl-5*H*-indolo[3,2-*c*]quinoline was obtained in a higher overall yield (57.7%) in only three synthetic steps. Besides the synthesis of the parent natural product, this approach looks very promising to prepare D-ring substituted analogues starting from easily accessible substituted 2-chloroanilines.

[1] Jonckers, T.H.M.; Maes, B.U.W.; Lemière, G.L.F.; Rombouts, G.; Pieters, L.; Haemers, A. and Dommisse, R.A. *Synlett* **2003**, 615.
[2] for the regioselective Buchwald-Hartwig amination of dichloropyridines see: Jonckers, T.H.M.; Maes, B.U.W.; Lemière, G.L.F. and Dommisse, R. *Tetrahedron* **2001**, *57*, 7027.

HETEROCYCLIC MESOMERIC BETAINES IN NATURE. ON STRUCTURAL ANALOGS OF ALKALOIDS FROM *NIGELLA SATIVA* AND *PUNICA GRANATUM*

Andreas Schmidt, Tobias Habeck, and Thorsten Mordhorst

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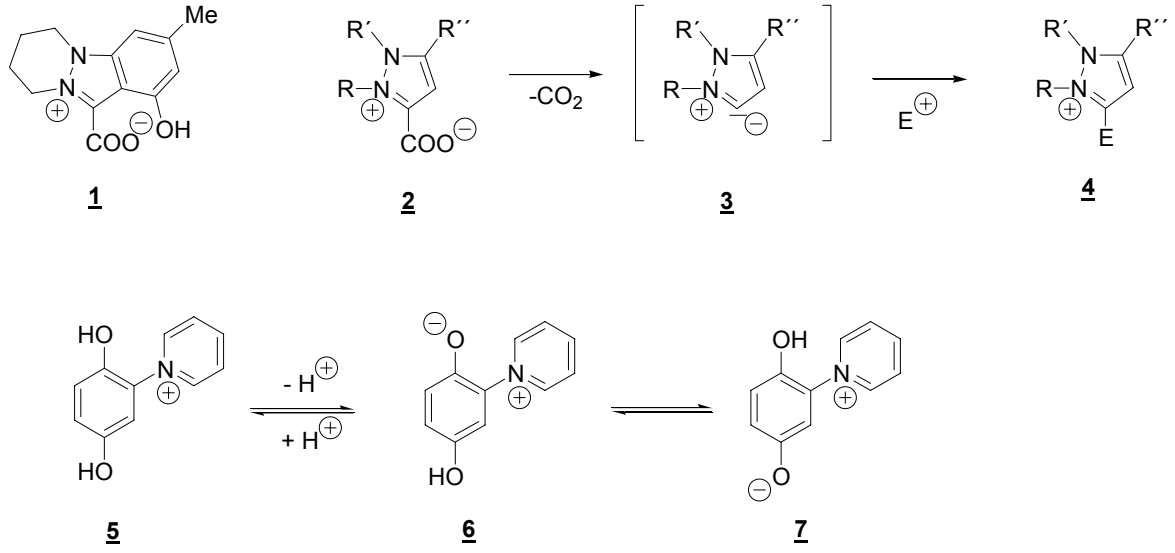
D-38678 Clausthal-Zellerfeld, Germany

Alkaloids which belong to the class of heterocyclic mesomeric betaines (MB) form a relatively small group of compounds with interesting biological activities [1],[2]. They are conjugated heterocyclic molecules which can only be represented by dipolar structures in which both the positive and the negative charge are delocalised within the common π–electron system. This class of compounds can be divided by their type of conjugation into conjugated (CMB), cross-conjugated (CCMB), and pseudo-cross-conjugated mesomeric betaines (PCCMB). The class of CMB, the charges of which are in mutual conjugation, include the well-known mesoions such as sydnones, münchnones and derivatives. Less is known about CCMB which form highly dipolar entities due to a charge-separation in the ground state. Pseudo-cross-conjugated heterocyclic mesomeric betaines PCCMB are very scarcely described in the literature.

We synthesized and studied some pseudo-cross-conjugated mesomeric pyrazolium-carboxylates **2** as model compounds for the alkaloid Nigellicine **1** which was isolated from black cumin (*Nigella sativa*). Decarboxylation resulted in the formation of ylides **3** which can be trapped by electrophiles to **4**. The pyridinium alkaloid **5** was isolated from *Punica granatum*. Deprotonation yields either a conjugated **6** or a cross-conjugated mesomeric betaine **7** so that this alkaloid gives rise to a direct comparison of these two types of conjugation.



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

5 **6** **7**

[1] A. Schmidt, *Adv. Heterocycl. Chem*. **2003**, in press.
[2] A. Schmidt, *Curr. Org. Chem*. **2003**, in press.

STEREOCONTROLED ACCESS TO GLYCOSIDES ANALOGUES VIA HETERO-DIELS-ALDER REACTION

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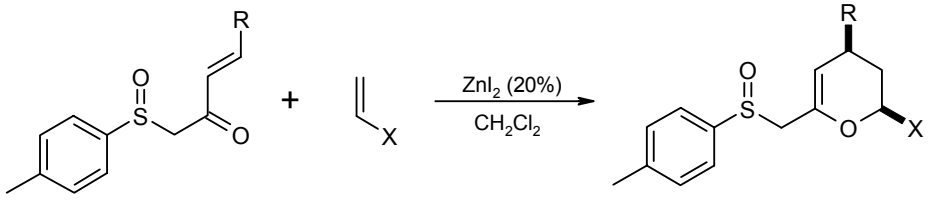
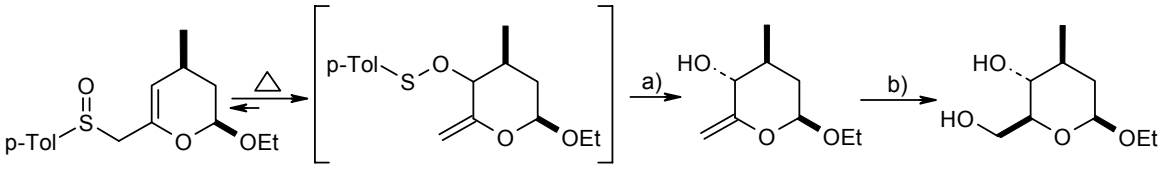
Previous work realised in our group showed that intermolecular Diels-Alder reactions of chiral 3-sulfinyloxabutadienes offer a convenient route to biologically active molecules such as insect [1] or mammal [2] pheromones. In order to develop the use of sulfoxydes, we were then interested in the reactivity of 2-methylsulfinyloxabutadienes. Indeed, when opposed to electron-rich dienophiles, this new type of heterodienes generate dihydropyran adducts that provide a valuable access to glycoside analogues.

Using the strategy developped by Wada and co-workers [3], we were able to prepare various heterodienes with good yields. Inverse electronic demand [4+2] cycloadditions using vinyl ethers and sulfides, under Lewis-acid catalysed conditions, led to the dihydropyran adducts with good *endo* selectivity and moderate facial selectivity.



I R = H, Me, Et, Ph, OMe; X = OR, SR **II**

In the presence of a thiophilic agent such as piperidine, the adducts **II**, bearing an allylic sulfoxyde, underwent easily a [2,3]-sigmatropic rearrangement to give stable methylenehydroxypyrans. Then, hydroboration of the latter compounds led to 2,3-dideoxy-3-alkylglycosides.



a) piperidine, THF, reflux b) i) $BH_3.Me_2S$, THF et ii) H_2O_2, NaOH

Moreover, heterodienes **I** and some alkylidene pyruvic acid esters have been successfully tested with a solid-supported vinyl ether, under Lewis acid conditions [4].

[1] P. Hayes, C. Maignan, *Tetrahedron : Asymmetry*, **1999**, *10*, 1041. [2] P. Hayes, C. Maignan, *Synthesis*, **1998**, *5*, 783. [3] E. Wada, W. Pei, H. Yasuoka, U. Chin, S. Kanemasa, *Tetrahedron*, **1996**, *52(4)*, 1205. [4] A. Arboré, G. Dujardin, C. Maignan, *Tetrahedron Lett.*, **2003**, submitted.

SYNTHESIS OF N-ACYLATED-2,5-DISUBSTITUTED PYRROLIDINES THROUGH A MULTI COMPONENT APPROACH

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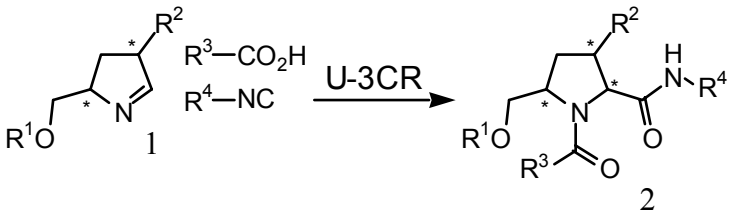
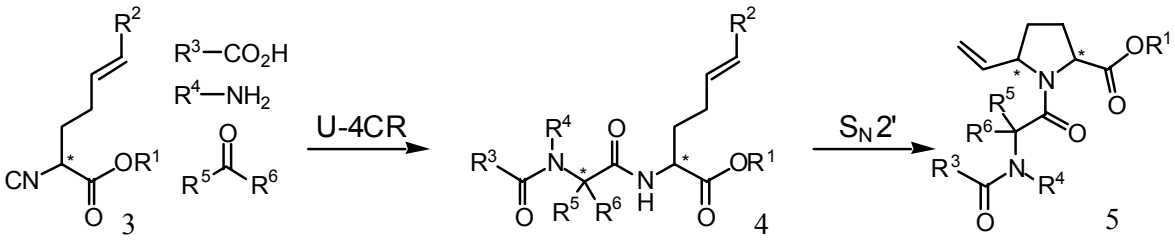
In the course of a project directed to the synthesis of bicyclic lactams to be used as β-turn mimics, we are exploring two alternative approaches for the multi component synthesis of functionalised pyrrolidines.
In the first one, chiral pyrrolines **1**, derived from L- or D-glutamic acid, have been prepared and used in the synthesis of pyrrolidines **2** exploiting a Ugi reaction in which, apart from pyrroline acting as a cyclic imine, several different isocyanides and carboxylic acids have been used.



In the second, one a classical Ugi 4 component reaction was planned to be used before the pyrrolidine ring formation. For the heterocyclic ring formation we planned to use an unprecedented intramolecular S_N2' reaction involving a secondary amide functionality as precursor of the internal nucleofile. First we explored the feasibility of this strategy on a simpler analogue of **4**, bearing an acetyl group bonded to the NH. We are now preparing a series of more complex amides through an Ugi condensation employing isocyanide **3** in the presence of suitable carboxylic acids, amines and carbonyl compounds.



Both methods show a certain degree of stereoselectivity. Moreover, R^1 - R^4 groups in **2** and R^5 and R^6 groups in **5** may contain suitable functional groups that allow formation of a fused bicyclic lactam.
Finally, the high variety of substrates that can be used in these multi component reactions make both strategies well suited for a combinatorial synthetic approach to bi- or even tricyclic derivatives.

MICROWAVE-PROMOTED HETERO-DIELS-ALDER REACTIONS OF 2(1H)-PYRAZINONES IN IONIC LIQUID DOPED SOLVENTS AND ON SOLID SUPPORT

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[a]Laboratory for Organic Synthesis, Department of Chemistry, University of Leuven, Celestijnenlaan 200F,
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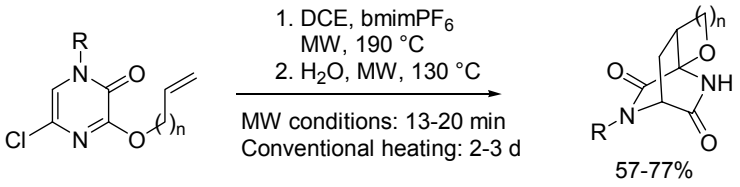
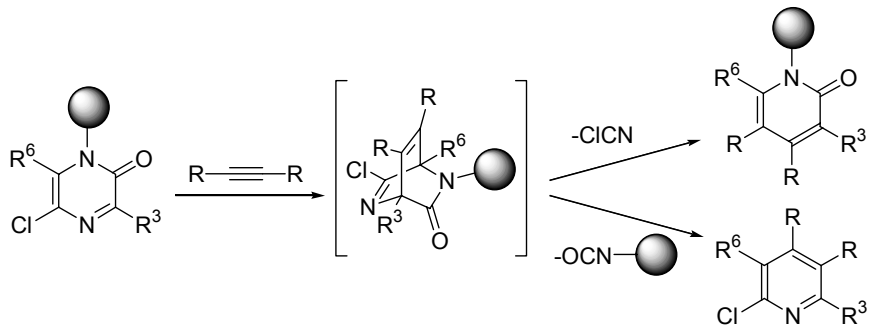
[b]Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Inter- and intramolecular hetero-Diels-Alder reactions in a series of functionalized 2(1*H*)-pyrazinones were investigated under controlled microwave irradiation.[1] The cycloaddition reactions were efficiently performed in sealed tubes, utilizing either a combination of 1,2-dichlorethane and a thermally stable ionic liquid, or 1,2-dichlorobenzene as reaction medium. In all cases a significant rate-enhancement using microwave flash heating as compared to thermal heating was observed.



Diels-Alder reactions of polymer-bound pyrazinones with acetylenes offer an efficient solid-phase methodology for the separation of the resulting products (i.e. pyridines and pyridones) using the concept of traceless linking. Upon reaction, pyridines are released into solution phase, whereas pyridones stay on the solid support and can be cleaved from the resin affording the final compounds in moderate to high purities. The microwave-assisted protocol will be compared with the conventional thermal method. We will also discuss the development of a new acid-labile linker used in the synthesis.[2]



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[2] Kaval, N.; Van der Eycken, J.; Caroen, J.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* accepted.

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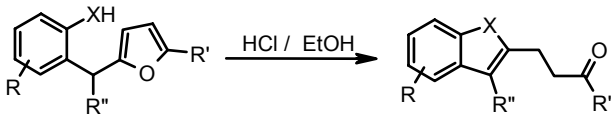
ISOCHROMONE DERIVATIVES SYNTHESIS VIA PROTOLYTIC FURAN RING OPENING REACTION

Artem C. Dmitriyev[a], Vladimir T. Abaev[b], Andrey V. Gutnov[b], Alexander V. Butin[a]

[a]Research Laboratory of Furan Chemistry, Kuban State University of Technology, Russian Federation
[b]Leibniz-Institute für Organische Katalyse an der Universität Rostock e. V., Buchbinderstr. 5-6, 18055 Rostock, Germany

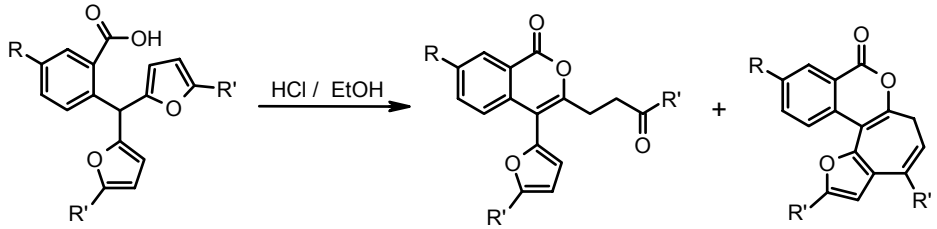
We have developed the general approach for the benzoannelated heterocycles synthesis from 2-substituted benzylfurans based on the protolytic furan ring opening reaction. The reaction was studied in details for the syntheses of benzofuran [1] and indole [2] derivatives.



R = H, NO2, Hal, OMe, Me; R' = Me, Et; R" = Ar, Alk, Fur; X = O, NTs

It is known that recyclization of furan ring can be followed with secondary cyclization reaction as it was showed earlier for isoquinolone derivatives synthesis [3]. Similar cyclization was observed for benzofuran derivatives [4] too.

Now we present an application of our methodology for the preparation of isochromone derivatives.



R = H, NO2, NH2, Hal, OMe; R' = Me, Et, t-Bu

Synthesis of the starting 2-carboxyaryldifurylmethanes and the effect of substituent in the position 5 of furan ring for the recyclization and secondary cyclyzation are discussed.

Acknowledgements: authors are grateful to *the Russian Foundation of Basic Research (RFBR)* (grant 03-03-32759) and *BAYER AG* (project "Synthon B001") for the financial support.

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HARTREE-FOCK AND DENSITY FUNCTIONAL STUDIES ON THE STRUCTURE AND VIBRATIONAL FREQUENCIES OF FUNCTIONALIZED QUINOXALINES.

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[1]University U.S.T.H.B, Algiers,Algeria
[2]University Paris VI,Paris,France.

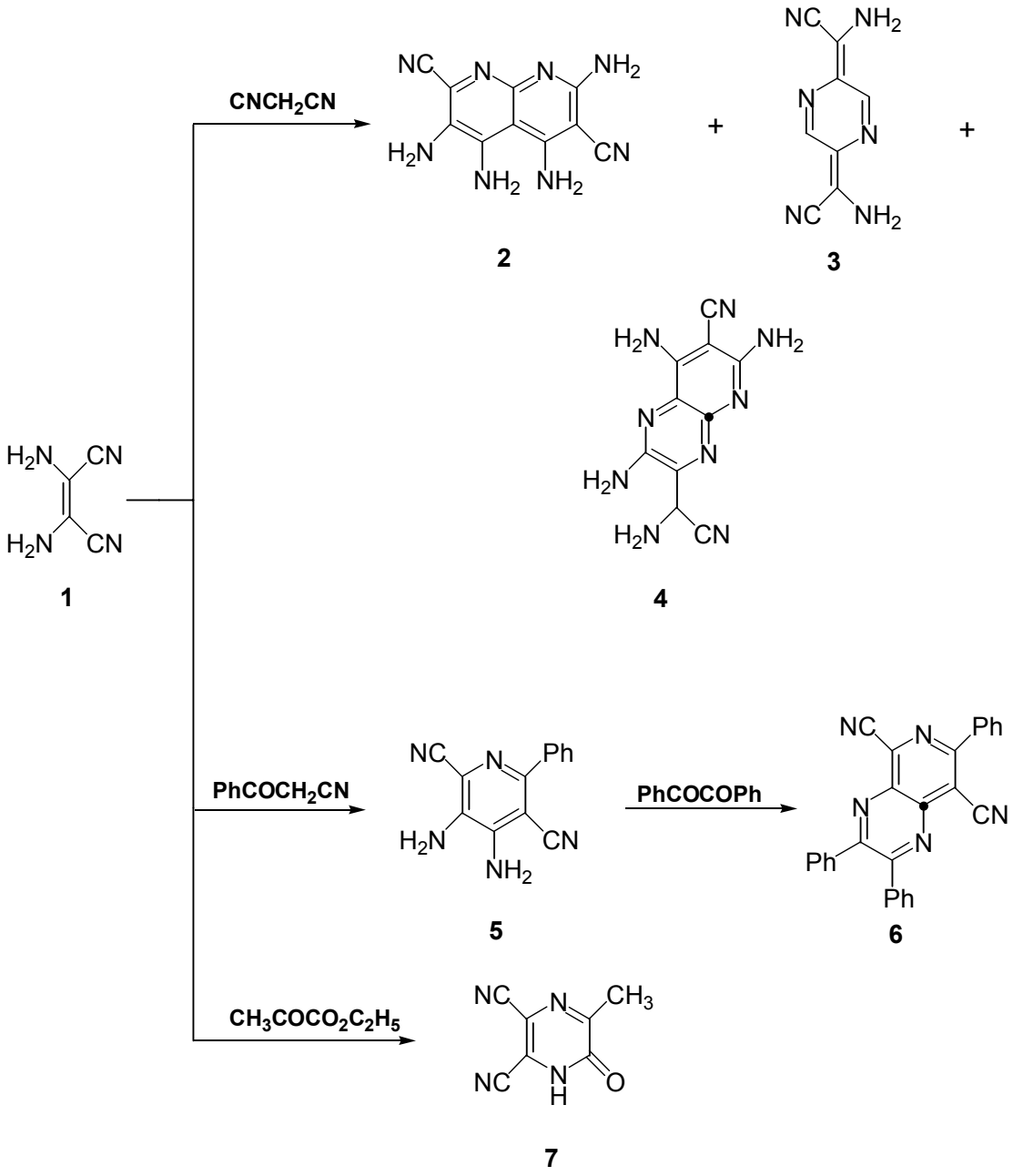
In recent years much attention has been focused on the development of functionlized quinoxalines which are useful in synthetic Chemistry and in Pharmacology as anti HIV and others.
The cycloadditions between maleimide and the o.phenylene diamine produced a range of geometrical variants which were characterised as quinoxaline derivates.
With the development of improved algorithms and increased computational facilities, the geometrical structures energies, vibrational frequencies and atomic charges for large molecular systems can be now studied with the quantum chemical methods.
Ab initio HF as well as the hybrid density functional B3LYP methods with the 6-31G* basis set are used in all calculations using the Gaussian 98 program.
For all the structures considered in this study, the optimized geometries, and the vibrational frequencies obtained from the HF and B3LYP calculations have been compared to the experimental data available in the literature.
The relative stability of products can be explained by their keto-enamine form with N-H..O intramolecular hydrogen bonds. Our theoretical results are in good agreement with the experiment.

ENAMINONITRILE IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRIDINE AND PYRIDAZINE DERIVATIVES

Abdel-Zaher A. Elassar and Amal Al-Azmi

Department of Chemistry, University of Kuwait, P.O. Box 5969, Safat 13060, Kuwait.

Diaminomaleontrile (DAMN) **1**, reacts with malononitirtile under basic conditions to give a mixture of 1,8-naphthyridine **2**, pyrazine **3** and aminopyrido[2,3-b]pyrazine **4** derivatives. Also, DAMN reacts with benzoylacetonitrile to furnish pyridopyrazine derivative **5**. Reaction of **5** with benzil gave 2,3,7-triphenylpyrido[3,4-b]pyrazine-5,8-dicarbonitrile **6**. In addition, reaction of ethyl pyruvate with DAMN **1** forms dicyanopyrazine **7**. All structures were established based on spectral analysis.



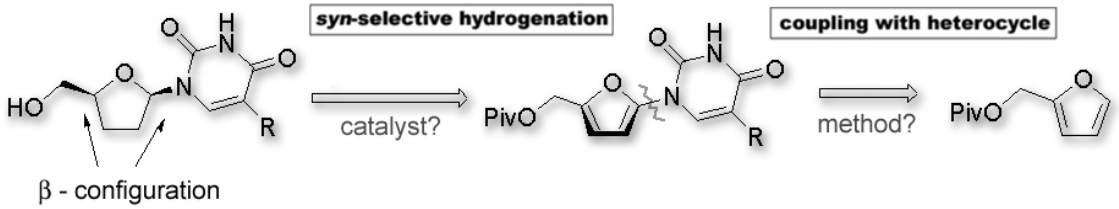
Acknowledgments: The financial support of University of Kuwait received through Project SC04/ 01 and SAF facilities through Projects GS01/01 and GS03/01 are gratefully acknowledged.

2',3'-DIDEOXYNUCLEOSIDES FROM 2-SUBSTITUTED FURANS

Martin Albert, Dominic De Souza, Petra Feiertag, and Helmut Hönig

Institut für Organische Chemie, Technische Universität Graz, A-8010 Graz, Austria

The interest in nucleoside analogues, and particularly in 2',3'-dideoxynucleosides is based on the finding that these compounds are potentially effective therapeutic agents for the treatment of AIDS and other virus-caused diseases [1]. Depending on strategy and target structure the existing methodologies for the synthesis of nucleoside analogues are usually limited by one or several factors, namely, highly priced starting materials, lack of control during the glycosylation, laborious syntheses or/and the use of toxic reagents.
The known high reactivity of furans towards hydrogenation and the ease of controlling the relative stereochemistry of 2,5-disubstituted furans motivated us to design a retrosynthetic concept with planar furyl nucleosides as key intermediates and with a *cis*-selective hydrogenation of these compounds as key step (scheme). Since 2-substituted furans already consist of the desired five-carbon skeleton of the final products, we anticipated that these commercially available compounds represent ideal starting materials for such a synthesis. A coupling reaction of a *N*-heterocycle with 2-substituted furans, followed by hydrogenation should yield racemic, exclusively β-configurated 2',3'-dideoxynucleosides in a short and efficient synthesis [2].



Concept for the synthesis of 2',3'-dideoxynucleosides

The realization of the concept, in particular the results for the fusion of a suitable nucleobase (pyrimidines and purins) with a furan by two different strategies as well as results for a series of chemoselective hydrogenations will be presented.

[1] Mansour, T. S.; Storer, R. *Curr. Pharm. Des.* **1997**, *3*, 227-264.
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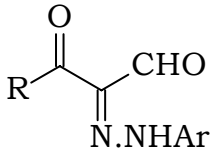
2-ARYLHYDRAZONOPROPANALS AS STARTING MATERIALS IN SYNTHESIS: EFFICIENT ROUTES TO 3-OXOALKANONITRINES, 3,5-DIACYLPYRAZOLES AND ARYLAZOPHENOLS

Balkis Al-Saleh, Moursy A. El-Apasery and Mohamed Hilmy Elnagdi

Department of Chemistry, Faculty of Science, Kuwait University, P.O. Box 5969, 13060 Safat, Kuwait.

The arylhydrazonopropanals **1a-c** are converted into nitriles (2) on treatment with hydroxylamine sulphonic acids. Reacting **1a-c** with α-haloketones afforded 3,5-diacylpyrazoloes (3). The reaction of **1a-c** with acetone gives the arylazophenols **4a-c.**



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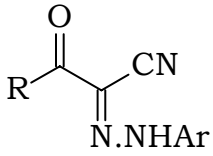

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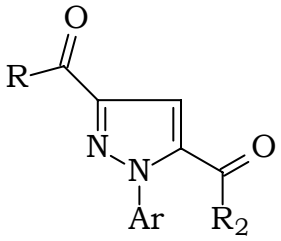

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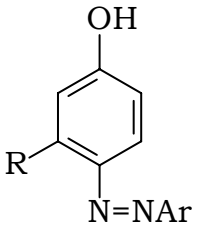


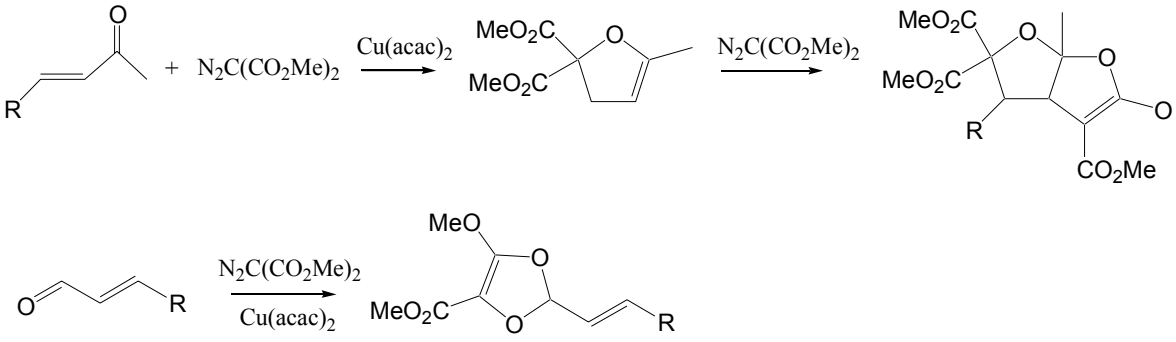
4

REACTION OF α,β-ENONES, ENALS AND ESTERS WITH DIAZO COMPOUNDS

Olcay Anac, Cigdem Kahveci

Istanbul Technical University, Department of Chemistry, Faculty of Science and Letters, Maslak, Istanbul 34469, Turkey
anac@itu.edu.tr

Carbonyl ylides arising from dimethyl diazomalonate and α,β-enones with mainly s-cis conformations underwent disrotatory cyclization to produce dihydrofuran [1,2] and furofuran derivatives. The corresponding ylides arising from rather s-trans α,β-enals yielded dioxole derivatives.



In this study: i) We aimed to obtain only dihydrofurans and to prevent the formation of furofurans starting from some specially designed bulky-enones.
ii) We also searched for the reactivities of α,β-esters towards dimethyl diazomalonate to form dihydrofurans.

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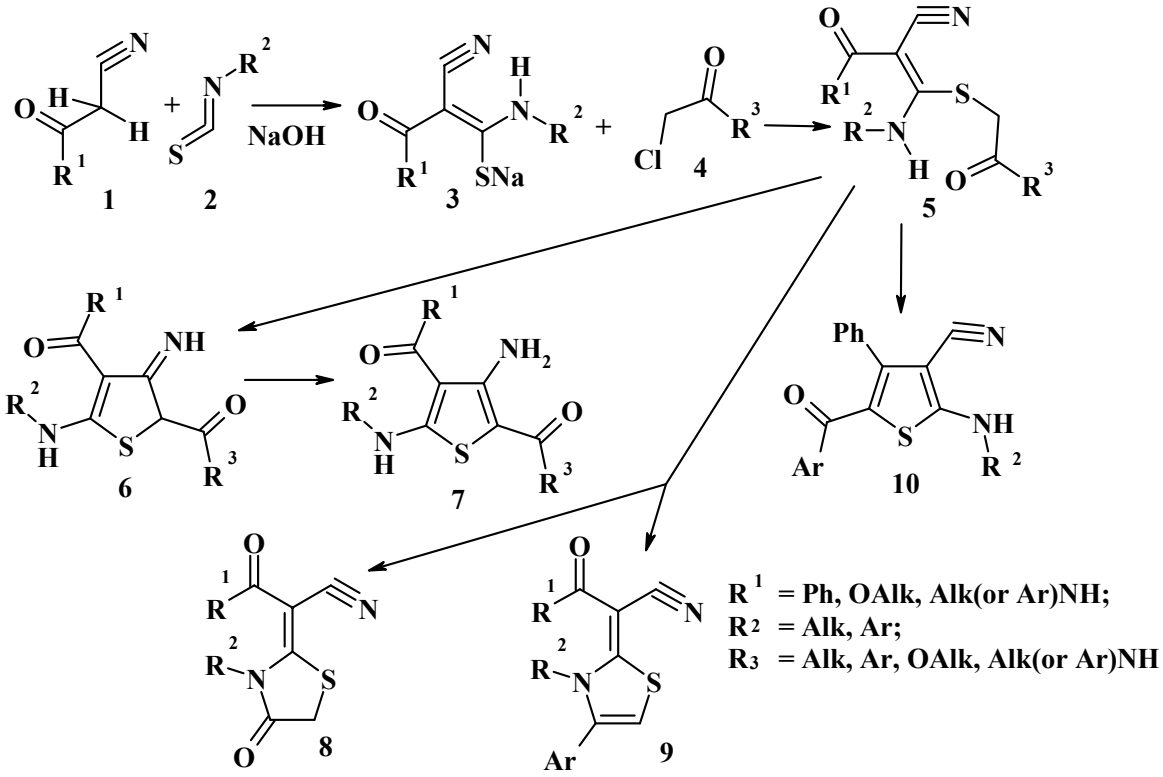
INVESTIGATION OF 3-AMINO-3-METHYLTHIO-2-ACYL(CARBAMOYL)PROPENENITRILES CYCLIZATION REACTIONS

Alexander P. Andrushko, Dmitry O. Sysoev, Albert K.Tyltin, Konstantin G. Nazarenko

Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033, Kiev, Ukraine;
e-mail: enamine@enamine.net



Active methylene nitriles **1** react with isothiocyanates **2** and α-halocarbonyl compounds **3** in the presence of bases leading to the title intermediates **5**. The latter are transformed into thiophene or thiazole derivatives dependently on reaction conditions and substituents nature.

It was found that starting from cyanoacetic acid esters and amides **1** (R^1= OAlk, NR_2) and chloroacetic acid amides **4** (R^3= NR_2) in the presence of Et_3N the diamonothiophenes **7** were obtained. They are formed via intermediate imines **6**, which were isolated in pure state and characterized in several cases. Instead, in the presence of NaOAc or AcOH the thiazolones **8** were formed.

The use of α-haloketones **4** (R^3= Alk, Ar) also resulted in diaminothiophenes **7** obtaining, however sometimes the thiazoles **9** formation was observed.

Noteworthy, when the aroylacetonitriles **1** (R^1 = Ar) were used as starting materials the ring closure occurred with participation of the carbonyl, but not the nitrile, group yielding the thiophenes **10**.

MICROWAVE-ASSISTED SYNTHESIS OF BIARYL-CONTAINING POLYCYCLES VIA PALLADIUM-CATALYZED REACTIONS

Prasad Appukkuttan, Wim Dehaen and Erik Van der Eycken*

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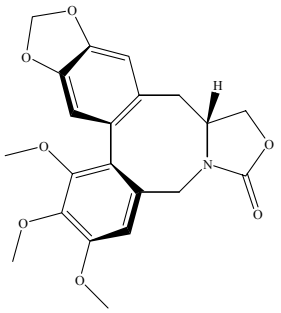
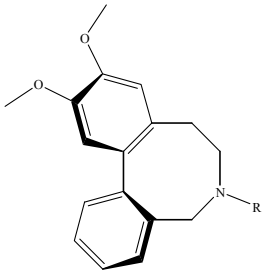
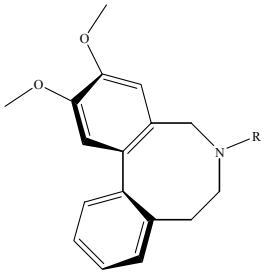
Palladium catalyzed C-C bond forming reactions are of extreme interest in present day chemistry, due to their widespread application in the synthesis of biologically active natural product analogues [1]. However, these reactions are proved to be slow and sluggish when applied to electron-rich and *ortho*-substituted aryl halides, because of the difficulty in transpalladation. *Amaryllidaece* alkaloids (Apogalanthamine, Buflavine, 7-aza Isopicrostegane) containing a unique 5,6,7,8-dibenzo[c,e]azocine skeleton have been shown to possess interesting biological activities including microtubulin growth inhibition, alpha-adrenergic -, anti-serotonin -, anti-HIV - and anti-hepatitic activities [2]. All of these compounds display a characteristic biaryl unit, the construction of which is the key step in their total synthesis.



7-aza Isopicrostegane



Apogalanthamines



Buflavines

It has been amply demonstrated in the literature that the use of focused microwave irradiations can dramatically improve the reaction rates. In this contribution, we wish to present the results of our studies towards the 5,6,7,8-dibenzo[c, e]azocine skeleton of the title natural products by using microwave-assisted Suzuki and Stille coupling strategies. Dramatic rate enhancements have been observed during the reaction, in comparison with the conventional heating conditions, and the commonly observed problem of dehalogenated side products during the palladium-catalyzed reactions of electron-rich substrates could efficiently be circumvented. This strategy also allows to substitute the aryl rings of the title molecules with heterocyclic rings, which, to the best of our knowledge, has not so far been investigated.

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[2] Kubota, Y.; Kawasaki, H.; Tomioka, K.; Koga, K.; *Tetrahedron* **1993,** 49, 3081-3090, Ishida, Y.; Watanabe, K.; Kobayashi, S.; Kihara, M.; *Chem.Pharm.Bull* **1977,** 25(8), 1851–1855, Hoarau.C, Couture. A, Deniau,E.; and Grandclaudon, P.; *J.Org.Chem.,* **2002,** 67, 16, 5846-5849.

ONE-POT AND SIMPLE SYNTHESIS OF BISSPIROPIPERAZINE DERIVATIVES VIA[3+3]CYCLOADDITION REACTIONS

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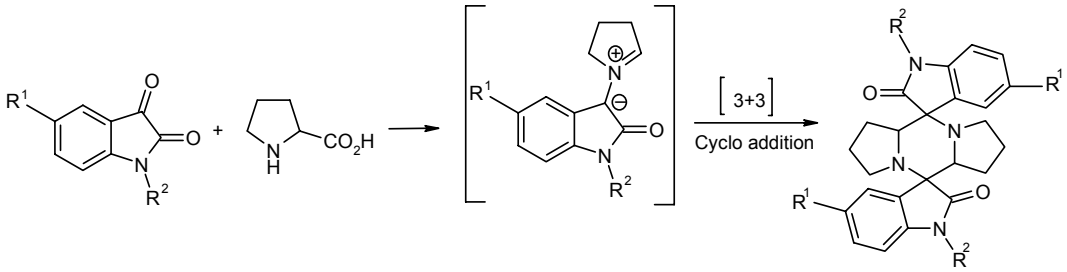
It is well known that compounds including piperazine ring in thier stracturs, such as clozapin, buspiron, mianserin and tandospirone have important biological activity[1]. Preparation of this compounds via [3+3]cycloaddition of azomethine ylides was reported[2].

In connection with our ongoing works on isatin derivatives [3] we found that reaction of proline and isatin derivatives gives rise to stereospecific formation of intermediate azomethine ylides via decaboxylation route which in absence of dipolarophiles does a [3+3]cycloaddition reaction to formation of new symmetrical heterocyclic compounds which structures were supported by elemental analysis, Mass, IR, 13CNMR and 1HNMR spectra of compounds.



[1] (a) Fitton, A.; Hett, R. C.; Drugs, **1990**, 40, 722. (2) Hamik, A.; Oksenberg, D.; Fishchette, c.; Peroutka, S., *J. Biol. Psycbioat*., **1990,** 28, 99. (c) Christipher, J. In "molecular mechanism of drug action" 2nd ed., Taylor and francis Ltd., London, **1994**, Chapter 9.

[2] (a) Frolich, J.; Habermalz, V.; Krohnke, F., *Tetrahedron Lett.*, **1967**, 3649. (b) Albrecht, A.; Frohlich, J.; Habermalz, V.; Krohnke, F., *Tetrahedron Lett*., **1967**, 3649.

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NEW TRANSFORMATIONS OF UNSATURATED POLYOLS CATALYSED WITH $PdCl_2$

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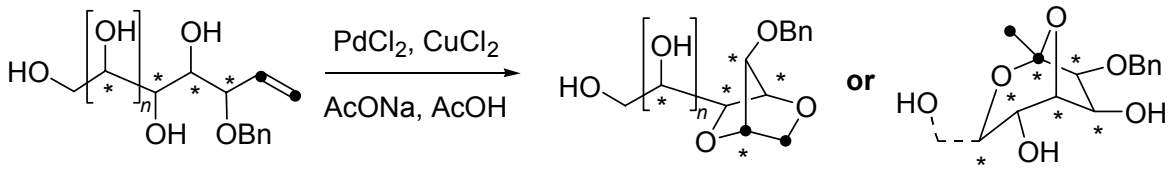
On our research course to new Pd(II) catalysed cyclisation reactions, employing intramolecular oxycarbonylation [1] or halogene/alcoholate introduction [2] as the terminal step, we have studied two types of bicyclization reactions on various α-benzyloxy-alkenitols (scheme 1):



Scheme 1

Reaction course depends strongly on substrate chain length and relative configuration, especially on carbons in α and γ positions to the terminal double bond. A mechanism based on the observed chemo- , regio- and stereo-selectivity in particular reactions and partially supported by semi-empirical calculations, will be discussed.

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[2] Koman, M.; Szolcsányi, P.; Gracza, T. *Acta Cryst.* C56, 138 (**2000**); Szolcsányi, P. *Disertation* STU, Bratislava (**1998**)

SYNTHESIS OF SEVERAL OPTICALLY ACTIVE IMIDAZO [1, 2-a] PYRIMIDINE-3(2H) -ONES

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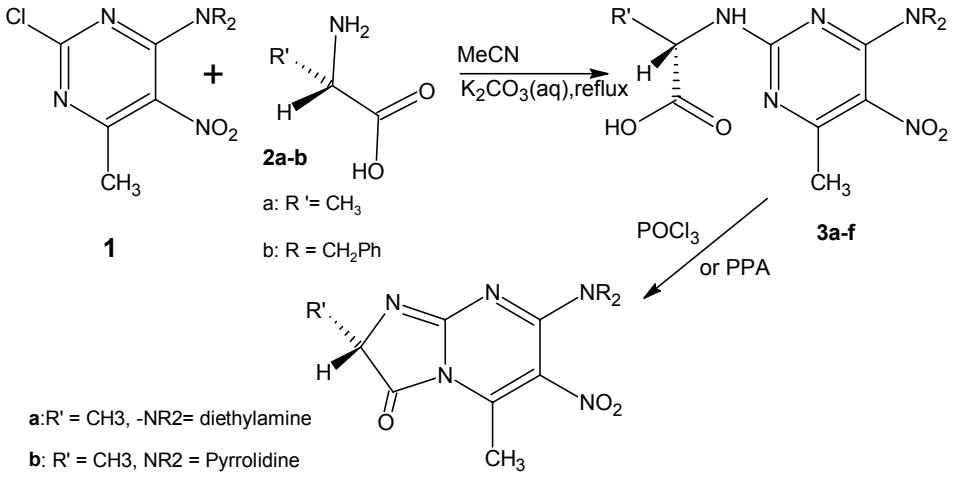
Several derivatives of the optically active imidazo[1,2-a]pyrimidin-3(2H)one were prepared from the appropriately substituted pyrimidine precursors. The reaction of 2-chloro-4-substitutedamino-6-methyl -5-nitropyrimidine **1** with few (L)-α-amino acids gave a high yield of the substituted derivatives **3**. These compounds were conveniently converted to their corresponding optically active imidazo[1,2-a]pyrimidines **4** on treatment with either phosphorus oxychloride or polyphosphoric acid at moderate temperatures.



1

2a-b

a: R '= CH_3

b: R = CH_2Ph

3a-f

4a-f

a:R' = CH3, -NR2= diethylamine

b: R' = CH3, NR2 = Pyrrolidine

c: R' = CH3, NR2 = morpholine

d: R' = CH2Ph, NR2 = diethylamine

e: R' = CH2Ph, NR2 = Pyrrolidine

f: R' = CH2Ph, NR2 = morpholine

Scheme **1**

THE DISCOVERY OF A NOVEL TANDEM PHOTOCHEMICAL REACTION AND ITS APPLICATION TO THE TOTAL SYNTHESIS OF STEMOAMIDE

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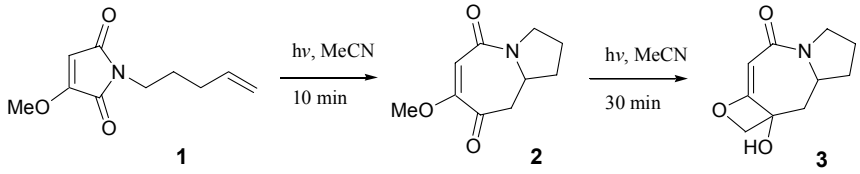
[b]Novartis, Horsham, UK

Introduction

A novel photochemical [5+2] cycloaddition has been reported for the construction of fused azepine ring systems from simple maleimide starting materials [1]. Whilst investigating the effect of substitution on the back of the maleimide moiety, a fascinating tandem photochemical reaction was discovered. This poster describes investigations into this reaction and its application to the total synthesis of stemoamide.

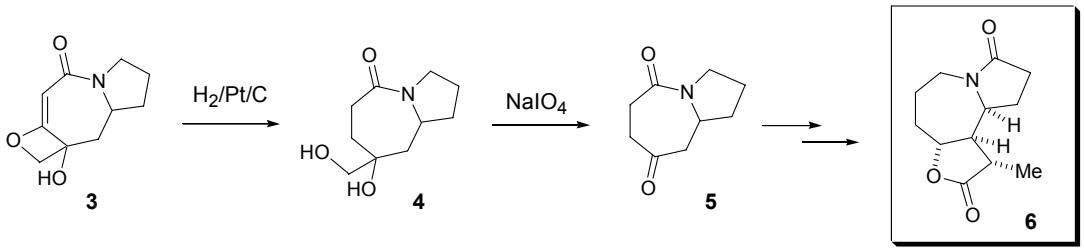
Results and Discussion

The irradiation of maleimide **1** resulted in an extremely rapid and high yielding [5+2] reaction to give **2**. Prolonged irradiation resulted in a Norrish II cyclization to give the highly strained oxetane **3**. The result is the construction of a complex tricyclic azepine in one step.



1 **2** **3**

A method was then developed for the reduction of the double bond and the oxetane moiety in one step to give **4**. Sodium periodate cleavage of the diol gave **5.** Extension of this methodology would allow a short total synthesis of stemoamide **6**.



3 **4** **5** **6**

Conclusion

The irradiation of maleimide moiety **1** has led to the discovery of a novel tandem photocycloaddition sequence. This reaction has been investigated with a range of alkoxy-maleimide substrates. A process has been developed to remove the oxetane functionality, allowing this methodology to be utilized in the synthesis of stemoamide.

[1] K. I. Booker-Milburn, C. E. Anson, C. Clissold, N. J. Costin, R. F. Dainty, M. Murray, D. Patel, A. Sharpe, *Eur. J. Org. Chem.,* **2001**, 1473-1482.

CYCLIZING NUCLEOPHILIC ADDITION TO AZINIUM SYSTEMS. PART 3.REACTION OF 3-ACYL QUINOLINIUM HYDRAZONES

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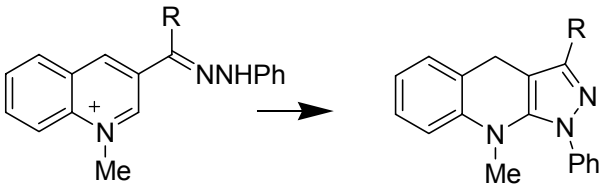
The N-phenylhydrazone of 3-acylquinolines were prepared,then were quaternized with iodomethane to give 3-acylquinolinium hydrazone methiodides(**1**).The salts were tranformed into desired neutral tricyclic product which were identified as pyrazoloquinolines(**2**) by generating as side chain N-anione by abstraction of N-hydrogen followed by an intramolecular nucleophilic addition following precedents in which bicycles were generated.[1,2]



(**1**) (**2**)

R=Ph

[1] M.M Baradarani and J.A.Joule,*J.Chem.Soc.,Perkin Trans. 1*,**1980,**72.
[2] J.D.Street,M.M.Baradarani,R.L.Beddoes,O.S.Mills,and J.A. Joule, *J.Chem.Res.,(s),***1987**,154;*(M),***1987**,1247.

CONVERSION OF ASCOMYCIN INTO 11-epi-ASCOMYCIN

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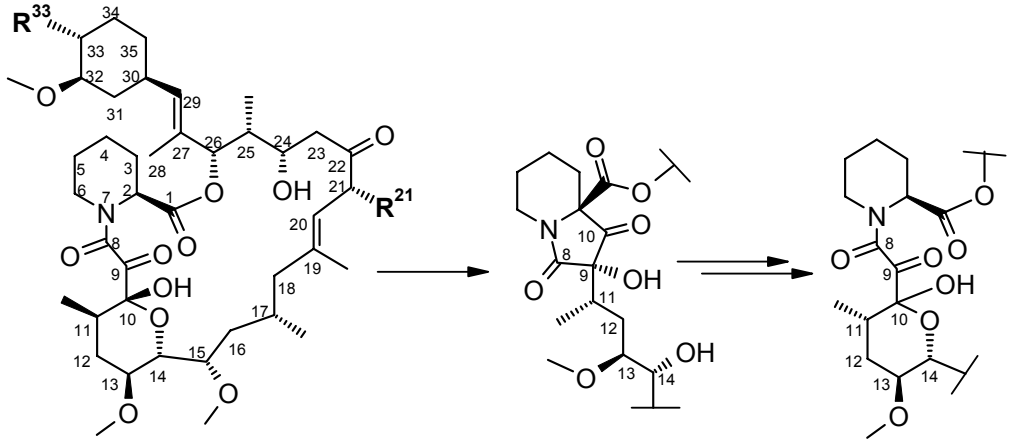
NOVARTIS Research Institute, Department of Medicinal Chemistry,
Brunner Strasse 59, A-1235 Wien, Austria.

The natural product Ascomycin (**1**) and the related compound FK 506 (**2**), represent highly functionalized 23-membered macrocycles with a polyketide backbone. Elidel®, a topical formulation of ASM 981 (**3**, pimecrolimus), the 33-*epi*-chloro-derivative of ascomycin, heralds major advances in the treatment of inflammatory skin diseases as compared to traditional treatment schedules.[1]



1 Ascomycin (R^{21} = ethyl; R^{33} = OH)
2 FK 506 (R^{21} = allyl; R^{33} = OH)
3 ASM 981 (R^{21} = ethyl; R^{33} = epi-chloro)

4 11-*epi*-ascomycin

Within the binding domain, ascomycin features the unusual pattern of a masked tricarbonyl moiety, which potentially allows for high structural diversity via simple isomerisation events. Herein, a cascade of diastereoselective rearrangement reactions, allowing the synthesis of 11-*epi*-ascomycin (4) is reported (fig.).

[1] (a) Harper, J.; Green, A.; Scott, G.; Gruendl, E.; Dorobek, B.: Cardno, M.; Burtin, P. *Br. J. Dermatol.* **2001**, *144*, 781-7. (b) Luger, T.; Van Leent, E. J. M.; Graeber, M.; Hedgecock, S.; Thurston, M.; Kandra, A.; Berth-Jones, J.; Bjerke, J.; Christophers, E.; Knop, J.; Knulst, A. C.; Morren, M.; Morris, A.; Reitamo, S.; Roed-Petersen, J.; Schoepf, E.; Thestrup-Pedersen, K.; Van der Valk, P. G. M.; Bos, J. D. *Br. J. Dermatol.* **2001**; *144*, 788-94.

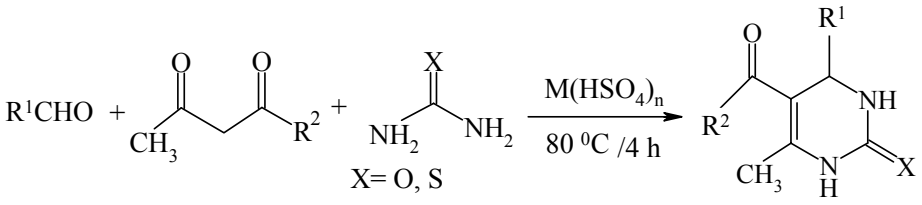
[2] For a review see: (a) Grassberger, M.A.; Baumann, K. *Curr. Opin. in Therapeutic Patents* **1993**, 931-37. (b) Stuetz, A.; Grassberger, M. A.; Baumann, K.; Edmunds, A.J.F.; Hiestand, P.; Meingassner, J.G.; Nussbaumer, P.; Schuler, W.; Zenke, G. **Immunophilins as Drug Targets**, in *Perspectives in Medicinal chemistry,* Testa, B.; Kyburz, E,; Fuhrer, W.; Giger, R. (Eds.), Verlag Helv. Chim. Acta, Basle and VCH, Weinheim, **1993**, Chapt. 27, 427-44.

SALTS OF HYDROGEN SULFATE CATALYSED ONE-POT SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES UNDER SOLVENT-FREE CONDITIONS

Ahmad Shaabani,* Ayoob Bazgir, Sakineh Arab-Ameri and Masoumeh Sharifi Kiasaraie

Department of Chemistry, Shahid Beheshti University, Zip Code 1983963113, Tehran, Iran

It is well known that 3,4-dihydropyrimidin-2-(1*H*)-ones and related compounds exhibit a wide range of biological activities [1] such as antiviral, antitumor, antibacterial and antiflammatory properties. In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature [2] and in potent HIVgp-120-CD_4 inhibitors.
Therefore, many synthetic methods for preparing such compounds including classical reflux or solid state conditions and microwave or ultrasonic irradiation have been reported [3].
As a part of our program towards green synthesis [4,5], the environment-friendly salts of hydrogen sulfate catalyzed the one-pot three component condensation reactions of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea under solvent-free conditions leading to 3,4-dihydropyrimidin-2(1*H*)-ones in fairly high yields at 80 °C.



R^1= Alkyl and Aryl

R^2= Alkyl-O and Alkyl

M=Mg, Li, Na, K

[1] Kappe, C. O. *Tetrahedron* **1993**, 49, 6937 and references cited there in
[2] a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. *J. Org. Chem*. **1995**, 60, 1182. b) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. *Tetrahedron Lett.* **1996**, 37, 6977.
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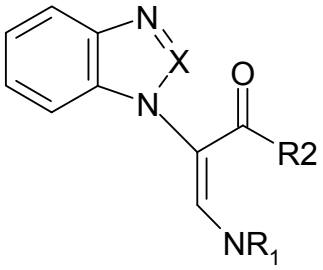
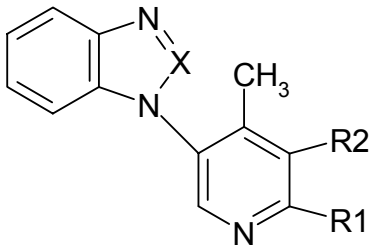
ENAMINONES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS : SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED 3-AZOLYL-PYRIDINES AND AZOLYL AZOLOAZINES VIA THERMAL AND MICROWAVE HEATING

Balkis Al-Saleh, Haider Behbehani, Morsy El-Abasery and Mohamed Hilmy Elnagdi

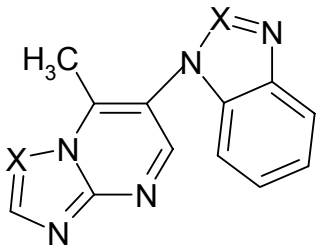
The reactivity of enaminoes 1 a-c toward active methylene reagents and amino-azoles to yield 2 and 3 will be demonstrated . A comparison of reaction time and product yields from reactions conducted by conventional heating and by microwave heating will be made. Structure elucidation of reaction products via utility of 2D NMR will also be demonstrated.



1



2



3

1 a, X= N ; R1 = R2= Me
b, X= CH ; R1 = R2= Me
c, X= N ; R1 = R2= Ph
d, X= CH ; R1 =H ; R2= Ph

REACTIONS OF ARYLHYDRAZONOACETTHIOAMIDES WITH BISELECTROPHILIC REAGENTS

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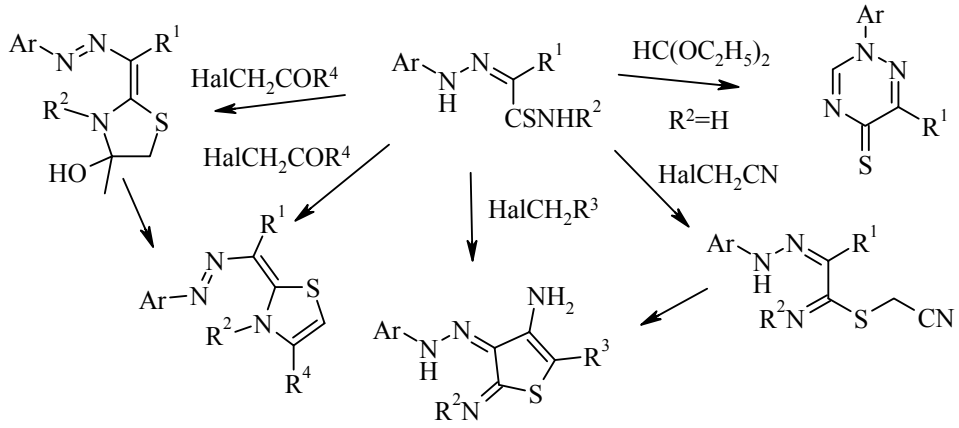
Chemistry Department, Urals State Thechnical University, 620002, Ekaterinburg, Russia

The research concerns a wide study on the reactions of arylhydrozonoacetthioamides with different electrophiles (haloketones, haloacetonitriles, haloacetates and orthoesters). It has been shown that the examine compounds ambident electrophilic substrates. Consequently in depending on the structures of thioamides and reagents, electronic and steric effects of some fragments and the reaction temperature were realized the different directions of the heterocyclization.



As a result of investigation it were synthesized the different type of the heterocycles (triazines, thiazolines, thiazoles, thiophenes). Possible mechanism of this reaction will be discussed.

Financial support from the Russian Foundation of Basic Research (grant 01-03-33173) is gratefully acknowledged).

S_N^H-REACTION IN THE SYNTHESIS OF THIENO- AND FUROQUINOXALINES

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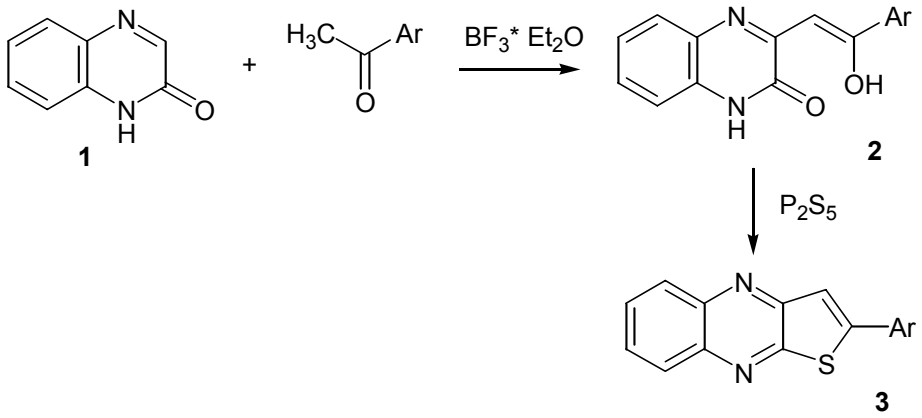
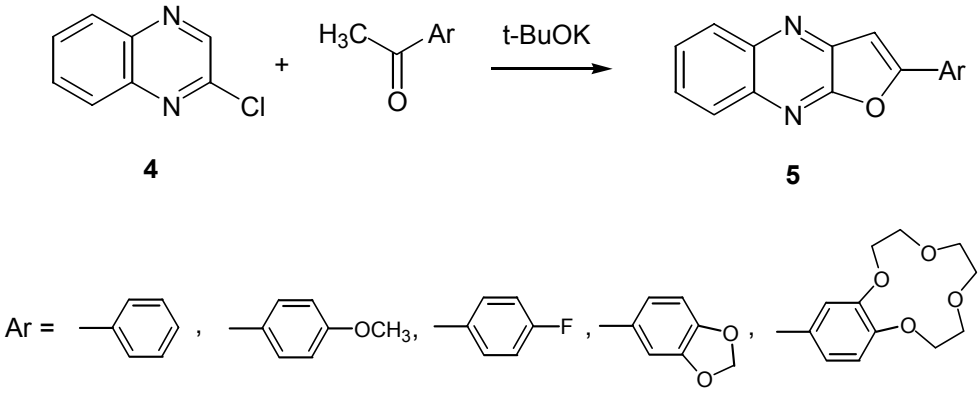
A new synthetic approach to condensed quinoxalines has been developed. The key step of this method is nucleophilic substitution of hydrogen (S_N^H).
Thus, the reaction of quinoxalin-2-one (**1**) with acetophenones takes place in the presence of BF_3 and results in the formation of compounds **2** as the S_N^H -products. The treatment of compounds **2** by phosphorus pentasulfide leads to thienoquinoxalines **3**.



The reaction of 2-chloroquinoxaline **4** with acetophenones appears to be a combination of the S_N^H and S_N^{ipso} processes leading to furoquinoxalines **5**.



This work was possible due to financial support of Russian Foundation for Basic Research (grants No 02-03-32332-a and 02-03-32627-a) and International Science & Technology Center (project No 708).

CRYSTALLIZATION-INDUCED ASYMMETRIC TRANSFORMATIONS. THE SYNTHESIS OF FUROYLALANINES.

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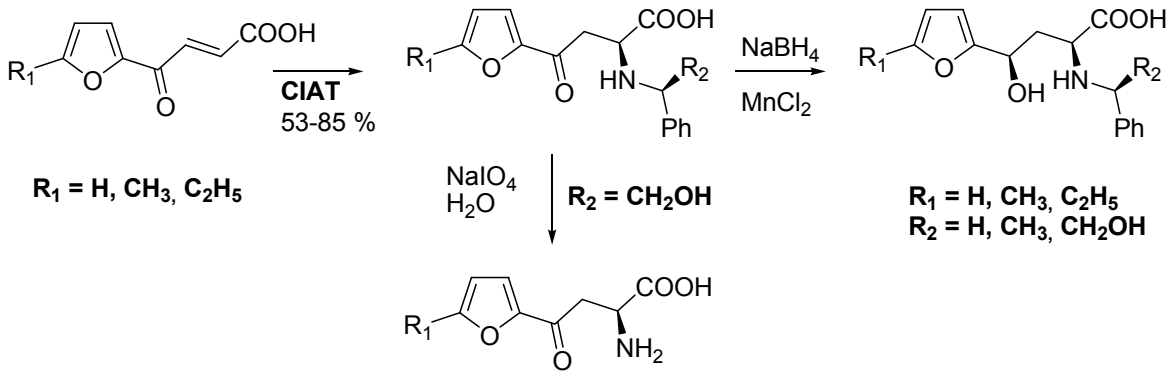
Radlinského 9, SK-81237 Bratislava, Slovakia

Crystallization-induced asymmetric transformation (CIAT) represents a powerful tool for the preparation of enantiomerically pure compounds (EPC) especially in the last decade, when its industrial potential has been uncovered.[1]

Recently we have developed the efficient application of CIAT based on *aza*-Michael – retro-*aza*-Michael addition of chiral amino derivatives on the aroylacrylic acids. The precipitated adducts serve as convenient EPC´s for a large variety of homophenylalanine derivatives.[2]

Here we would like to present an extension of this methodology to the synthesis of optically pure L-furoylalanines and their derivatives.



3-(2-Furoyl)-L-alanine as a naturally occuring compound has been isolated from *Fagopyrum esculentum Moench*.[3] Its synthesis from α-amino acid precursors has been published recently.[4]

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[3] Ichihara, A.; Hasegawa, H.; Sato, H. *Tetrahedron Lett.* **1973**, 37-38.

[4] Golubev, S.A.; Sewald, N.; Burger, K. *Tetrahedron*, **1996**, *52*, 14757-14776.

SYNTHESIS OF PYRAZOLO[4,3-c]PYRIDINES

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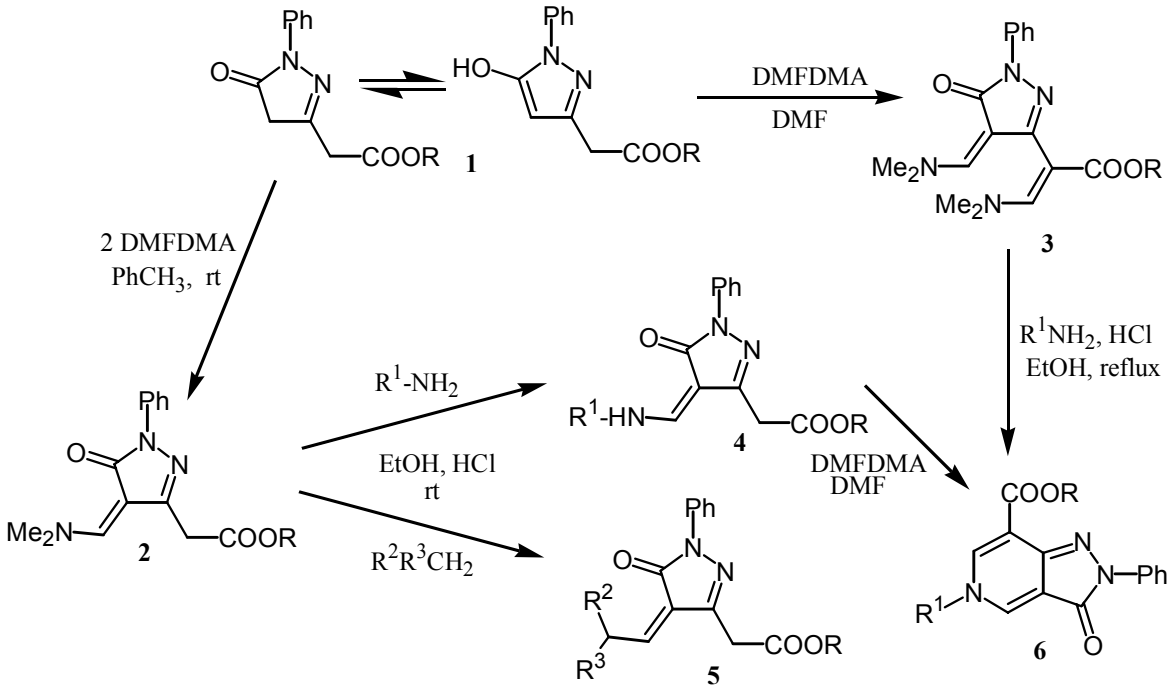
Aškerčeva 5, 1000 Ljubljana, Slovenia

Alkyl (1-phenyl-4,5-dihydro-pyrazol-3-yl)acetates (**1**) react with DMFDMA at room temperature or at reflux temperature, to give mono- or bis- dimethylaminomethylidene derivatives **2** or **3**, respectively. Reactions of *N*- nucleophiles with **2** furnished aminosubstituted products **4**, while reactions with *C*- nucleophiles furnished products **5**. By heating of products **4,** with DMFDMA in DMF, pyrazolo[4,3-c]pyridines (**6**) were obtained. Products **6** can also be obtained from reagent **3** in single step with good yields.



[1] (a) H. V. Pechmann, *J. Liebigs Ann. Chem.*, **1891**, *261*, 171. (Beil. H *25*, 213); (b) Jpn. Kokai Tokkyo Koho JP 82 40,407 (*Chem. Abstr.* **1982**, *97*, P92271z); (c) F. W. Short, E. J. Schoeb, *J. Heterocycl. Chem.*, **1969**, *6*, 723.

[2] D. Bevk, R. Jakše, J. Svete, A. Golobič, L. Golič, and B. Stanovnik, to be published.

DIASTEREOSEECTIVE DIELS-ALDER REACTION OF 2-THIENYL AND 2-FURYL SUBSTITUTED 3-PROPENETHIOAMIDES WITH ELECTRON DEFICIENT DIENOPHILES

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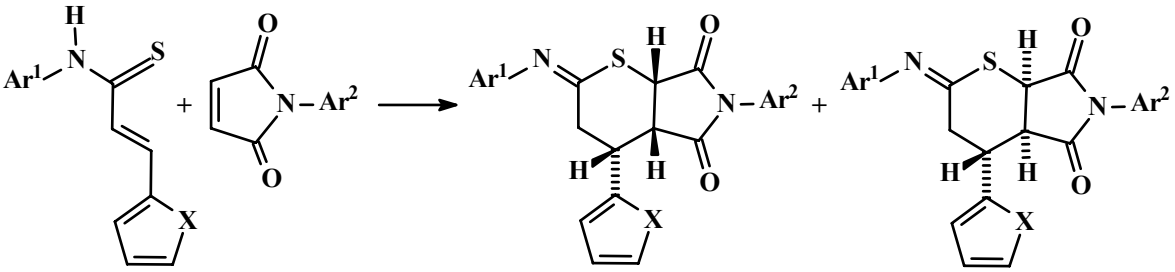
Reaction of α,β-unsaturated thiocarbonyl compounds with electron deficient dienophiles represents a straightforward and useful route to sulphur containing six membered heterocycles. Its efficiency and versatility combined with regio- and stereochemical control renders the thia-*Diels-Alder* reaction an attractive approach to 3,4- dihydro-*2H*-thiopyrans, which are potential precursors of a wide range of sulphur heterocycles, which exhibit an interesting biological properties [1-3].

The aim of our study was to investigate the influence of 2-thienyl and 2-furyl substituents at C-3 in α,β-unsaturated thioamides **3** and **4** on yield and on diastereoselectivity of cycloadditions to N-arylmaleimides and diethyl fumarate. All reactions of thioamides **3** and **4** with N-arylmaleimides furnished cycloadducts in moderate to good yields with the favoured formation of *endo* cycloadducts as major products.



3, 4 **5, 6** **7, 8**

3, 5, 7: X = S, 4, 6, 8: X = O

The both diastereoisomers revealed in their ^{1}H NMR spectra the presence of two diastereotopic protons of CH_2 group at C-6 and did not exhibit amine proton, this indicated that both compounds existed in tautomeric arylimine form.

Heterodienes **4** containing 2-furyl substituent were more reactive than **3**, and furnished almost exclusively *endo* cycloadducts in high yields.

[1] Vedejs E., Stults J. S; J. Org. Chem. **53**: 2226, 1998.

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AN UNUSUAL TAUTOMERISM IN SOME METHYL DERIVATIVES OF 2,3-DIHYDRO-1H-PYRROLE-2,3-DIONE

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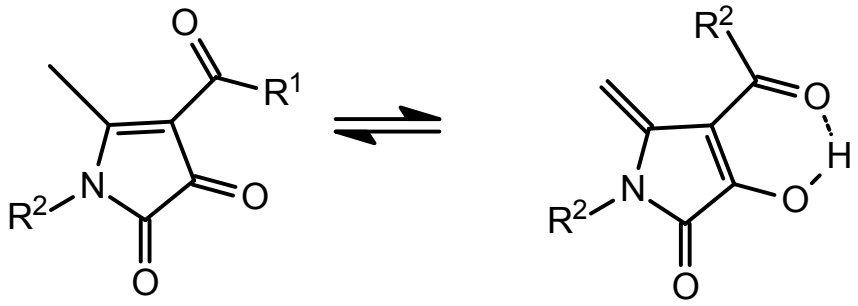
A series of *N*-substituted 4-acetyl-, 4-benzoyl- or 4-carboethoxy-5-methyl-2,3-dihydro-1*H*-pyrrole-2,3-diones was synthesised staring from the respective Schiff bases, derivatives of acetylacetone [1], benzoylacetone or ethyl acetylacetate and oxalyl chloride. Their structure was elucidated by means of spectral techniques and crystallographic data [2]. NMR and IR investigations of these compounds proved an unusual tautomerism that involves a methyl group attached to heterocyclic ring (examples shown below). The reactivity of an exocyclic double bond and the dependence of the tautomeric equilibrium on phenyl ring substitution will be discussed.



R^1= CH_3, C_6H_5, OC_2H_5

R^2= X-C_6H_4, X-CH_2

[1] J.Golus, PhD Thesis, Kraków, 1983

[2] J. Grochowski, P. Serda, Z. Dauter, A. Kolasa, *Z. Kristallogr.,*1996, **211**, 622

A NEW CLASS OF LIGANDS EASILY OBTAINED BY HYDROGENATION OF CALIX[4]PYRROLE

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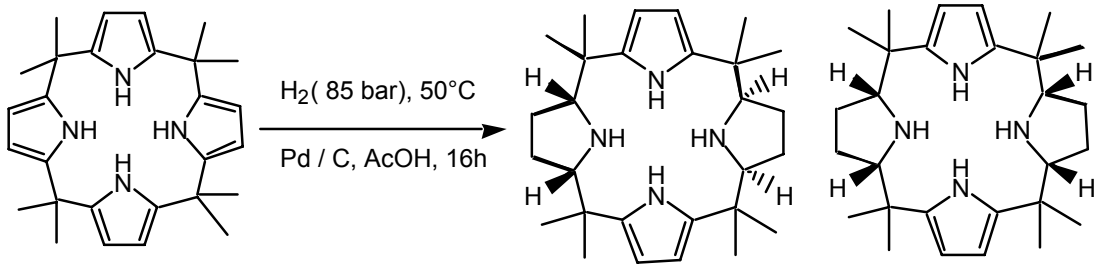
[b]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK

The calix[4]pyrroles (**1**), first synthesized in 1886 by Baeyer, as the result of an acid-catalyzed condensation between acetone and pyrrole, are not very efficient ligands and special conditions have to be applied to obtain metal complexes[1].
The catalytic hydrogenation of calix[4]pyrrole resulted in partially reduced calix[4]pyrroles (**2a** and **2b**), new possible ligands for complexation with metal ions.
Various metal catalysts on different supports have been screened for this reaction. The best results were obtained with a carbon supported palladium catalyst, in acidic medium, under mild reaction conditions (85 bar, 50°C). Ruthenium on carbon also showed activity in this hydrogenation. Scope and limitations of this reaction will be discussed.



1 **2a** **2b**

References:
[1] J. Jubb, G. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Inorg. Chem*., **1992**, 31, 1306-1308.

GELPHASE ^{13}C NMR SPECTROSCOPY OF SELECTED SOLID PHASE SYSTEMS

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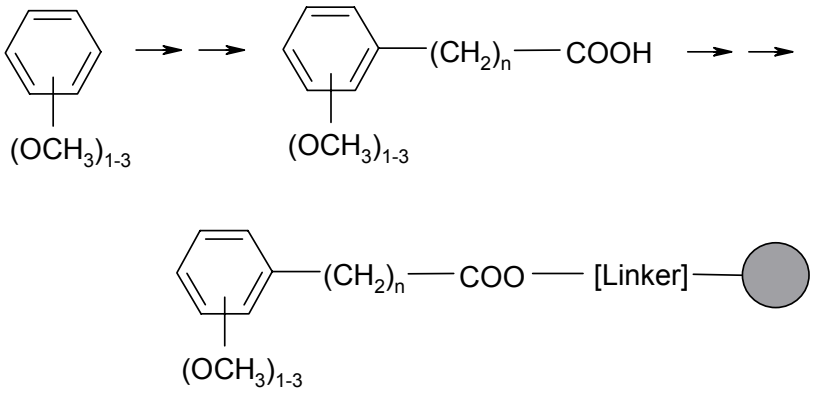
Getreidemarkt 9/163, 1060 Vienna, Austria

Studies on the applicability of usual liquid nmr spectroscopy for the analysis of solid phase reactions directly on the resin will be described. For a systematic investigation small and easily assignable molecules substituted with a chain of varying length were synthesised. In the next step these sensor-molecules were attached to different resins by appropriate methods. After swelling experiments ^{13}C nmr spectra of the solid phase systems were recorded using various puls techniques.



The quality of the resulting ^{13}C nmr spectra was analysed using the linewidth of the signals as the most important criterion. Scope and limitation of the method will be discussed.

STEREOSELECTIVITY IN PINACOL-HOMOCOUPLINGS MEDIATED BY SAMARIUMIODIDE

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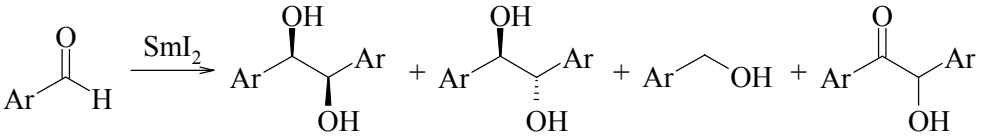
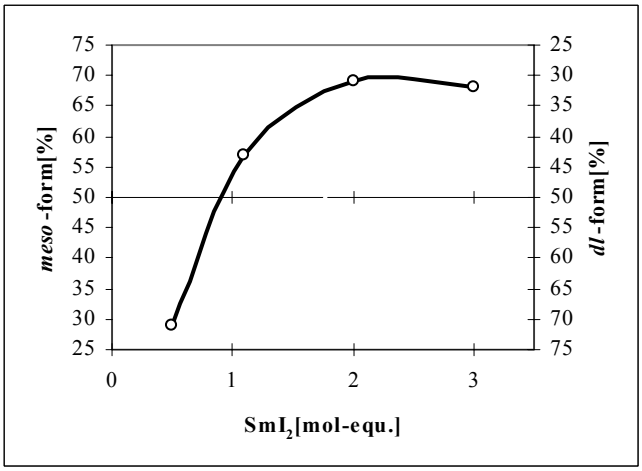
Being interested in a general approach to arylsubstituted meso-hydrobenzoins direct pinacol-coupling mediated by samariumdiiodide seemed to be a promising alternative to benzoin-condensation and subsequent reduction. Furthermore, checking the literature very carefully we found that described stereoselectivities vary in a broad range which seemed to be due to different reaction conditions, but no general investigation on this matter has been performed so far.[1] Thus the pinacol-coupling of different nitro-, methoxy- and unsubstituted derivatives was tested with regard to the dependence of stereoselectivity on the substrate-reagent-ratio as well as other reaction conditions.





The results of this investigation including the possibility to control the stereoselectivity via variation of the substrate-reagent-ratio (see above) will be presented.

[1] J.L. Namy, J. Souppe, H.B. Kagan, *Tetrahedron Lett.* **1983**, 24, 765-766; R. Annunziata, M. Tenaglia, M. Cinquini, L. Raimondi, *Eur. J. Org. Chem.* **1999**, 3369-3374

NUCLEO-β-LACTAMS: USEFUL INTERMEDIATES FOR THE SYNTHESIS OF SELF-ASSEMBLING β-PEPTIDES

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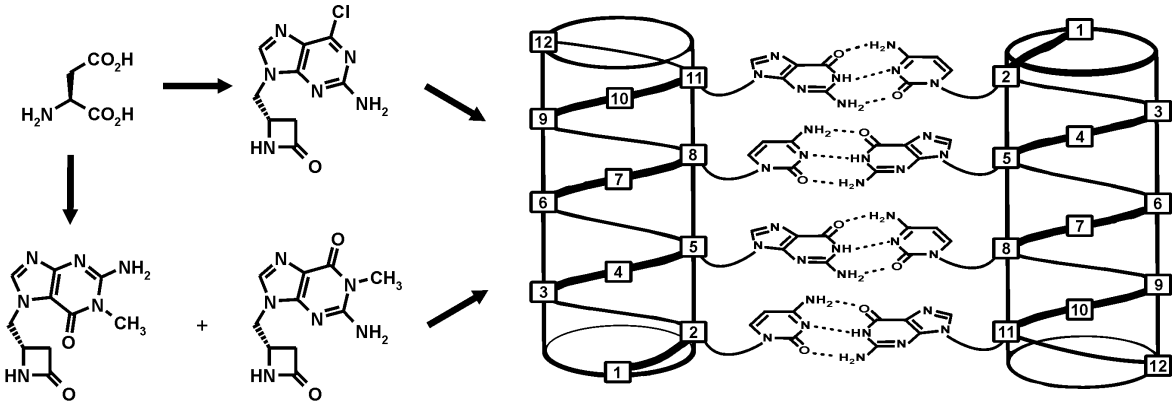
β-Amino acid oligomers ("β-peptides") form much more stable secondary structures in solution than their α-peptidic counterparts.[1] β-Peptidic backbones therefore offer useful scaffolds to probe and mimic the functionality of biomolecules. The 14-helix requires three β-amino acids for one turn, orienting every fourth side chain in the same direction. If this side chain contains a nucleobase it should be possible to create a helix with a nucleobase pairing site. This suggests the possibility to control structure and function of leucine zipper and helix bundle analogs by nucleobase pairing.



We report the synthesis of nucleobase containing β-amino acids[2] *via* nucleo-β-lactams. β-Lactams provide ideal protection of the nitrogen atom in β-position during purine alkylation. The prepared β-amino acids were incorporated into β-peptides. The formation of right-handed helices was demonstrated by CD spectroscopy. Investigations with mass spectrometry and temperature dependent UV spectroscopy showed the formation of stable pairing complexes between the complementary nucleo-β-peptides.

[1] R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219.
[2] A. M. Brückner, H. W. Schmitt, U. Diederichsen, *Helv. Chim. Acta* **2002**, *85*, 3855.

SYNTHESIS OF 13-METHYL EPOTHILONE A

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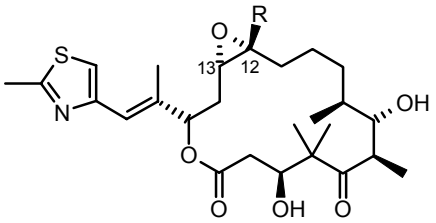
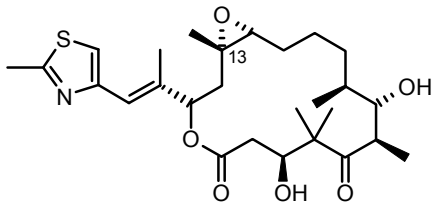
Wolfgang Schwede, and Werner Skuballa

Schering AG, Müllerstr. 170 - 178, D-13342 Berlin

The new natural product class of Epothilones excert cytostatic activity in a picomolar range in the NCI tumor cell panel with selectivity to tumors (colon, breast, NSCLC) with high medical need.
Compared to epothilone A the additional methyl group at position 12 in Epothilone B enhances the in vitro activity by one order of magnitude.
According to molecular modeling, the formal transposition of the methyl group from C-12 to C-13 should maintain the conformation.





R = H: Epothilone A

R = Me: Epothilone B

13-Methyl-Epothilone A

The synthesis of 13-Methyl-Epothilone A and its biological results are described.

*Corresponding author. E-mail: bernd.buchmann@schering.de

THE SYNTHESIS AND STUDY OF THE CYCLIZATION REACTIONS OF 1,2-DIHYDRO-3-[2-AMINO-3-(6-AZAURACIL-5-YL)-PHENYL]-QUINOXALIN-2-ONE

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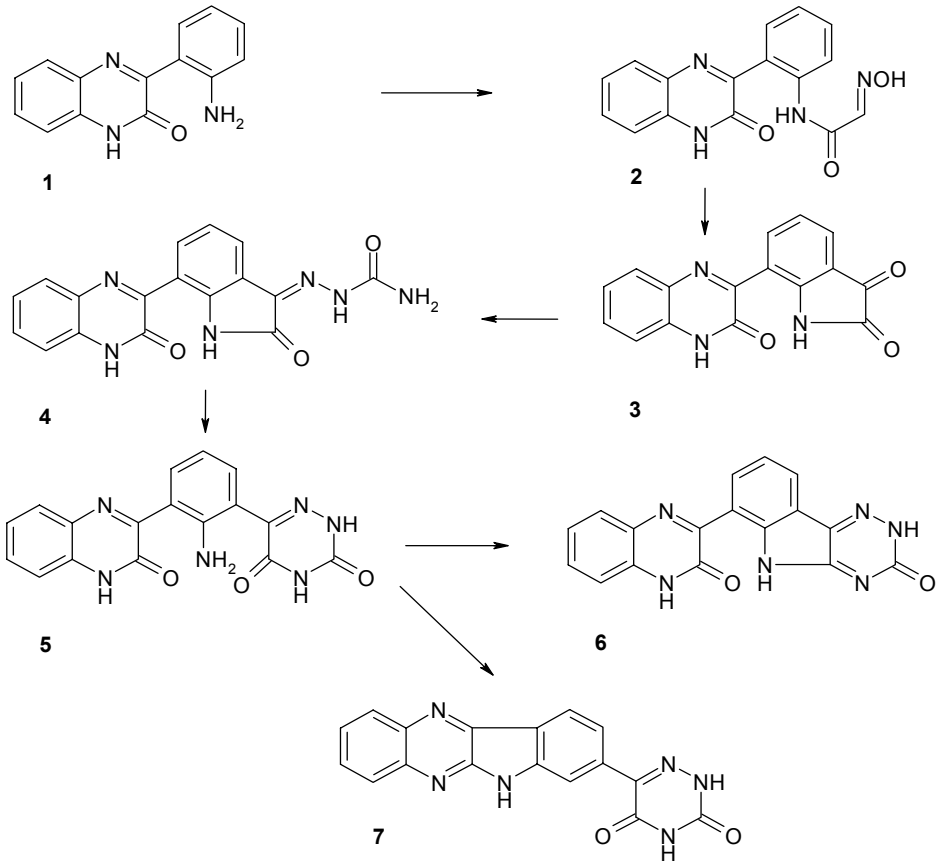
Department of Organic chemistry, Faculty of Science, Palacký University, Tr. Svobody 8, 771 46 Olomouc, Czech Republic, E-mail: rammon@postmaster.co.uk

In the context of our recent investigation [1,2] in the field of polycyclic heterocyclic N-H acids, we focused on compounds containing 6-azauracil and quinoxaline cycle.

3-(2-Aminophenyl)-quinoxalin-2-one (**1**) was transformed to corresponding isatine (**3**) by Sandmeyer method. Alkaline recyclization of its semicarbazone (**4**) afforded 1,2-dihydro-3-[2-amino-3-(6-azauracil-5-yl)-phenyl]-quinoxalin-2-one (**5**). Further we have studied cyclization of this compound to derivative (**6**) or to isomeric indolo [2,3-b] quinoxaline as well (**7**).



References:

[1] Bílek P. and Slouka J., *J. Heterocycl. Chem.* 39, 357 (2002)

[2] Hlaváč J., Buchtík R., Slouka J., Hradil P. and Wiedermannová I., *ARKIVOC* 2003, 22

SYNTHESIS AND REACTIONS OF BENZIMIDAZO[1,2-C][1,2,3]THIODIAZOLES

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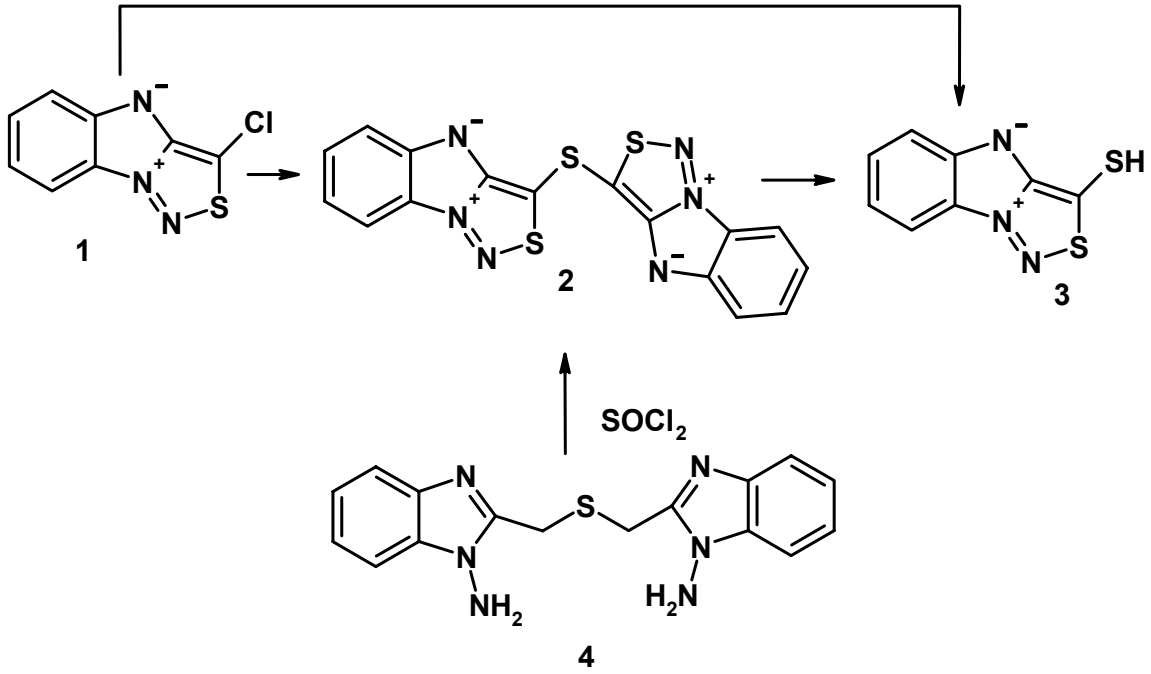
Department of Organic Chemistry,
Faculty of Chemistry, Vilnius University,
Naugarduko 24, 2006 Vilnius, Lithuania

1,2,3-Thiadiazole ring is a component of a large number of biologically active molecules [1]. Moreover, 1,2,3-thiadiazoles are widely used in the synthesis of heterocyclic compounds.

3-Chloro-4-benzimidazo[1,2-c][1,2,3]thiadiazole (**1**) was synthesised from (1-amino-1*H*-benzimidazol-2-yl)methanol or 2-chloromethyl-1*H*-benzimidazolyl-1-amine hydrochloride by treating with thionyl chloride (Hurd-Mori reaction [2]). Compound **1** was treated with various nucleophilic reagents. Surprisingly compound **2** was oftenly afforded instead of the expected products of nucleophilic substitution. Later compound **2** was synthesised from compound **4**. In some cases compound **3** was obtained from sulfide **2** or directly from compound **1.**



Some chemical properties of **1** and **2** were investigated and new derivatives were synthesised.

References:

1. Gommaa, Al.; Selhdar, M. *Alexandria J. Pharm. Sci*. **5**, 153 (1991).
2. Hurd, C. D.; Mori, I. R. *J. Am. Chem. Soc*. **77**, 5359-5364 (1955).

REACTION OF PROTOLYTIC FURAN RING OPENING FOR TETRACYCLIC INDOLE DERIVATIVES SYNTHESIS

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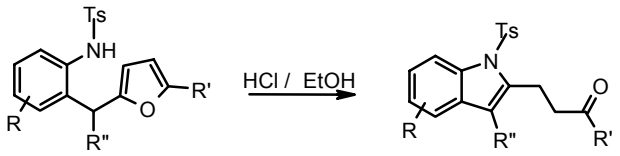
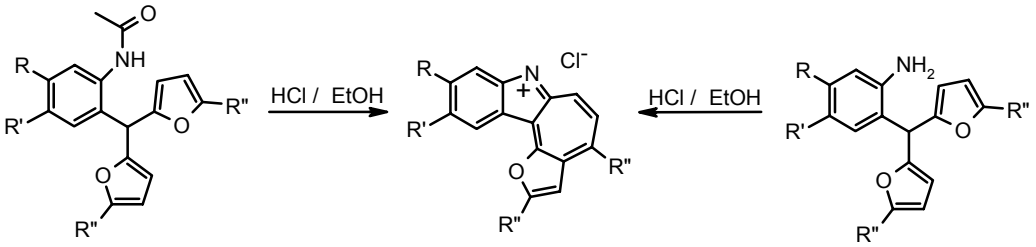
Earlier we showed that 2-tosylaminobenzylfurans were transformed into indoles under the action of HCl (gas) in ethanol [1]. In this reaction we have used the initial compounds containing the single furan ring and synthesized indoles bearing alkyl and aryl substituent at position 3 of indole system only.



R = H, Hal, OMe; R' = Me, Et; R" = Ar, Alk

To prepare indoles with furan ring at position 3 we have synthesized 2-aminoaryldifurylmethanes, which in turn were treated under above conditions. However our attempts were failed. But we found new approach to the tetracyclic indole derivatives synthesis from 2-acetylaminoaryldifurylmethanes. It is established that this transformation follows with acetyl protective group cleavage.



R=R'=H; R=R'=OMe; R=R'=OCH_2O; R=R'=OCH_2CH_2O; R = Br, R'=H; R"=Me, Et

We have proposed to use 2-aminoaryldifurylmethanes in the reaction and obtained the same results. Earlier we prepared the similar perchlorates by treatment 2-acylaminoaryldifurylmethanes with triphenylcarbenium perchlorate [2].

Acknowledgements: authors are grateful to *the Russian Foundation of Basic Research (RFBR)* for the financial support (grant 03-03-32759).

[1] Butin A.V., Stroganova T.A., Lodina I.V., Krapivin G.D., *Tetrahedron Lett.*, **2001**, *42*. 2031.

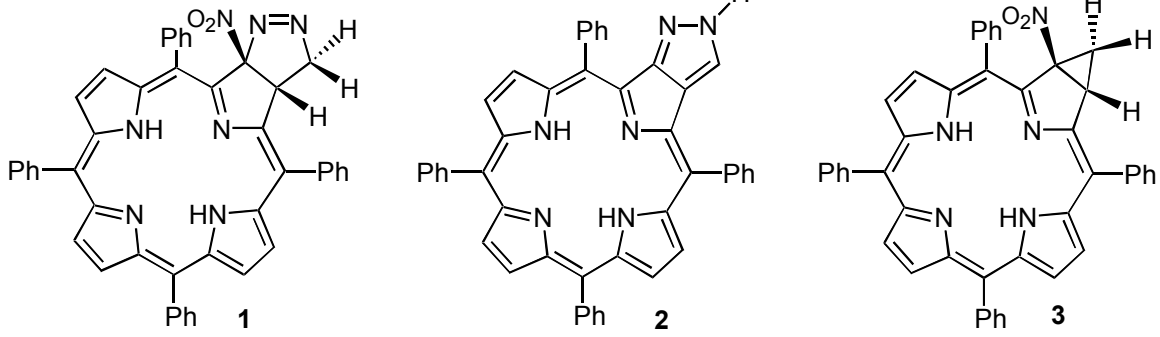
[2] Butin A.V., Stroganova T.A., Abaev V.T., Zavodnik V.E. *Khim. Geterotsikl. Soedin.* **1997**, 1614. [*Chem. Heterocycl. Compd.*, **1997**, *33*, 1393 *(Engl. Transl.)*].

SYNTHESIS OF NEW PYRAZOLINE / PYRAZOLE-FUSED TETRAPYRROLIC DERIVATIVES

A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves and J. A. S. Cavaleiro

Department of Chemistry, The University, 3810-193 Aveiro, Portugal

Porphyrin and chlorin (dihydroporphyrin) heterocycles are being used in the detection and treatment of neoplastic situations. Similar compounds have demonstrated promising applications as anti-bacterial/anti-virus agents. In such way new and more efficient molecules fulfilling certain structural features should become available for biological assessment. We are studying new synthetic routes leading to porphyrin derivatives; cycloaddition transformations are also being considered since the obtained adducts can become potential new drugs. We have shown that *meso*-tetraarylporphyrins can react as dienophiles and as dipolarophiles in Diels-Alder and other cycloaddition processes involving, respectively, reactive dienes (like *o*-quinodimethanes) [1] and 1,3-dipoles (like azomethine ylides and nitrones) [2,3]. Further studies were extended to the reactions of beta-nitroporphyrins with diazomethane as another 1,3-dipolar species. Pyrazoline-fused chlorin, pyrazole-fused porphyrin and methanochlorin type compounds (e.g., **1**, **2**, **3**) have been the isolated products. These results will be shown and discussed in this communication.



Acknowledgements:
Thanks are due to "Fundação para a Ciência e a Tecnologia -FCT" for funding (POCTI/1999/QUI/32851). One of us (AMGS) also thanks FCT for a PhD grant.

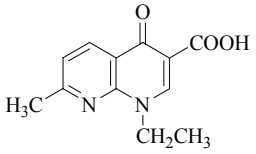
References:
[1] A. C. Tomé, P. S. S. Lacerda, M. G. P. M. S. Neves and J. A. S. Cavaleiro, *Chem. Commun*., 1997, 1199-1200
[2] A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva and J. A. S. Cavaleiro, *Chem. Commun.,* 1999, 1767-1768
[3] A. M. G. Silva, A. C. Tomé, M. G. P. M. S. Neves, A. M. S. Silva, J. A. S. Cavaleiro, D. Perrone and A. Dondoni, *Tetrahedron Lett*., 2002, **43**, 603-905

SOLVENT-FREE SYNTHESIS OF QUINOLONE DERIVATIVES USING MICROWAVE IRRADIATION.

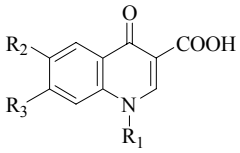
Petra Černuchová[a], Viktor Milata[a], Giang Vo-Thanh[b], André Loupy[b]

[a]Department of Organic Chemistry, Faculty of Chemical and Food Technology, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic
[b]ICMMO, Laboratoire des Réactions Sélectives sur Supports, Université Paris-Sud, Bât 410, F-914 05 Orsay-Cedex, France

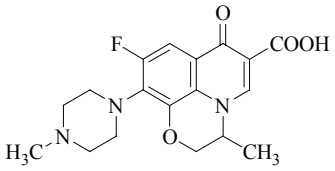
Nalidixic acid **1** and its quinolone analogues, for example oxolinic acid **2**, norfloxacin **3**, pefloxacin **4**, ciprofloxacin **5** and ofloxacin **6**, have been used for a long time for treatment of various bacterial infections (in urology, ophthalmology,...) [1]



1

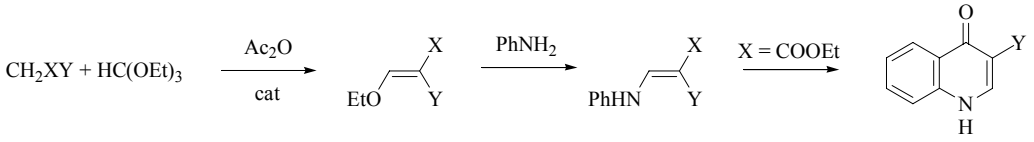


2 $R_1 = CH_2CH_3$, $R_2,R_3 = -CH_2-O-CH_2-$
3 $R_1 = CH_2CH_3$, $R_2 = F$, R_3 = 1-piperazinyl
4 $R_1 = CH_2CH_3$, $R_2 = F$, R_3 = 4-methyl-1-piperazinyl
5 R_1 = cyclopropyl, $R_2 = F$, R_3 = 1-piperazinyl



6

We present here the synthesis of the quinolone derivatives **11** under solvent-free microwave irradiation [2]. The solvent-free method is by far more efficient and constitutes an evident simplification of work-up and treatments within the frame of "Green Chemistry".



7 **8** **9** **10** **11**

X, Y = COOEt, COMe, CN

Alkoxymethylenemalonates **9** were prepared by condensation of triethyl-orthoformiate with activated ethylene derivatives (125°C, 15-120 min, 82-93%) [3]. The influences of the presence of acetic anhydride and catalyst (KSF montmorillonite, $ZnCl_2$) in the reaction were studied. The displacement of alkoxy group by nitrogen nucleophile produces a series of disubstituted aminoethylene derivatives **10** (70°C, 2 min, 90-99%). Intramolecular cyclization of **10** (X = COOEt) by Gould-Jacobs reaction [4] under microwave irradiation and by thermal cyclocondensation will be also presented.

This work was financially supported by Grant Agency of Slovak RepublicNo. 1/9254/02 and 1/0058/03.

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[2] a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D.; *Synthesis,* **1998**, 1213.
[3] Milata, V. ; *Aldrichimica Acta,* **2001**, *34*, 20.
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DNA FOLDING AND VISUALIZATION BY NOVEL POLYAMINE DERIVATIVES OF PTERIDINE

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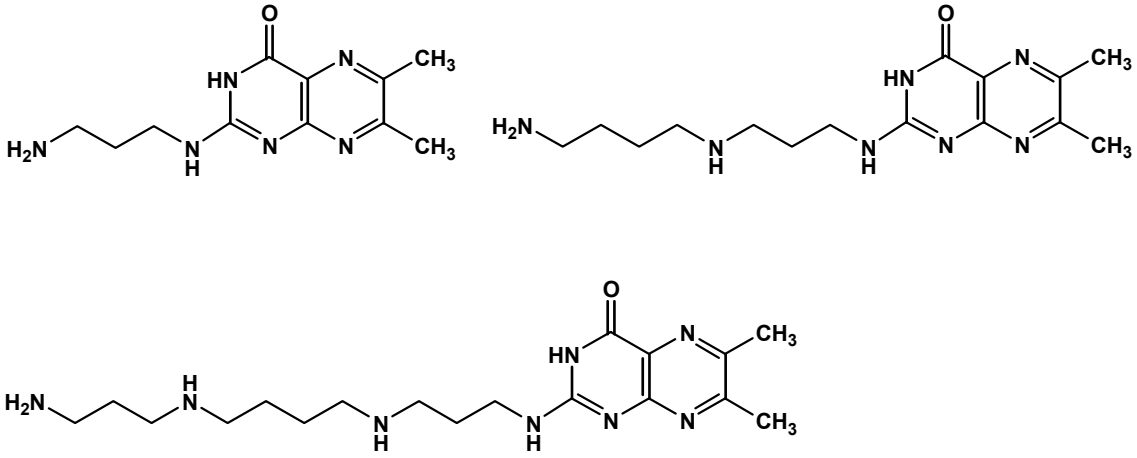
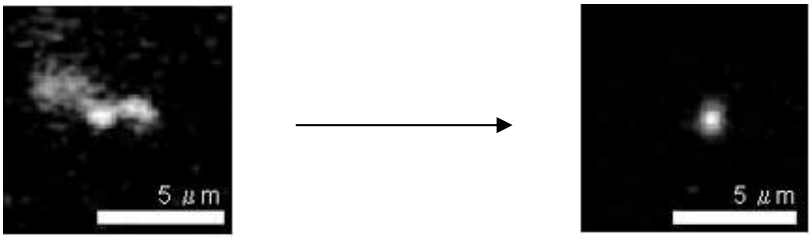
[a]Graduate School of Environmental Studies and CREST, JST (Japan Science and Technology), Nagoya University, Chikusa Nagoya, 464-8601 Japan
[b]Department of Physics, Kyoto University, Sakyo, Kyoto, 608-8501 Japan

Several types of polyamine derivatives of pteridine were synthesized by substitution on the 2-, 4-, or 6-position of pterin (2-amino-4-hydroxypteridine) with 1,3-diaminopropane, spermidine, and spermine. These compounds strongly interacted with DNA and fold the DNA molecule from the extended coil state to the compacted globule state. And, in addition, the compounds could selectively visualize the compacted DNA molecule without the help of a fluorescent dye in the fluorescent microscope observation.





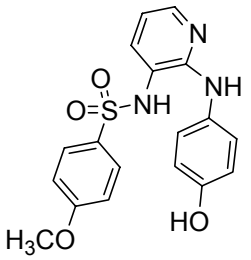
DNA coil **DNA Globule**

DESIGN AND SYNTHESIS OF CARBAZOLYLBENZENESULFONAMIDE DERIVATIVES AS POTENTIAL TARGETING CELL CYCLE INHIBITORS

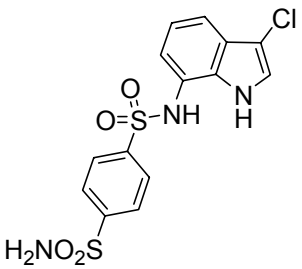
Grace Shiahuy Chen, Kuan-Yu Chen, Pei-Yu Chen, Feng-Yi Chen, Ji-Wang Chern*

School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

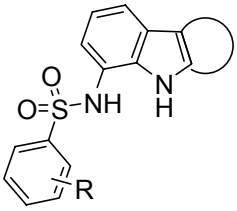
Intact components of cell cycle arrest checkpoints are potential targets for novel antineoplastics. Many antitumor agents act at multiple steps in the cell cycle. The sulfonamide derivatives have been shown to possess diverse biological activities such as antibacterial, insulin releasing, carbonic anhydrase inhibitory, and antihyroid. Various sulfonamide drugs were reported to interact with many kinds of cellular protein targets. The first antitumor sulfonamide, **E7010**, was found to cause cell cycle arrest and apoptosis in M phase and to demonstrate good antitumor activity.[1] Interestingly, the same group reported that the other related series of antitumor sulfonamides, *N*-(7-indolyl)benzenesulfonamides such as **E7070**, showed prominent antitumor activity targeting in G1 phase not in M phase.[2] In the course of our study, we designed and synthesized a series of carbazolylbenzenesulfonamides **I** as novel potential antitumor agents in which the hydrophobicity may be expected to be increased by expanding the 2 and 3 positions of **E7070**. It was hoped that these compounds could serve as new cell cycle inhibitors. The preliminary cytotoxicity assays of the target compounds exhibited potentiality against many cancer cell lines. More importantly, our designed carbazolylbenzenesulfonamide derivatives are almost all more potent than the corresponding indole derivative.



E7010
Targeting M phase



E7070
Targeting G1 phase



I
Potential cell cycle inhibitors

1. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitoh, K. *J. Med. Chem.* **1992**, *35*, 2496-2497.

2. Owa, T.; Yosihino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999**, *42*, 3789-3799.

ELECTROPHILE-INDUCED CYCLIZATION REACTIONS OF VINYLALLENIC SULFOXIDES AND SULFONES

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Department of Chemistry, University of Shoumen, BG-9700 Shoumen, Bulgaria
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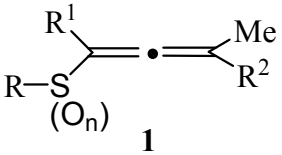
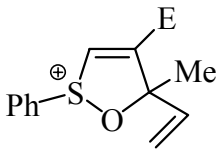
Results on the examined electrophile-induced cyclization reactions of the 3-methyl-1,2,4-pentatrienyl and 5-methyl-1,3,4-hexatrien-3-yl sulfoxides and sulfones **1**, possessing a vinyl group on the 1- or 3-place in the allenic system, will be discussed in the report [1]. We investigated the reactions with different electrophilic reagents such as chlorine, bromine, alkyl- or phenylsulfenyl chlorides and phenylselenenyl chloride. It has been established that a heterocyclization of vinylallenic system of double bonds proceeds in more cases. Halogenation of **1** occurs with formation of different products depending on the place of the vinyl group. We isolated the heterocyclic 4-halo-5-ethenyl-5*H*-1,2-oxathiol-2-ium salts **2** and **4** or the highly unsaturated 3-methylene-2-halo-1,4-pentadienyl sulfoxides and sulfones **3** and 3-halo-1,3,5-hexatriene-4-yl sulfones **5**. Reaction of vinylallenic sulfoxides and sulfones **1** with sulfenyl and selenenyl chlorides proceeds with oxathiolic (**2** and **4**), thiophenic (**6** and **7**) or selenophenic (**6** and **7**) heterocyclization depending on the kind of the electrophile and the place of the vinyl group.



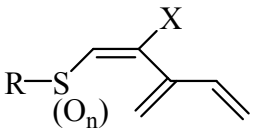
1

R = Ph, n = 1
R = Me, n = 2
R^1 = H, CH=CH_2
R^2 = CH=CH_2, Me



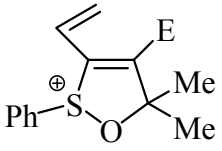
2

E = Br, SR, SePh



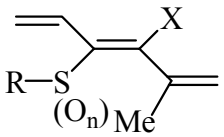
3

X = Cl, Br
R = Ph, n = 1
R = Me, n = 2



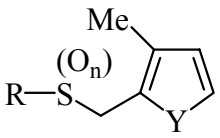
4

E = Cl, Br, SR, SeP



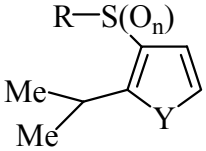
5

X = Cl, Br
R = Me, n = 2



6

R = Ph, n = 1
R = Me, n = 2
Y = S, Se



7

R = Ph, n = 1
R = Me, n = 2
Y = S, Se

Probable reaction schemes for formation of the above mentioned unsaturated and heterocyclic compounds will be discussed.

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THE SYNTHESIS OF NEW 2'R-2R_1-4R_2-5,4' DITHIAZOLES

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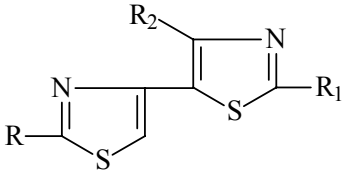
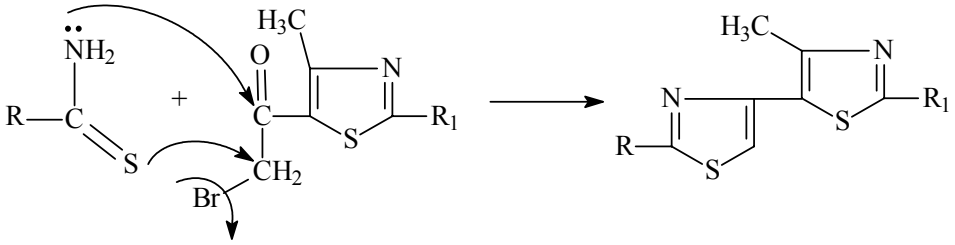
Department of Pharmaceutical Chemistry, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

Continuing our preocupations for the study of the poliheterocycle sistems with isolated rings, we proposed to obtain new series of 5,4'-dithiazoles with the following structure:



The obtaining of the compounds had been realized through Hantzsch reaction between 5-bromoacetyl-2R^1-4-methyl-thiazole as α-halocarbonil compound and various thioamides compounds.



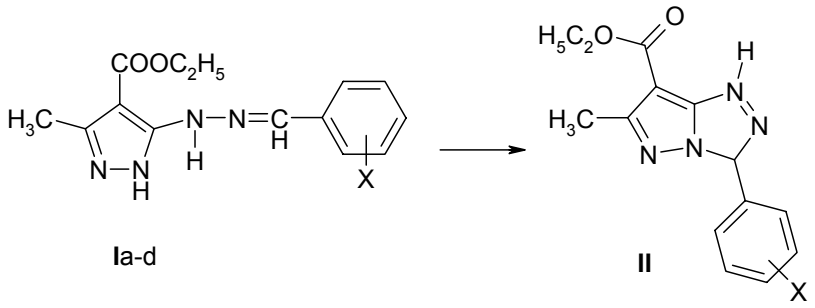
Structural analysis of our dithiazoles was realized by ^{1}HRMN and mass spectrometry.

ELECTROCHEMICAL PROPERTIES OF SOME 1H - 3 - METHYL - 4 - ETHOXYCARBONYL - 5 - SUBSTITUTED - ARYLIDENEHYDRAZONO - PYRAZOLES

Liviu Virgil Costea[a], Vasile Bercean[a], Valentin Badea[a], and Ioan Ţăranu[b]

[a]University "Politehnica" Timişoara, Faculty of Industrial Chemistry and Environmental Engineering, 1900 Timişoara, Romania
[b]National Institute for Research and Development in Electrochemistry and Condensed Materials Timişoara, 1900 Timişoara, Romania

1H-3-methyl-4-ethoxycarbonyl-5-substituted-arylidenehydrazono-pyrazoles (I) are key intermediates in obtaining 1H-3-aryl-6-methyl-7-ethoxycarbonyl-pyrazolo[5,1-c][1, 2, 4]triazoles (II). The latter are used in obtaining color photographic light sensitive materials, toners and ink jet printer dyes.
In the presence of bromine and sodium acetate in glacial acetic acid, the hydrazones (I) substituted with -NO_2, -Cl, and methyl yield the corresponding pyrazolo-triazoles (II) [1]. If the starting materials contain substituents like -OH and -OCH_3 respectively, the brominated pyrazolo triazoles (II) are formed [2].
In order to obtain -OH and -OCH_3 substituted pyrazolo triazoles without the bromine attached to the benzene ring, we investigated the electrochemical properties of 1H-3-methyl-4-ethoxycarbonyl-5-benzylidenehydrazono-pyrazole (Ia) [3] in order to accomplish the anodic cyclisation of the latter compound.
In this paper we present the voltammetric behaviour of 1H-3-methyl-4-ethoxycarbonyl-5-substituted-arylidenehydrazono-pyrazoles (I) in nonaqueous media, having the following substitutents attached to the benzene ring: 4-$N(CH_3)_2$, 4-OH, 4-OCH_3 and 3-OH respectively.
The synthesis of the 1H-3-methyl-4-ethoxycarbonyl-5-substituted-arylidenehydrazono-pyrazoles (I) has been carried out according to an own method [4].



Ia-d II

Selective references:

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[2] Carol Csunderlik, Vasile Bercean*, Francisc Peter, Valentin Badea *ARKIVOC* 2002 (ii) 133-141 http://arkat.org./arkat/
[3] 11th Physical Chemistry Conference, Timişoara ROMANIA, september 2-5,2003
[4] Vasile Bercean – unpublished results.
[5] G. M. Abou-Elenien, N. A. Ismail, A. A. El-Maghraby, and G. M. Al-abdallah, Electroanalysis 2001, 13, 1022.
[6] X. Wei, B. Speiser, Electrochimica Acta, 1997, 42, 73.

RHODIUM (II) CATALYZED INTRAMOLECULAR INSERTION OF CARBENOIDS DERIVED FROM 2-PYRROLYL α-DIAZOALKANONES AND α-DIAZO-β-KETOESTERS.

Erick Cuevas-Yañez,[a] Joseph M. Muchowski[b] and Raymundo Cruz-Almanza[a]

[a]Instituto de Química,UNAM. Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.
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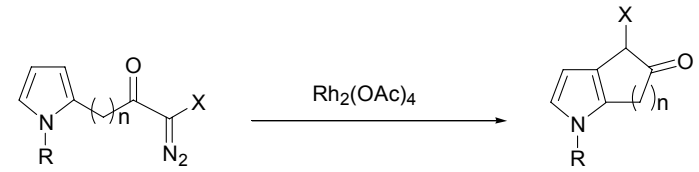
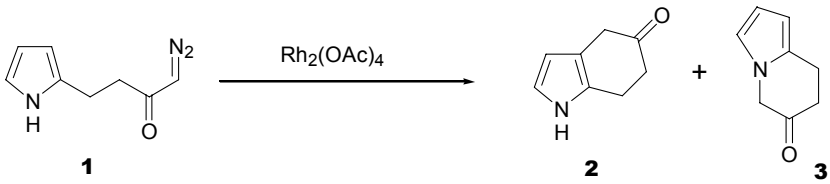
The rhodium (II) catalyzed processes using N-pyrrolyl-α-diazoketones as carbenoid precursors have been utilized to synthesize several naturally occurring indolizine derivatives [1]. Nevertheless there are few examples about the insertion of α-keto carbenoids into the C-3H bond of pyrroles [2].

Exposure of several α-Diazoketones and α-diazo-β-ketoesters derived from 2-pyrrolylacetic and 2-pyrrolylpropionic acids to catalytic amounts of rhodium (II) acetate in dichloromethane solution at room temperature or 1,2-dichloroethane at reflux, rapidly produced. C-3 subtituted bicyclic ketones as the only isolable products in 50-70% yields.

In contrast, the α-diazobutanone **1** gave a mixture of ketones **2** (30% yield) and **3** (15% yield) derived from intramolecular insertion into the C-3H and N-H bonds of the pyrrole ring. This product ratio was independent of both the reaction temperature and the catalyst concentration.





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1. (a) Jefford, C.W.; Kubota, T.; Zaslona, A.; *Helv. Chim. Acta*, **1986**, *69*, 2048. (b) Jefford, C.W.; Tang, Q.; Zaslona, A.; *Helv. Chim. Acta*, **1989**, *72*, 1749. (c) Jefford, C.W.; Tang, Q.; Zaslona A.; *J. Am. Chem. Soc*., **1991**, *113*, 3513. (d) Jefford, C.W.; Wang, J.B.; *Tetrahedron Lett*., **1993**, *34*, 3119.
2. Capretta, A.; Salim, M.; *Tetrahedron*, **2000**, *56*, 8063.

THE SYNTHESIS OF METHOXYBRASSENIN B DERIVED NUCLEOSIDE ANALOGS

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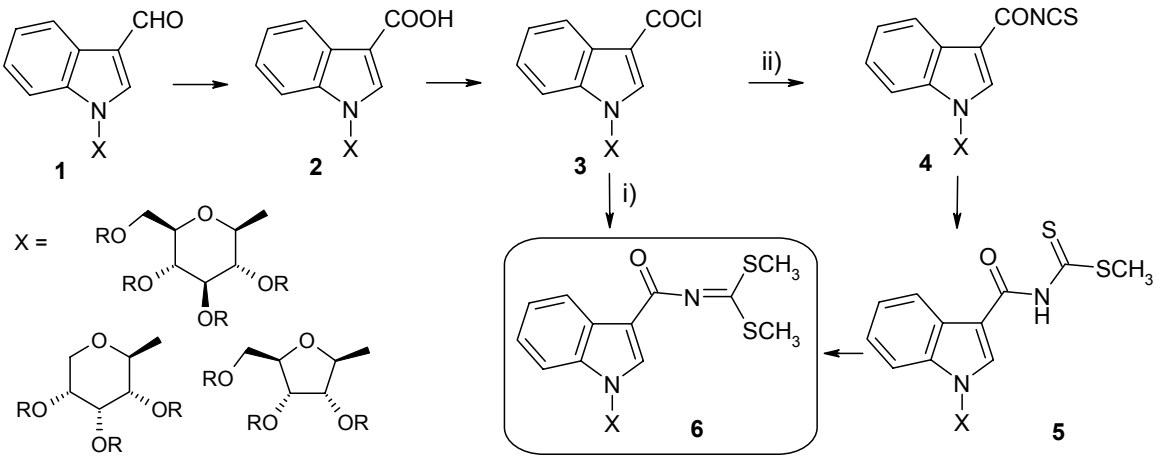
Institute of Chemical Sciences, Faculty of Science, P. J. Šafárik University, Moyzesova 11, 041 67 Košice, Slovak Republic

Indole nucleosides, for example rebeccamycin and its analogs, represent a rare type of natural products with interesting biological properties [1,2]. Very recently 1-(β-*D*-glucopyranosyl)camalexin, the first naturally occurring indole phytoalexin derived nucleoside analog has been isolated as a detoxification product of indole phytoalexin camalexin, produced by fungus *Sclerotinia sclerotiorum* [3]. The linear synthesis of a new type of 1,3,7-trideaza analogs of purine nucleosides derived from β-*D*-glucopyranose, β-*D*-ribopyranose, β-*D*-ribofuranose and indole phytoalexin methoxybrassenin B [4] (**6** X=OMe) will be presented, using hitherto not described ribopyranosyl- and ribofuranosylindole-3-carboxaldehydes (**1**) and indole-3-carboxylic acids (**2**) as a key intermediates. In these syntheses two synthetic pathways has been studied: i) acylation of methyl(methylsulfanyl)methanimidothioate with acyl chlorides **3**; ii) transformation of chlorides **3** to acyl isothiocyanates **4** and their treatment with NaSH and CH_3I, followed by methylation of **5**.



for **1**-**5** R=Ac, for **6** R=Ac or H

[1] Nettleton DE, Doyle TW, Kirshnan B, Matsumoto GK, Clardy J (1985) Tetrahedron Lett **26**: 4011
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[3] Pedras MSC, Ahiahonu PWK (2002) Bioorg Med Chem **10**: 3307
[4] Monde K, Sasaki K, Shirata A, Takasugi M (1991) Phytochemistry **30**: 3921

SYNTHESIS OF NEW TRICYCLIC SPIROBISPIDINES VIA RING CLOSING METATHESIS REACTION

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Institute of Applied Synthetic Chemistry
Vienna University of Technology
Getreidemarkt 9/163, 1060 Vienna, Austria
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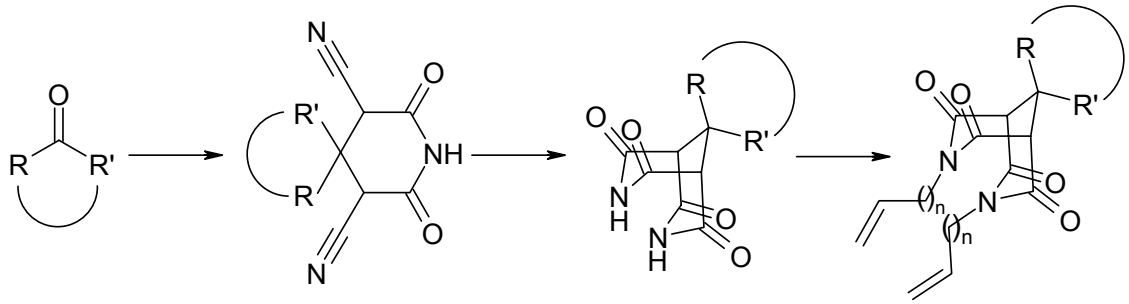
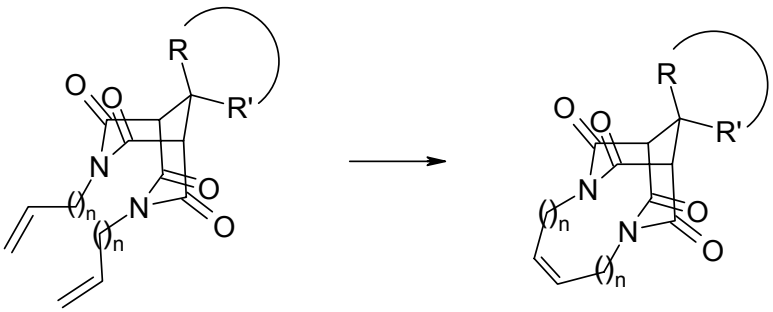
The synthesis of new tricyclic spirobispidines via Ring Closing Metathesis Reaction (RCM) of N,N'-disubstituted Spirobispidines carrying terminal double bond substituents is described.

Starting from a cyclic ketone, a Guareschi reaction followed by an acidic hydrolysis led to a spirotetraoxo bispidine, which subsequently was N-alkylated:



Ring Closing Metathesis was carried out at the tetraoxo stage varying the reaction conditions (e.g. conventional heating *vs.* microwave heating) and the chain lengths of the olefins:



Yields and selectivities of the compounds thus obtained dependent on the reaction conditions will be discussed.

RUTHENIUM-CATALYZED FORMATION OF PYRANE-2-ONE AND THIOPYRANE-2-THIONE - A THEORETICAL STUDY

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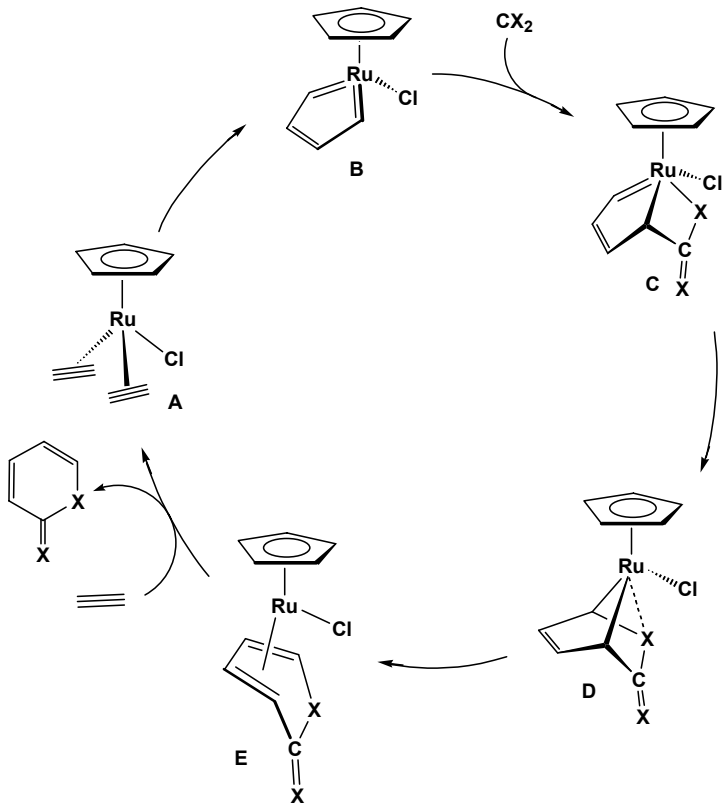
Itoh and coworkers have shown [1] that RuCp*(COD)Cl is an efficient catalysts for the coupling of 1,6-diynes and CS_2 to yield thiopyrane-2-thiones. In the present contribution a complete catalytic cycle for the coupling of acetylenes with CO_2 and CS_2 [2] catalyzed by the CpRuCl fragment is proposed and discussed based on DFT/B3LYP calculations. Thereby a couple of uncommon intermediates are suggested. A key species is the metalla-cyclopentatriene complex **B**, generated through oxidative coupling of two alkyne ligands. This complex adds both CO_2 and CS_2 directly to the Ru=C bond. Two successive intermediates could be located for the subsequent formation of pyrane-2-one and thiopyrane-2-thione. The unusual five and four-membered bicyclic ring system **D** which undergoes reductive elimination to form via **E** the title compounds. The conversion of **D** to **E** is the rate determining step of the overall catalytic cycle requiring activation energies of 28.1 and 17.7 kcal/mol for CO_2 and CS_2, respectively. Thus the formation of pyrane-2-one is much more difficult.



[1] Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 28.
[2] Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F.; *J. Am. Chem. Soc.* **2003**, *125*, submitted for publication.

EFFECT OF METAL COORDINATION AND MICROWAVE IRRADIATION ON SELECTIVE CYCLOADDITION LEADING TO HETEROCYCLIC COMPLEXES

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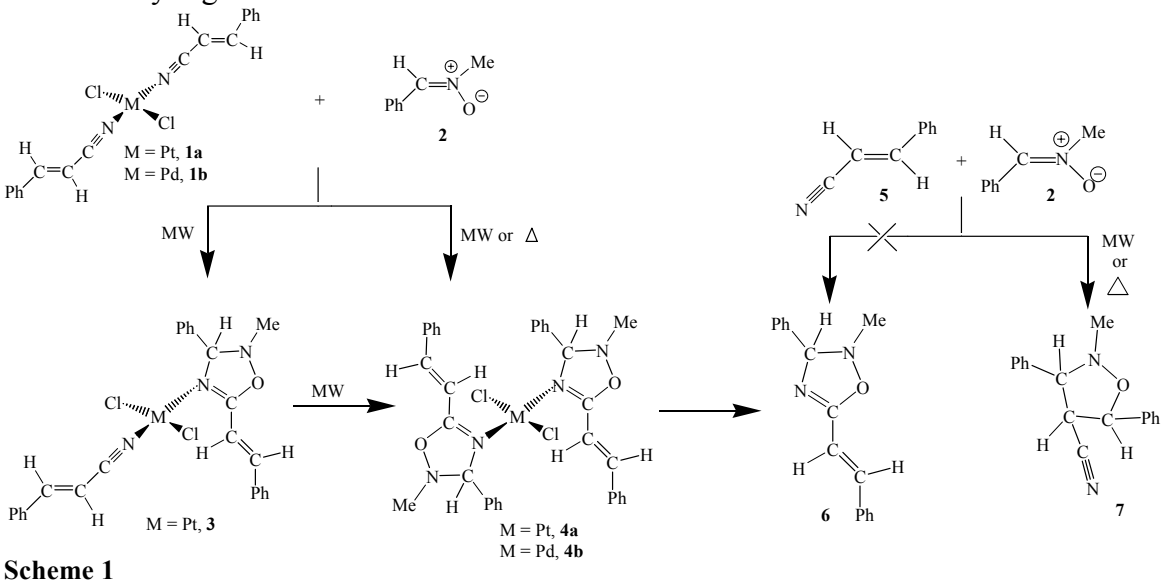
[1]Institute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria.
[2]The Oratory School, Woodcote, Reading, Berkshire RG8 0PJ, United Kingdom.
[3]Chemistry, University of Surrey, Guildford, Surrey GU2 7XH.
Email: [1] bimbisar.desai@uni-graz.at, [3] G.Wagner@surrey.ac.uk

Many organic molecules are not sufficiently reactive and require use of activating agents like Lewis acids. Activation of such organic molecules can be done by their coordination to a metal centre (M) [1]. In this context, Platinum (Pt) and Palladium (Pd) complexes have proven useful in studying important transformations like [2+3] cycloaddition of nitrones to metal coordinated nitriles leading to synthetically important heterocycles viz. Δ^4-1,2,4-oxadiazoline complexes [2]. In our studies, we found that coordination of organic molecules to metal centres does not only change the reactivity of the functional groups but also modifies the selectivity of the reactions. In bifunctional organonitriles such as *E*-cinnamonitrile **5**, the selectivity of the cycloaddition switches from across the C=C bond of the free organonitrile to an exclusive reaction across the C≡N bond in the metal-mediated case (see Scheme 1). Microwave irradiation does not change the chemoselectivity with respect to the thermal reaction but notably accelerates cycloadditions both under uncoordinated and metal mediated cases. Moreover, the stepwise cycloaddition to the metal complex becomes more pronounced in microwave conditions, thus allowing for the selective synthesis of the mono-cycloaddition product **3**. The newly formed ligands by cycloaddition on metal mediated organonitriles could be easily displaced, allowing an easy method for the preparation of heterocycles of substitution patterns that were not previously accessible by organic methods.



Scheme 1

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SYNTHESIS OF ENANTIOMERICALLY PURE 5,5-DISUBSTITUTED 2-AZABICYCLO[2.2.1]HEPTANE DERIVATIVES

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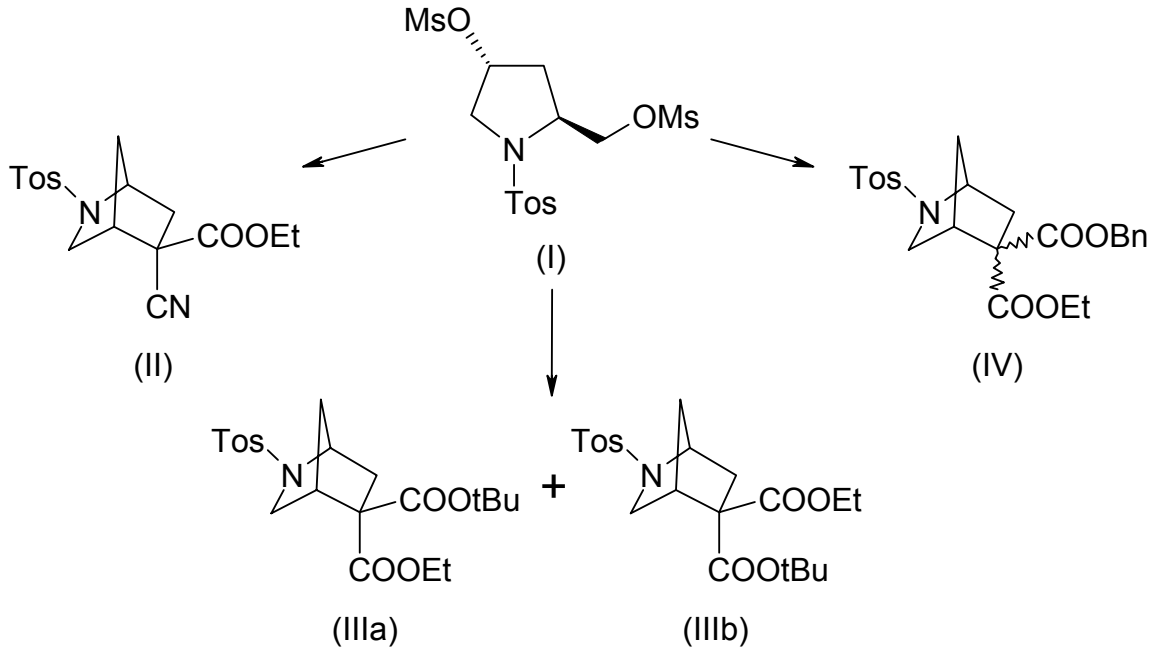
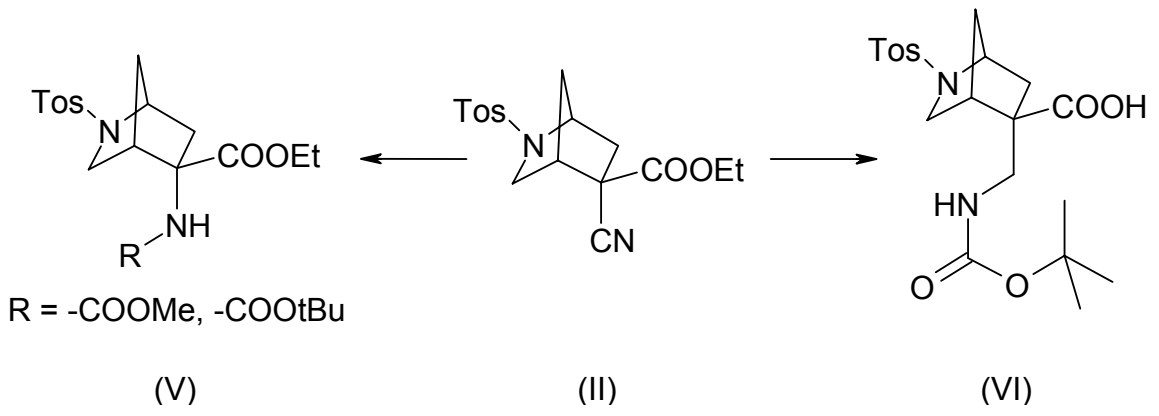
The synthesis of 2-azabicyclo[2.2.1]heptane derivatives (II – IV) from N-tosyl-hydroxyprolinol dimesylate (I) by cyclisation with malonic acid derivatives is described. Optimized reaction conditions and crystal structures of the resulting products (II, IIIa) are shown.



Starting from (II) the synthesis of bicyclic α- and ß-amino acids (V, VI) of potential biological interest is illustrated.



CYCLISATION REACTIONS GIVING 5,5-DIMETHYL-2-PHENYLIMIDAZOLIN-4-THIONES AND 4,4-DIMETHYL -2 -PHENYLTHIAZOLIN-5-ONES

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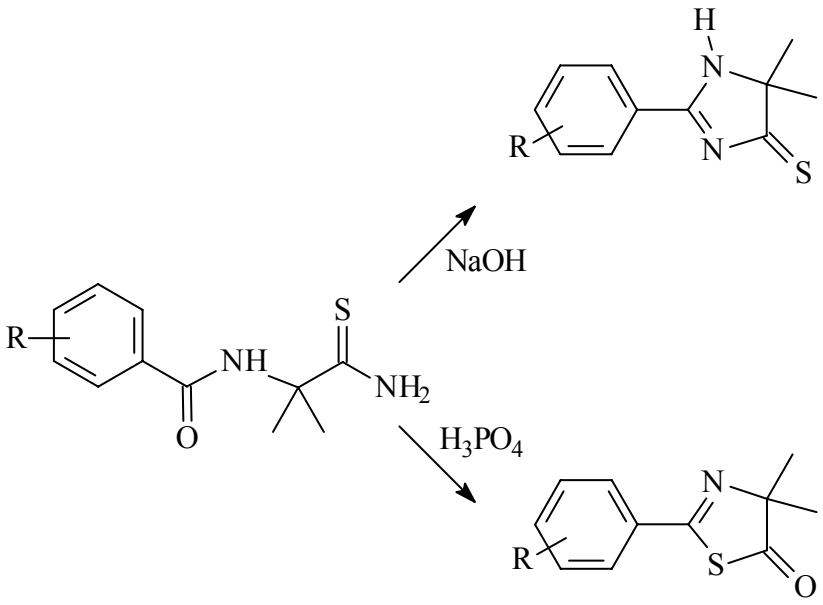
Six substituted 2-benzoylamino-2-methyl-thiopropanamides have been prepared and their ring-closure reaction studied in basic and strongly acid media. In bases the ring closure takes place at the terminal nitrogen atom of thioamide group to give the corresponding 5,5-dimethyl-2-phenylimidazoline-4-thiones, while in strongly acid medium the reaction involves the sulphur atom to give the substituted 4,4-dimethyl-2-phenylthiazolin-5-ones (Scheme 1). The 5,5-dimethyl-2-phenylimidazoline-4-thiones are stable in both acid and base media. The 4,4-dimethyl-2-phenylthiazolin-5-ones undergo hydrolysis to 2-methyl-2-thiobenzoylamino-propionic acids. The mechanism of ring closure in basic medium has been studied in detail: its rate-limiting step is the decomposition of tetrahedral intermediate [1].



Scheme 1

Acknowledgement: The authors thank to Ministry of Education, Youth and Sports of the Czech Republic (project No. CI MSM 253 100 001) for financial support.

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SYNTHESIS OF 2,4,6,8,10,12-HEXANITRO-2,4,6,8,10,12-HEXAAZAISOWURTZITANE (CL-20, HNIW)

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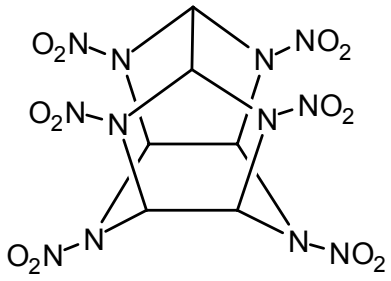
Increasing of explosive charge performance is a permanent trend. Performance characteristics of energetic materials are very dependent on the material density, that is why the research in the area of individual compounds with high energy nearly entirely focuses on the substances with high density (High Energy/Density Materials). The compounds with three-dimensional cage structure are at present as the most perspective substances in this way. 2,4,6,8,10,12-Hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW, CL-20) is their typical representative.
Synthesis route of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane is described. HNIW was prepared by 3-step reaction. The basic cage structure of isowurtzitane (HBIW) was prepared at the first step. Intermediate TADFIW was synthesised by reductive debenzylation of HBIW using of hydrogen, acetanhydride and formic acid. HNIW was prepared by nitrolysis of TADFIW at the last step of this process.



HNIW (CL-20)

STEREOSELECTIVITY OF D-ERYTHROSE DERIVED NITRONE CYCLOADDITIONS IN THE PRESENCE OF LEWIS ACIDS

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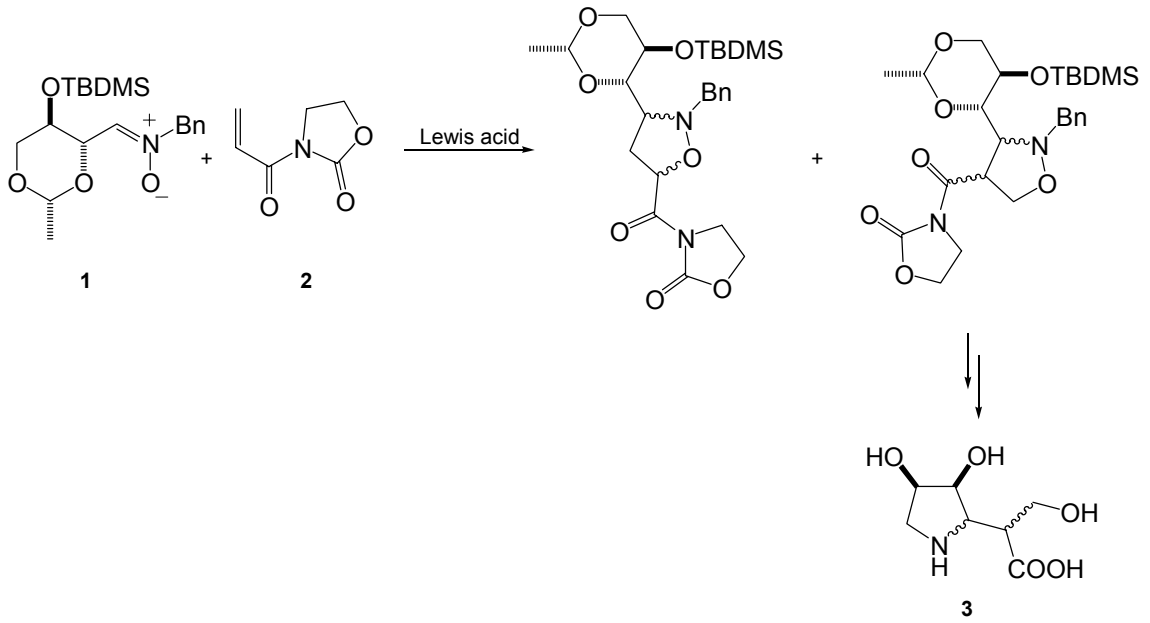
The way of classical 1,3-dipolar cycloadditions between nitrones and alkenes has been changed in last decade, the numerous works dealing with the Lewis acid catalysis have been published [1]. On the other hand, the cycloadditions of *C*-chiral sugar derived nitrones in the presence of Lewis acids remain unexplored.
Recently 1,3-dipolar cycloadditions of nitrone **1** in the absence of any Lewis acids were realized [2]. With our continuing effort to utilize chiral 1,3-dipolar cycloadditions we report the influence of Zn(II), Mg(II), Ti(IV) Lewis acids on regio- and the diastereoselectivity of the cycloaddition between acrylamide **2** and D-erythrose derived nitrone **1**. The cycloadducts thus obtained are interesting synthetic building blocks and were utilized in the synthesis of polyhydroxylated pyrrolizidine **3**.



1 2 3

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THE SYNTHESIS OF 1,2,3-THIADIAZOLE DERIVATIVES

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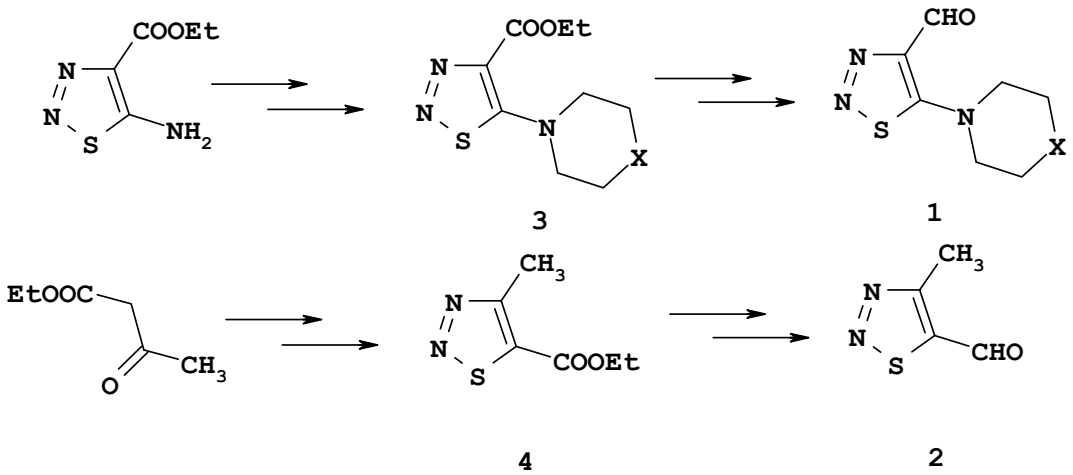
1,2,3-Thiadiazoles are known to be useful synthons in organic synthesis. Very active cotton defoliant and plant activator were found among them recently [1-3]. In the course of our research work we were interested in functionalized 1,2,3-thiadiazoles as potential fungicides.

Herein we report the synthesis 1,2,3-thiadiazolecarbaldehyde derivatives **1, 2**. The 5-amino-thiadiazoles **3** were prepared in our previsions work [4]To prepare 1,2,3-thiadiazole **4** we used Hurd and Mori reaction.



The carbaldehyde **1,2** were prepared by several methods. The details and more examples will be presented on the poster.

We thank the US Civilian Research and Development Foundation (REC-005) and the Russian Foundation for Basic Research (Grant 02-03-96421a) for financial support of this work.

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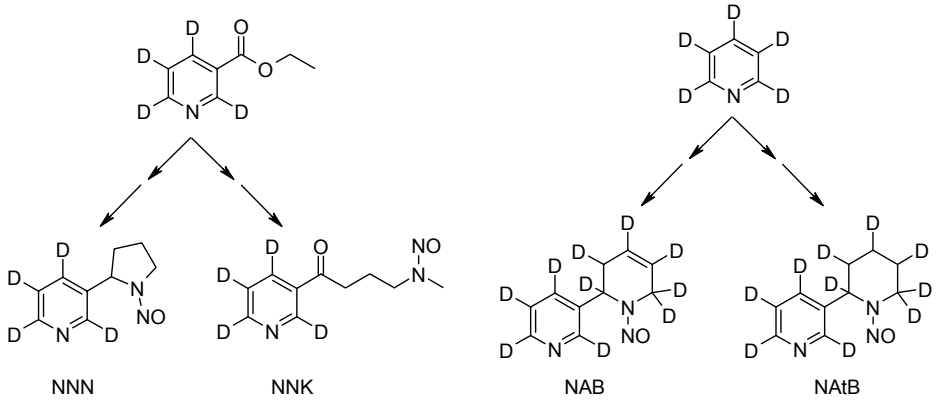
SYNTHESIS OF PARTIALLY DEUTERATED N-NITROSOAMINES - STANDARDS IN TOBACCO SMOKE ANALYSIS AND TRANS-3´-HYDROXYCOTININE-O-GLUCURONIDE – A MAJOR NICOTINE METABOLITE

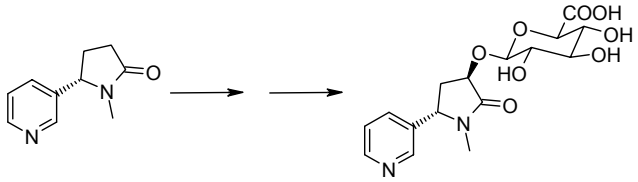
Peter Gärtner, Katharina Bica and Christian Einzinger

Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria

Abstract. Concerning the toxicity of major tobacco-specific N-nitrosoamines, their partially deuterated derivatives can be highly useful standards in tobacco smoke analysis and for the measurement of their carcinogenic and mutagenic activity after incorporation.
Starting from commercially available deuterated d_4-nicotinic acid ethyl ester, racemic d_4-N-nitrosonornicotine (NNN) and d_4-4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) were synthesized in 5 and 3 steps in an overall yield of 45 and 30%, respectively [1],[2].
In order to obtain d_{10}-N-nitrosoanatabine (NAB) and d_{10}-N-nitrosoanabasine (NAtB) we started from d_5-pyridine and lithium aluminum deuteride. A major step in this reaction pathway was the oxidation of the initially formed lithium tetrakis-(N-dihydropyridyl)aluminate (LDPA) [3].



As a major nicotine metabolite found in the urine of tobacco users, trans-3´-hydroxycotinine-O-glucuronide is a useful standard for metabolic studies. First results of the synthesis, starting with optically pure (-)-cotinine via asymmetric hydroxylation [4], will be presented.



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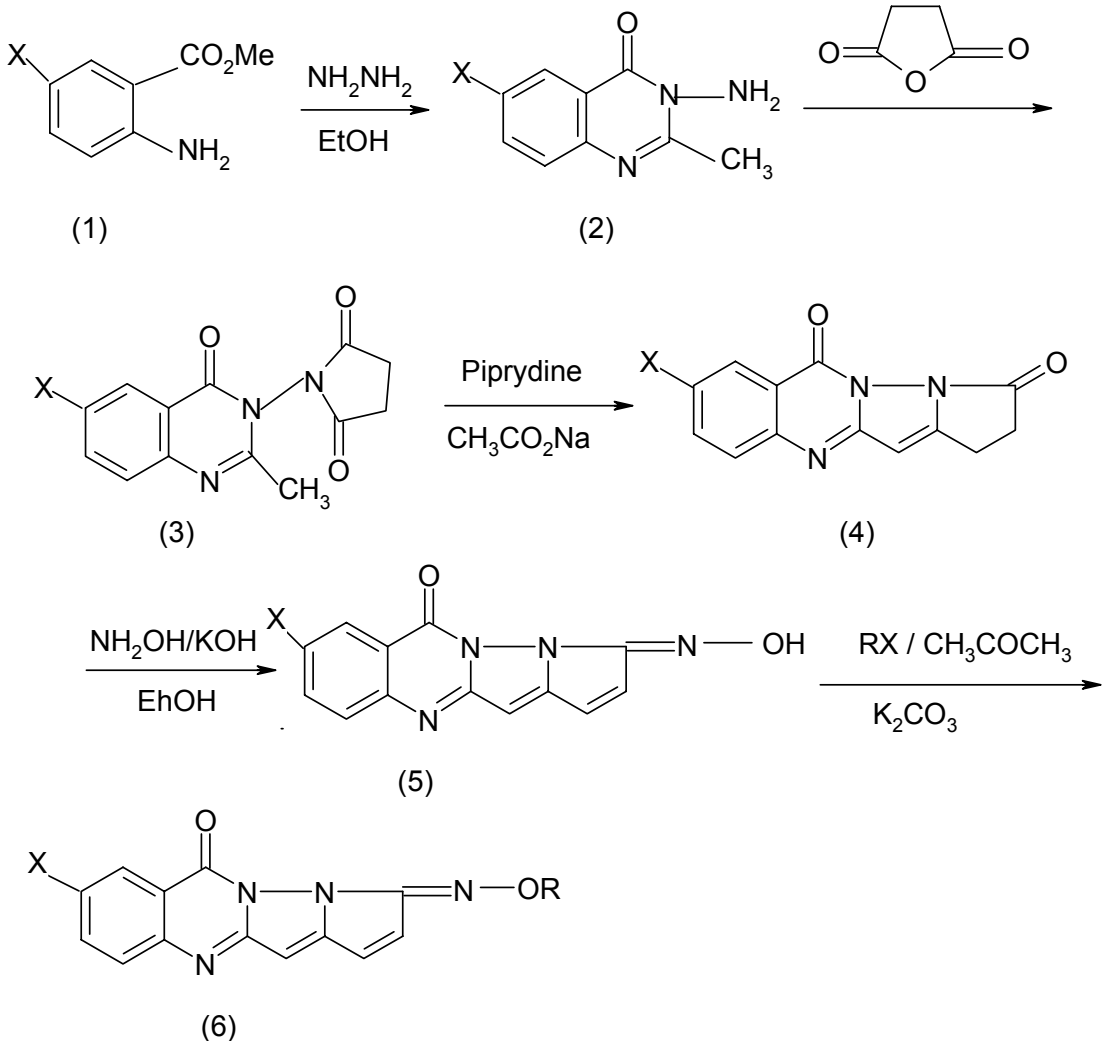
SYNTHESIS OF TETRACYCLIC ANTIDEPRESSANT ANALOGOUS

Ahmed M.El-Khawaga, M.M.Kandeel, and Walid El-Sayed

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

The tetracyclic antidepressant analogous (6) were synthesize according to the following to the following scheme:



HETEROCYCLES FROM CARBOHYDRATE PRECURSORS: STUDIES ON DEHYDRO-L-ASCORBIC ACID HYDRAZONES: CONVERSION INTO TRIAZOLE, PYRAZOLE, QUINOXALINE AND ISOXAZOLINE DERIVATIVES.

M.A. El-Sekily and S.H. Mancy

Department of Chemistry, faculty of Science, University of Alexandria, Ibrahimia, P.O. Box: 426, Alexandria, 21321, Egypt. E-mail ElSekily@hotmail.com

Much attention has been made for the synthesis of heterocyclic compounds in the quest for new chemotherapeutic drugs. This attracted our attention – and in continuation of our work – to the synthesis of some triazole, pyrazole, quinoxaline and isoxazoline derivatives form dehydro-L-ascorbic acid and from D-glucose. Thus, 2-arylhydrazone-3-oximes of dehydro-L-ascorbic acid were converted into triazole derivatives upon treatment with dehydrating agent. In the same time dehydro-L-acid 2-arylhydrozones were converted into olefinic derivatives upon treatment with Ac_2O or with benzoyl chloride, and these were converted into 4,5-pyrazolinedione pyrazole derivatives upon treatment with arylhydrazines. Reaction of equimolar amounts from dehyro-L-acorbic acid, o-phenylenediamine and arylhydrazine gave quinoxialine hydrzones that were converted into chloroquinoxaline pyrazole derivatives. These were converted into a number of heterocycles upon treatment with hydrazine, arylhydrazines or thiosemicarbazide. Sodium borohydride reduction of 2-arylhydrazones of dehydro-L-ascorbic acid at low temperature gave the bicyclic 3,6-anhydro derivatives. Pyrazole-thiadiazoline and triazolo pyrazole derivatives were obtained form dehydro-L-ascorbic acid 2-arylhdydrazones-3-thiosemicarbazones. D-Glucose reacted with p- sulphamylphenylhydrazine, afforded the bishydrzones that were converted into triazole derivatives.

NEW METODS FOR SYNTHESIS OF 1-SUBSTITUTED-1,2-ALKADIENEPHOSPHONATES

Dobromir D. Enchev

"Bishop Konstantin Preslavsky" University , Faculty of Natural Sciences, Department of Organic Chemistry and Technology, 9700 Shumen, Bulgaria

The high unsaturated organophosphorus compounds are good precursors for synthesis of variety of cyclic compounds, which have direct application as growth regulators on the agriculture plants. The heterocyclization of the 1, 2-alkadienephos-phonates is one of the most convenient ways for obtaining of the cyclic organophos-phorus compounds with remarkable physiological activity. The modification of the starting compounds i.e. 1, 2-alkadienephosphonates, is one of the ways, leading to cyclic compounds with structures known in advance.

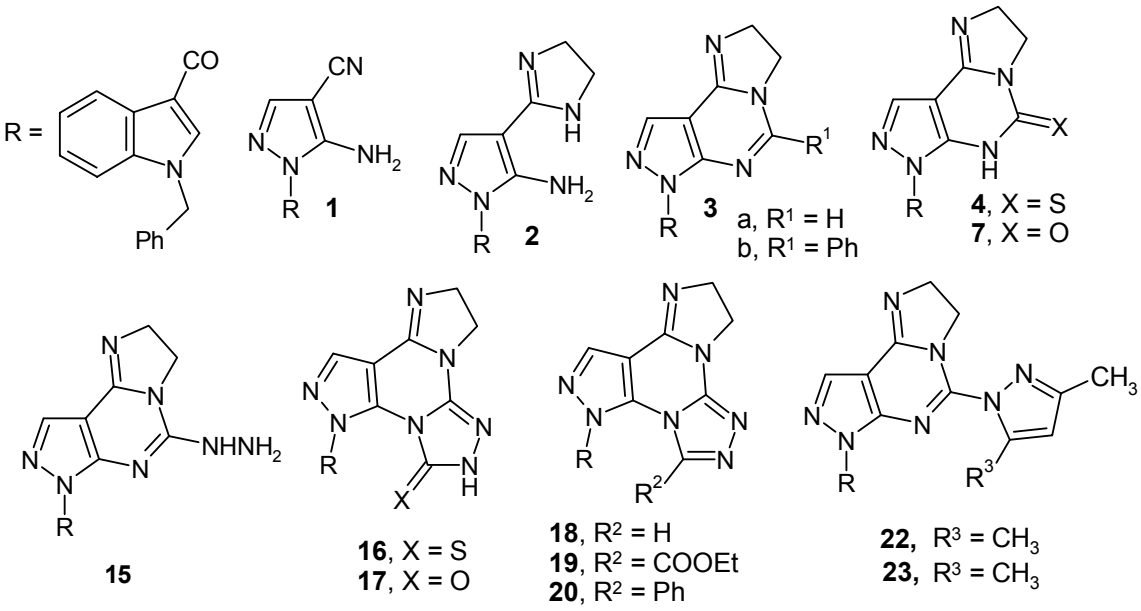
The article described some new and high effective methods for preparation of 1-sub-stituted-1, 2-alkadienephosphonates.

SYNTHESIS OF SOME IMIDAZO[1,2-C]PYRAZOLO[4,3-E] PYRIMIDINES DERIVED FROM INDOLE RING AND RELATED HETEROCYCLES OF POTENTIAL PHARMACEUTICAL INTEREST

H. S. El-Kashef and A. A. H. Farghaly

Chemistry Department, Faculty of Science, Assiut University, Assiut-Egypt

The starting material **2** was prepared by the reaction of amino nitrile derivative **1**[1] with ethylenediamine in the presence of a catalytic amount of carbon disulfide [2]. Compound **2** could be ring closed to the tricyclic system imidazopyrazolopyrimidine in different ways. Thus, compound **2** was allowed to react with triethylorthoformate, carbon disulfide, 1,1`-carbonyl diimidazole (CDI) and benzaldehyde to afford the corresponding imidazopyrazolopyrimidine derivatives **4-6**. While its reaction with sodium nitrite afforded the imidazopyrazoltriazine **7**. The interaction of the thione derivative **4** with hydrazine hydrate gave the corresponding hydrazine compound **15**. This latter **15** was incorporated into pyrazolo- and triazolo derivatives **16-23**. The biological evaluation of newly synthesized compounds is in progress.



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ISOXAZOLIDINYL SPIRO NUCLEOSIDES: 1,3-DIPOLAR CYCLOADDITIONS OF 7-METHYLENEPYRROLO [1,2-C]PYRIMIDIN-1(5H)-ONES

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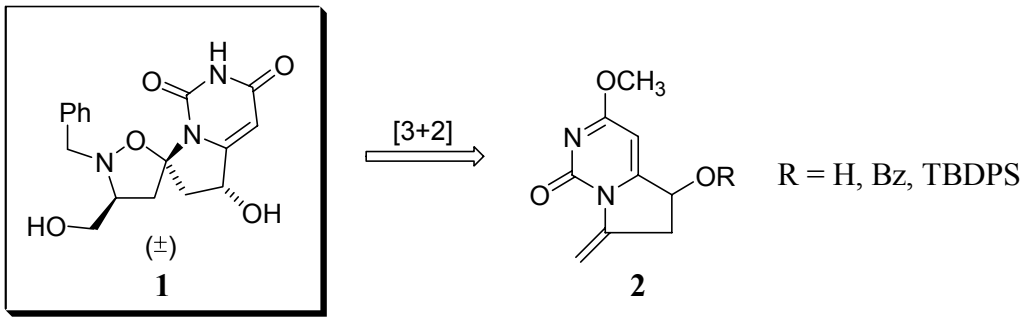
Spiro nucleosides are useful modifications of the natural nucleosides with the fixed base around the *N*-glycosidic bond [1]. Stereochemical factors such as *cis*/*trans* glycosyl configurations are important for biological activity and can be changed when the molecules are binded to enzyme, but not in nucleosides, whose torsion angles are fixed. Nucleosides containing nitrogen as a second heteroatom receive considerable interest for their potential anti-HIV effect over the last 10-years [2]. Based on the previous work [3], we focused our attention to the preparation of the spiro isoxazolidinyl nucleoside **1** *via* 1,3-dipolar cycloadditions of the 7-methylenepyrrolo[1,2-*c*]pyrimidin-1(5*H*)-ones **2**. The preparation of the starting dipolarophiles **2**, stereochemical aspects of their 1,3-dipolar cycloadditions with nitrile oxides and nitrones as well the synthetic solutions will be discussed.



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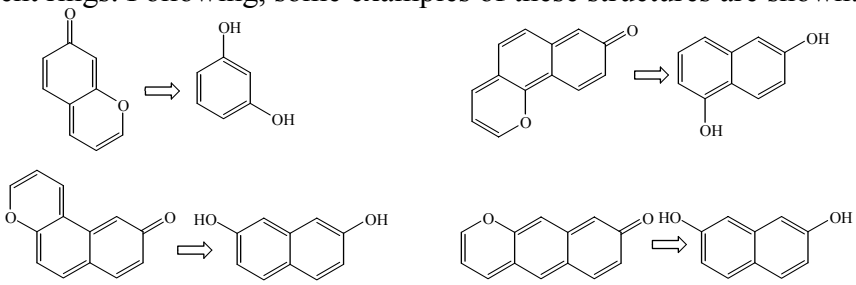
PYRONE-LIKE STRUCTURES WITH SUPERBASE ACTIVITY PRESENT ON CARBON MATERIALS

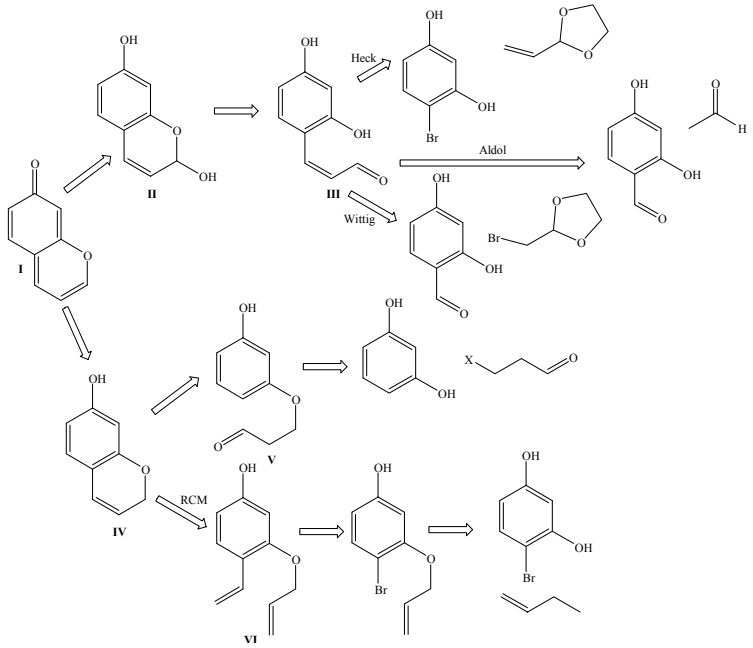
José Flórez-Álvarez[a], M[a] Dolores González-Azpíroz[a], Carlos Gutiérrez-Blanco[a], Miguel A. Montes-Morán[a], Dimas Suárez[b] and Enrique Fuente[a]

[a] Instituto Nacional del Carbón (INCAR), Consejo Superior de Investigaciones Científicas(CSIC), Francisco Pintado Fe, 26 La Corredoria,33011 Oviedo (Asturias), Spain
[b]Departamento de Química Física y Analítica, Universidad de Oviedo, Julián Clavería, 8, 33006, Oviedo (Asturias), Spain

The possibility of designing new organic compounds of elevated protonic affinity has great practical interest, since processes that involve proton transference and, in general, acid-base interactions have an important role both in Chemistry and Biochemistry. In this context, theoretical work done previously in our group has shown that some pyrone-like model structures could present an extraordinarily enhanced basic character. These structures would represent the first example of organic superbases in which the atom that accepts protons is oxygen (carbonylic). It is believed that these structures are present on the surface of carbon materials. The objective of this work is to develop a general, flexible and selective synthetic strategy for a new family of heterocyclic pyrone-like compounds with two or more aromatic rings, in which the carbonyl and ether functionalities are located on different rings. Following, some examples of these structures are shown:



The approach will involve the synthesis of the bicyclic system at the first instance followed by subsequent use of the same methodology for preparation of the rest of compounds. The possible routes that can be employed are shown in the following scheme:



THE SYNTHESIS OF STAUROSPORINONE

S. P. Gaudêncio, M. M. M. Santos, A. M. Lobo and S. Prabhakar

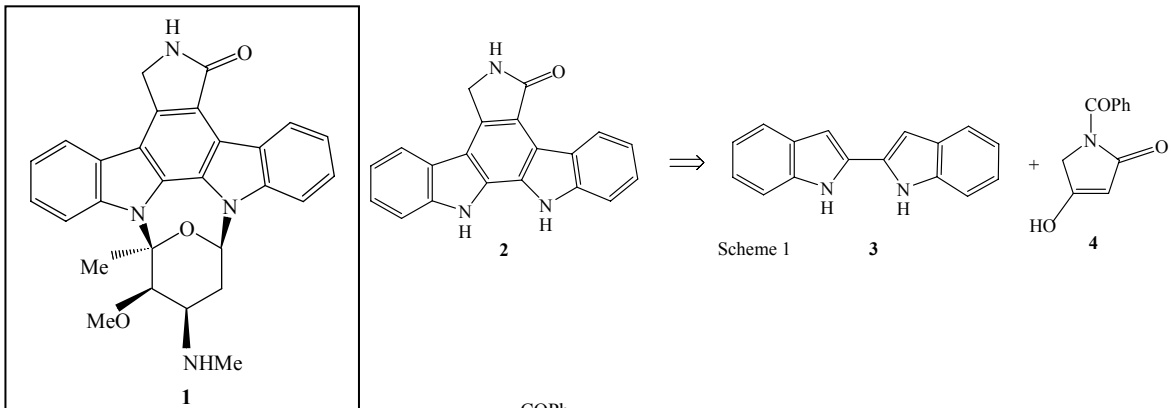
Secção de Química Orgânica Aplicada, Departamento de Química, CQFB-REQUIMTE and SINTOR-UNINOVA, campus Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, 2829 Monte de Caparica, Portugal

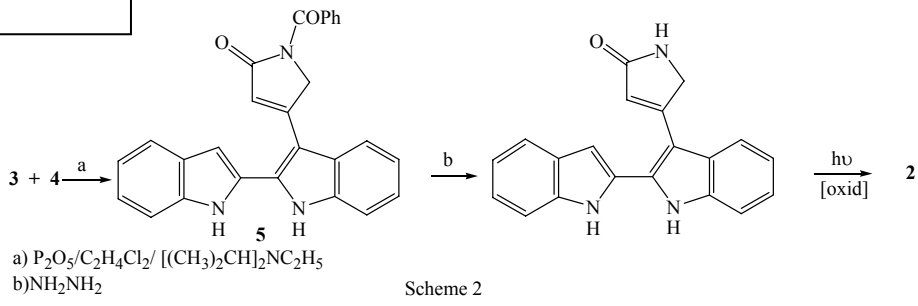
The indolocarbazole alkaloids are a structurally rare, but biologically interesting, class of natural compounds. Staurosporine **1** is one of the most well known members of this family owing to is very interesting biological activity such as antimicrobial, hypotensive, cell cytotoxic, inhibition of protein kinase C and platelet aggregation[1]. Thus, there is great interest in the synthesis of staurosporinone **2**, since this staurosporine aglycone retains much of the activity and is essential to the total synthesis of the indolocarbazoles alkaloides[2].

Method	**5**,Yield (%)
BF_3Et_2O, CH_2Cl_2 * [3]	57.0
CF_3SO_3H, $C_2H_4Cl_2$*	34.0
CH_2Cl_2, $InCl_3$*	45.6
P_2O_5, $C_2H_4Cl_2$, $[(CH_3)_2CH]_2NC_2H_5$	70.2

* molecular sieves

We report a significant modification of the method previously employed for a short, high-yield synthesis of staurosporinone **2**,[3] which employs as starting materials the bis-indole **3** and the keto lactam **4** (Scheme 1), using P_2O_5 and N,N´-diisopropyl-ethylamine to achive **5** in a simple and high yield step (Scheme 2).





Aknowledgements. We thank Fundação para a Ciência e a Tecnologia (FEDER, POCTI) (Lisbon, Portugal) for the award of a doctoral fellowship to two of us (S. P. G. and M. M. M. S.) and partial financial support.

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SYNTESIS OF NEW DERIVATES OF SILYBIN WITH IMPROVED BIOLOGICAL PROPERTIES

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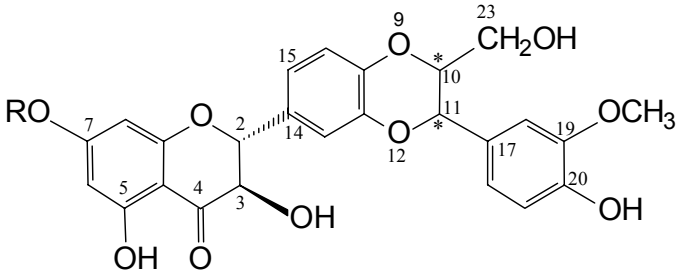
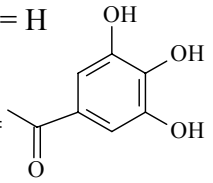
Silybin isolated from seeds of the milk thistle (*Silybum marianum*) is an active component in a number hepatoprotective and cytoprotective preparations. Silybin shows strong antioxidant and antiradical effects. Natural silybin is a mixture of two nearly inseparable diastereoisomers (2*R,* 3*R,* 10*S,* 11*S* and 2*R,* 3*R,* 10*R*, 11*R*).



silybin (**1**) R = H



Bioavailability of silybin is rather limited by its low water solubility. Selective oxidation of primary hydroxy group at C-23 of silybin into the carboxyl is a good possibility to increase silybin bioavailability without affecting its total biological activity (increase of water solubility). The connection of silybin molecule with another antioxidant (e. g. gallic acid, ascorbic acid, α-tocopherol) represents other approach for improvement of its bioavailability. 7-*O*-Galloylsilybin (**2**), a new compound, shows in our preliminary tests significant increase of its antioxidant properties comparing to silybin itself.
Antioxidant properties of the prepared substances were characterised by the value of half wave anodic potential determined by cyclic voltammetry (CV), the scavenging effect in the reaction with stable 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) and by deoxyribose oxidation assay and inhibitory effect on microsomal lipid peroxidation.

Compound	CV	DPPH	Oxidation of deoxyribose	Microsomal lipoperoxidation
	$E_{1/2}$ (mV)	IC_{50} (mM)	Inhibition (%)	IC_{50} (μM)
Silybin (**1**)	458	1.777	47.4	30.56
7-*O*-Galloylsilybin (**2**)	235	0.025	64.8	1.15

All four antioxidant parameters for the new compound **2** are substantially better than the starting compound **1**.

Acknowledgement: This work was supported by the grants No. 303/02/1097 from the Grant Agency of the Czech Republic, Grant No. NL/6713-3 from Ministry of Health of the Czech Republic and No. FD-K/096 from the Ministry of Industry and Commerce of the Czech Republic.

NEW REDOXACTIVE HETEROCYCLES POSSESSING AN OXALAMIDINE SUBSTRUCTURE

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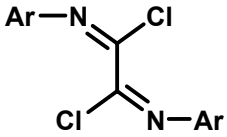
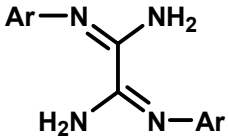
In our work group a construction set for the synthesis of numerous types of heterocycles was developed. Fundamental building blocks are the bifunctional electrophile (1) and binucleophile (2) obtainable by conversion of (1) with ammonia. By simple one-step-reactions multifunctional systems can be produced, which colourfulness, redoxactivity and the ability to chelatization are the topic of our current interest.



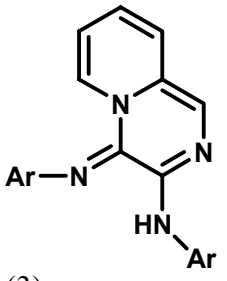
(1)



(2)

Pyrido[1,2-a]pyrazines can easily be synthesized by cycloacylation of 2-picolylamine with (1) [1]. Via a cycloaddition-ringtransformation cascade of (3) with quinones a convenient access to highly functionalized azaanthraquinones (4) is given [2]. By cyclization of the exocyclic NH-functions planar, fluorescent derivatives are obtained.

High yields of 4H-imidazoles with a wide variety of the aromatic substituents are achievable either by reaction of acylchlorides not containing an α-hydrogen atom with (2) [3] or by conversion of benzamidine hydrochloride with (1) [4]. The redox activities and the cyclisation of the exocyclic nitrogen atoms with borane are object of our present research.



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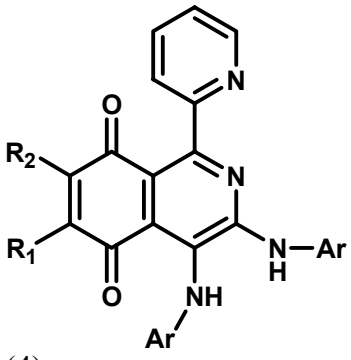

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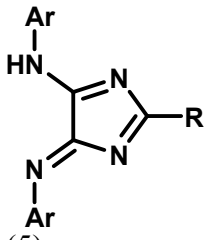

(5)

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4,5-DICYANOPYRIDAZINE: A POWERFUL HETERODIENE FOR PERICYCLIC DOMINO PROCESSES

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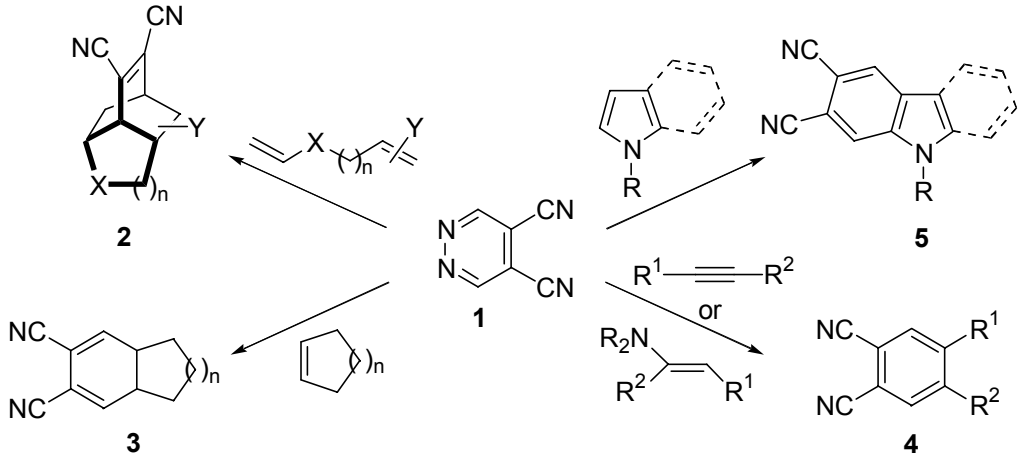
Despite the poor reputation enjoyed by electron-deficient 1,2-diazines in the realm of polyazine heterodienes as potential 4π electron components for intermolecular inverse electron-demand Hetero Diels-Alder (HDA) reactions [1], 4,5-dicyanopyridazine (DCP) (**1**) behaved as an excellent ***heterocyclic azadiene*** with a variety of dienophiles.
Reactions of **1** as ***masked bis-diene*** with different bis-dienophiles opened the way to a general strategy for the one-pot synthesis of carbo- and hetero-cage compounds **2**, through purely pericyclic, three-step homodomino processes [2].



Treatment of DCP with alkene dienophiles afforded cyclohexa-1,3-dienes **3** [3], while the employ of alkynes [4] or enamines [5], under different reaction conditions, provided a straightforward complementary route to substituted phthalonitriles **4**.
Moreover, the possibility of direct benzoannelations of heterocyclic dienophiles through HDA reactions with DCP was also investigated, providing a new entry into indole and carbazole derivatives **5** [6].
Synthetic applications as well as mechanistic features will be conveniently discussed.

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REACTIONS OF 2,13-DIHYDROXYDINAPHTHOFURANOFURAN AND 6,9-DIHYDROXYDINAPHTHOFURANOFURAN COMPOUNDS WITH FORMALDEHYDE

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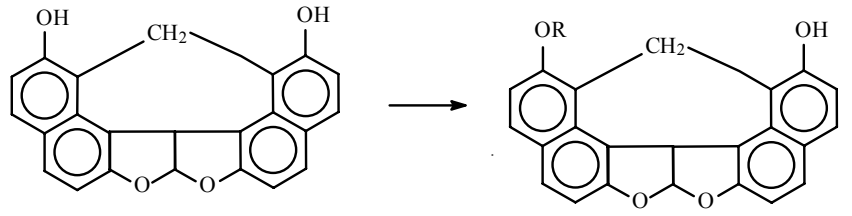
A calixarene like compound (1,14-Methylene-2,13-Dihydroxy-7a,14c-dihydronaphthofuro[2,1-b]naphthofuranofuran) (I), is synthesized by the reaction of 2,13-Dihydroxy-7a,14c-dihydronaphthofuro[2,1-b]naphthofuranofuran with formaldehyde in the presence of different catalysts such as morpholine, dimethylamine, triethylamine, HCl. The compound I is reacted with allylbromide, acetylchloride and P,P-dichlorophenylphosphine to produce appropriate mono subtituted derivatives.



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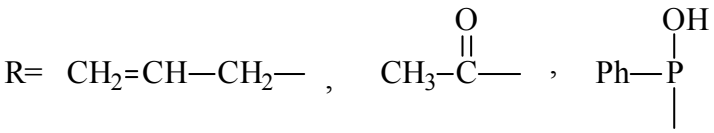
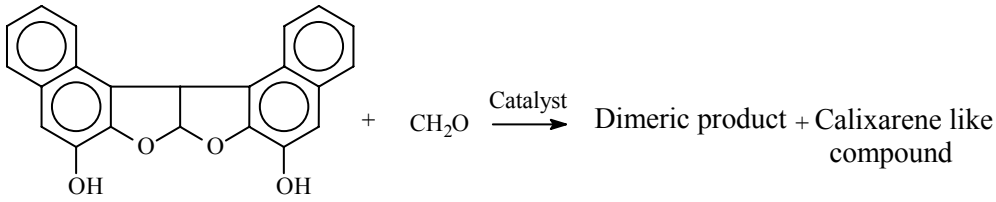


6,9-Dihydroxy-7a,14c-dihydronaphthofuro[2,1-b]naphthofuran is reacted with formaldehyde in the presence of a base catalyst of morpholine and triethylamine, a dimeric product and a calixarene like compound is formed .



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NAPHTHALENE ETHYLATION USING REACTION MEDIA BASED ON IONIC LIQUIDS

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[a]Instituto Nacional del Carbón (INCAR), Consejo Superior de Investigaciones Cientírficas (CSIC), 330012 Oviedo, Spain

Alkylation is one of the most used reactions in Organic Chemistry. Searching for new feasible alternatives is quite necessary since most of the organic solvents employed present dangerous and toxic properties, specially chlorinated hydrocarbons, and also because it causes serious environmental problems (atmospheric emissions and aqueous effluents contaminations).

The use of room temperature ionic liquids (RTIL) is a really good alternative for the future because of the advantages that they present. Ionic liquids are salts with low melting points, constituted by a wide range of organic cations like tetraalkylamonium, tetraalkylphosphonium, N-alkylpyridinium, 1,3-dialkylimidazolium and trialkylsulfonium combined with a metallic anion.

Methylbuthylimidazole aluminium trichloride salt is synthesised in a two step process. The first reaction is carried out mixing 1-methylimidazole and an excess of chlorobutene (1:1.1) in a round flask under inert atmosphere of nitrogen with continuous stirring, around 80ºC, for 24 hours. The excess of chlorobutene is removed by vacuum distillation. The crystals of 1-buthyl-3-methylimidazolium chloride are added to aluminium (III) chloride powder in a flask equipped with a Teflon stirrer bar. After the melt is partially formed it is stirred until all the aluminium chloride reacts. (This salt is noted Bmin).

A similar process was developed to synthesize the correspondent salts from 1,5diazabyciclo(4,3,0)non-5ene (noted DBN), and 1,8diazabyciclo(5,4,0)undec-7-ene (noted DBU). All the process for each salt is studied by 1H and 13C NMR spectrometry with a Brucker 300Mhz instrument.

Alkylation of naphthalene is carried out in a double round flask with a thermostate bath with continuous stirring and inert atmosphere of nitrogen. A reflux tower is used to condense gases. Ethylbromide is used as the alkylation agent at 70ºC. A sample is collected each sixty minutes. Adding water the action of the catalyst is stopped. Finally, the organic phase is separated with dichloromethane.

Each sample is analysed by Gas Chromatography in a Hewlett-Packard 5890 Series II, with a flame ionised detector (FID). Operating conditions: Stationary phase OV-1701; Length 25m; Internal diameter 0.25mm; Carrier gas(H2) flow 1,8 ml/min; Splitting ratio 1:65; Injector temperature 350ºC; Detector temperature 300ºC; Oven temperature 50ºC to 290ºC; Oven program temperature 4ºC/min.

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SYNTHESIS OF HETARYL SUBSTITUTED BENZO- AND HETEROANNELATED OCTAHYDROINDOLIZINES AND -QUINOLIZINES

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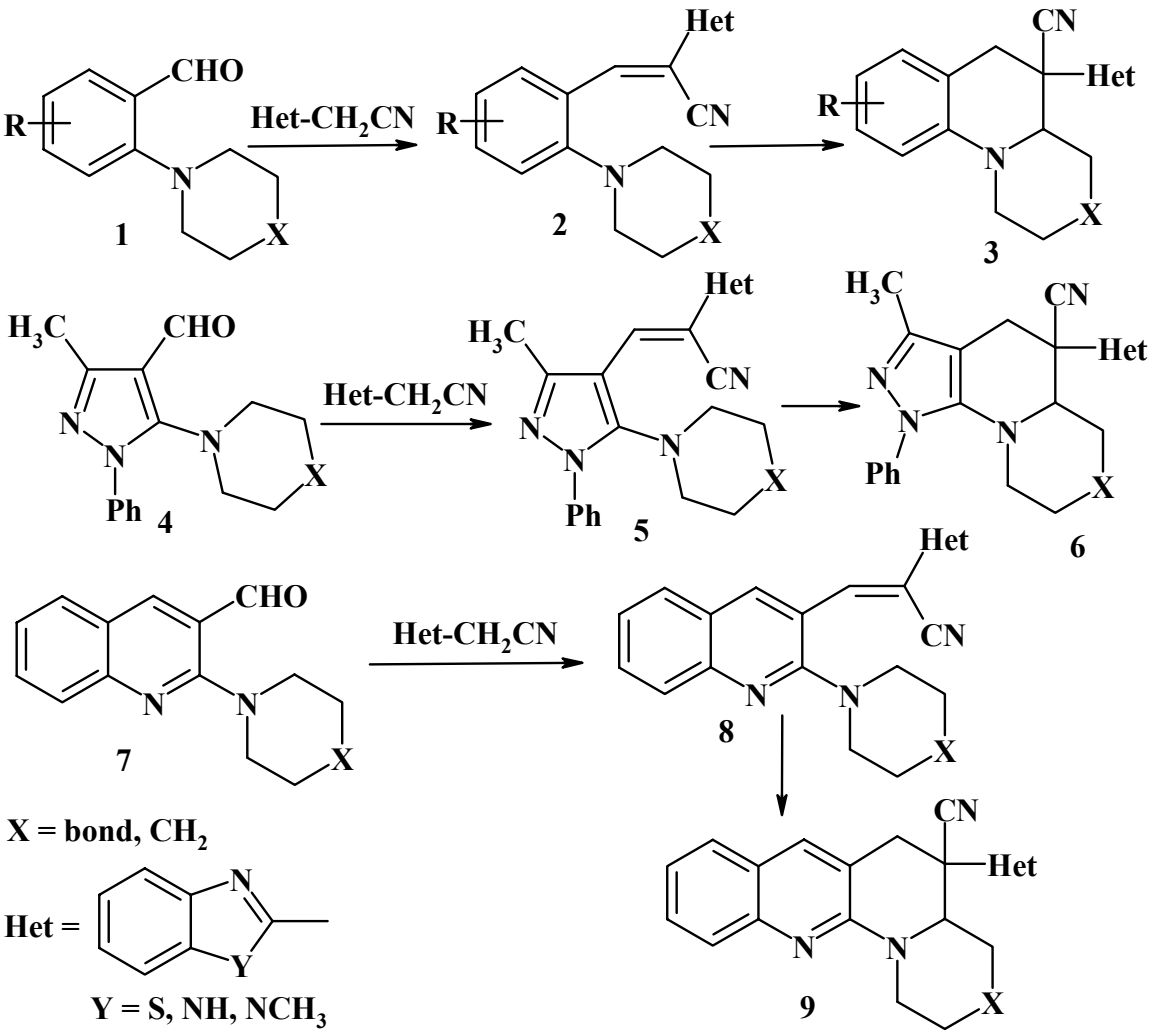
Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033, Kiev, Ukraine; e-mail: atver@mail.univ.kiev.ua



Compounds **2** easily obtained from *o*-pyrrolidino- and *o*-piperidinobenzaldehydes **1** and hetarylacetonitriles were found to undergo cyclization reaction upon reflux in AcOH or DMF yielding the title derivatives **3**. Similarly, pyrazolecarboxaldehydes **4** and quinolinecarboxaldexydes **7** were transformed into corresponding heteroannelated analogues **6** and **9**. These type cyclizations of 2-vinyl-N,N-dialkylanilines are known in organic chemistry as so called "*tert*-aminoeffect" [1]. Present investigation is the first application of this approach to the hetaryl substituted and heteroannelated systems preparation.

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A NOVEL CLAISEN SEQUENCE FOR THE SYHTHESIS OF 3,3-SUBSTITUTED-2-OXINDOLES

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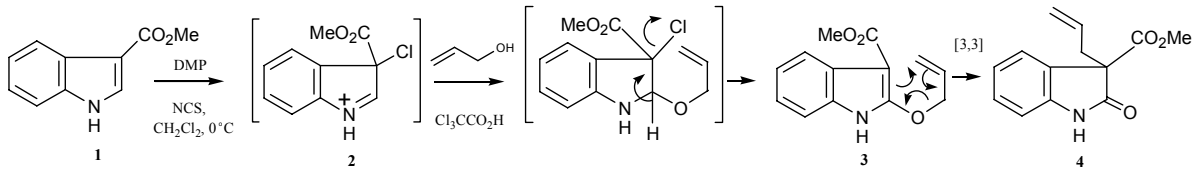
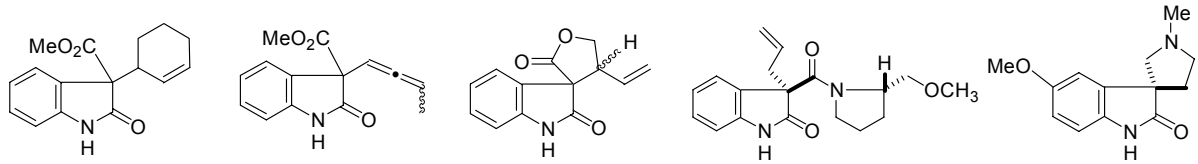
The oxindole system is a key structural feature of many naturally occurring alkaloids which exhibit biological properties. This poster describes a novel one-pot synthesis of functionalised oxindoles with a view to application in natural product synthesis.

Reaction of 3-methoxycarbonyl indole **1** with *N*-chlorosuccinimide (NCS) in the presence of 1,4-dimethylpiperazine (DMP) gives chloroindolenine **2**. When this reactive intermediate is added to a solution of allyl alcohol and a catalytic amount of Cl_3CCO_2H, ether **3** is generated which undergoes a Claisen rearrangement to give oxindole **4** in excellent yield. [1]



The scope and limitations of this reaction are investigated with respect to the substituents at the 3-position of the indole and the allylic alcohol partner. The sequence tolerates a variety of alkenol substitution leading to oxindoles such as **5**, alkynols which rearrange to oxindole-3-allenes **6**, and various diols which can undergo spontaneous lactonisation to yield oxindole-3-spirolactones **7**. A wide variety of indole-3-amides rearrange under the standard conditions to give the corresponding oxindoles. The use of chiral amides allow investigation into the diastereoselectivity of the rearrangement to give oxindoles such as **8**.



5 97% **6** 66% **7** 79%, 3:1 **8** 70%, 95:5 **9** Horsfiline

This sequence may potentially lead to an extremely efficient diastereoselective preparation of a relatively simple oxindole alkaloid such as Horsfiline **9**. [2]

[1] K. I. Booker-Milburn, M. Fedouloff, S. J. Paknoham, J. B. Strachan, J. L. Melville and M. Voyle, *Tetrahedron Lett.*, **2000**, 41, 4657.
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SYNTHESIS OF NEW [1,2,4]TRIAZINE-FUSED TETRACYCLIC RING SYSTEMS

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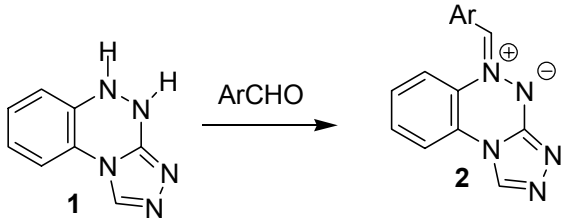
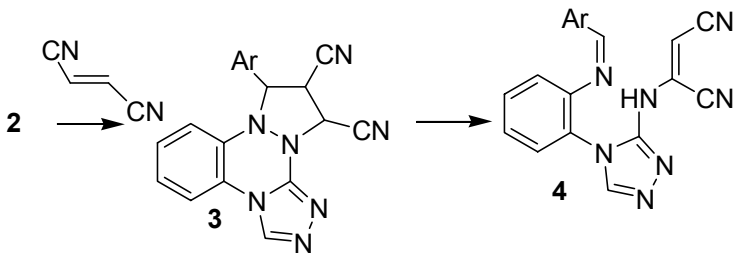
bUniversity of Ljubljana, Askerceva 5, 1000 Ljubljana, Slovenia

Earlier we elaborated a facile synthetic route to 4,5-dihydro[1,2,4]triazolo[3,4-c]benzo-as-triazine[1] (**1**) and found that - similar to a recent recognition with five-membered dihydropyrazolones[2] - these compounds readily react with aromatic aldehydes to give zwitterionic azomethine imines, a group of new derivatives highly appropriate for 1,3-cycloaddition reactions.





We report now that 1,3-dipolar cycloadditions of **1** with a great variety of dipoplarophiles can take place and, thus, various new tetracyclic derivatives can be obtained. Thus, **2** reacts with fumaronitrile in dichloromethane under smooth conditions to yield the expected cycloadduct. If the transformation, however, is carried out in acetonitrile as a solvent, an unexpected ring opening takes place and the phenyltriazole derivative **4** is formed in acceptable yield.

Extenstion of the reactivity of the new azomethine imines for other dienophiles as well as the mechanism of the unexpected ring opening to **4** will be discussed.

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2. Preseren A, Svete J, Stanovnik B. J. Het. Chem., **1999**, *36*, 799.

PREPARATION OF NOVEL, CAMPHOR-DERIVED CHIRAL COMPOUNDS

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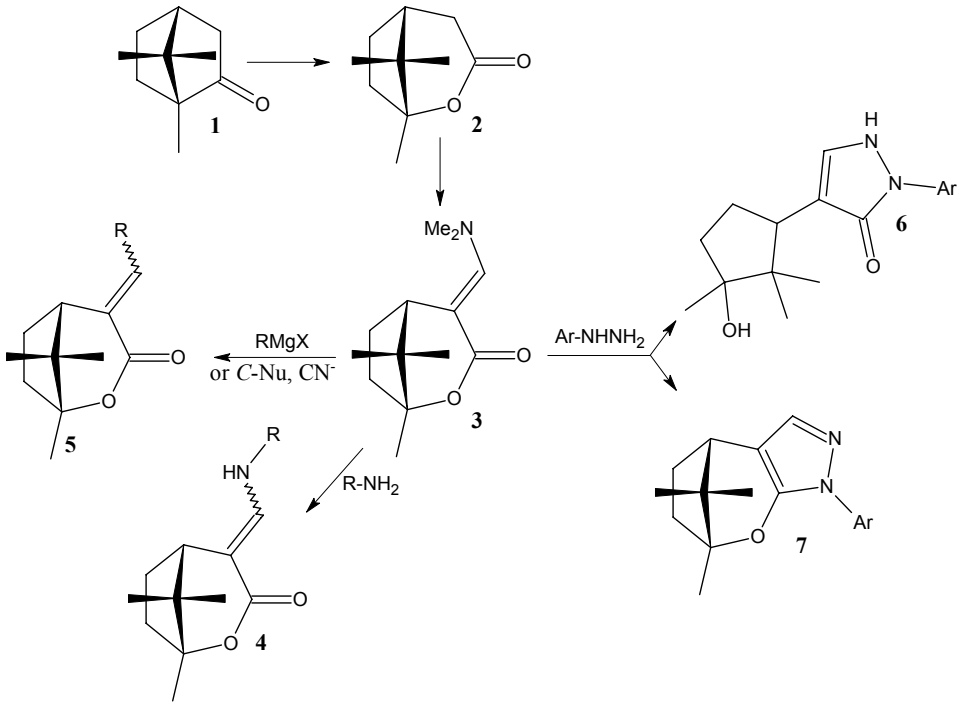
Interest in the chemistry of camphor is associated with the fact that (+)- or (-)-camphor is readily available and undergoes a wide variety of transformations. Various compounds that are derived from camphor have been used as key intermediates in organic synthesis [1]. In this connection a new enaminon reagent (1*R*,4*E*,5*S*)-4-[(dimethylamino)-methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one **3** was prepared in two steps from (1*R*)-(+)-camphor **1** *via* Baeyer-Villiger oxidation to (1*R*)-(+)-camphor lactone **2** [2] followed by treatment of **2** with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) in decaline under reflux. Compound **3** reacted with various types of *C*- and *N*-nucleophiles. Reactions with primary aliphatic, aromatic, and heterocyclic amines, amino acid esters, Grignard reagents, 2-methylindole and potassium cyanide gave the corresponding substituted products **4** and **5,** respectively. On the other hand, compound **3** reacts with aromatic hydrazines to form either 2-aryl-4-(3-hydroxy-2,2,3-trimethylcyclopentyl)-1,2-dihydro-3*H*-pyrazol-3-ones **6** or (1*S*,8*R*)-5-aryl-8,11,11-trimethyl-7-oxa-4,5-diazatricyclo-[6.2.1.$0^{2,6}$]undeca-2(6),3-dienes **7**. This depends on the position and type of the substituent attached to the phenyl ring. The structures were determined by 2D NMR techniques and NOESY spectroscopy as well as by X–ray diffraction.



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SUBSTRATE SCREENING OF MICROBIAL BAEYER-VILLIGER MONOOXYGENASE PRODUCING RECOMBINANT WHOLE-CELLS

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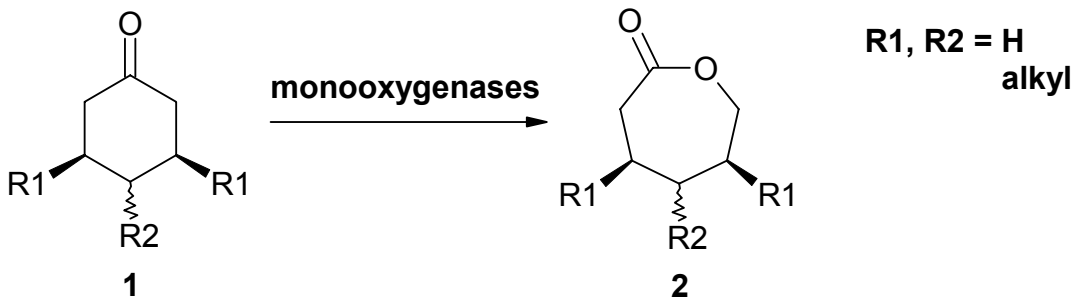
Baeyer-Villigerases have been established as versatile tools for the conversion of cyclic ketones to lactones. A key feature beside the regio- and chemoselectivity is the possibility of introducing chirality on a large number of non natural substrates[1].

Based on our previous reports on recombinant whole cell mediated oxidations[2] of carbocyclic prochiral ketones[3], we investigate the enantiodivergency of 11 different Baeyer-Villiger Monooxygenases producing whole cells[4].



In this contribution we discuss our latest results on the conversion of prochiral ketones of type **1** to the corresponding lactones **2** and a usefull synthetic approach towards the substrates **1**. The enantiodivergency of the used enzymes will be studied.

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SYNTHESIS OF SOME [1,2,4]TRIAZINO[6,5-B]QUINOLINE DERIVATIVES

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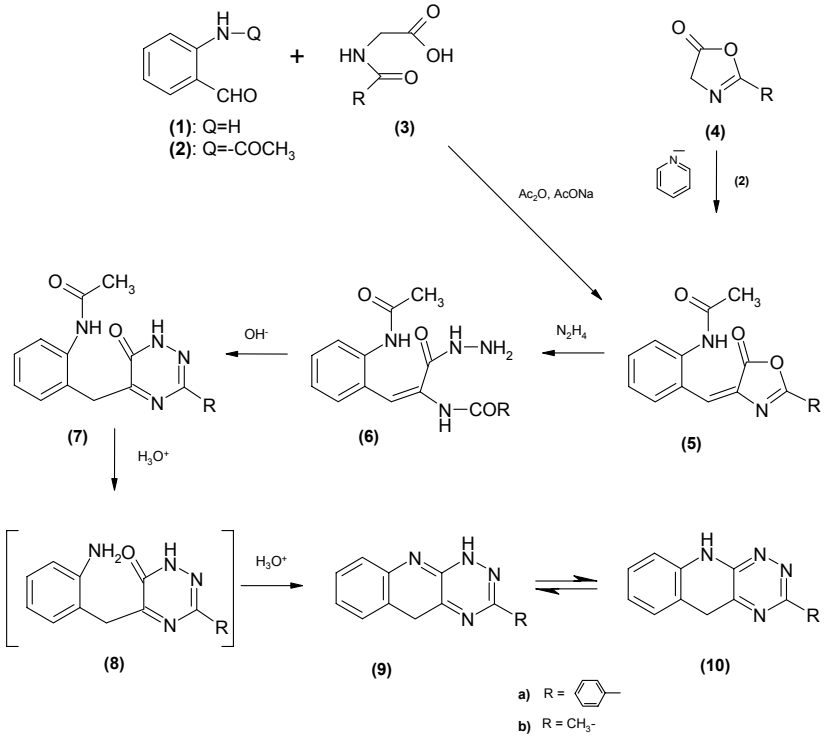
This communication deals with the use of 6-oxo[1,2,4]triazine cyclocondensation reaction for synthesis of some [1,2,4]triazino[6.5-b]quinoline derivatives. The only synthesis of this heterocyclic system known is the cyclization reaction of some 2-hydrazinoquinoline derivatives[1].

2-Phenyl-4-(2-acetylaminobenzylidene)-4,5-dihydrooxazol-5-one **5a**, resp. its analogous 2-methyl derivate **5b** were converted into the 2-benzoylamino-, resp. 2-acetylamino-3-(2-acetylaminophenyl) acrylic acid hydrazides **6a**, resp. **6b**. These hydrazides were cyclized to the 3-phenyl-, resp. 3-methyl-5-(2-acetylaminobenzyl)-1,6-dihydro-[1,2,4]triazin-6-ones **7a**, resp. **7b**. The acidic hydrolysis of acetyl group was followed by the cyclocondensation of derivates **8a**, resp. **8b** into 3-phenyl, resp. 3-methyl-1,5-dihydro-[1,2,4] triazino[6,5-b]quinolines **9a**, resp. **9b**[2].

Scheme



References:

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A NOVEL ONE-POT SYNTHESIS OF 2-IMIDAZOLINES

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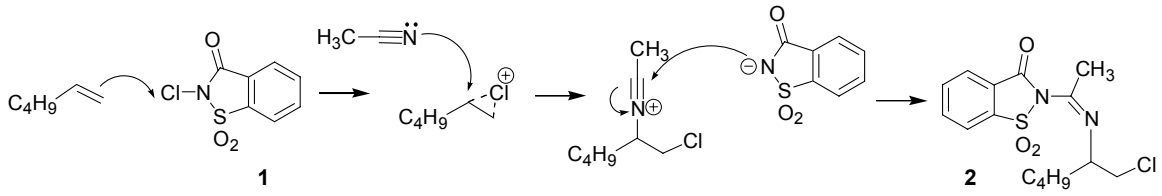
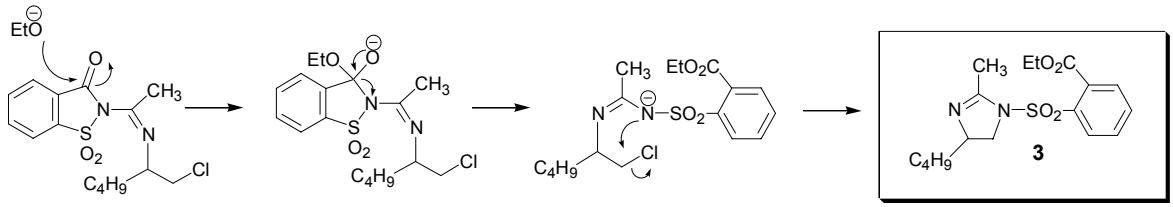
In the course of our work on nitrogen centred radicals, *n*-hexene was treated with *N*-chlorosaccharin **1** in acetonitrile solvent. Thin-layer chromatography indicated the formation of a single product, but all attempts to isolate and characterise it led to decomposition. Based on literature precedent with other chloroamine species the product was tentatively assigned the structure **2** [1]. The proposed mechanism involves a Ritter-type interception of a chloronium ion by acetonitrile (Scheme 1).



Scheme 1

It was expected that treatment of **2** with potassium ethoxide *in situ* would give an imidazoline **3** *via* ethanolysis of the saccharin moiety and concomitant ring closure (Scheme 2). Satisfyingly, this one-pot reaction was successful for a variety of simple alkenes, giving imidazolines in up to 60 % yield. The imidazoline nucleus is common in biologically active natural products and so is of considerable interest in medicinal chemistry [2]. Imidazolines have also been used as catalysts and ligands [3].



Scheme 2

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STEREOELECTRONIC EFFECTS ON THE 1,5-RING CLOSURE REACTIONS OF ENON-CARBONYL YLIDES ARISING FROM CARBENES

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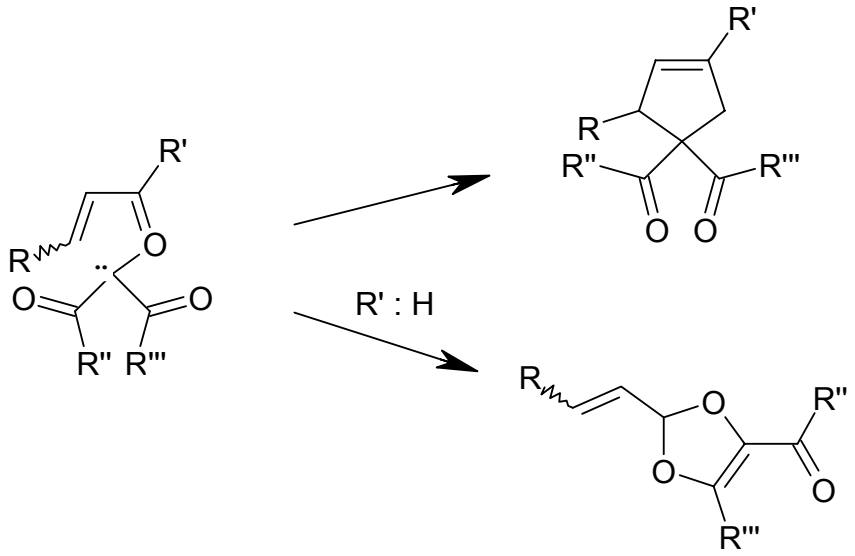
1,5-Electrocyclic reactions constitute an important principle of heterocyclic chemistry [1,2]. Electrocyclic 1,5-ring closure reactions of carbonyl ylides generated from metalo-carbenes and α,β-unsaturated carbonyl compounds has recently gained interest [3,5]. Our group also contributed to this topic. These reactions generally yield dihydrofurans and dioxalenes that are important heterocyclic in natural compounds chemistry (scheme-1). The reaction is also known to go further steps in several occasions. The cyclization is believed to be pericyclic and this character results in sensitivities to steric and even to some electronic effects. In this proposed research, several unsaturated carbonyl compounds will be reacted with several diazo compounds in metal-catalyzed medium and changes in the reaction course will be investigated.

Scheme 1.



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PHOTOCATALYZED [2+2+2]-CYCLOADDITION OF NITRILES AND ACETYLENES: A CONVENIENT ROUTE TO PYRIDINES UNDER MILD CONDITIONS

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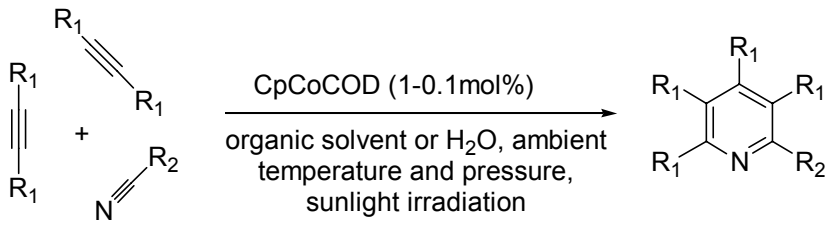
[2]Grünenthal GmbH, Center of Research, P.O. Box 500444, 52088 Aachen, Germany
[3]Laboratorios Dr. Esteve S.A. Av. Mare de Déu de Monserrat, 221, 08041 Barcelona, España

The Co(I)-catalyzed synthesis of pyridines from acetylenes and nitriles usually requires high temperature and pressure. The approach doesn't tolerate many functional groups, it causes racemization of chiral centers, and also safety risks should be taken into account. The pyridine ring participates in many pharmacologically active compounds, and any progress in the pyridine synthesis can potentially ease the task of the preparation of such molecules.



The Co(I)-catalyzed pyridine synthesis can be conveniently carried out at room temperature and atmospheric pressure under continuos irradiation with visible light [1]. Thus, the drastic reaction conditions of the thermally initiated variant of the reaction can be avoided. It is important since gaseous acetylene has to be dealt with, so the mild conditions of the reaction are preferable.
Lamp irradiation as well as sunlight can be used for the ideal wavelength range (350-500 nm). The light seems to promote the conversion of the precatalyst (CpCoCOD, for example) into active species through the dissociation of COD from cobalt and creation of free coordination sites. It likely facilitates also the formation of the central catalytic intermediate (metallocyclopentadiene) through the addition of two acetylene molecules.

It should be noticed that water can be used as a media for the reaction. Besides the costs reduction it allows reducing the amount of side benzenes to a minimum [2].

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INTRAMOLECULAR [4+2] CYCLOADDITION REACTIONS OF INDOLYLALKYLPYRIDAZINES: SYNTHESIS OF ANNULATED CARBAZOLES

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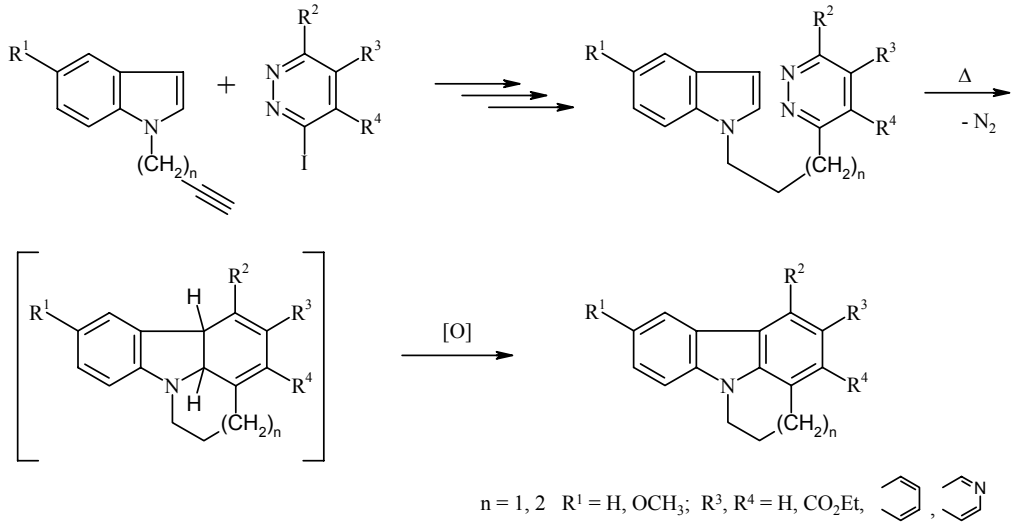
In the course of a research program aiming at the synthesis of polycyclic hetarenes as potential cancer chemotherapeutic agents [1], *b*-fused carbazoles with an alkylene bridge between the nitrogen and the adjacent ring C became an object of interest. A synthetic pathway leading to such compounds was developed which is based on an intramolecular inverse-electron-demand Diels-Alder reaction of the electron-rich C(2)-C(3) unit of an indole as the dienophile with an electron-deficient pyridazine azadiene, tethered together by a three- or four-carbon linker. Comparable cyclization reactions had been previously known only for (more reactive) 1,2,4-triazines with similar side chains [2]. Different methods for the preparation of the cycloaddition educts were elaborated, e.g. employing N-alkynylindole derivatives and iodopyridazines for Sonogashira coupling and subsequent reduction of the triple bond.



n = 1, 2 R^1 = H, OCH_3; R^3, R^4 = H, CO_2Et,

The thermally induced cycloaddition reactions take place in refluxing triisopropylbenzene at 232 °C, giving the tetra- or pentacyclic products in yields which strongly depend on the presence and nature of substituents at the pyridazine ring and on the chain length of the tether. Cyclization of diesters (R^3 = R^4 = CO_2Et) with hydrazine or amines gives further pentacyclic target compounds.

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COMPARISON OF REACTIVITY OF S-[1-(4-METHOXYPHENYL)-PYRROLIDIN-2-ON-3-YL]ISOTHIURONIUM BROMIDE WITH ITS N-METHYL AND N,N-DIMETHYL DERIVATIVE

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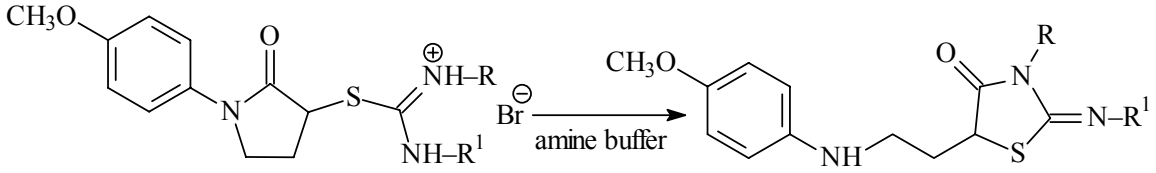
In our previous work we have dealt with the synthesis [1] and detailed mechanism [2] of the tandem recyclisation reaction of *S*-[1-(4-methoxyphenyl)pyrrolidin-2-on-3-yl]-*N*-methylisothiuronium bromide and *S*-[1-(4-methoxyphenyl)pyrrolidin-2-on-3-yl]-*N*,*N*′-dimethylisothiuronium bromide. It was found that the methyl group(s) on the nitrogen(s) markedly influenced type of acid-base catalysis and rate determining step (Scheme 1). In the case of derivative carrying R = H, $R^1 = CH_3$ the reaction was mainly subject to general base catalysis ($k_B >> k_{BH}$) whereas in the case of derivative carrying R = CH_3, $R^1 = CH_3$ the general acid catalysis makes itself felt ($k_{BH} >> k_B$). Therefore we have decided to study parent non-methylated compound and evaluate which type of catalysis and mechanism prevails in this case.



R, R^1 = H, H; H, CH_3; CH_3,CH_3

Scheme 1

The authors thank to Grant Agency of the Czech Republic (grant No. 203/02/D170) for financial support.

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ADVANCES IN SYNTHESIS OF HETEROCYCLES VIA OXIMES

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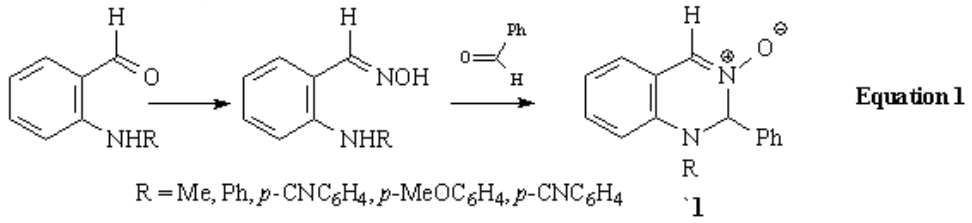
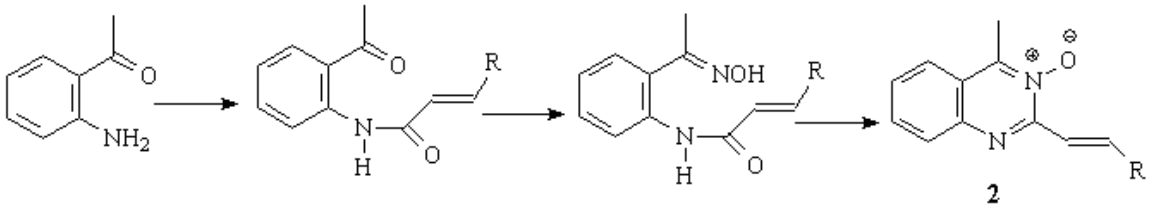
o-Aminoarylaldehydes/ketones have been shown to be versatile platforms for the construction of heterocyclic nitrones. In the first approach dihydroquinazoline *N*-oxides 1 result from a domino condensation/annulation reaction sequence between benzaldehyde and secondary *o*-aminobenzaldoximes (Equation 1). In a second approach aromatic quinazoline *N*-oxides 2 are formed from *o*-aminoacetophenone. The reaction involves initial condensation with α,β-unsaturated acid chlorides. The resulting *o*-amido derivatives undergo an oximation cyclodehydration sequence to yield nitrones (Equation 2). The new dipoles show some unexpected reactivity during efforts to effect their cycloaddition which will be discussed, for example the aromatic dipole 2b on reaction with dimethyl acetylenedicarboxylate affords a benzodiazepine, Figure 1, as the major product, xray crystallographic analysis has confirmed its structure. The proposed mechanistic origin of the benzodiazepine will be discussed.



Equation 1



2

a. R = Me, b. R = Ph **Equation 2**

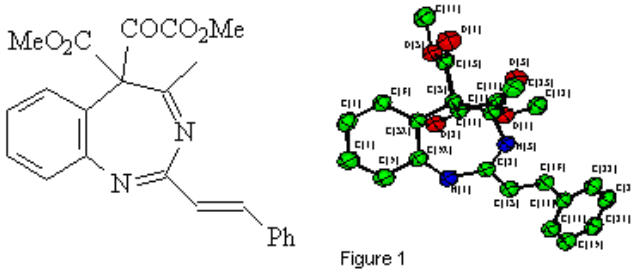


Figure 1

REGIOSELECTIVE SYNTHESIS OF 3-BENZYLTHIAZOLO[3,2-a]PYRIMIDONES AND 3-BENZYL-THIAZOLO[3,2-c] PYRIMIDONES THROUGH PALLADIUM-CATALYZED HETEROANNULATION OF ACETYLENIC COMPOUNDS

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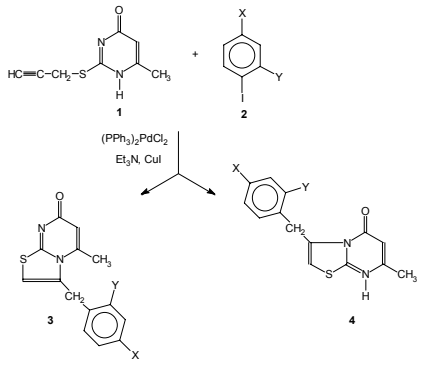
Up until now, the general method for synthesizing thiazolo[3,2-a] pyrimidines has been basically dependent on starting from 2-aminothiazoles [1]. Many thiazolo[3,2-a] pyrimidines have been synthesized to evaluate their biological activities. However, these synthetic methods have the disadvantages of giving another regioisomer, thiazolo [2,3-b] pyrimidines. Although palladium-catalyzed cyclization reactions of 2-propynyl sulfanylpyrimidones has reported to give thiazolo[3,2-a]pyrimidone [2], all attempts made so far to reach pure regioisomeric thiazolo [3,2-a] pyrimidone have invariably led to failure or poor yield [1,2]. Moreover none of these methods led to the synthesis of substituted thiazolo [3,2-a] pyrimidones.

Palladium-catalyzed annulation strategy has been successfully utilized for the synthesis of carboxylic [3] and heterocyclic compounds. In continuation of our recent studies [4] on the palladium-catalyzed reactions of acetylenic substrate leading to heterocyclic compounds of biological significance, we became interested in developing a regioselective synthesis of substituted thiazolopyrimidines.

In this communication we wish to report that when 6-methyl-2 (prop-2-ynylsulfanyl) pyrimidone-4-one **1** was treated with 4-nitro-1-iodobenzene **2a** in triethylamine in the presence of bis(triphenylphosphine) palladium chloride and copper iodide, 5-methyl-3(4-nitrobenzyl)-1H-thiazolo[3,2-a] pyrimidon-7-one **3** was obtained in good yield. It means that carbometalation/anion capture, cyclization and aromatization have been occurred in an one pot reaction.



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SYNTHESIS OF A SPIROCYCLIC INDOLINE LACTONE

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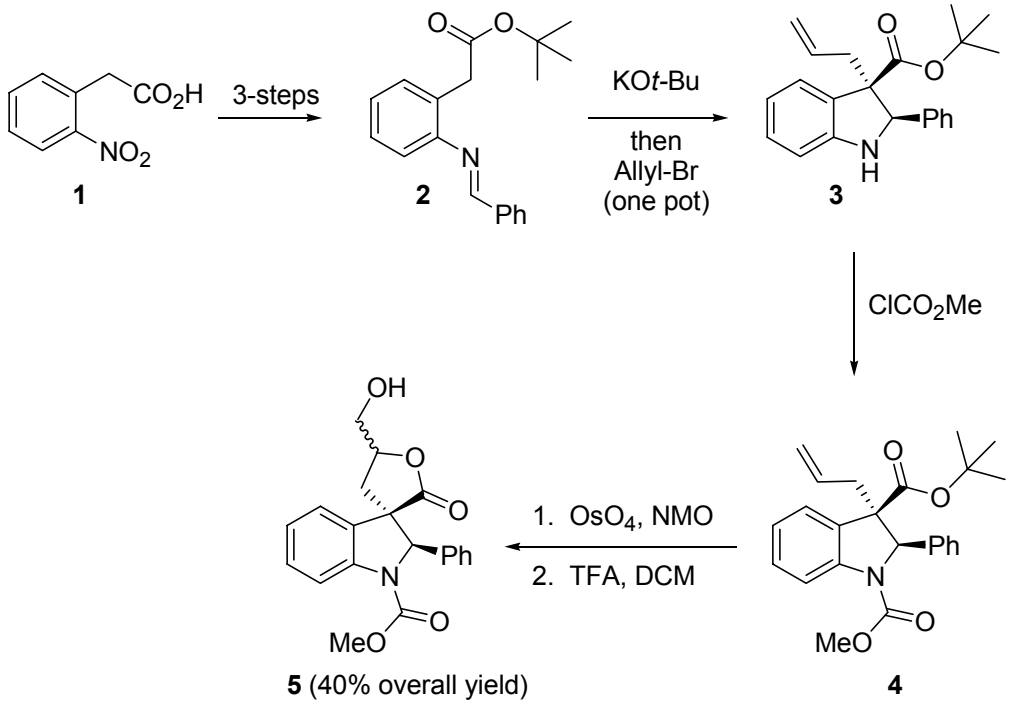
As part of an effort to synthesize natural product-like compounds for biological screening, a route to the spirocyclic indoline lactone, **5**, was developed. Base promoted cyclization of [2-(Benzylidene-amino)phenyl]-acetic acid *t*-butyl ester (**2**) and subsequent trapping of the resulting enolate with allyl bromide affords 3-allyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic acid *t*-butyl ester (**3**) in high yield as a single diastereomer. This result is contrary to a prior publication that describes failed cyclization under basic conditions utilizing an analogous ethyl ester and poor diastereoselectivity for Lewis acid promoted cyclization [1]. N-acylation, olefin dihydroxylation, and *t*-butyl ester cleavage affords spirocyclic lactone **5** as a pair of diastereomers. Separation of these two diastereomeric products by preparative HPLC, stereochemical assignment, and spectral characterization will be reported. This synthesis provides a high yield alternative to the photochemical route for analogous spirocyclic indoline lactones reported by Ibrahim-Ouali, *et al.* [2].



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LIBERATION OF THE TRICARBONYL PORTION OF ASCOMYCIN

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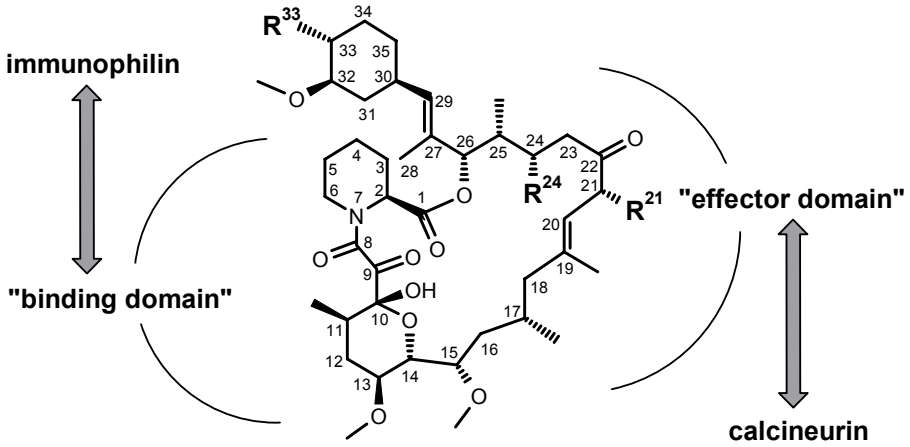
The natural product ascomycin (**1**) and the related compound FK 506 (**2**), represent highly functionalized 23-membered macrocycles with a polyketide backbone. Elidel®, a topical formulation of ASM 981 (**3**, pimecrolimus), the 33-*epi*-chloro-derivative of ascomycin, heralds major advances in the treatment of inflammatory skin diseases as compared to traditional treatment schedules.[1] The left hand part of the macrolactams mediate binding to their common immunophilin (FK 506-binding protein) and has therefore been termed "binding domain".[2] The right hand part of the macrocycles, together with elements of the immunophilin, interact with the protein phosphatase calcineurin, which plays a key role in the Ca^{2+} dependent activation of lymphocytes, and thus represent the "effector domain".



1 Ascomycin (R^{21} = ethyl; R^{33} = R^{24} = OH)
2 FK 506 (R^{21} = allyl; R^{33} = R^{24} = OH)
3 ASM 981 (R^{21} = ethyl; R^{33} = epi-chloro; R^{24} = OH)
4 24,33-bis-OTBDMS-ascomycin (R^{21} = ethyl; R^{33} = R^{24} = -OTBDMS)

Within the binding domain, ascomycin features the unusual pattern of a masked tricarbonyl moiety, which potentially allows for high structural diversity *via* simple isomerisation events. Methodologies, allowing the liberation of the tricarbonyl unit by blocking the 14-hydroxy group will be reported.

[1] Luger, T.; Van Leent, E. J. M.; Graeber, M.; Hedgecock, S.; Thurston, M.; Kandra, A.; Berth-Jones, J.; Bjerke, J.; Christophers, E.; Knop, J.; Knulst, A. C.; Morren, M.; Morris, A.; Reitamo, S.; Roed-Petersen, J.; Schoepf, E.; Thestrup-Pedersen, K.; Van der Valk, P. G. M.; Bos, J. D. *Br. J. Dermatol.* **2001**; *144*, 788-94.
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SYNTHESIS OF MEDIUM-SIZED HETEROCYCLIC RINGS PROMOTED BY SAMARIUM DIIODIDE

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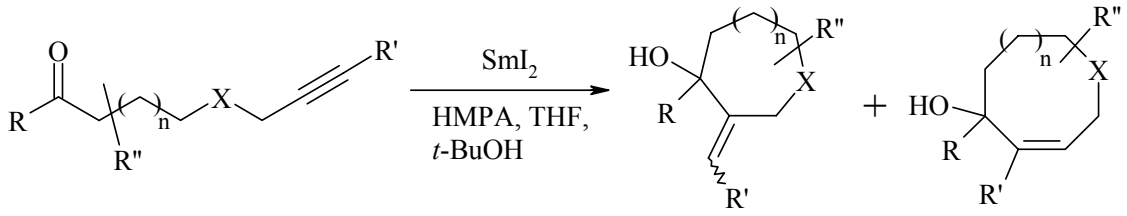
Since its introduction to synthetic organic chemistry by Kagan,[1] samarium diiodide (SmI_2) has become an extremely useful and powerful reagent. It serves as a mild and selective one-electron transfer reductant promoting a wide range of synthetically important transformations.[2] By transferring an electron to aldehydes and ketones, SmI_2 generates ketyl radical anions, which can undergo reductive coupling reactions often with excellent yields and high diastereoselectivity.[3] This method offers a highly efficient way to cyclic and bicyclic systems. The utility of this process is not only due to the variety of ring sizes, which can be prepared, but also to the ability of SmI_2 to initiate sequential reactions.[2]
Medium-sized ring systems are important (sub)structures in various natural products[4] or are often used as precursors in the synthesis of natural products.[5] Therefore, efficient syntheses of these units have been investigated for a long time.[6] As previously shown by our group,[3b] SmI_2 has been employed in intramolecular ketone-alkyne coupling reactions offering an efficient way to medium-sized carbocyclic ring systems. This method has now been extended to the synthesis of various medium-sized heterocyclic compounds. In the presence of hexamethylphosphoramide (HMPA), alkynylketones **1** (X = NBoc, O) undergo reductive cyclization to give heterocyclic compounds **2** and **3** in moderate to good yields depending on the substituents. Further studies investigate scope and limitations of this method.



1 **2** **3**

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NITROPYRIDYL ISOCYANATE

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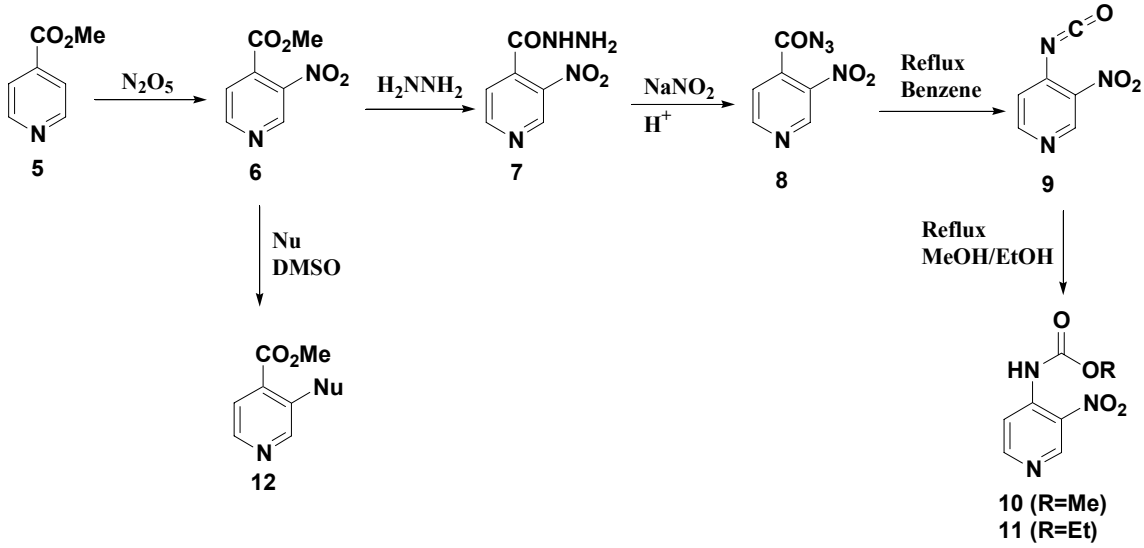
Isocyanates constitute an important class of compounds in organic chemistry. They undergo a series of reactions to yield a variety of interesting products including heterocyclic derivatives.
Heterocyclic isocyanates have however not got the same attention as the respective aromatic compounds in synthesis and reactivity studies because of their instability and high reactivity [1]. Attempts to generate 2-pyridyl isocyanate led to the formation of its dimer [6] while the 4-isomer trimerizes to an isocyanurate [2].
We have studied the preparation, stability and reactivity of nitropyridyl isocyanates. The introduction of an electronegative substituent like the nitro group [3,4,5] is expected to reduce the basicity of the pyridine nitrogen, hence retarding the trimerization, but also increase the reactivity of the isocyanate carbon towards nucleophiles. We hereby present the preparation of 3-nitro-4-pyridyl isocyanate **9**.



The nitro group in methyl 3-nitro-4-pyridine carboxylate **6** seems to be a good leaving group in nucleophilic aromatic substitution reactions. Different nucleophiles have been tested to yield new products **12**.

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PYRAZOLONE TAUTOMERISM: THE GEMINAL ^{2}J(PYRAZOLE C-4,H-3(5)) COUPLING CONSTANT AS A STRUCTURAL PROBE

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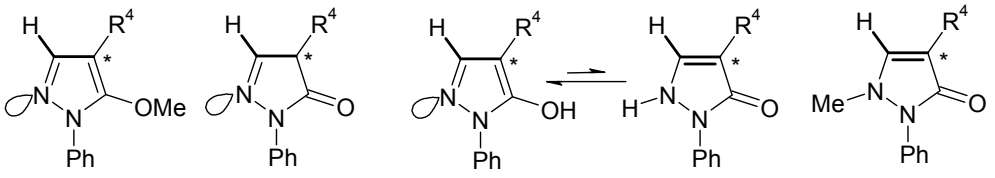
The tautomerism of N-phenylpyrazolones unsubstituted at position 3(5) was investigated by ^{13}C- and ^{1}H-NMR spectroscopy. Apart from chemical shift considerations and observed NOEs the magnitude of the geminal ^2J(pyrazole C-4,H-3(5)) spin coupling constant permits the unambiguous differentiation between 5-hydroxypyrazole (**1A**) and 1,2-dihydro-3*H*-pyrazol-3-one (**1B**) tautomers, forms which usually are difficult to discriminate due to fast interconversion resulting in only one averaged set of signals.
Whereas 5-methoxypyrazoles **2** ('fixed' OH-isomers) have ^2J(C-4,H-3) coupling constants in the range between 8.6 and 10.6 Hz, in the corresponding 1,2-dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-ones **3** ('fixed' NH-isomers) the values are considerably reduced to 4–6 Hz. This phenomenon can be mainly attributed to the removal of the lone-pair at pyrazole N-1 in the latter due to alkylation. An analysis of literature data confirms this suspicion as protonation, N-oxidation and complexation of the 'pyridine-type' N2-atom in 1-substituted pyrazoles - analogously - leads to a comparable reduction of the regarded coupling constant. Accordingly, with the 'free' pyrazolones **1** those forms having an 'intact' lone-pair (OH-forms **A** and CH-forms **C**) exhibit large ^2J values of approximately 9–11 Hz. Considering the obtained data, 4-acylpyrazolones **1** exist predominantely as hydroxypyrazoles **1A** in $CDCl_3$ or benzene-d_6 solution, in DMSO-d_6 also minor amounts of NH tautomer **1B** may contribute to the tautomeric composition. 1-Phenylpyrazol-5-one (**1**, R^4 = H) turned out to exist solely in the CH-form **1C** in benzene-d_6, in $CDCl_3$ a mixture of CH (**1C**) and OH-form (**1A**) was found, whereas in DMSO-d_6 a fast equilibrium between OH (**1A**) and NH isomer (**1B**) (with **1A** far predominating) is probable.

Observed ^2J(pyrazole C-4,H-3(5)) coupling constants in Hertz



2 **1C** **1A** **1B** **3**

2	**1C**	**1A**	**1B**	**3**
9.6 -10.1 (R^4 = COR)		9.8 -11.2 (R^4 = COR)		4.0 - 5.0 (R^4 = COR)
10.7 (R^4 = H)	11.1 (R^4 = H)	8.1 (R^4 = H)		6.3 (R^4 = H)
8.7 (R^4 = CO_2Et)		9.6 (R^4 = CO_2Et)		4.3 (R^4 = CO_2Et)

NUCLEOPHILIC SUBSTITUTION REACTIONS OF 1-PENTAFLUOROPHENYL-1-H-PYRROLE DERIVATIVES

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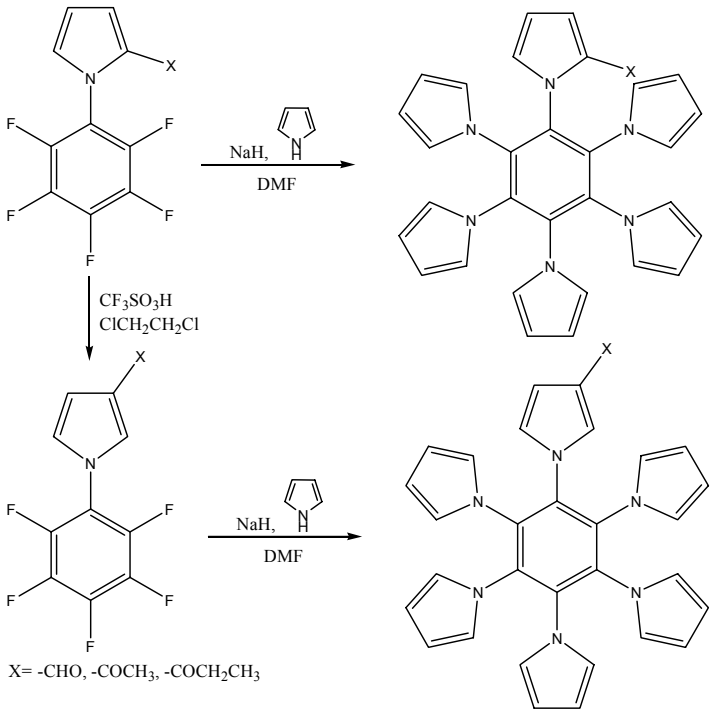
Highly symetrical, propeller-shaped, hexasubstituted benzenes have received considerable interest due to their intriguing properties as sterically congested polycyclic aromatic compounds [1]. A synthesis of hexapyrrolyl benzene [2] is based on the multiple nucleophilic substitution of perfluroaromatic with the corresponding nucleophile. The electrophilic substitution reactions of hexapyrrolyl benzene such as Vilsmeyer-Haack formylation and acylations with aliphatic acid anhydrides leads to non separable mixtures. The synthesis of wanted products important starting materials for the synthesis of naturally occuring porphynoid compounds and other porphyrins, potential chemotherapeutics agents and conducting polymers was realized by nucleophilic substitution reaction of appropriate 1-[1-(pentafluorophenyl-6-yl)pyrrole-2-yl]alkanones and 1-[1-(pentafluorophenyl-6-yl)pyrrole-2-yl]alkanones with pyrrolylsodium.



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SYNTHESIS OF PHOTOCHROMIC 1,2-DITHIENYLETHENES WITH THE RIGID FRAME

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Arkady A. Dudinov, Lyudmila G. Vorontsova

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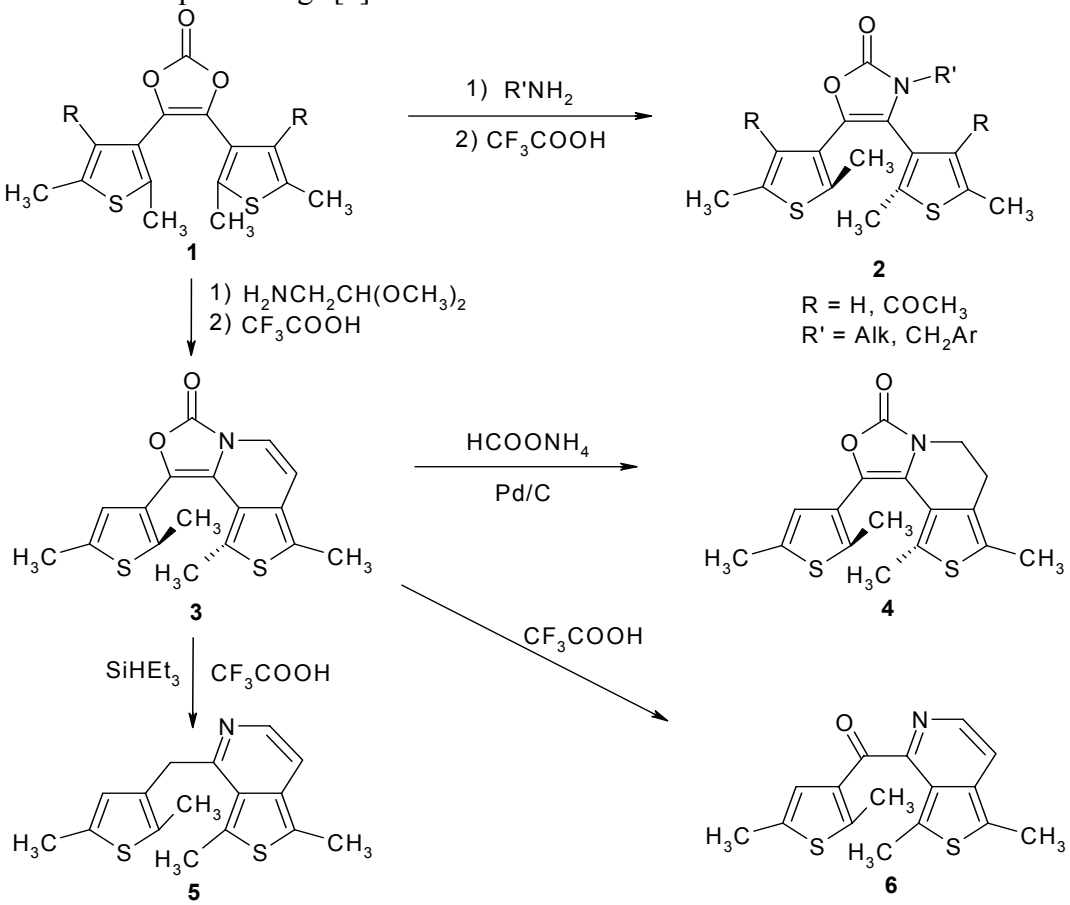
In recent years the considerable efforts has been made towards thermally stable 1,2-dihetarylethenes [1]. Earlier we have synthesized a series of 1,2-dithienylethenes based on the 1,2-dioxol-2-one moiety **1** and have demonstrated that those compounds are suitable for preparation a wide range of photochromic dihetarylethenes **2** with unsymmetrical orientation of thiophene rings [2].



1 **2** **3** **4** **5** **6**

A novel approach was elaborated to design a rigid dithienylethene system **3-4**, in which one of the thiophene rings is locked in antiparallel conformation favorable for photocyclization. Furthermore the synthesized thienopyridines **5-6** are of interest to develop the chemistry of photochromic 1,2-dithienylethenes with rigid conformation of thiophene units.

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SYTHESIS AND APPLICATIONS OF DIPEPTIDES IN THE SYNTHESIS OF HYDANTOIN DIMETHYAMINOPROPENOATES

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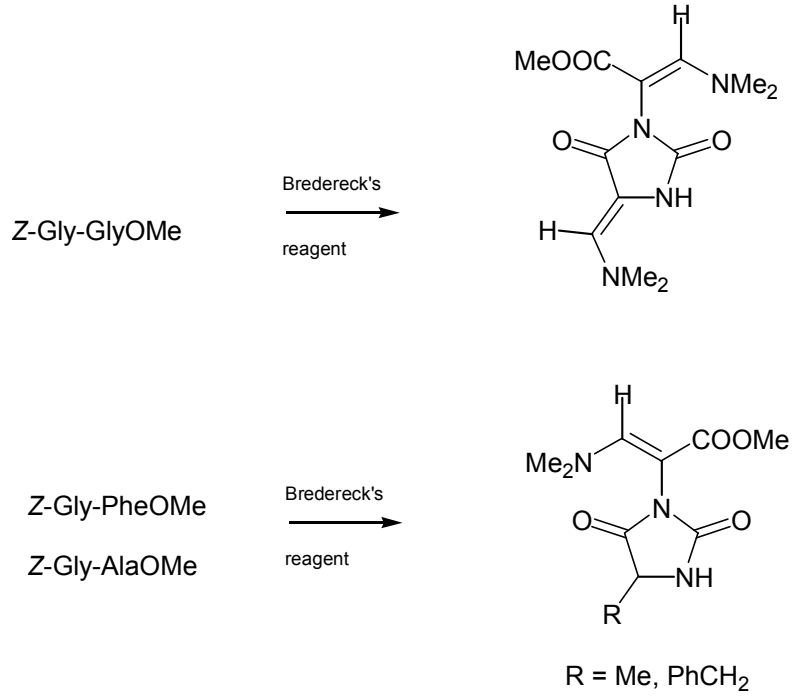
A series of dipeptides was prepared and transformed to methyl 3-dimethyamino-2-(4-alkyl-2,5-dioxoimidazolidine-1-yl)acrylates. Their reactivity with different nucleophiles was studied.



Hydantoins belong to significant heterocycles, since many of hydantoin containing natural and synthetic products exhibit diverse biological activities, such as antitumor, antiarrhytmic, anticonvulsant, herbicidal, and others [1]. *Z*-Glycine was coupled to various amino acid esters using the standard procedure and dipeptides were obtained in good yields. They reacted further with tert-butoxy-bis(dimethylamino)methane (Bredereck's reagent) yielding compounds which turned out to be useful reagents in the synthesis of heterocyclic systems with the hydantoin and unsaturated α,β-amino acid moiety [2-3].

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[3] R. Jakše, J. Svete, B. Stanovnik, *unpublished results.*

SYNTHESIS OF SPIROHETEROCYCLES VIA 1,3-DIPOLAR CYCLOADDITIONS

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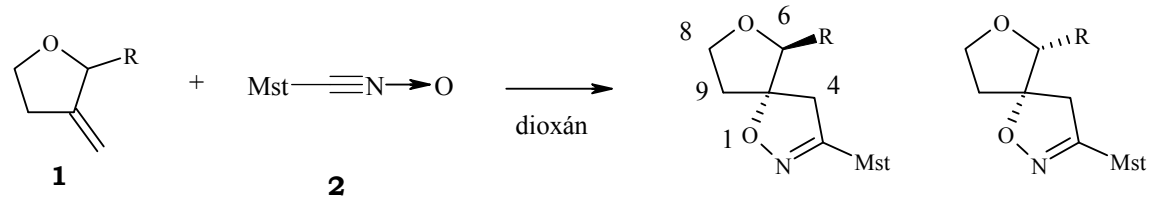
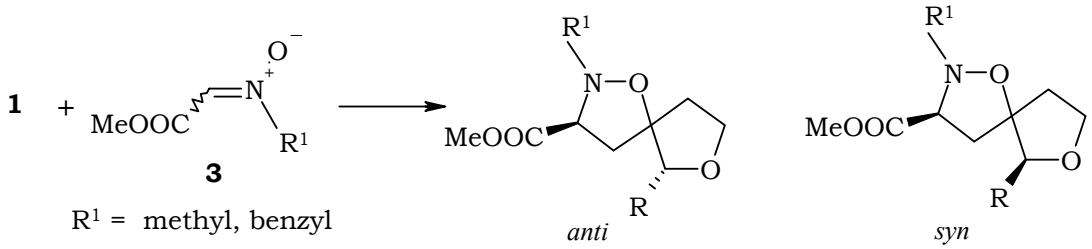
1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety different five-membered heterocycles, e.g. isoxazole and isoxazoline rings-substructures with inherent biological activity. In a continuation of our study to use the heterocyclic compounds possesing an exocyclic double bonds in 1,3-dipolar cycloadditions as dipolarophiles [1,2], we report here the preparation of some new spiroisoxazolines and spiroisoxazolidines *via* 1,3-dipolar cycloaddition. Our synthetic effort started with synthesis of substituted 3-methylidenetetrahydrofurans **1** which were used in 1,3-dipolar cycloadditions to nitrile oxide **2** and nitrones **3** (scheme 1). The cycloadditions proceeded with excelent regioselektivity.



1 **2**

R	*anti* : *syn*	yield / %
Ph-	92 : 8	52
2-tienyl	90 : 10	68
3,4-diCH_3OPh-	84 : 16	77



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IMPROVED SYNTHESIS OF THE P38 KINASE INHIBITOR 1-(3-BUTYLISOXAZOL-5-YL)-3-[4-(4-HYDROXYPHENOXY)-PHENYL]UREA

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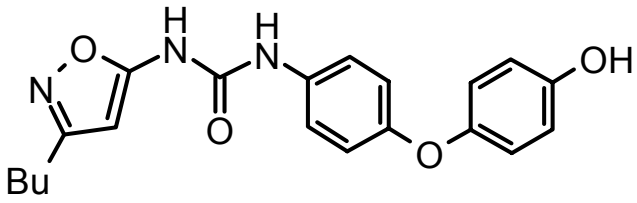
Compounds similar to the urea **1** are potent p38 and raf kinase inhibitors[1,2]. P38 kinase belongs to the family of mitogen-activated protein (MAP) kinases, and has been implicated in cytokine signaling. Members of the MAP kinase family are implicated of a wide variety of transcription factors and proteins involved in the control of cytokine production. Raf kinase is a downstream effector of the ras signal transduction pathway which transmits signals from groth factor and cytokine receptors on the cell surface to the nucleus, resulting in the regulation of cell differentiation and division. Inhibitors are potentially useful treatments against diseases of inflammation and cancer. In the context of the ongoing collaboration with the DrugMatrix program[2] we needed a reference sample of **1**. Analogous procedures disclosed in Bayer patents[1a] **1** were unsatisfactory in our hands.



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[2] http://www.iconixpharm.com/products/products_main.html

ONE POT SYNTHESIS OF 4-HETARYL-SUBSTITUTED 2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINES

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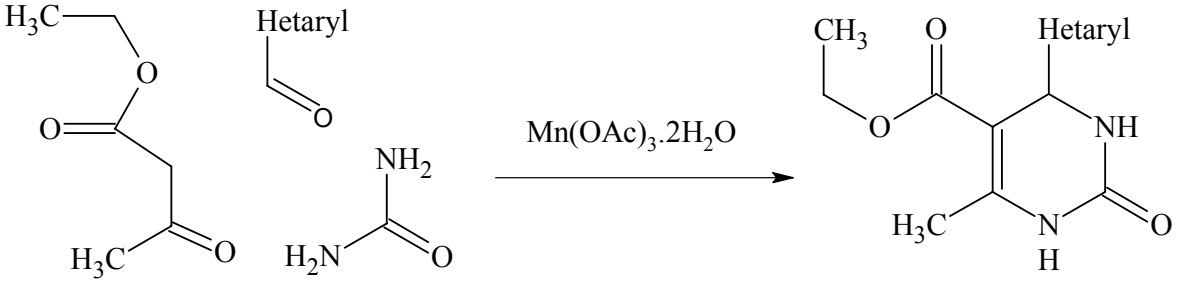
The reaction of numerous aldehydes with urea and β-keto ester to give a tetrahydropyrimidine derivatives (THPMs) was first discovered and formulated by Biginelli [1], therefore all these multi-functionalized pyrimidines are named as Biginelli compounds. In recent years, THPMs have become increasingly significant due to their therapeutic and pharmacological properties, because they show a diverse range of biological activities [2]; and nearly every day additional new structures are added to this list [3] .

We describe a work in this paper as a preliminary contribution dealing with synthesis and chemistry of 4-hetaryl-substituted compounds via Biginelli reaction. Thus, a series of THPMs were obtained via one-pot condensation reaction of various quinolinecarboxaldehydes in the presence of manganese(III) acetate by using excess amount of both ester and urea.



Hetaryl = quinol-2-yl , quinol-4-yl , quinol-8-yl , 6-methyl-quinol-2-yl

4,6-dimethylquinol-2-yl , 4,7-dimethylquinol-2-yl

The structures proposed for the new THPMs are consistent with data obtained from their ir, uv, ms, pmr and ^{13}C nmr spectra; moderate to excellent yields and uncorrected melting points of the crystallised products are reported.

* Correspondence.

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BASE CATALYSED THERMAL CONVERSION OF FURO[2,3-C]QUINOLINE-2,4(3AH,5H)-DIONES

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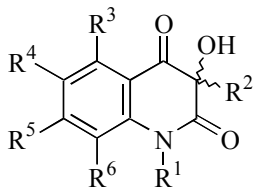
[a]Faculty of Technology, Tomas Bata University in Zlín, 762 72 Zlín, Czech Republic
[b]Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia

We previously demonstrated that Wittig olefination of 3-alkyl/aryl-3-hydroxyquinoline-2,4(1*H*,3*H*)-diones (**1**) unsubstituted at benzene ring with ethyl (triphenylphosphoranylidene)acetate in boiling xylene afforded mainly ethyl (2*E*)-(3-alkyl/aryl-3-hydroxy-2-oxo-2,3-dihydroquinolin-4(1*H*)-ylidene)acetates (**2**) whereas furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-diones (**3**) were isolated as side products.[1] On the other hand, 5,8-disubstituted compounds (**1**) reacted under the same reaction conditions in a completely different manner yielding mainly products of indoline and benzoxazinone structural types.[2] In the presence of catalytic amounts of benzoic acid compounds **3** and, moreover, isomeric furo[3,4-*c*]quinoline-3,4(1*H*,5*H*)-diones (**4**) were obtained.[2] It has been shown that compounds **4** are formed by molecular rearrangement of **3**, and an independent synthesis of the latter, based on intramolecular Wittig reaction, has also been described.[2,3]



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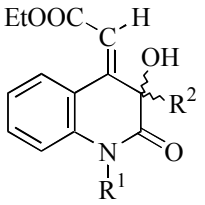

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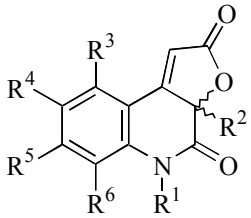

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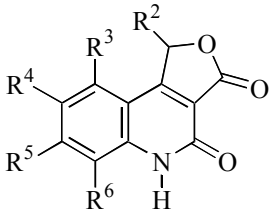

4

With the aim of investigating conditions for the synthesis of novel lactones **4** we now focused our attention to the rearrangement of **3**. Initial, experiments were conducted in boiling cyclohexylbenzene: (*a*) without any catalyst, and (*b*) in presence of triphenylphosphine or 4-dimethylaminopyridine as basic catalysts. So far, the rearrangement of **3** only took place with N-unsubstituted precursors **3** and in the presence of catalyst. The reactions were completed within one hour and the yields of the products **4** were satisfactory to good. The reaction mechanism has been proposed.

Acknowledgements.
The Ministry of Education, Youth and Sports of the Czech Republic and The Ministry of Education, Science and Sport of Slovenia supported this study.

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GENERATION OF BICYCLO[3.2.1]KETONES BY SONOCHEMICAL [4+3] CYCLOADDITIONS

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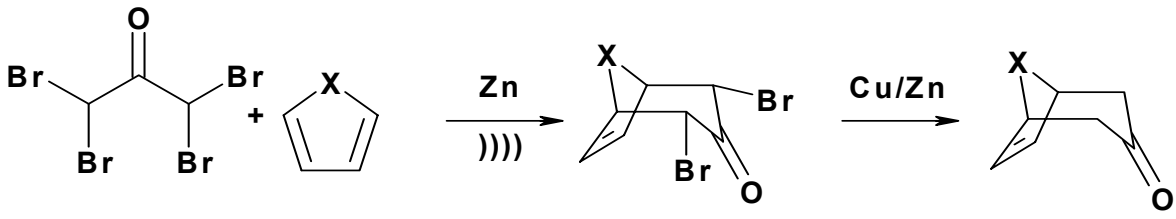
Bicyclo[3.2.1]ketones are important precursors for a broad scale of pharmacological active compounds.[1] One of the major pathways to this class of compounds is the [4+3] cycloaddition via an in situ generated oxallyl cation and a diene. Although new methods have been developed, the preparative setup is excessive and only moderate yields have been obtained.

Sonochemistry is a versatile tool for various types of cycloadditions[2]. The first [4+3] cycloadditons via ultrasound has been performed by *Montaña*[3], generating 2,4-substituted bicyclo[3.2.1]oct-6-en-3-ones. Based on this report, we investigated a new method of generating unsubstituted bicyclo[3.2.1]ketones, which are notoriously difficult to obtain, with different heteroatoms on position 8.



X = O, C, N-COOMe

In this contribution we discuss our latest results about cyclizations via ultrasound and compare them with common ways of generating bicyclo[3.2.1]ketones.

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MICROBIAL BAEYER-VILLIGER OXIDATIONS USING RECOMBINANT CELLS BIOTRANSFORMATION OF FUSED KETONES

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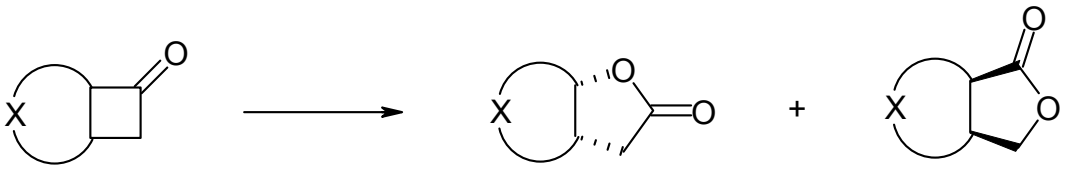
Baeyer-Villiger-type oxidation reactions using biocatalysts represent a powerful methodology for the one-step asymmetric synthesis of chiral lactones [1].
In a kinetic resolution process fused bicyclic ketones **1** with a cyclobutanone structural motif were transformed into bicyclic γ-lactones in high enantioselectivity using whole-cell cultures of *Acinetobacter* NCIB 9871 [2]. These lactones are important chiral synthons for preparation of prostaglandins, pheromones, and nucleosides [3].



1 **2** **3**

X = C, O

In this contribution we present new microbial transformations of fused ketones **1** using *E.coli* expression systems [4] for Baeyer-Villiger monooxygenases originating from several different bacteria. The biotransformation produces regioisomeric lactones from the two enantiomeric starting compounds: using different enzymes both the expected "normal" lactone **2**, and its regioisomeric "abnormal" lactone **3** are obtained in good yields and excellent enantiomeric excesses up to 95%ee.
A detailed discussion of the different substrate acceptance profiles and biotransformation trends of the utilized monooxygenases will be presented.

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ANNULATED PYRAZOLO[4,3-e][1,2,4]TRIAZINES NEW HETEROCYCLIC RING SYSTEMS

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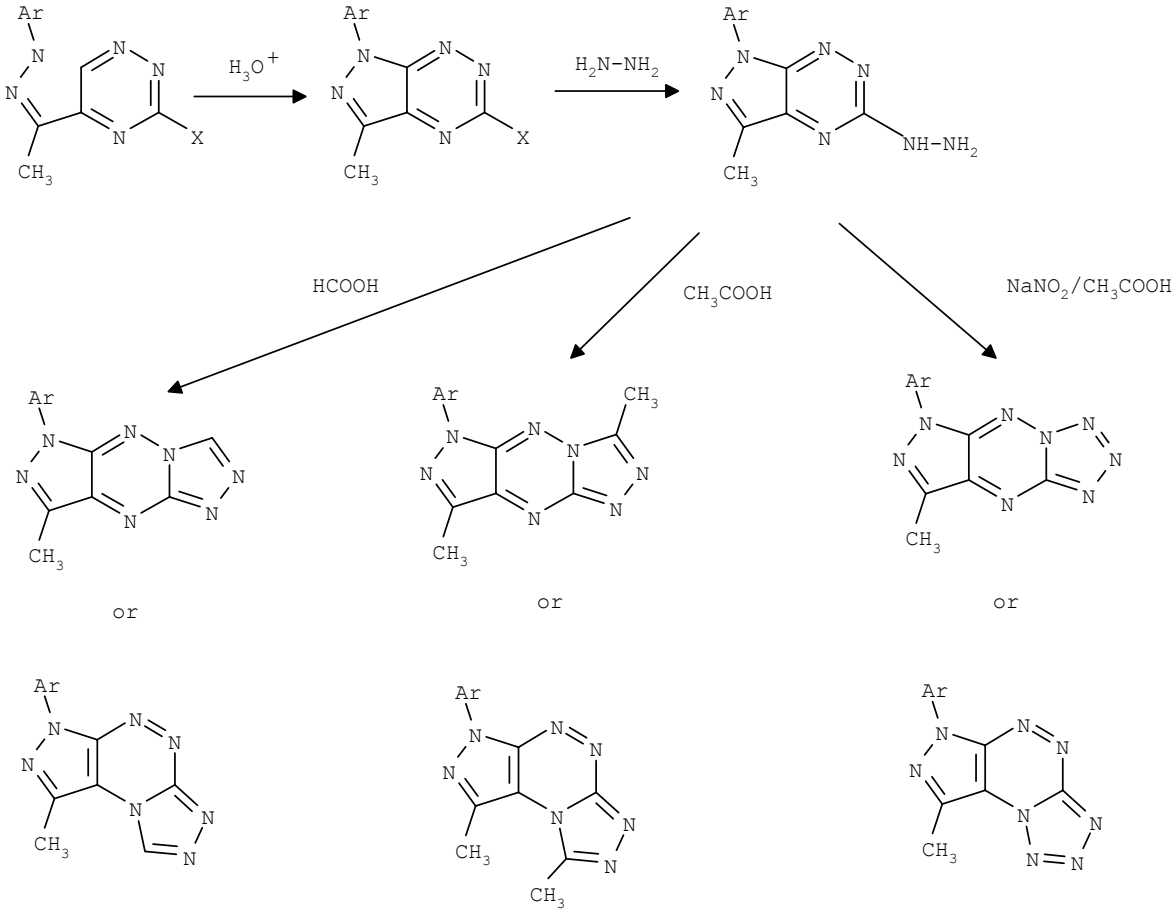
Pyrazolo[4,3-*e*][1,2,4]triazines (fluviols) exhibiting both antibacterial and antifungal activity were found in metabolites of strains of *Pseudomonas fluorescens var pseudoiodinum* and *Nostoc spongiaeforme* [1]. Recently we reported a novel one-pot synthesis of various substituted pyrazolo[4,3-*e*][1,2,4]triazines *via* acid promoted ring closure of the phenylhydrazones of 5-acyl-1,2,4-triazines [2]. The present paper deals with the synthesis and structure of novel triazolo- and tetrazolo-fused pyrazolo[4,3-*e*]-[1,2,4]triazines by the reaction of their functionalized derivatives, bearing an hydrazino group, with some cyclization agents.



To differentiate between such obtained linear or angular structures the advanced spectroscopic methods, X-ray analysis and theoretical calculations were applied.

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SYNTHESIS OF SOME NOVEL γ-SPIROLACTONES

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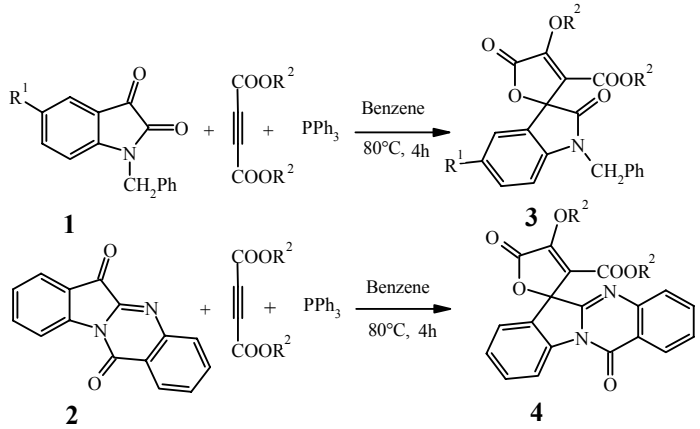
The addition of dialkyl acetylenedicarboxylate to 1-alkyl isatins or tryptanthrine in the presence of triphenylphosphine leading to highly functionalised novel unsaturated γ-spirolactones is reported.

γ-spirolactones have been shown an important class of molecules owing to their interesting structures and biological activities [1]. The lactone moiety is also present in many natural products [2], especially insect pheromones [3], antifungal substances, and flavor components that occurs in the essential oils of plants [4]. Recently, γ-spirolactones have been the subject of great consideration because of their effect as aldostrone inhibitors [5].

In view of our general interest in the chemistry of isatin and tryptanthrine [13], because of their bioactivity effects, and as a continuation of our work [13a], we have examined the reaction of *DMAD* with isatin derivatives or tryptanthrine in the presence of *TPP* and our preliminary results are reported here.

In this experiment, we observed that a mixture of 1-alkyl isatin derivatives or tryptanthrine and dialkyl acetylenedicarboxylates at 80 ˚C in benzene or toluene when treated with *TPP* afforded the products that were characterised as **3** and **4 (scheme 1)**.



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SYNTHESIS OF NOVEL β-LACTAM CONTAINING N-THIOCARBAMATE GROUPS

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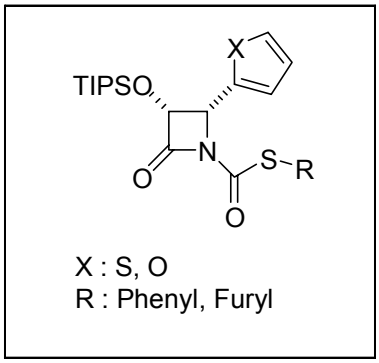
Since Gilman and Speeter reported the Reformatsky addition reaction to imines in 1943 it has been employed as a method to synthesize β-Lactams, β-aminoacids and their derivatives. β-Lactams are very important compounds existing widely in various antibiotics and other natural products [1,2].

However, to the best of our knowledge, there seems to be no reports on the synthesis of β-Lactam containing N-Thiocarbamate in high yield. Therefore, we extended our study to prepare β-Lactam containing N-Thiocarbamate which might show better antibiotic effect than the typical β-Lactams.

In this work, we produced imines which are used various aldehydes, react smoothly with acetoxyacetyl chloride to make cyclization . During that reaction, enantiomeric products are separated by using lipase amano enzyme hydrolysation. Final β-Lactams derivatives were coupled with various thiochloro formate to reach novel β-Lactams N-thiocarbamate contaning analogues which have been synthesized in high yield.



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SUPRAMOLECULARLY ASSISTED FUNCTIONALIZATION OF CARBOHYDRATES

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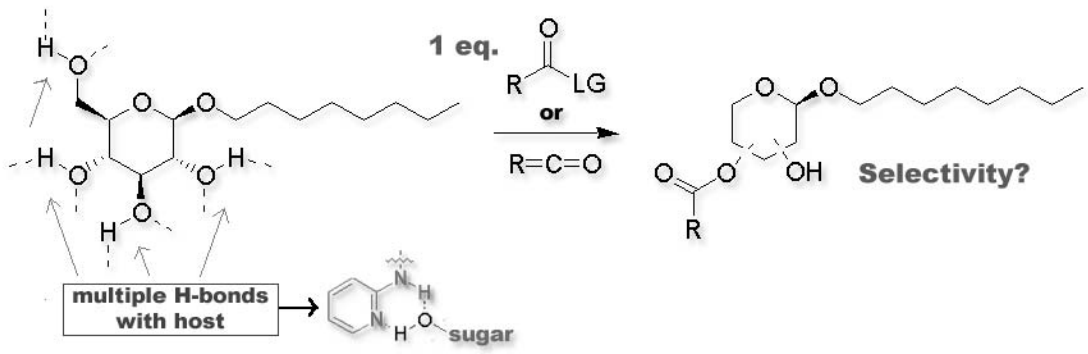
One major goal in modern carbohydrate chemistry consists in finding systems, that are able to recognize carbohydrates by non-covalent interaction. Strong interactions are desired, even in protic solvents [1]. The first host-designs were based on complex, rigid cage structures, which were believed to be a prerequisite for the formation of multiple and strong hydrogen bonds. Recently, Mazik [2] and others [3] disclosed some new, non-cage heterocyclic systems with unexpected strong affinities towards carbohydrates in aprotic systems.
Another major target in carbohydrate chemistry is to find ways for a selective manipulation of unprotected sugars. Bearing these two facts in mind we started a program to investigate the influence of multiple intermolecular hydrogen bonds on the selectivity of simple acylation reactions. First results will be reported.



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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NETROPSIN ANALOGUES

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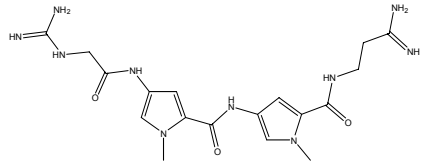
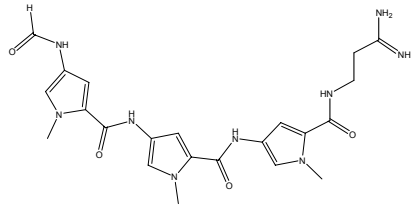
Distamycin and Netropsin (Lexitropsins) are pyrrole polyamides. These are naturally occurring anticancer antibiotics and well-known DNA binding agents. They bind reversibly to the minor groove of double helical B-DNA at regions with at least four AT base pairs. The high cytotoxicity of these compounds prevents them from being used as drugs. However, this class of pyrrole polyamides have attracted large interest, focused at the possibilities of modifying and improving the pharmaceutical usefulness of the minor groove binders. Large amounts of work have also been carried out aiming to increase the sequence specificity and selectivity of these DNA binding compounds.

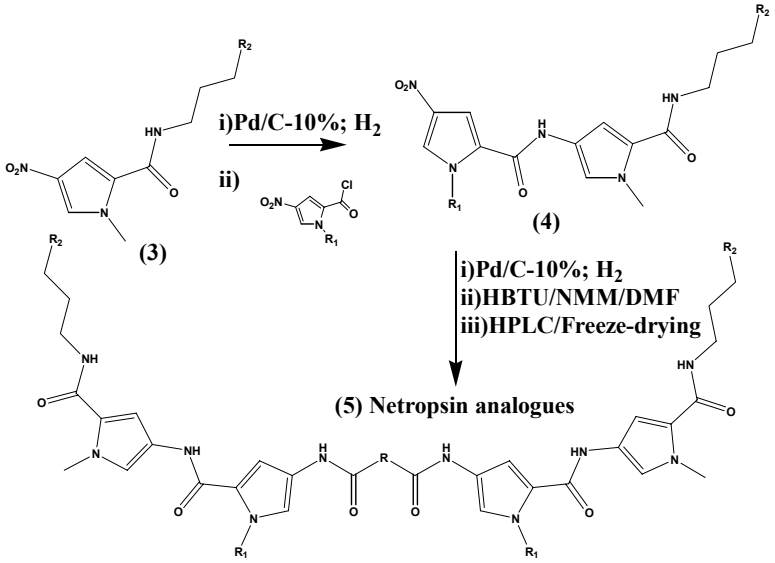


(1) Netropsin



(2) Distamycin

Our group and others are actively pursuing several ways of improving the antiviral, anti-fungal and antibacterial activity of netropsin analogues. The N-terminal ends were joined with a wide range of dicarboxylic acid linkers in a head to head fashion as illustrated in the scheme below. Reduction of the nitro group, followed by coupling to the carboxylic acid (or acid chloride), gave rise to the dimer, which was reduced and coupled to the dicarboxylic acid (linker) to afford the desired netropsin-like material. These compounds were tested against bacteria (gram positive and gram negative) and fungi, such as E. coli, S. aureus and MRSA. Some of the netropsin analogues showed comparable activity to the existing drugs such as Amoxicillin, Fluconazole and Streptomycin.



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SYNTHESIS OF A NOVEL HETEROCLES VIA THE REACTION OF 3-AMINO-1H,3H-QUINOLINE-2,4-DIONES WITH UREA

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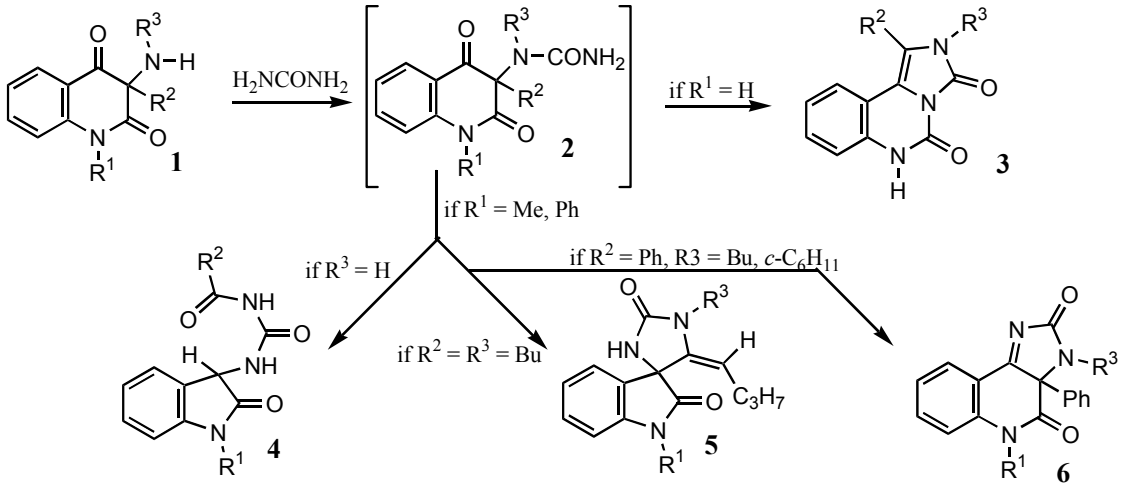
[b]Research Institute of Organic Syntheses, CZ-53218 Pardubice, Czech Republic
[c]Department of Analytical Chemistry, Faculty of Chemical Technology, University of Pardubice, CZ-53210 Pardubice, Czech Republic

3-Alkyl/aryl-3-amino-1*H*,3*H*-quinoline-2,4-diones (**1**) [1] react with urea in boiling acetic acid to give products depending on the type of substitution in positions 1 and 3 and also at the nitrogen atom of the 3-amino group. In most cases, a molecular rearrangement of the transiently formed 3-ureido-1*H*,3*H*-quinoline-2,4-diones (**2**) proceed.
Starting compounds unsubstituted at lactam nitrogen rearrange in high yields to 2,6-dihydro-imidazo[1.5-*c*]quinazoline-3,5-diones (**3**) [2]. Compounds **1** substituted at lactam nitrogen and bearing a primary amino group in position 3 give [3] 3-(3-acylureido)-2,3-dihydro-1*H*-indol-2-ones (**4**). Starting compounds bearing a secondary amino group in position 3 react according to the character of the other substituent in position 3. If there is a hydrogen atom α to the carbon atom C-3, 4-alkylidene-1′*H*-spiro[imidazolidine-5,3′-indole]-2,2′-diones (**5**) arise [3]. If a hydrogen atom is not present in this position, the reaction leads [3] to 3,3*a*-dihydro-5*H*-imidazo[4,5-*c*]quinoline-2,4-diones (**6**). Reaction mechanisms for these transformations will be presented.



Acknowledgements: This study was supported by the Ministry of Education of the Czech Republic (Grant No. MSMT 265200015) and the Grant Agency of the Czech Republic (Grants No. 203/02/0023 and 203/03/0356).

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REACTIONS OF STERICALLY CROWDED (1-ARYL-3,5-DIPHENYL-1H-PYRROL-2-YL)PHENYLMETHANONES WITH ORGANOLITHIUM REAGENTS

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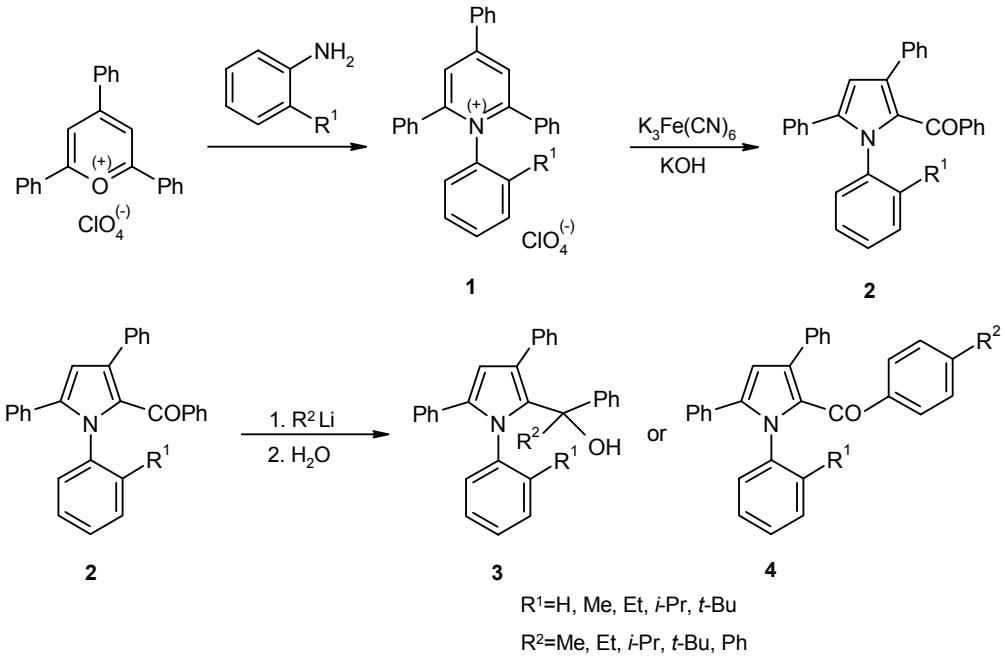
Extended Decker oxidation of 1,2,4,6-tetraarylpyridinium salts represents suitable synthetic procedure for the preparation of atropoisomeric aryl-(1,3,5-triaryl-1*H*-pyrrol-2-yl)methanones. Axial chirality of some pyrrole derivatives prepared using this method has been studied in the past [1].

1-Aryl-2,4,6-triphenylpyridinium-perchlorates (**1**) were converted to (1-aryl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanones (**2**) by treatment with potassium ferricyanide and potassium hydroxide.

Sterically crowded (1-aryl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanones (**2**) were treated with selected organolithium reagents to give corresponding tertiary alcohols (**3**) or 4´-substituted ketones (**4**). The influence of structure of organometallic reagent on regioselectivity of the reaction was studied. The diastereoselectivity was investigated in the case of the reactions of methyllithium and (1-aryl-3,5-diphenyl-1*H*-pyrrol-2-yl)phenylmethanones with restricted rotation around C-N bond. Some tertiary alcohols (**3**) were submitted to dehydration and dehydroxymethylation.



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IMPROVED SYNTHESIS OF THE TYROSINE KINASE INHIBITORS CT-53518 AND GEFITINIB

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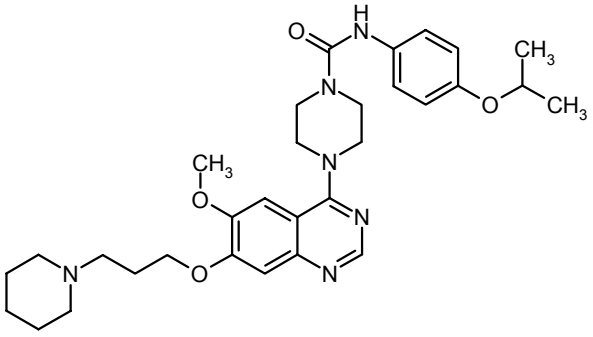
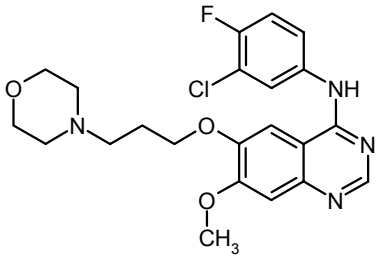
4-[4-(N-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazolines can function as potent and selective inhibitors of platelet-derived growth factor receptor (PDGFR) phosphorylation. A series of highly potent, specific, orally active, small mol. kinase inhibitors directed against members of PDGFR receptor have been developed recently. CT-53518 inhibits Flt-3, bPDGFR, and c-Kit receptor phosphorylation with IC50 values of 50-200 nM. Oral administration of CT-53518 promotes mice survival and significantly delayed disease progression in a Flt-3/ITD-mediated leukemia mouse model and shows efficacy in a nude mouse model of chronic myelomonocytic leukaemia [1,2].
We will report an optimized synthesis of CT-53518 that we developed in the context of the collaboration with the DrugMatrix program [3], the world's largest chemogenomics reference database and informatics system.
Gefitinib (=Iressa) has already shown its capacity as modern anticancer agent [3].

We will present optimized syntheses of the title compounds.



CT-53518



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AN ACCESS TO α-C-(1→3)-LINKED DISACCHARIDES CONTAINING DEOXYHEXOPYRANOSES.

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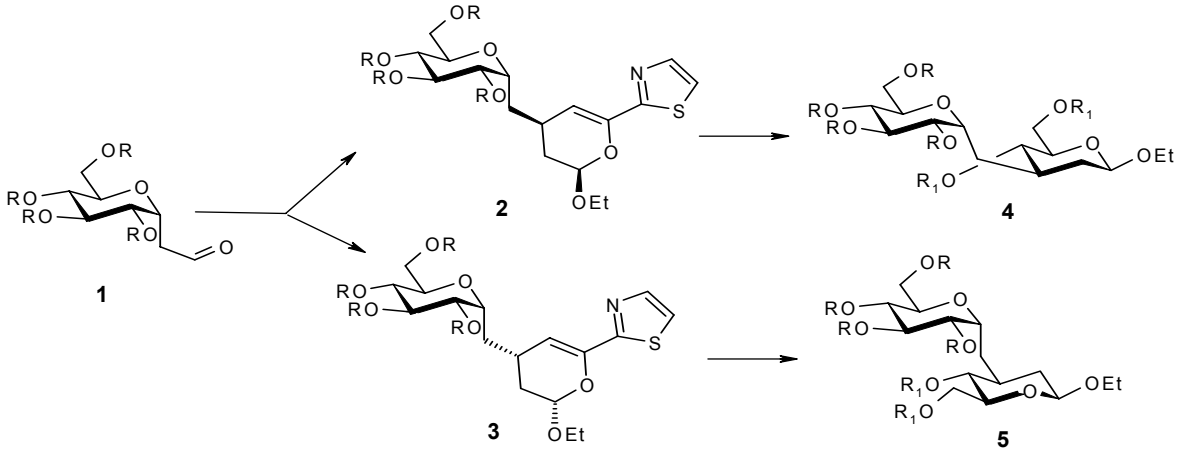
Formal replacement of the glycosidic oxygen atom by methylene group in disaccharides leads to a group of compounds denoted trivially as *C*-disaccharides. It is assumed that *C*-disaccharides mimic well the structure of the natural disaccharides but – unlike them – they resist acidic as well as enzymic hydrolysis. Therefore, *C*-disaccharides are potential inhibitors of glycosidases or glycosyltransferases. Since these enzymes play a crucial role in the biosynthesis of cell-surface oligosaccharides that are important for intercellular communication, we can expect that some *C*-disaccharides could find use as compounds with therapeutic effects [1].

For these reasons, there is an increased interest in the search for new synthetic pathways leading to various types of *C*-disaccharides and in the study of their properties. Here we report our approach to new type of *C*-(1→3) disaccharides containing deoxyhexopyranoses. Protected α-D-glucopyranosylacetaldehyde **1** was converted by Wittig reaction with (thiazol-2-yl)carbonylmethylenetriphenyl phosphorane into the corresponding substituted 1-oxa-1,3-butadiene which by hetero-Diels-Alder reaction with ethyl vinyl ether afforded a mixture of two diastereoisomeric dihydropyran derivatives **2** and **3**. These were separated by chromatography and the thiazol ring was transformed into an aldehyde group. Subsequent hydroboration afforded α-*C*-(1→3)-linked disaccharides **4** and **5** containing 2-deoxyhexopyranoses of D- and L- configuration, respectively.



References:

[1] (a) Du, Y.; Linhardt, R. J.; Vlahov, I.R. *Tetrahedron* **1998**, *54*, 9913. (b) Vogel, P. *Chimia* **2001**, *55*, 359.

Acknowledgement: This work was supported by Ministry of Education, Youth and Sports of the Czech Republic, Project No. 22330006

A NEW SIMPLE SYNTHESIS OF BENZO[4,5]IMIDAZO[1,2-a]PYRIDINE-4-CARBONITRILES

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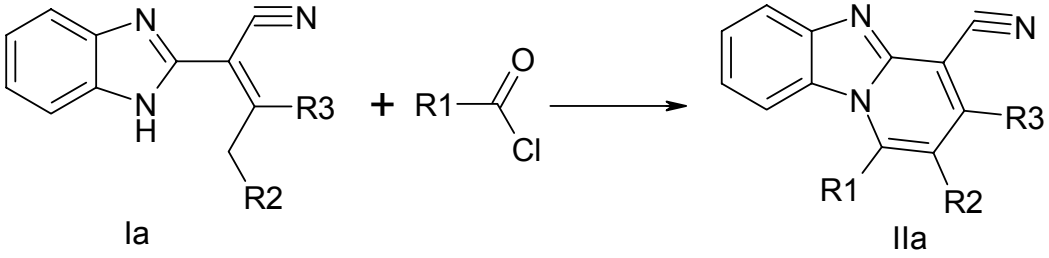
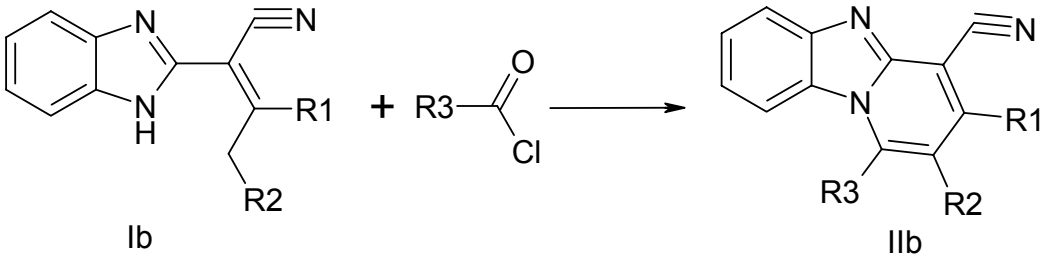
A typical synthetic approach to benzo[4,5]imidazo[1,2-*a*]pyridine-4-carbonitriles via cyclocondensation 2-benzimidazoleacetonitrile with β-diketones have been described Mencke and co-workers [1]. This method can not be successfully applied to the synthesis of target compounds with different substituents in positions 1 and 3 in case of unsymmetrical diketones or their derivatives and leading to the mixture isomers II a,b. To our knowledge, there is only one route described by Zimmerman [2] leading to such type of compounds. Thus, cyclocondensation and ring opening of triarylpyrylium salts with 2-benzimidazoleacetonitrile gave IIa or IIb. The convenient method for preparation of various 1,3-disubstituted benzo[4,5]-imidazo[1,2-*a*]pyridine-4-carbonitriles II has been elaborated in our laboratory. It consists of acylation of 2-alkylidene or 2-arylidene-2-benzimidazoleacetonitriles (I) with 1.2-fold excess of acid chlorides.



Ia IIa



Ib IIb

R1,R3 = alkyl, aryl
R2 = H, alkyl, aryl

The structure of prepared products was confirmed by analytical and spectral data. Moreover, some of the obtained compounds turned out to be the same with those described in literature [1, 2]. Furthermore, this approach can also be applied for synthesis of derivatives of a novel heterocyclic system, namely 13H–benzo[4,5]imidazo[1,2-*a*] chromeno[3,4-*c*]pyridin-13-one.

[1] Mencke; Schmitt; Arch.Pharm.Ber.Dtsch.Pharm.Ges.; 300; 6; 1967; 481.
[2] Zimmermann, T.; J.Pract.Chem./Chem.-Ztg. 1993, 335(8), 717-20(Ger).

THE SYNTHESIS OF 1,3-SELENAZOLE BY REACTION USING SELENAZADIENE

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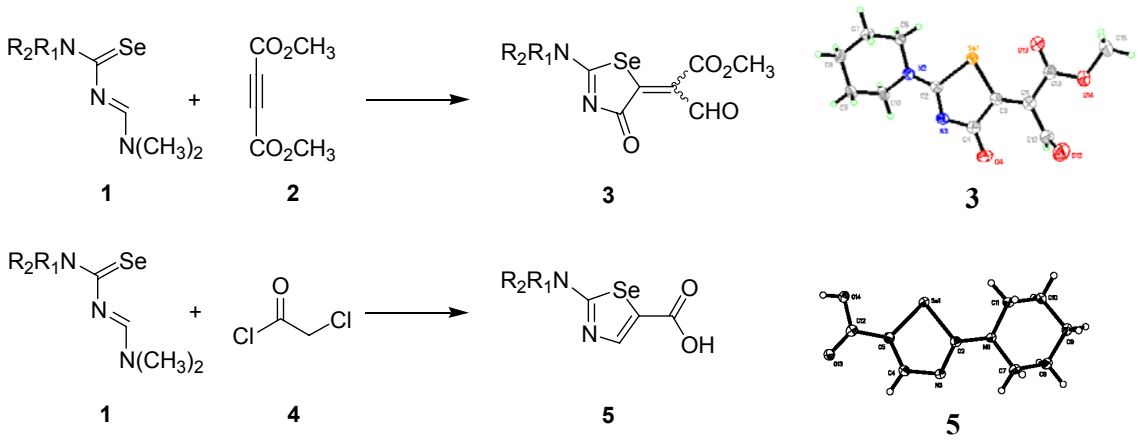
Hetero Diels-Alder reaction of selenazadiene with dimethyl acetylenedicarboxylate yielded 4-selenazolone instead of the expected Diels-Alder adduct. Reaction of the selenazadiene with chloroacetyl chloride gave 1,3-selenazolyl-5-carboxylic acid.

Many syntheses of heterocyclic compounds containing selenium have been extensively investigated because of their interesting reactivities and potential pharmaceutical significance. We are interested in the synthesis of novel cyclic compounds containing selenium.[1] In the present study, we have confirmed a pathway to 1,3-selenazol-4-one **3** *via* cycloaddition and elimination by the reaction of selenoazadiene **1** with dimethyl acetylenedicaboxylate **2**. Interestingly, the reaction did not give the expected Diels-Alder adduct but instead a separable mixture of *E*/*Z* isomers of **3** was obtained. The crystal structure of the obtained 1,3-selenazol-4-one **3** was determined by X-ray diffraction. We also confirmed that reaction of the selenoazadiene **1** with chloroacetyl chloride **4** gave 1,3-selenazolyl-5-carboxylic acid **5**. The crystal structure of the obtained 5 was confirmed by X-ray diffraction. We discuss their structural characterization and reaction mechanisms.



[1] (a) Koketsu, M.; Nada, F.; Mio, T.; Ishihara, H. *Heterocycles*, **2003**, *60*, 1211. (b) Koketsu, M.; Ishihara, H. *Curr. Org. Chem.*, **2003**, *7*, 175. (c) Koketsu, M.; Kanoh, M.; Ishihara, H. *Synlett*, **2002**, 805. (d) Koketsu, M.; Nada, F.; Hiramatsu S.; Ishihara H. *J. Chem. Soc., Perkin Trans. 1*, **2002**,740 (e) Ishihara, H.; Koketsu, M.; Fukuta Y.; Nada F. *J. Am. Chem. Soc.* **2001**, *123*, 8408. (f) Koketsu, M.; Takenaka, Y.; Ishihara, H. *Synthesis* **2001**, 731. (g) Koketsu, M.; Yang, H.O.; Kim, Y.M.; Ichihashi M.; Ishihara, H. *Org. Lett.*, **2001**, *3*, 1705.

SYNTHESIS OF PYRIDO[1,2-A]PYRIDIMIDINONE, PYRIMIDO[2,1-B]THIAZOLONE AND PYRAZOLONE FROM DEHYDRO ACETIC ACID

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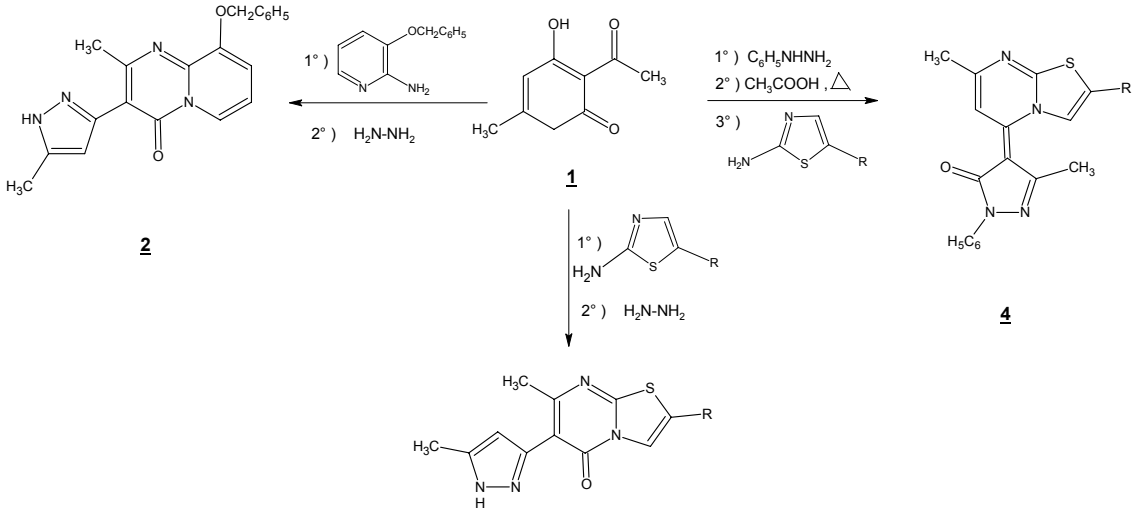
b : Université Paul Sabatier, Bat. De Chimie, 118, route de Narbonne, 31062 Toulouse, France.

In an extention of our study on the reactivity of dehydro acetic acid [1] **1**, we have developped the synthesis of fused heterocyclic series **2**, **3** and **4**.
These reactions provided convenient access to a variety of condensed heterocyclic systems known by their biological activities.
Under below conditions, each reaction case involves intermediate forms, via cleavage of dehydro acetic acid heterocycle, wich were then converted into products **2**, **3** or **4**.
The synthetic and mecanistic aspects of these sequences will be described in detail.



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

The structures of different products were assigned and confirmed on the basis of their elemental analysis and spectral data.

[1]. M. Amari, M. Fodili, B. Nedjar-Kolli, P. Hoffmann and J. périé, J. Heterocyclic Chem. 39, 1 (2002).

DIRECTED ORTHO-METALLATION AND COUPLING REACTIONS WITH 3-SUBSTITUTED FURANS.

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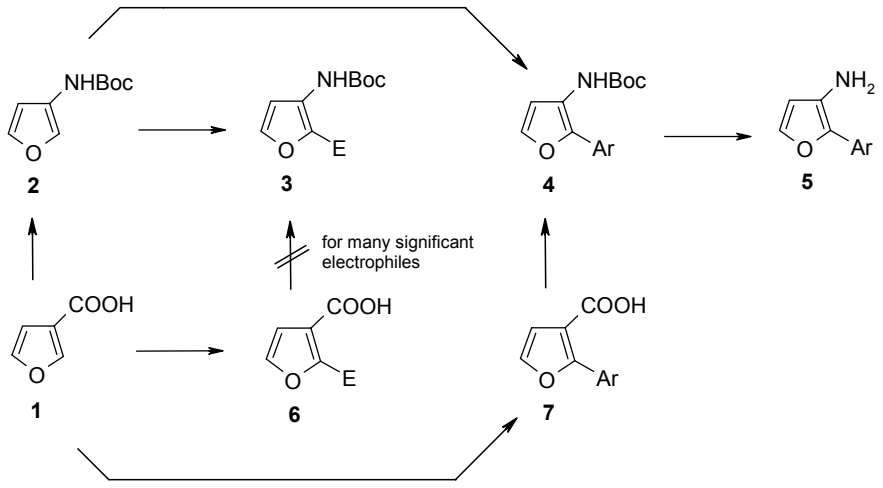
Directed *ortho*-metallation (D*o*M)[1] adjacent to heteroatom containing functional groups is a very efficient methodology for the construction of aromatic substitution patterns and has overtaken the classical electrophilic aromatic substitution as the principal means of making regiospecifically substituted aromatic compounds. Since 1980 when the N-*tert*-butylcarbamate group was reported the first time as a directing group[2], no paper appeared where this directed metallation group (DMG) was used in furan chemistry. Although a moderate DMG, the NHBoc-group is of high synthetic value as it can by transformed to the amino group under very mild conditions. In the course of a long-term project in collaboration with Syngenta Crop Protection AG we became interested in 2-substitued 3-aminofurans. Looking for a general and efficient route to this target compounds we developed two sequences as shown in Scheme 1:



Scheme 1

1) Lithation of 3-furoic acid **1**[3] which after introduction of appropriate substituents is not generally transformable to the corresponding 3-N-Boc-aminofurans **3**.
2) Curtius rearrangement of the acid **1** to 3-N-Boc-aminofuran **2** followed by lithation and quenching the dilithio-intermediate with appropriate electrophiles, leading to a series of target compounds **3**.
3) Finally, sterically hindered 2-aryl-3-aminofurans **5** were available by application of palladium-catalyzed cross-coupling reactions, preferably *via* lithiation of **2**.

[1] V. Snieckus, *Chem. Rev.* 1990, *90*, 879-933.
[2] J. M. Muchowski, M. C. Venturi, *J. Org. Chem.* 1980, *45*, 4798-4801.
[3] D. W. Knight, A. P. Nott, *J. Chem. Soc. Perkin Trans.1* 1981, 1125-1131.

SYNTHESIS AND PROPERTIES OF NEW LIQUID CRYSTALS BASED ON [1]BENZOTHIENO[3,2-B][1]BENZOTHIOPHENE CORE

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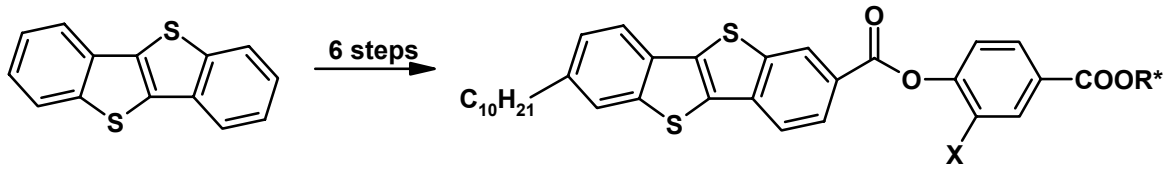
[b]Institute of Physics, Academy of Sciences of the Czech Republic, Na Slovance 2, CZ-182 21 Prague 8, Czech Republic

Recently we showed [1] that [1]benzothieno[3,2-*b*][1]benzothiophene (**1**) heterocyclic system elongated only with simple alkyl chains exhibits smectic phases. Presence of a chiral alkyl residue led even to formation of the antiferroelectric SmC_A* phase in a broad temperature interval.

In order to extend the number of studied chiral derivatives a convenient method for introduction of carboxyl moiety into the molecule of heterocycle **1** was devised. This procedure enabled us to prepare chloride of 7-decyl[1]benzothieno[3,2-*b*]-[1]benzothiophene-2-carboxylic acid in high yield after five synthetic steps. Based on this chloride, series of chiral aromatic esters of 7-decyl[1]benzothieno[3,2-*b*]-[1]benzothiophene-2-carboxylic acid bearing various lateral substituents were prepared and their liquid crystalline properties studied.



X = H, F, Cl, Br, OCH_3, NO_2

The work is financially supported by Grant Agency of Czech Republic (Project No. 202/02/0840) and grant COST D14-WG0015.

[1] Košata B., Kozmík V., Svoboda J., Novotná V., Vaněk P., Glogarová M.: *Liq. Cryst.* **2003**, *30*, in press.

SCOPE, MECHANISM AND APPLICATION OF CATALYTIC AND REGIOSELECTIVE SULFONYLATION OF α-CHELATABLE ALCOHOLS

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[b] Chemical Process R&D, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285-4813, USA

The regioselective sulfonylation of hydroxy groups in polyol substrates has been of considerable interest to organic chemists and the stannylene acetals have been widely employed substrates. However, the unavoidable co-production of a stoichiometric amount of lipophilic tin waste poses a significant problem. Our investigation into a catalytic approach has revealed that a convenient protocol for regioselective sulfonylation of α-chelatable alcohols in a catalytic fashion typically employs 2 mol% of Bu_2SnO, 1 equiv of *p*-TsCl and 1 equiv of Et_3N and rapidly leads to exclusive mono-tosylation.[1]

Herein we would like to show the effect of solvent, base and structure on the reaction rate as well as a plausible mechanism for this reaction, based on ^{119}Sn NMR studies.

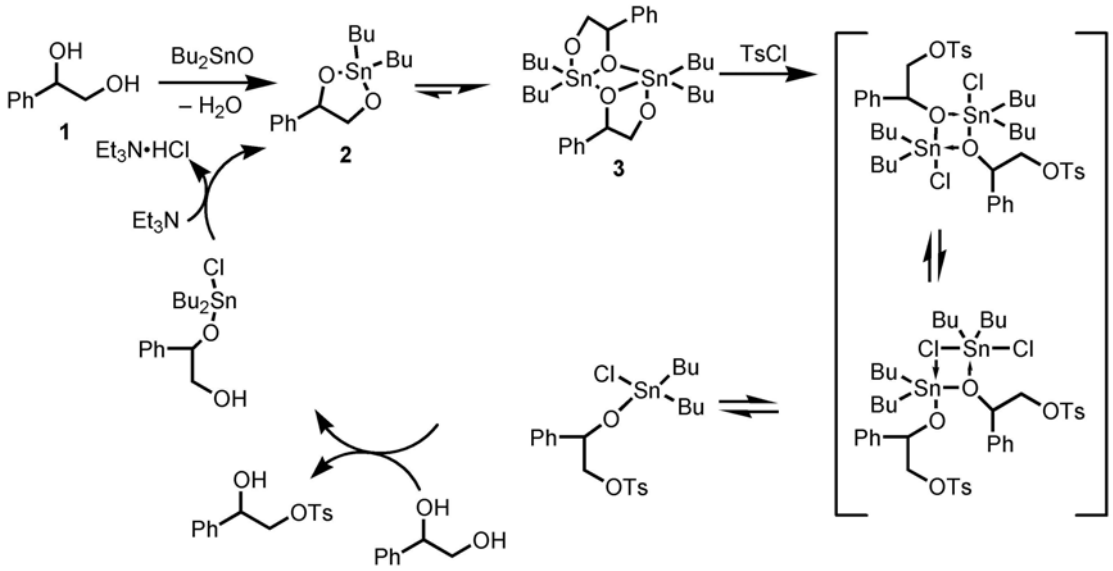

Figure Proposed mechanism of the Bu_2SnO-catalyzed tosylation reaction

[1] *J. Am. Chem. Soc.* **2002**, *124*, 3578–3585.

A NEW EFFICIENT ROUTE TO PYRIDAZINOINDOLES BY THE APPLICATION OF SUZUKI CROSS-COUPLING REACTIONS

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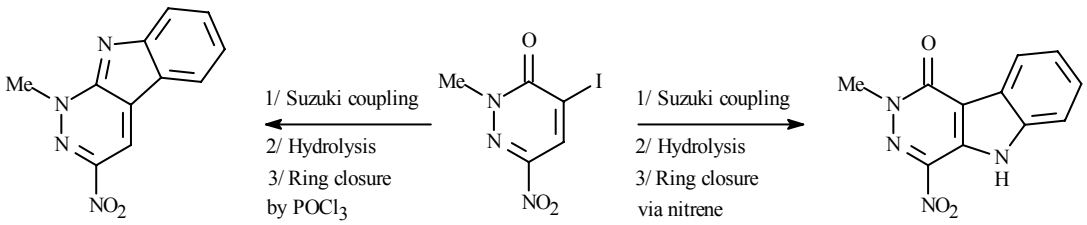
In our previous studies we reported on a new synthetic approach to pyridazino[3,4-*b*]indole [1] and pyridazino[4,5-*b*]indole-4(3*H*)-one [2] ring systems by Pd(0)-catalyzed cross coupling reactions of 4-iodo-2-methyl-6-nitro-3(2*H*)-pyridazinone and 5-iodo-2-methyl-3(2*H*)-pyridazinone, respectively, and the subsequent ring closures of the arylpyridazinones. In this communication, we report on the preparation of 2-methyl-4-nitropyridazino[4,5-*b*]indol-1(2*H*)-one by Suzuki reaction of 4-iodo-6-nitropyridazinone precursor obtained from 4,5-dichloro-6-nitropyridazinone. The structure of 4-iodopyridazinone was established by ^{1}H-^{15}N heteronuclear chemical shift correlation measurements, and it was also supported by chemical transformations.



References:

[1] G. Krajsovszky, P. Tapolcsányi, Gy. Horváth, P. Mátyus, Zs. Riedl, G. Hajós: A Novel Efficient Synthesis of Pyridazino[3,4-*b*]indole and Pyrimidino[5,4-*c*]cinnoline Ring System. *9th Blue Danube Symposium on Heterocyclic Chemistry* 16th-20th June 2002 Tatranska Lomnica (Slovak Republic)

[2] G. Krajsovszky, Zs. Riedl, D. Csányi, P. Mátyus, G. Hajós, *Heterocycles* **55**, 1105-1111 (2001)

THE SYNTHESIS OF 8-HYDROXYQUINAZOLINE DERIVATIVES AND THEIR ACID–BASE INTERACTIONS

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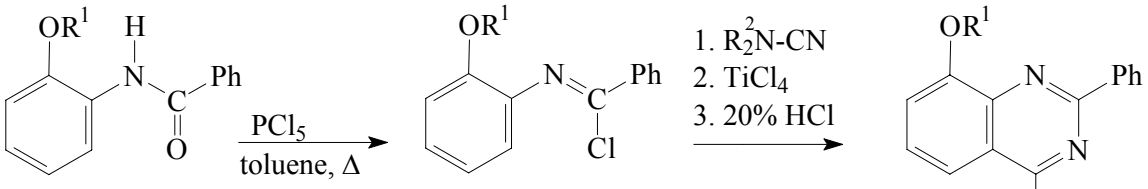
Quinazolines have been attracting attention for a few decades due to a wide range of biological activity [1]. Particular attention has been focused on amino and methoxy derivatives which demonstrate anti-malaria and cancerogenic properties and are used to work out medicines against hypertension [2].

A group of 4-amino-8-hydroxy-2-phenylquinazoline derivatives has been synthesized from well-known compounds: *N*-(2-hydroxyphenyl)benzamide and *N*-(2-methoxyphenyl)benzamide. The synthesis consists in converting of *N*-(2-R^1-oxyphenyl)benzamide derivatives to the appropriate benzimidoyl chlorides in the reaction with PCl_5. Such chlorides react then with cyanamide derivatives yielding probably acyclic linear products which undergo cyclization with the use of $TiCl_4$ to final 8-R^1-oxyquinazolines (scheme).



R^1 = H, Me, CPh_3
R^2 = H, Me, Et

Unfortunately, the unsubstituted *N*-(2-hydroxyphenyl)benzamide reacts with PCl_5 in anhydrous toluene yielding mainly 2-phenyl-1,3-benzoxazole. It was necessary to protect the hydroxy group in amide using Ph_3CCl to avoid such side reaction and then transfer the protected amide into the benzimidoyl chloride and finally to quinazoline.

Considering the fact that a biological activity of compounds is also greatly dependent on their ability to acid-base interactions, the pK_a values of the synthesized compounds have been also determined.

Some aspects of the synthesis, spectral characteristic of the compounds and the pK_a measurements are going to be presented.

[1] W. L. Armarego, 'Fused Pyrimidines: Part I-Quinazolines', Interscience Publishers, New York-London-Sydney, 1967.
[2] R. O. Dempcy, E. B. Skibo, *Biochemistry*, 1991, **30**, 8480.

IMPROVED SYNTHESIS OF THE P38 INHIBITOR 3-[3-(4-CHLOROPHENYL)-3-(NAPHTHALEN-2-YLAMINO)-PROPANOYL]-4-HYDROXY-1-METHYLQUINOLIN-2(1H)-ONE

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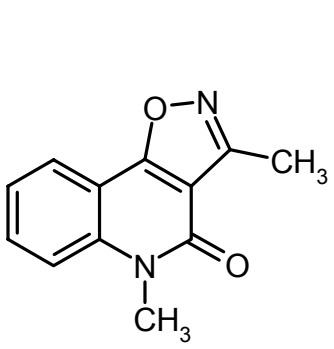
P38 mitogen-activated protein (MAP) kinase is supposed to be responsible for inflammatory and neurological diseases. Inhibitors of this key enzyme are suitable pharmaceutical targets as potential drugs. P38 MAP kinase is a specific member of the MAP kinase family which is involved in signal transduction and the amplification of cellular responses to stimuli and it is associated with the onset and progression of inflammation. The heterocyclic compounds **1** and **2** are known p38 MAP kinase inhibitors. While **1** has an assigned CAS registry number [2] with no associated references, the literature procedure for **2** was inadequate for preparation of multi-gram quantities. [3].
We will report an optimized synthesis of **1** and **2** that we developed in the context of the collaboration with the DrugMatrix program [4], the world's largest chemogenomics reference database and informatics system.



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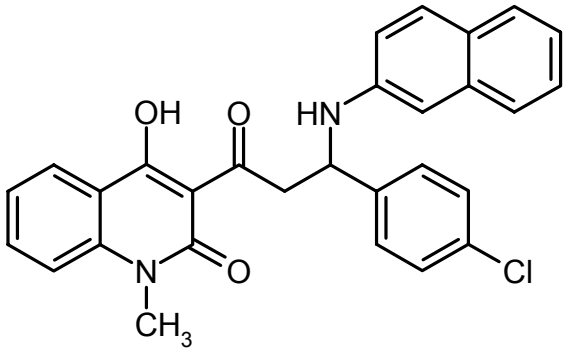

2

ICX-56319223

Leading references: [1]. (a) Ambrosino, C.; Nebreda, A. R., **Cell cycle regulation by p38 MAP kinases**. *Biology of the Cell* **2001**, *93*, 47-51; (b) Adams, J. L.; Gallagher, T. F.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Gum, R. J.; Webb, E. F.; Sorenson, M. E.; Smietana, J. M.; Garigipati, R. S.; Hall, R. F.; Ayrton, A.; Badger, A.; Griswold, D. E.; Young, P. R.; Lee, J. C., **P38 MAP kinase inhibitors: Progress, pitfalls and possibilities.** *Special Publication - Royal Society of Chemistry* **2001**, *264 (Medicinal Chemistry into the Millennium)*, 163-173; (c) Underwood, D. C.; Griswold, D. E., **Inhibition of p38 MAP kinase**. *Progress in Respiratory Research* **2001**, *31 (New Drugs for Asthma, Allergy and COPD)*, 342-345
[2]. CAS [359907-66-7].
[3] Melese, Teri; Perkins, Edward L.; Nguyen, Allen T. Q.; Sun, Dongxu. **Quinolin-2-ones and isoxazolo[3,4-c]quinolin-2-ones as modulators of phosphoinositide 3-kinase.** PCT Int. Appl. **2003** WO 0335618 CAN 138:353971.
[4] http://www.iconixpharm.com/products/products main.html

CHIRAL α-DIAZOKETONES AS PRECURSORS FOR SYNTHESIS OF CHIRAL DERIVATIVES OF 2-PHENYLIMIDAZOLES

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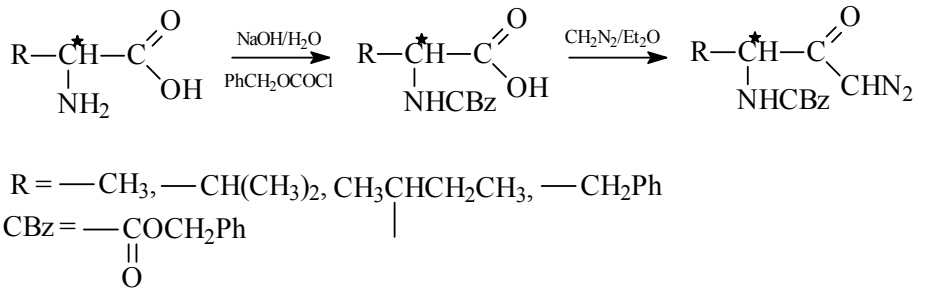
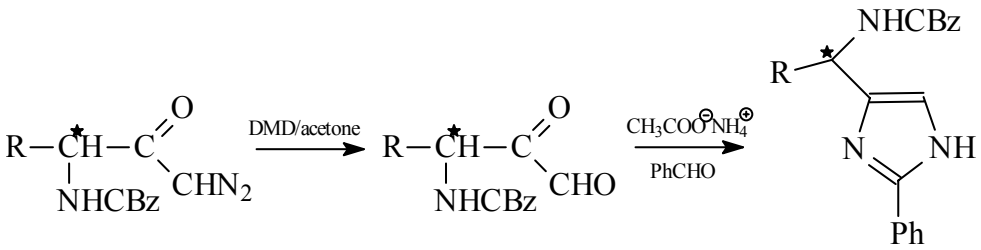
We have investigated synthesis of chiral α-diazoketones (**Scheme 1)**. The available L-amino acids have been used as starting compounds. All used amino acids have been protected in the first step. Benzyloxycarbonyl (CBz) group, as protecting group, we have selected. Arndt-Eistert method on L-amino acids (reaction of N-protected amino acids with etheric diazomethane solution [1,2]) has been applied in the next step of synthesis. The α-diazoketones with retention of configuration have been prepared.



Scheme 1

α-Diazoketones are good precursors for synthesis of chiral derivatives of 2-phenylimidazoles. It is possible to oxidate these α-diazoketones to chiral derivatives of glyoxal using dimethyldioxiran (DMD) solution as it is described in **Scheme 2**. Condensation of glyoxals prepared this way with ammonium acetate and benzaldehyde [3] has been used as a key step of synthesis. Deprotection of amino group by hydrogenation has been selected as next and last step. So, the chiral derivatives prepared this way can be used, after complexation with suitable metal, as a potential ligands of catalysts for enantioselective synthesis.



Scheme 2

This work was supported by Grant Agency of the Czech Republic, Nr. 203/02/0750.

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SYNTHESIS OF DIHYDROXYMETHYL CARBONYL COMPOUNDS VIA BIS-OXAZOLINES

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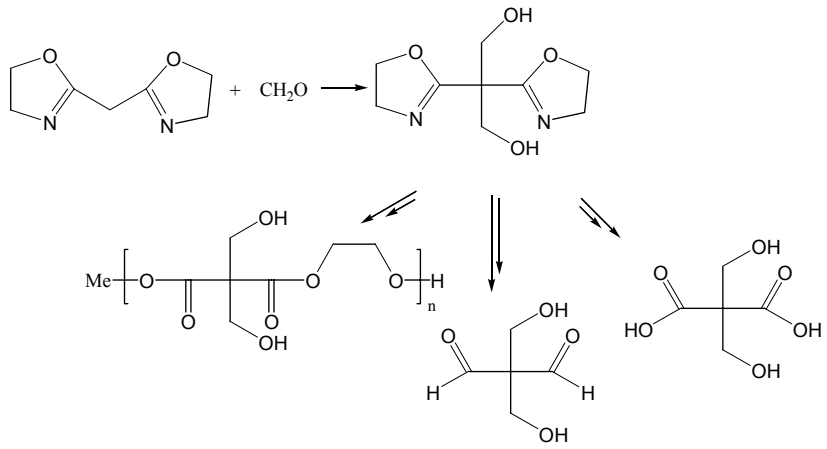
In this work, α,α'-dihydroxymethyl (dimethylol) aldehyde, α,α'-dihydroxymethyl (dimethylol) carboxylic acid and α,α'-dihydroxymethyl (dimethylol) polyester which were synthesized via bis oxazolines.

As known, α-mono and α,α'-dihydroxymethyl (dimethylol) aldehydes are obtained by condensation reaction of formaldehyde and the suitable aldehydes which have α-hydrogens. But poor yields are obtained because of many by-products. This study suggests a new synthetic method which provides high yields.

The starting dicarboxylic acid has been converted to corresponding bis oxazoline. Bis oxazoline has been reacted with paraformaldehyde to yield mono and dihydroxymethyl (dimethylol) derivatives [1,2]. Hydrolizes of bis oxazoline derivative at different conditions gave α,α'-dihydroxymethyl (dimethylol) aldehyde, dicarboxylic acid, diester and α,α'-dihydroxymethyl (dimethylol) polyester [3].



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[1] A.I. Meyers, E. Mihelich Angew, *Chem. Int. Ed. Engl* **1976** vol: 15 270-280
[2] John A. Frump *Chemical Reviews* **1971** vol: 71 483-505
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COMPETING FORMATIONS OF OXONIUM AND CARBONYL YLIDES WITH CARBONYLCARBENES

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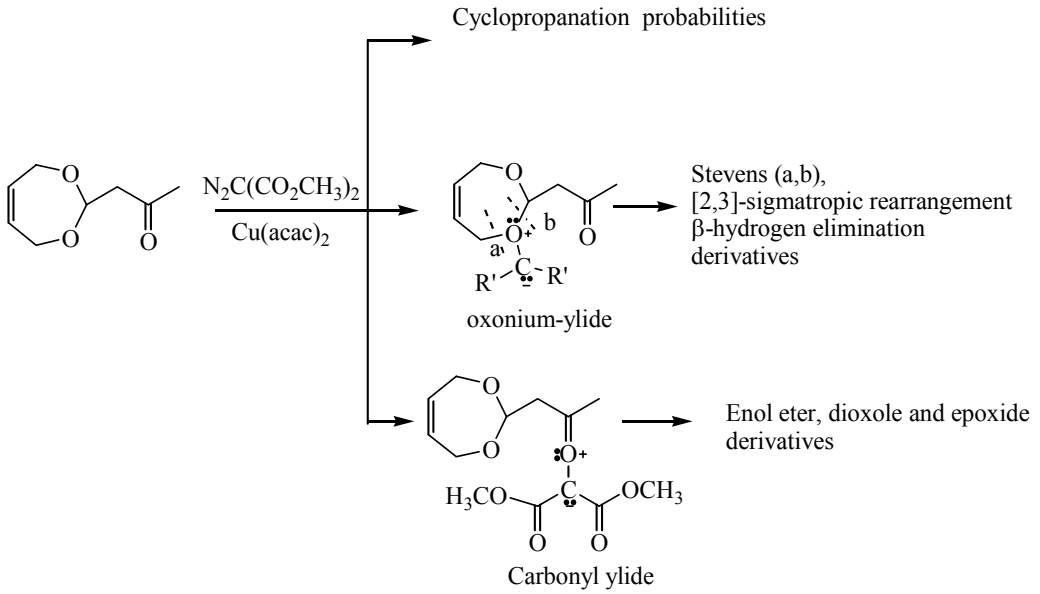
In our previous work, we reacted 1,3-dioxepin derivatives with dimethyl diazomalonate (dmdm) using copper (II) acetylacetonate [$Cu(acac)_2$] as catalyst to investigate the formation of oxonium ylide originated products, along with cyclopropanation and ß-hydrogen elimination reactions [1].

As a part of our continuing interest in this particular field, we worked on the similar reactions of 2-mono- and 2,2-disubstituted 1,3-dioxepin derivatives. Furthermore, we investigated the probabilities of additional pathways via carbonyl ylides in the case of 2-R groups having carbonyl functions, and also wanted to compete the ylide formation of allyl ether and carbonyl functions residing on the same molecule [2].



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A NEW TYPE OF LIQUID CRYSTALS WITH A BENZOTHIOPHENE CORE

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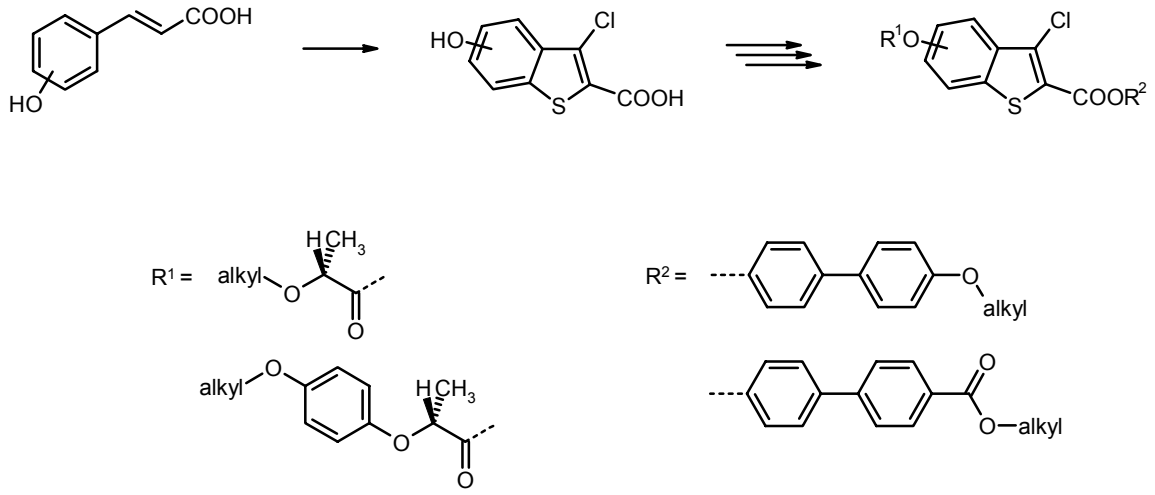
[b]Institute of Physics, Academy of Sciences of the Czech Republic, Na Slovance 2, CZ-182 21 Prague 8, Czech Republic

Recently we have shown[1,2] that thieno[3,2-b][1]benzofuran skeleton can be applied as a heterocyclic core for construction of new types of ferroelectric liquid crystals (FLC´s). As a continuation of this study we wish to report results of synthesis and physical evaluation of new series of liquid crystals possessing a little exploited benzothiophene system.

Synthesis of the LC´s was based on derivatization of easily accessible 3-chloro-5-hydroxybenzothiophene-2-carboxylic acid. Using appropriate protective groups the heterocyclic cores were further derivatised by linking to the alkyl or acyl chain, inserting of chiral group and elongation of the core with biphenyl unit (Scheme 1).



Scheme 1

Mesomorphic properties were determined by DSC study and by observation of textures in polarizing microscope.

Financial support of the Grant Agency of Czech Republic (projects No. 106/00/0580 and 202/02/0840) is gratefully acknowledged.

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SYNTHESIS OF PHENACYL ESTERS OF 5-AMINO-1-SUBSTITUTED PYRAZOLE-4-CARBOXYLIC ACIDS AND THEIR CYCLIZATION.

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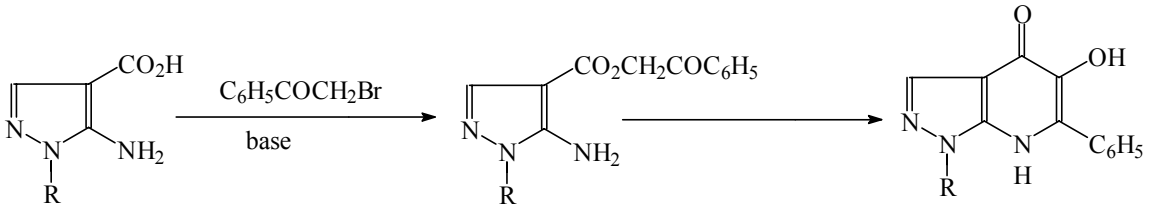
[b]Palacky University, Department of Organic Chemistry, Tř. Svobody 8; Olomouc, 771 46 Czech Republic, ph.1@tiscali.cz

A series of phenacyl esters of 5-amino-1-substituted pyrazole-4-carboxylic acids **2** were prepared from corresponding 5-amino-1-substituted pyrazole-4-carboxylic acids **1**.



1 2 3

Cyclization of **2** at different conditions to pyrazolopyridones **3** will be discussed. The dependense of cyclization rate of **2** and yields of **3** on characteristics of R-substituents were observed.

This work was financially supported by the Grant Agency of the Czech Republic. (Grant No. 203/01/1360)

DIPOLAR CYCLOADDITIONS WITH PORPHYRINIC AZOMETHINE YLIDES

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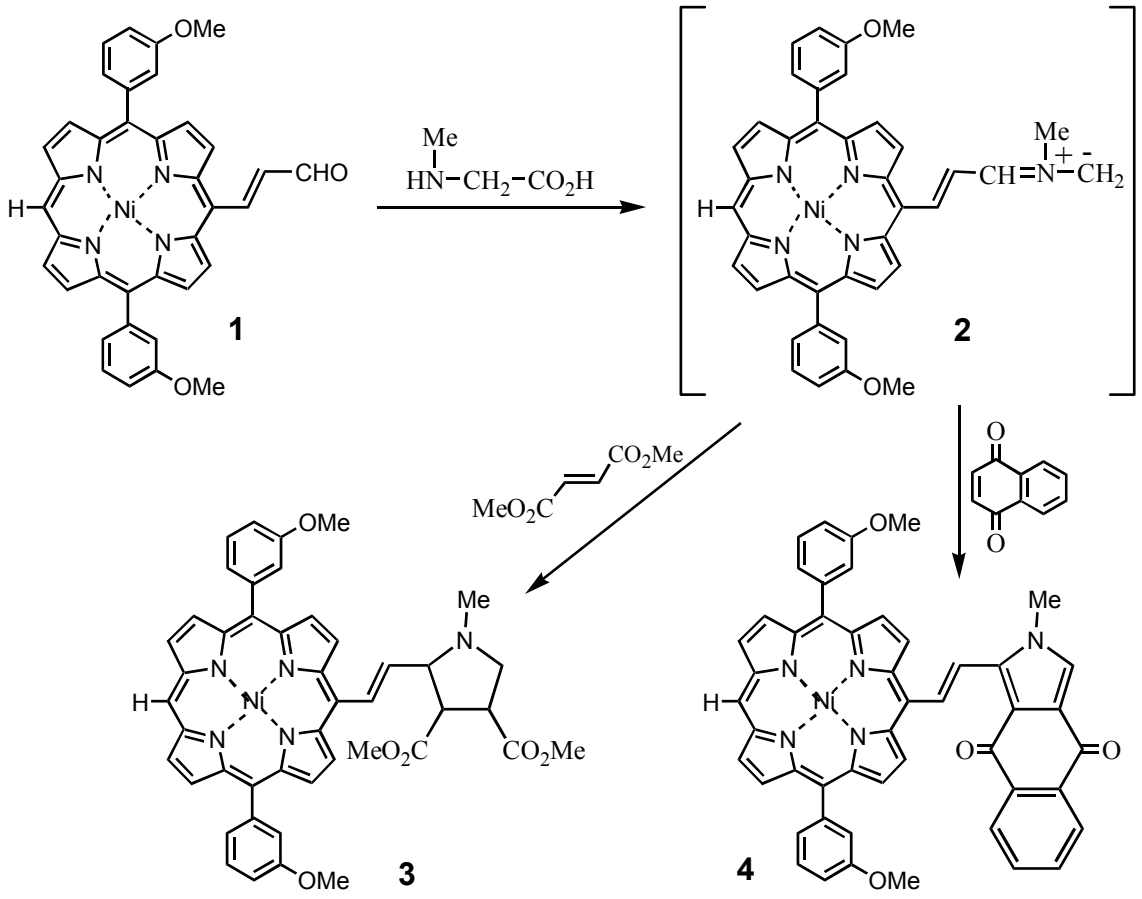
During the last decades a considerable effort has been put on the design and synthesis of novel porphyrins, due to their promising applications in medicine, in solar energy conversion, in catalysis, and others. 1,3-Dipolar cycloadditions are effective methods for the synthesis of five-membered heterocycles [1]. In recent years, we have reported the use of tetraarylporphyrins and β-formyl tetraarylporphyrins in 1,3-dipolar cycloadditions [2]. Here we wish to report the 1,3-cycloaddition of porphyrinic azomethine ylide **2** with two dipolarophiles, namely dimethyl fumarate and naphthoquinone. The 1,3-dipolar species is generated *in situ* from the reaction of Ni(II) complex of the 10-(2-formylethenyl)-5,15-bis(3-metoxyphenyl)porphyrin **1** and *N*-methylglycine.



Thanks are due to the University of Aveiro, to "Fundação para a Ciência e a Tecnologia" and FEDER for funding the Organic Chemistry Research Unit and the POCTI/QUI/ 32851/99 Project. One of us (P. Lacerda) thanks FCT for a PhD grant.

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CONCERNING THE SYNTHESIS OF HETEROCYCLIC HYPERICIN DERIVATIVES

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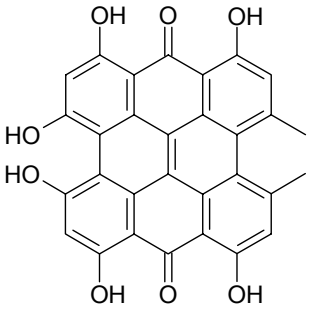
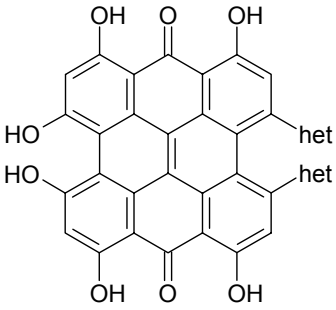
Following the quest for hypericin derivatives as photodynamic therapy agents [1-3] experiments were undertaken to prepare a series of heterocyclic ω,ω´-substituted hypericin derivatives. The aim of these efforts was to gain a shift of the long wavelength absorption band of hypericin ($\lambda_{max.}$ ~ 598 nm; **1**) to the wavelength range of medicinal lasers ($\lambda_{max.}$ ~ 650 nm).

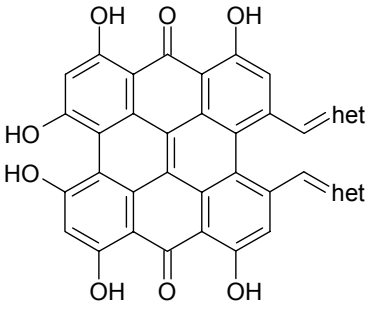
The derivatives broadly fall into two categories. Due to synthesis reasons, the first contains derivatives in which the parent methyl carbon is part of the heterocyclic system (**2**). The second one contains derivatives in which the heterocycle was appended to the former methyl group by means of a double bond (**3**). For derivatives of type **2** heterocycles like tetrazole, oxazole, oxazoline and the benzo condensed analogs were chosen as well as the 3,4-dimethylpyrrolinone and 5-methylisatin moiety for type **3**.



1



2



3

The synthesis started with the recently prepared tri-*O*-methyl protected emodin aldehyde or nitrile [4]. These were transformed into the corresponding heterocyclic derivatives by conventional means. After reduction and deprotection the corresponding anthrones were eventually dimerized to get the desired hypericin derivatives. A summary of the results attained will be presented.

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SYNTHESIS, CONFORMATION AND RING-CHAIN TAUTOMERISM OF SUBSTITUTED PYRIMIDO[6,1-a]ISOQUINOLINES

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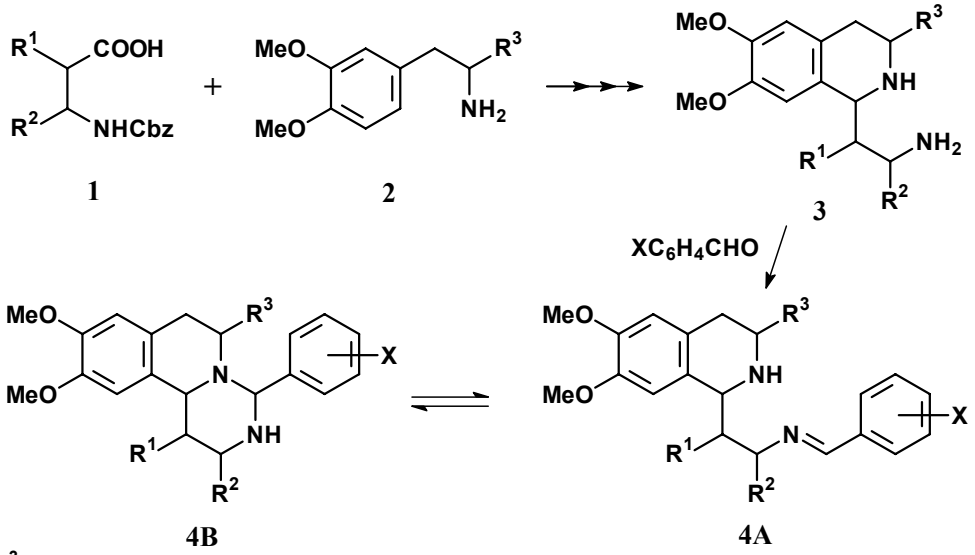
A large number of examples have emerged in recent years demonstrating that ring-chain tautomerism occurs not only among *N*-unsubstituted saturated 1,3-*O*,*N* heterocycles, but also among their 1,3-*N*,*N* analogues. Our previous studies on 2-aryl-1,3-*N*,*N*-heterocycles revealed that the ring-chain tautomeric character of these compounds is influenced by the ring size, the steric effect of the *N*-substituents and the electronic effects of the 2-aryl substituents [1,2].



1 **2** **3**

4B **4A**

R^1, R^2, R^3 : H, Me; X = *p*NO_2, *m*NO_2, *p*Cl, H, *p*Me, *p*OMe, *p*NMe_2

Starting from *N*-protected β-alanine derivatives (**1**, R^1 = H, Me, R^2 = H, Me) and homoveratrylamine (**2**, R^3 = H) or α-methylhomoveratrylamine (**2**, R^3 = Me), tetrahydroisoquinoline 1,3-diamine diastereomers (**3**) were prepared, which were converted to 3-aryl-substituted pyrimido[6,1-*a*]isoquinolines (**4**) by condensations with aromatic aldehydes. NMR investigations indicated that the substituents proved to exert strong effects on both the ring-chain tautomeric equilibria and the predominant conformation of these compounds.

[1] L. Lázár, A. Göblyös, T. Martinek, F. Fülöp: *J. Org. Chem.* **2002**, *67*, 4734.
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SYNTHESIS OF 2,4-DISUBSTITUTED 2,3-DIHYDRO-1,5-BENZOTHIAZEPINES AND THEIR CONVERSION INTO 2,2-DISUBSTITUTED 3-ACETYL-2,3-DIHYDROBENZOTHIAZOLES

Albert Lévai

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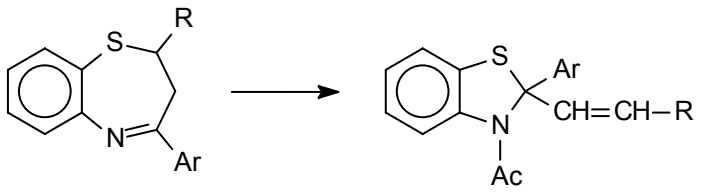
In the course of our studeis on the chemical transformations of 2,3-dihydro-1,5-benzothiazepines their unprecedented ring contraction has been demonstrated which made available a convenient preparation of previously unknown 2,2-disubstituted 3-acetyl-2,3-dihydrobenzothiazoles under acetylating conditions [1]. This procedure was then generalized for the synthesis of a wide variety of 3-acyl-2,3-dihydrobenzothiazoles under acylating conditions by using various acylating agents [2].

In our present work, new 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines bearing a 3-chromonyl or a styryl goup at position 2 have been synthesized ring contraction of which has been accomplished under acetylating conditions to afford new 2,2-disubstituted 3-acetyl-2,3-dihydrobenzothiazoles.



The major aim of this study was to investigate the influence of the substituent at the C-2 atom of the 2,4-disubstituted 2,3-dihydro-1,5-benzothaizepines. These results provide new examples for a better understanding of this ring contraction of the above-mentioned 1,5-benzothiazepines. Reaction conditions and structure elucidation of all new compounds will be presented and discussed in our poster.

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[2] A. Lévai: *Monatsh. Chem.* **1998**, *129*, 909-914.

PHENYL(HYDROXY)ETHYLGUANINES

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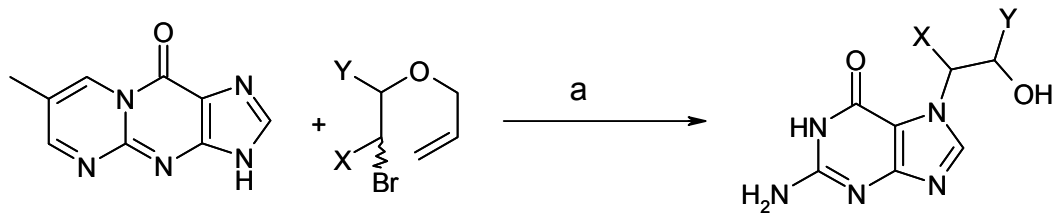
[b]Central Laboratories, Institute of Chemical Technology Prague, CZ-166 28 Prague

Phenyl(hydroxy)ethylguanines, in particular 7-(2-hydroxy-1-phenylethyl)-guanine (N7αG) and 7-(2-hydroxy-2-phenylethyl)guanine (N7βG), are important markers of exposure to styrene as well as indicators of DNA damage caused by styrene 7,8-oxide, a styrene metabolite. An improved synthetic procedure leading to these compounds has been developed. As a rule, the alkylation reactions of guanine and guanine derivatives are rather unselective. The selectivity of alkylation was improved by using 7-methyl-10-oxo-9,10-dihydropyrimido[1,2-a]purine as a protected guanine compound [1], and allyl-protected bromohydrins as synthetic equivalents of styrene 7,8-oxide (Scheme). This procedure gives a better selectivity and better yields of 7-[phenyl(hydroxy)ethyl]guanines N7αG and N7βG than the alkylation of 2-amino-6-chloropurine, as a precursor to guanine [2].



X = Ph, H; Y = H, Ph

a, (i) K_2CO_3/DMF, (ii) aqueous NaOH, reflux, (iii) $(Ph_3P)_4Pd$, PMHS, $ZnCl_2$, DMF

Acknowledgement. The authors are grateful to the Grant Agency of the Czech Republic for the financial support by grant No. 310/03/0437.

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REGIOSELECTIVE Pd-CATALYZED AMINATIONS ON CHLORO-IODOPYRIDINES UNDER MILD REACTION CONDITIONS [1]

Bert U.W. Maes[a], Tim H.M. Jonckers[a], Kristof T.J. Loones[a], Guy L.F. Lemière[a], Roger A. Dommisse[a] and A. Haemers[b]

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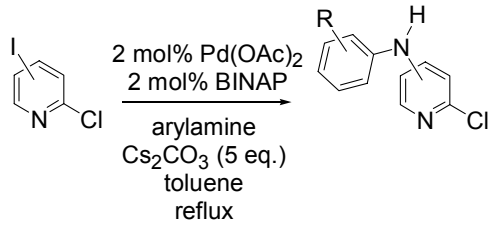
Diarylamines are of synthetic importance since several applications as pharmaceuticals are known. As a consequence a part of our research interest deals with the synthesis of arylamino- substituted pyridines, quinolines and naphthyridines. We previously described a very efficient and mild regioselective palladium-catalyzed amination protocol for the arylamination of dichloropyridines [2]. 2,3- 2,5- And 2,6-dichloropyridine were regioselectively aminated in the 2-position with an arylamine yielding 3-, 5- and 6-chloro substituted 2-arylaminopyridines respectively.



As a continuation of this selective amination study we wanted to prepare isomeric 3-arylamino-2-chloro- and 5-arylamino-2-chloropyridines under mild reaction conditions allowing a large functional group tolerance. Therefore we studied regioselective palladium-catalyzed amination on easily accessible 2-chloro-3-iodo- and 2-chloro-5-iodopyridine. Selective palladium-catalyzed C-C bond forming cross-coupling reactions on 2-chloro-3-iodopyridine and 2-chloro-5-iodopyridine have already been reported but no report of a similar selective Buchwald-Hartwig C-N bond formation has been published. More generally, to the best of our knowledge no palladium-catalyzed aminations on azaheteroaryl iodides under mild reaction conditions have been described in the literature yet. We found that Pd(0)/BINAP catalyst in the presence of *a large excess of Cs_2CO_3 (5 equivalents)* is an ideal combination to obtain sufficiently fast reactions with a low catalyst loading. Interestingly, a regioselective reaction with the carbon-iodine bond is observed, although the same catalyst as on dichloropyridine substrates is used.

Although the large excess of carbonate does not dissolve in the reaction mixture, faster reactions were observed in comparison with experiments where smaller amounts of the same base were used. At the present time it is our conviction that interphase interactions are responsible for this observation. Some experiments are currently carried out to further investigate this matter and to determine the role of the contact surface area of the insoluble base.

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SOLUTION NMR AND X-RAY CRYSTAL STRUCTURES OF NEW CHIRAL 1,4-OXAZEPINIUM HETEROCYCLES AND THEIR INTERMEDIARIES FROM THE REACTION OF 2,4-PENTANEDIONE WITH α-L-AMINOACIDS AND (R)-(-)-2-PHENYLGLYCINOL

M. Concepción Lozada[a], Carlos E. Lobato[a], Raúl G. Enríquez[a], Benjamín Ortíz[a], Rubén A. Toscano[a], Dino Gnecco[b], Alberto Galindo[b], William F. Reynolds[c]

[a] Instituto de Química, UNAM, Cd. Universitaria, Coyoacan, México, D. F. 04510
[b] Centro de Química del Instituto de Ciencias, BUAP, Puebla 72000, México
[c] Department of Chemistry, University of Toronto, Ontario M5S1A1, Canada.

The reaction of 2,4-pentanedione **1** with (R)-(-)-2-phenylglycine methyl ester **2**, (R)-(-)-2-phenylglycinol **3** and the proteinogenic aminoacids (2S,3R)(-)-2-amino-3-hydroxybutyric acid (L-Threonine) **4**, and (R)-(-)-2-amino-3-mercaptopropionic acid (L-cysteine) **5** methyl esters was investigated. The corresponding enamines **6**, **7, 8** were isolated and characterized spectroscopically while **9,** unstable, was transformed *in situ* into **13**. Furthermore, treatment of **7, 8** and **9** with Boron trifluoride etherate, afforded the new [1,4] oxazepines **10**, **11,** and [1,4] thiazepine **12** as their BF_3O^- salts (Fig. 1).

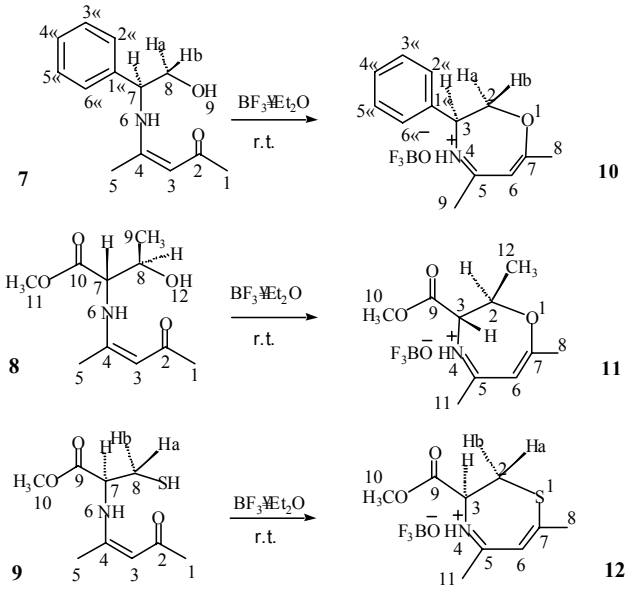


Figure 1
The structure of enamines and their corresponding seven member heterocycles was assessed by 1D and 2D NMR spectroscopy and by X-ray crystalographic determinations. Variable temperature experiments showed different molecular mobility among these heterocycles.

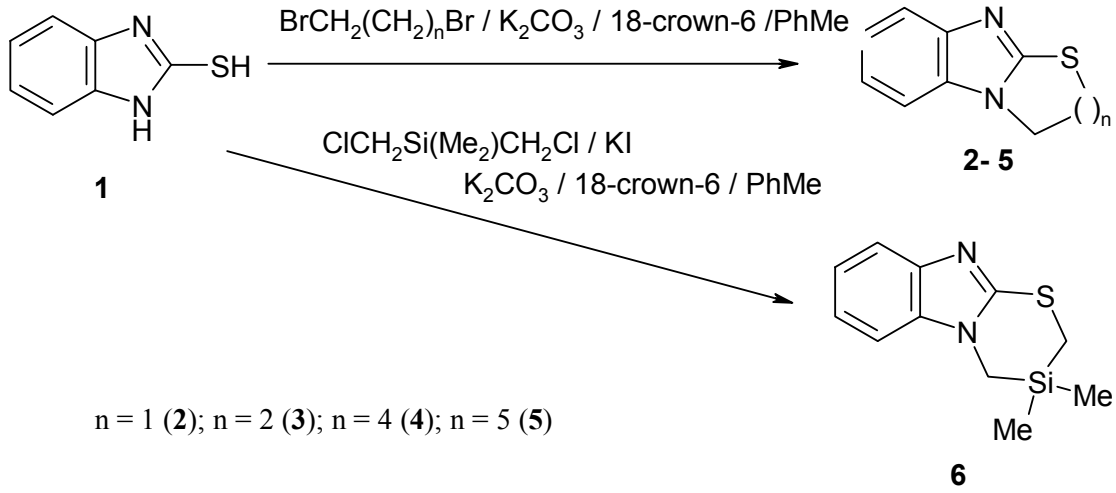
SYNTHESIS, STRUCTURE AND CYTOTOXICITY OF METAL COMPLEXES OF TRICYCLIC BENZIMIDAZOLE SULFIDES

Edmunds Lukevics, Ramona Abele, Edgars Abele, Pavel Arsenyan, Irina Shestakova, Sergey Belyakov, Juris Popelis

Latvian Institute of Organic Synthesis, 21 Aizkraukles street, Riga, LV-1006, Latvia, E-mail: sinta@osi.lv

Thiazolobenzimidazole and similar tricyclic benzimidazole sulfides have received considerable attention owing to their biological activity [1].

Tricyclic benzimidazole derivatives **2-6** were prepared in high yields by interaction of 2-mercaptobenzimidazole with α,ω-dihalogenalkanes in the system solid K_2CO_3 / 18-crown-6 / toluene in high dilution. The structure of novel heterocyclic system - of 3,3-dimethyl-3,4-dihydro-2H-1-thia-4a,9-diaza-3-sila-fluorene (**6**) was confirmed by X-ray crystallographic data.



n = 1 (**2**); n = 2 (**3**); n = 4 (**4**); n = 5 (**5**)

Complexes of metal salts ($CuCl_2$, $ZnCl_2$, $AgNO_3$, $CoCl_2$) with heterocyclic ligands **3** or **6** of structure 1:2 were prepared. The metal complexes exhibit high cytotoxicity on human fibrosarcoma (HT-1080) and mouse hepatoma (MG-22A) cell lines.

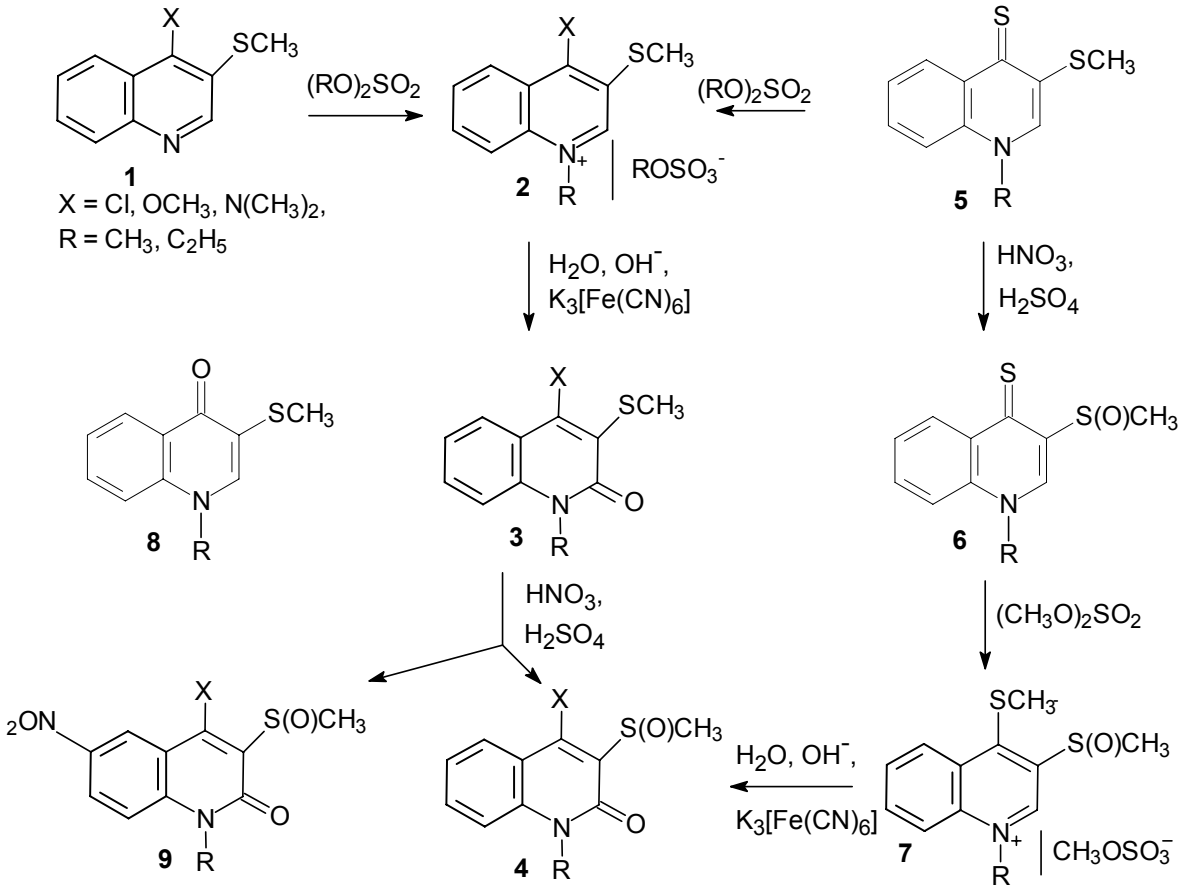
1. Chimirri A, Grasso S, Romeo G, Zappala M, *Heterocycles* 1988; **27**: 1975-2003.

1-ALKYL-3-METHYLTHIO- AND 3-METHYLSULFINYL-4-SUBSTITUTED-2(1H)-QUINOLINONES

Elwira Chrobak and Andrzej Maślankiewicz

Department of Organic Chemistry,The Medical University of Silesia
Sosnowiec, Poland

In order to extent our studies on 4-substituted-3-quinolinyl sulfides we attempted to transform compounds of type **1** and **5** to the title 2-quinolinones **4**. The later are close structural analogs of 2-quinolinones exhibiting antiosteoporetic acivity. [1]



Substrates **1** were quaternized with dialkyl sulfates to 1-alkylquinolinium salts **2**, salts **2** with 4-methylthio substituent were obtained by *S*-alkylation of thiones **5**. Then salts **2** were treated with aqueous $K_3[Fe(CN)_6]$ / OH^- system. It led to the expected 2-quinolinones **3**, however they were accompanied by 4-quinolinones **8**. When 2-quinolinones **3** were subjected to the reaction with nitrating mixture (1 mol.eqv. of HNO_3), the reaction gave sulfoxides **4**; but with an excess of HNO_3 (3 mol.eqvs.) nitro-sulphoxides **9** were obtained. The second route for the preparation of sulfoxides **4** ($X=SCH_3$) was studied as well. It was based on the oxidation of thionosulfides **5** to the sulfoxides **6** followed by alkylation of **6** to quinolinium salt **7** and final oxidation of **7** to 4-methylthio-2-quinolinone **4**.

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THE REACTIONS OF THIOQUINANTHRENE 7-OXIDE WITH O-CENTERED NUCLEOPHILES

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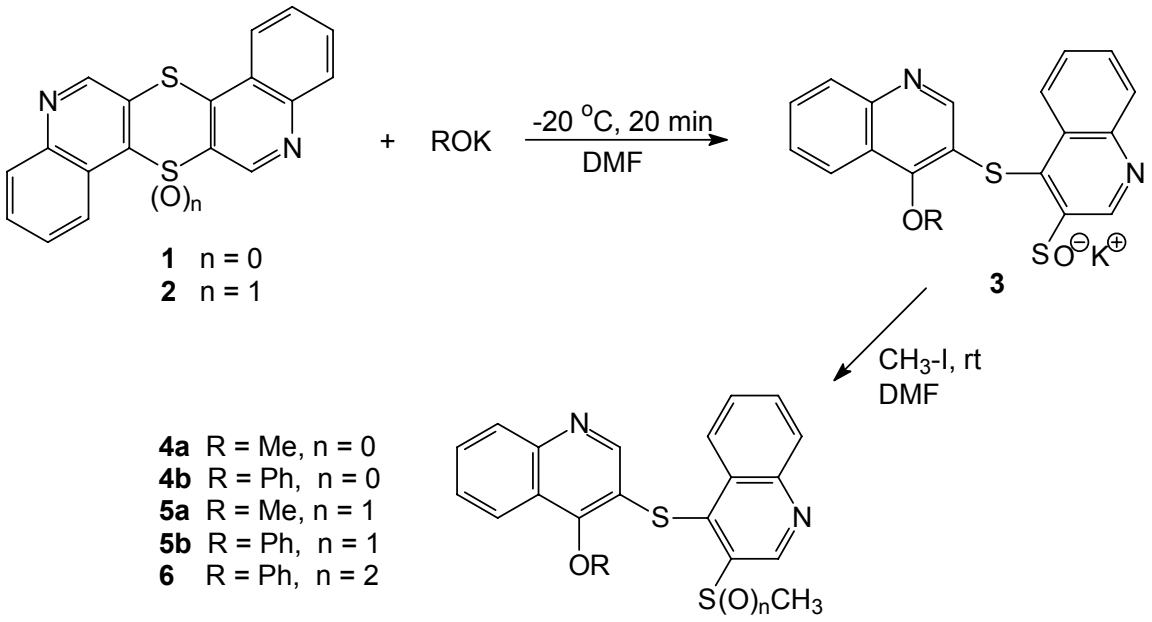
The reactions of thioquinanthrene **1** (n = 0) with nucleophiles are source of numerous 4-substituted 3-quinolinyl sulfides including compounds of type **4** (R = Alkyl, n = 0).

In the case of alkoxide ions, the reactions proceed easily (0.5 h, 70 °C, DMSO or DMF) with a 100 % dithiin **1** conversion [1], but no reaction with phenoxide and acetate ions was observed.

In order to enhance the nucleophilic susceptibility, thioquinanthrene **1** was converted to thioquinanthrene 7-oxide **2** (n = 1) [2]. It appeared to be high sensitive toward O-centered nucleophiles as the reactions with sodium methoxide and even potassium phenoxide proceeded at –20 °C (15 min, DMF or DMSO). The primary formed sulfenate **3** was characterized by alkylation with methyl iodide. The product mixtures consisted mainly of sulfoxides **5** (42 %) which were accompanied by sulfides **4** (11 %) and sulfones **6** (10 %).



1 n = 0
2 n = 1

3

4a R = Me, n = 0
4b R = Ph, n = 0
5a R = Me, n = 1
5b R = Ph, n = 1
6 R = Ph, n = 2

The formation of compounds **5**, **4** and **6**, confirms the formation of **3** and indicates that the sulfenate group is better leaving group that the sulfide one in nucleophilic displacement at $C_{4\text{-quinolinyl}}$ -S bonds in 1,4-dithiin ring of **2**.

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PREPARATION OF ALLENYL PRECURSORS FOR CRISS-CROSS CYCLOADDITIONS

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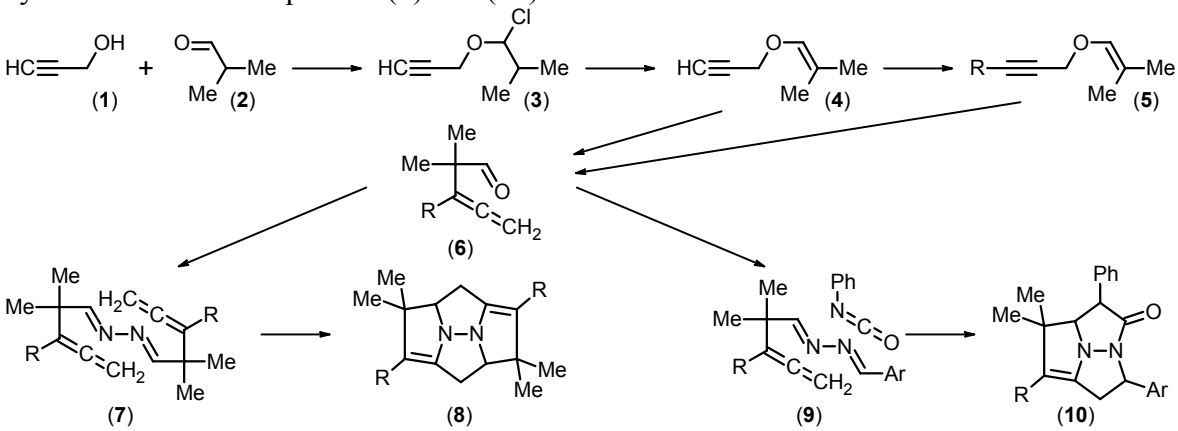
Criss-cross cycloaddition reaction is a unique method for preparation of fused five-membered heterocycles. The first criss-cross reaction published was the intermolecular reaction of benzaldazine with phenyl isocyanate [1,2]. Later an intramolecular variation leading to four fused five-membered heterocycles (**8**) has been developed [3] and much later an intra-intermolecular variation leading to three fused five-membered heterocycles (**10**) was introduced [4].

The last two mentioned criss-cross cycloadditions were carried out with allenyl azines. The intramolecular variation started from symmetrical azine (**7**) with two allenyl groups in one molecule. The combined intra-intermolecular reaction, on the other hand, started from nonsymetrical azine (**9**) containing only one allenyl.

To the preparation of allenyl precursors a reaction of propargylalcohol (**1**) and isobutyraldehyde (**2**) with HCl(g) (modified procedure [5]) was employed. The product (**3**) when treated with pyridine gave the important ether (**4**) intermediate. Substitution of ether (**4**) was carried out by two different procedures. The first method applied treatment of ether (**4**) with $NaNH_2$ in NH_3(l) and subsequent alkylation by MeI or EtBr leading to products (**5**) R = Me, Et. The second method was Manich reaction of ether (**4**) with paraformaldehyde and a secondary amine. The products were ethers (**5**) where R = -CH_2-$N(Et)_2$, -CH_2-morfolino, etc.

Ethers (**4**) and (**5**) when heated to high temperature underwent Claisen-Cope rearrangement to allenylaldehydes (**6**). These when treated with hydrazine gave symmetrical azines (**7**). Nonsymmetrical azines (**9**) were prepared by Zwierzak method [6] from (**6**) with protected aromatic hydrazones in presence of NaH. Products of criss-cross cycloaditions are compounds (**8**) and (**10**).



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A NEW CONVENIENT SYNTHESIS OF INDOLIZINES AND BIPYRIDINYLS FROM 2-FORMYL-1,4-DIHYDROPYRIDINES

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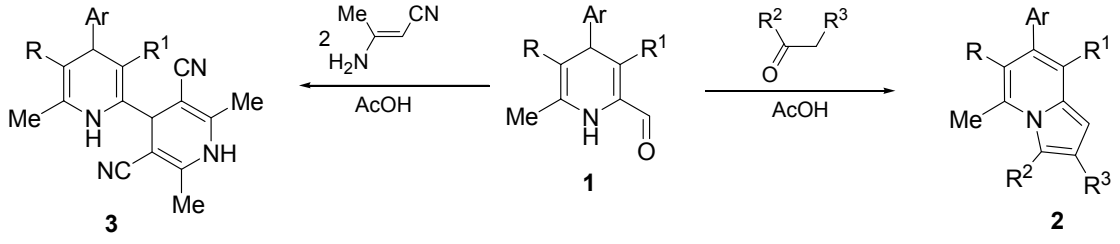
2-Formyl-1,4-dihydropyridine (DHP) derivatives undergo the tandem reaction with activated methylene reagents to afford highly functionalised indolizines and bipyridinyls in acidic conditions in good yields.

Reaction of 2-formyl-1,4-DHP substrates **1** and activated methylene reagents in a basic medium, constitutes a new and competitive methodology to access efficiently indolizines with different degrees of unsaturation [1]. Because of the exceptional biological potential of theses species allied with our great interest to develop this chemistry fully, we decided to investigate, evaluate and compare the regiocontrol features of this process in acidic conditions.



R: CO_2Me, CO_2Et, COMe, CN; R^1: CO_2Me, CO_2Et; R^2: Me, Ph; R^3: CO_2Me, CN; Ar: 2-thienyl, 5-X-2-furyl, 3-nitrophenyl.

The convenient one step synthesis of polysubstituted indolizines **2** by ring transformation of the formyl group containing 1,4-DHPs **1** by reaction with active methylene reactants in acidic medium has been found. These 1,4-DHPs **1** have also been allowed to react with 3-aminocrotonitrile and, to our surprise, afforded the bis-1,4-DHPs **3** accompanied by indolizines **2** as minor products. A mechanism performing these transformations was proposed [2].

Acknowledgements. This work was financially supported by the Grant Agency of Slovak Republic, Grant No.1/9249/2002.

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SYNTHESIS OF 8,8-DIMETHYL-3-X-5,7,9,10-TETRAHYDRO-6*H*,8*H*-6A,10-DIAZA-NAPHTHO[2,1-A]AZULEN-11-ONES

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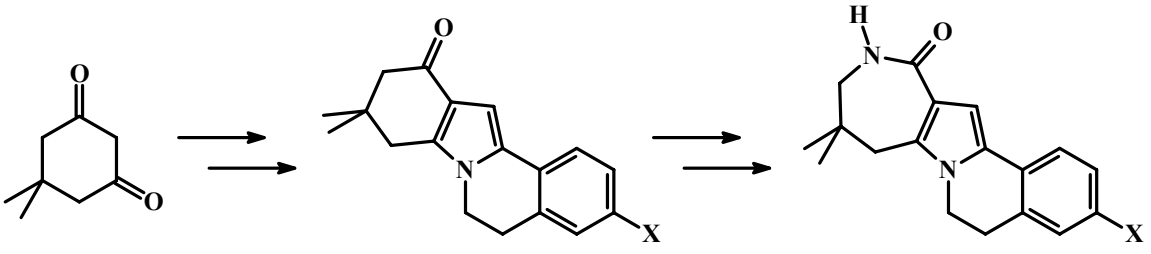
The synthesis of the title compounds **3** was achieved in 6 steps using 5,5-dimethyl-1,3-cyclohexanodione (dimedone) **1** as starting material.

This work describes a synthetic route to get some derivatives of diaza-naphtho[2,1-a]azulenone **3**. To our knowledge this is a novelty tetracyclic system.



1 **2** **3**

X = H, F, Cl, Br, CH_3, OCH_3, NO_2

Initially the dimedona **1** was alkylated with the suitable α-bromo ketone in the presence of potassium hydroxide. Then, the alkylated derivatives were reacted with ethanolamine by a Paal-Knorr reaction to obtain the tetrahydroindolones derivatives in moderate yields. Reaction of these indolones with iodine, triphenylphosphine and imidazole gave the substitution of the hydroxyl group by iodine. The key step of this synthesis was the free radical cyclization of the iodine derivatives to give the tetracyclic system **2**. This reaction was accomplished with dicumyl peroxide as initiator. Finally the diaza-naphtho[2,1-a]azulenones **3** were prepared by Beckman rearrangement of the corresponding oximes with poliphosphoric acid. **2**.

This kind of compounds has a structure similar to paullones. The paullones have recently been reported to inhibit the growth of cancer cells and they represent a novel class of molecule cyclin-dependent kinase (CDK) inhibitors[1].

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ξ We thank DGAPA-UNAM (IN-211601) and PAEP (208316) for financial support.

SYNTHESIS OF NEW THIENO[3,2-B]INDOLE DERIVATIVES AND ELECTROCHEMICAL PREPARATION OF THEIR CONDUCTING OLIGOMERS

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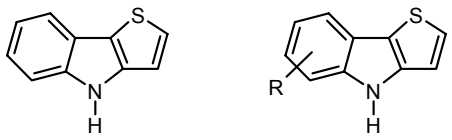
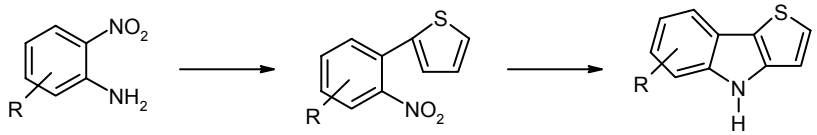
Since many years pyrrole, thiophene and their functionnalized derivatives have been studied intensively with the aim of electrochemically preparing of novel conducting polymers with important electrochemical, optical and anticorrosive properties [1,2]. As shown recently, the fused polycyclic system of thieno[3,2-b][1]benzothiophene and its derivatives can lead also to a group of semiconducting oligomers possessing interesting electrochemical and fluorescence characteristics [3,4].
In this work we have extended successfully the obtained results to another 1,4-diheteropentalene system, thieno[3,2-b]indole (**1**) and its derivatives. Our main goals were to prepare compound **1** and a series of their substituted derivatives **2** (R = methoxy, hydroxy, dimethylamino).



1 **2**

Synthesis of **2** was based on the procedure known for the parent **1** [5] (Scheme 1).



Scheme 1

The electropolymerization, and the electrochemical and spectral behaviour of coumpounds **1** and **2** were investigated. The electropolymerization was performed in organic media and in an anionic micellar solution. We also describe the structure of these new oligomers and their physicochemical properties was described by suitable methods (IR, UV-visible, MALDI-TOF, scanning electron microscopy).

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PREPARATION, SPECTRAL AND BIOLOGICAL PROPERTIES OF SULFONES OF 2-HETARYLCINNAMONITRILES

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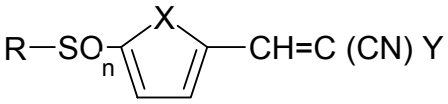
Aromatic or heterocyclic compounds containing an aryl, furan, thiophene or pyrrole ring and an ethylene substituent are frequently studied objects because of their preparation, spectral or biological properties or synthetic exploitation. Within a series of these substances correlation analyses of substituents on these (hetero)aromatic systems towards their spectral properties are often carried out.
In the frame of study of the physico-chemical and biological properties of heterocyclic five-membered compounds three series of the same types of compounds on the basis of thiophene, furan and N-methylpyrrole of the general formula:



R = Me, Ph; n = 0, 2; X = O, S, NMe; Y = CN, COOMe

has been prepared using a basically catalyzed reaction of the corresponding 5-R-SO_n-2-furane-/thiophenecarbaldehydes with malonodinitrile or methyl cyanoacetate in ethanol or by a nucleophilic substitution of a suitable substituent in position 5 of the hetaryl ring. These compounds bear in position 2 of the heterocyclic ring the strongly polarized 2-substituted prop-2-enoic nitrile chain and in the opposite side sulfur containing substituents such as methylthio or phenylthio or the corresponding sulphones, respectively. Spectral (^{1}H, ^{13}C, ^{15}N and ^{17}O NMR) and antibacterial properties will be presented and discussed.

Authors([a,c]) would like to thank Slovak Grant Agency for financial support (1/9254/02 and 1/0058/03).

A NEW SYNTHESIS OF PYRROLO[1.2-B]PYRIDAZINES

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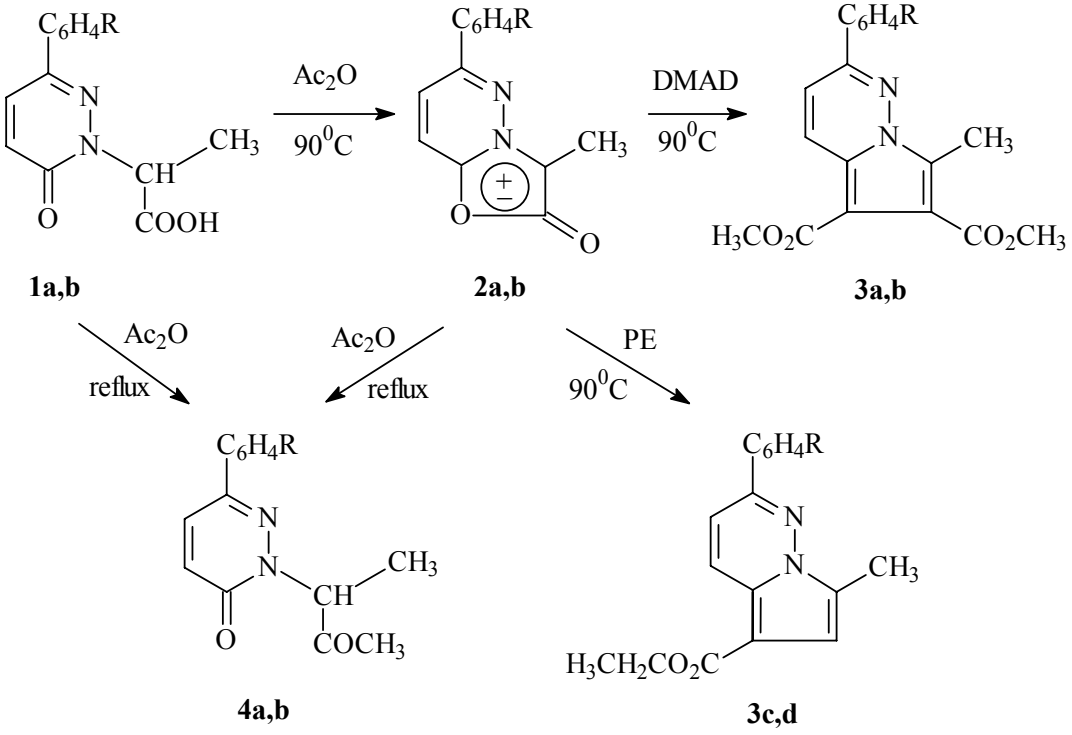
The 1,3-oxazolium-5-olates, commonly known as münchnones [1-3] are readily prepared by cyclodehydration of *N*-acyl-*N*-substituted α-aminoacid derivatives and are generally utilized *in situ* being too unstable to be isolated.

1,3-Dipolar cycloaddition reactions between bicyclic oxazolones **2a,b**, generated *in situ* from pyridazinone acids **1a,b** and dimethyl acetilenedicarboxylate (DMAD) gave pyrrolo[1.2-b]pyridazines **3a,b**. In the same reaction conditions, ethyl propiolate (PE) gave regiospecifically pyrrolo[1.2-b]pyridazines **3c,d**.

Notably, the mesoionic compounds **2a,b** could be isolated in pure state and were unambiguously assigned by NMR spectroscopy (^{1}H- and ^{13}C-NMR). By refluxing in acetic anhydride both **1a,b** and **2a,b** derivatives provided compounds **4a,b** by Dakin-West reaction. The fluorescence of compounds **2** and **3** in solution and solid state has been studied.



R = H; 4-Cl

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This work was supported by CERES Grant 31/12.11.2002.

POTASSIUM ALUMINUM SULFATE(ALUM): AN EFFICIENT CATALYST FOR SYNTHESES OF SOME DERIVATIVES BENZIMIDAZOLES AND BENZOXAZOLES UNDER MICROWAVE IRRADIATION

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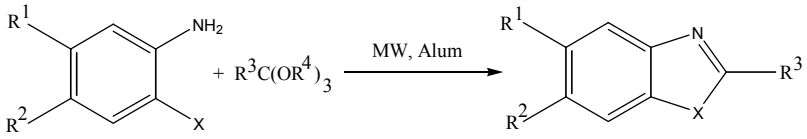
Varius methods for the synthesis of benzimidazoles and benz oxazoles have been reported in a number of papers [1]. These molecules would have enhanced biological properties and interesting industrial application [2].
In connection with our ongoing work on Alum [3] and microwave [4], we now wish to report of the preparation of some derivatives benzimidazloes and benzoxazoles from condensation of 1,2-phnylenediamin with orthoesters in the presence of Alum under microwave irradiation. (Scheme).



$R^1 = R^2$=H, Me
X=OH, NH_2
R^3=H, Me, Et, n-Pr, n-Bu, Ph
R^4=Me, Et

Scheme

The method offers several advantages including high yield of products, short reaction times, cleaner reaction, interestingly, the catalyst was recovered and recycled in subsequent reaction without reduction in activity.

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MICROBIAL BAEYER-VILLIGER OXIDATION OF BICYCLO[4.3.0]- AND BICYCLO[3.3.0] KETONES USING RECOMBINANT WHOLE-CELLS

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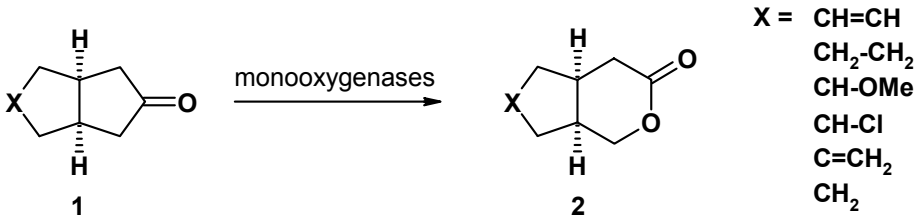
Over the last few years Baeyer-Villigerases have gathered increased attention for their ability to convert a large number of cyclic ketones in a regio- and chemoselective manner. But the most interesting feature for a synthetic chemist is the possibility to introduce chirality. The chiral lactones obtained, represent useful intermediates for the synthesis of natural products[1].

Based on our previous reports on recombinant whole cell mediated oxidations[2], we were interested in the prepartion of chiral lactones of type **2.**



1 **2**

In this contribution we discuss our results for the conversion of bicyclic ketones of type **1**. Both 5- and 6-membered fused carbocycles represent substrates for *Cyclohexanone monooxygenase (EC 1.14.13.22)*[3] and *Cyclopentanone monooxygenase (EC 1.14.13.16)*[4]. The stereoselectivity of the microbial transformation will be studied together with a survey of spatial requirements of the active site of the enzymes investigated based on substrate acceptance.
This enables a novel approach to yohimbine-type alkaloids as potential α_2-adrenoceptor antagonists. An improved synthetic procedure to the corresponding ketones **1** will be presented together with conditions for the whole-cell biotransformation.

KEYWORDS: BIOCATALYSIS / BAEYER-VILLIGER OXIDATION / MONOOXYGENASE / ENATIOSELECTIVE SYNTHESIS / ENANTIODIVERGENCE

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COORDINATION COMPOUNDS OF AMINOACRIDINE-N-OXIDES WITH THIOCYANATES OF THE 3D METALS

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New pestizides can be developed by two main ways. The first way uses known universal or selective pestizides as model molecules and vary substituents and structure unite or some atoms in the fundamentally structure. In the second way there are to be combined such structure units and/or molecules for which already biological activity are known to a new compound. We proofed the later way in the field of biocoordination compounds and found often not only addition of the effects regarding to physical, chemical and biochemical data. Continuing our previous work on biochemical synergistic metal Thiocyanate mixed ligand complexes we report here on such complexes containing acridines and triazines as ligands or cations (if they are protonated).

Reactions of thiocyanates of the 3d metals with selected aminoacridine N-oxides in homogeneous dilutions of N, N-dimethylformamide form compounds of the type [1].

$[M(AAcNO)_a(DMF)_b(NCS)_2]$ cDMF and $[M'(AAcNO)_d(DMF)_e(NCS)_3]$ fDMF,
M = Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}; M' = Cr^{3+}, Fe^{3+};
$AAc^{I}NO$ = 3,6-diamino-2,7-dimethylacridin-N-oxide,
$AAc^{II}NO$ = 3,6-bis(dimethylamino)acridin-N-oxide,
$AAc^{III}NO$ = 2-ethoxy-6,9-diaminoacridin-N-oxide;
a=1,2,3,4; b=0, 1;
c=0,1,2,3; d=1,2,3;
e=0,1,2; f=0,1,2,3.

The complexes are characterized by IR (4000-200cm^{-1}) and UV-VIS spectra in solutions and solids and by EPR and conductivity investigations [2].

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[2] Müller, R., Böhland, H., Anke, M. und K. Fröbus, Mengen- und Spurenelemente, Friedrich-Schiller-Universität Jena 2002, 21. Workshop, S. 1435, „Biochemical synergistic acridine and triazine metal thiocyanate mixed ligand-complexes“

THEORETICAL STUDIES ON DIHYDROPTERINS

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Sepiapterin with the 7,8-dihydropterin structure and quinonoid dihydrobiopterin are key intermediates in tetrahydrobiopterin biosynthesis and metabolic hydroxylation of aromatic aminoacids. Chemically, quinonoid dihydrobiopterin is the labile compound which quickly isomerizes to 7,8-dihydrobiopterin under bodily fluid conditions (pH 7.6) and is produced by chemical oxidation of tetrahydrobiopterin. 5,6-Dihydrobiopterin has not been reported in metabolic schemes of biopterin but is produced by chemical synthesis of biopterin. Indeed, however, it cannot exist as the dihydropterin structure but as the tetrahydropterin structure formed by intramolecular addition of the hydroxyl group. The retro aldol type side chain cleavage easily occurs on quinonoid and 5,6-dihydrobiopterin to give unsubstituted pterin, and Fikushima-Nixon procedure to evaluate concentrations of tetrahydrobiopterin in biological samples employs this reaction. There are several possibilities for structures of dihydropterin other than quinoniod, 7,8- and 5,6-dihydropterin, but existence of the other dihydropterin has not been reported. In order to understand chemical characters and structures of the dihydrobiopterins, semi empirical (PM3) and *ab-initio* MO calculations were carried out on the possible isomers of dihydro-6-methylpterin, 7,8-dihydrobiopterin, quinonoid dihydrobiopterin and sepiapterin.

A NOVEL SYNTHESIS OF DIHYDRODINAPHTHOPYRANO PYRANS WITH 2-NAPHTHOL AND DIMETHYLOL ALDEHYDE DERIVATIVES.

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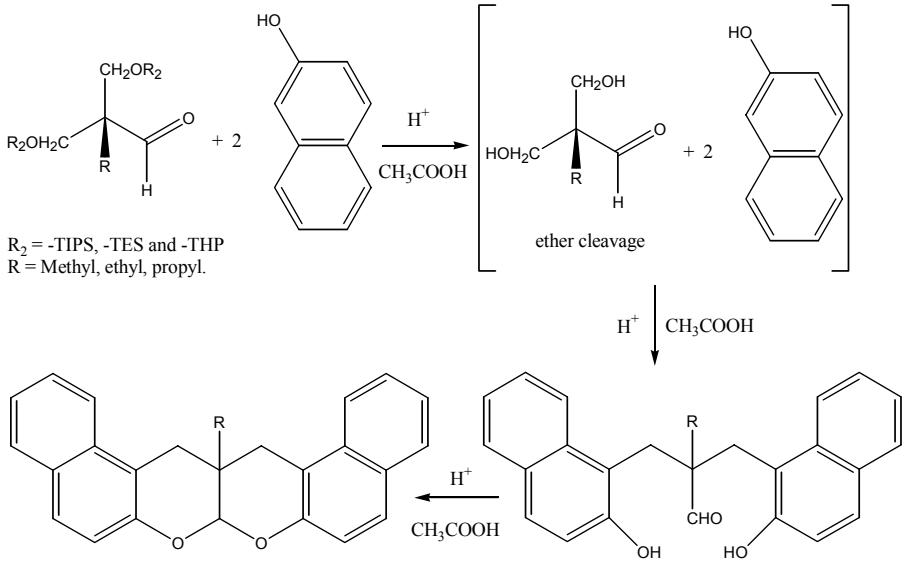
The synthesis of 7a,15a-dihydro-7a-alkyl-15a-alkylnaphtho[2,1-b]naphtho [1',2':5,6] pyran from 2-naphthol and corresponding dimethylol aldehydes derivatives in one step in the presence of acid catalyst in high yield[1].

We extended our study and in this work, we synthesised dimethylolpropanal, dimethylolbutanal and dimethylol pentanal with typical aldol condensation reaction but monomethylol and dimethylol aldehyde was not so stable under normal condition and it has been created intramolecular acetalization reactions itself . In order to prevent this acetalization reaction, and reach to aimed products, we wanted to protect the hydroxy group by selectively converting it to an mainly THP , trimethylsilyl and triisopropylsilyl ether. And than condensation of dimethylol ether aldehydes with 2-naphthol in the presence of acid catalyst, pyranopyran type compounds were obtained.



R = methyl, ethyl, propyl.

References.

[1] Naciye Talinli, Ahmet Akar, A.Cevdet Aydoğan.; Tetrahedron , 43,15 (1987), 3505-3508.

SYNTHESIS AND TRANSFORMATIONS OF HETARYLDIENES

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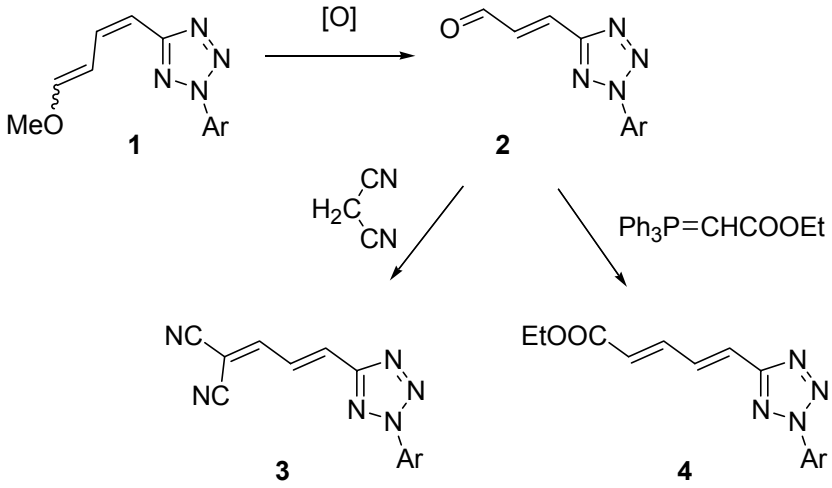
Institute of Chemistry Chemical Research Center of Hungarian Academy of Sciences, H-1025 Budapest, Pusztaszeri út 59-67.

In the course of our earlier investigations we have recently found[1] that oxidative degradation of tetrazolyldiene ethers (**1**) affords tetrazolylacroleins (**2**) which can serve as starting compounds for various structural modifications. Investigation of this group of derivatives is of especial importance because utilization of the reactivity of the diene chain may result in formation of novel derivatives containing the hetaryl group[2].



We found now that condensation reaction of the carbonyl function of **2** can be usefully applied for the above purpose. Thus, reaction of **2** with malonitrile affords the 1,1-dicyano-4-tetrazolyldiene compound (**3**), whereas the Wittig reaction of 2 with ethoxycarbonylmethyl phosphorane gives rise to the ester substituted diene compound **4**.

Extension of these transformations as well as subsequent reactions of the new derivatives will be discussed.

1. I. Nagy, D. Kónya, Zs. Riedl, A. Kotchy, G. Timári, A. Messmer and Gy. Hajós, submitted for publication,
2. Gy. Hajós and A. Kotschy, *Acta Chimica Slovenica*, **45**, 285-354 (1998)

SYNTHESIS OF PYRROLE AND PYRIDINE DERIVATIVES WITH CYCLISATION OF ENAMINES AND UNSATURATED CARBONYLS

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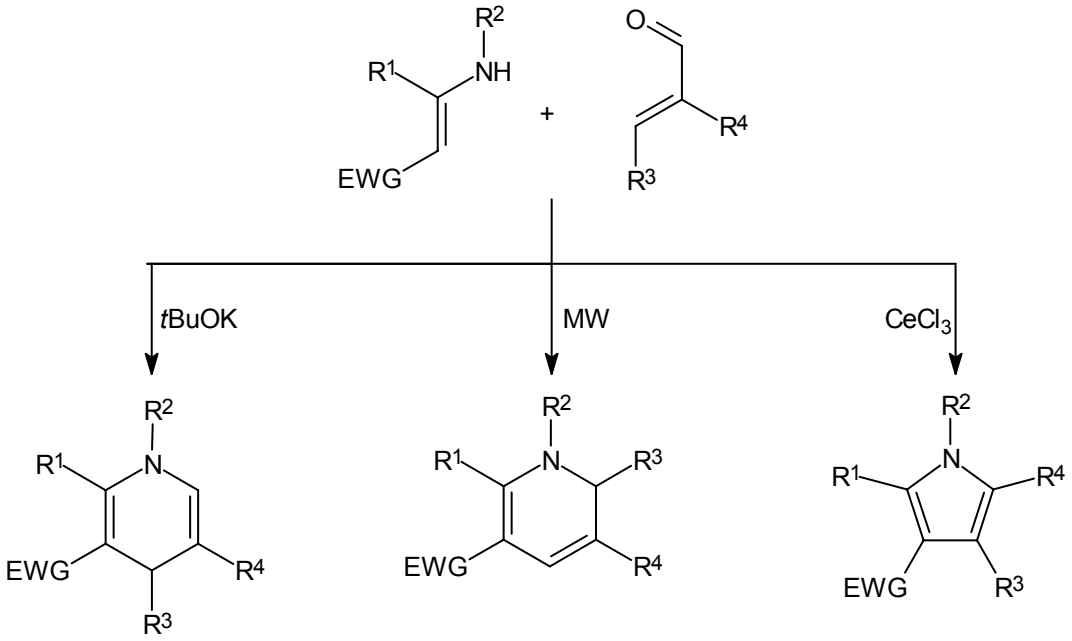
Enamines substituted with an electron withdrawing group in β-position are useful building blocks in the synthesis of various N-heterocycles.
In our present work we describe base or Lewis acid catalysed, and microwave assisted [3+3] cyclocondensations with different enamines and α,β-unsaturated carbonyls affording either 1,4- or 1,2-dihydropyridines regioselectively [1,2]. Surprisingly, Lewis acid supported reactions with unsaturated aldehydes having an alkyl group in α-position resulted in pyrrole derivatives. The variability of both the enamine and the carbonyl component provides a useful method for the preparation of numerous simple and condensed pyrroles or pyridines.



R^1, R^2 = H, Ph, or cyclic; R^3, R^4 = H, alkyl, aryl or cyclic

Further transformations of the new N-heterocycles were investigated as well. Structure elucidation and detailed stereochemical analysis were made by application of two-dimensional NMR techniques.

[1] Nemes, P.; Balázs, B.; Tóth, G.; Scheiber, P.: Synthesis of Fused Heterocycles from β-Enaminonitriles and Carbonyl Compounds *Synlett,* **1999,** 222.
[2] Nemes, P.; Vincze, Z.; Balázs, B.; Tóth, G.; Scheiber, P.: Novel Microwave-assisted [3+3] Cyclocondensations with 1-Cyanomethylene Tetrahydroisoquinoline *Synlett,* **2003,** 250.

DEVELOPMENT OF ODORLESS THIOLS AND SULFIDES AND THEIR APPLICATIONS TO ORGANIC REACTIONS

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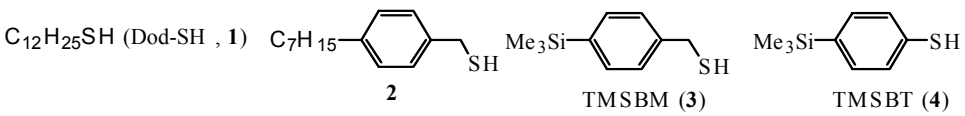
Thiols and sulfides are fundamental and important functional groups in organic chemistry, and the literature contains ample reports of organic and bioorganic chemistry on this group. Among them, benzenethiol is a significant component for the syntheses of some heterocycles containing sulfur atom. Commonly used thiols and sulfides like ethanethiol, benzyl mercaptan, benzenethiol, and dimethyl sulfide have a foul smell making them difficult and unpleasant to use in the laboratory without fume hoods. The problem becomes even worse in industry where these malodorous reagents are used on a large scale. Odorless substitutes are therefore always required. We report here the development of new odorless thiols and sulfides to replace the usual foul-smelling ones, as well as several applications in organic reactions.

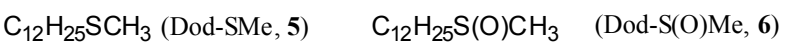
By testing the odor of a number of alkanethiols purified by HPLC, we found that 1-dodecanethiol (Dod-SH, **1**) [1] was odorless. On the base of this finding, 4-heptylphenylmethanethiol (**2**) [1] has been developed as an odorless substitute for benzyl mercaptan. Both odorless thiols **1** and **2** have the same carbon chains (C_{12}), which is a general phenomenon of a thiol to be odorless. The Dod-SH (**1**) was applied to the dealkylation of ethers (Me, benzyl, and MOM ethers) as a substitute for offensive EtSH with assistance of aluminum trichloride. Odorless thiol **2** was also utilized for the synthesis of 1,3-mercapto alcohols from α,β-unsaturated ketones.

Odorless Thiols



The other important findings is that *trimethylsilyl* (TMS) group on benzene ring has a remarkable effect for reducing malodor of the parent thiols, like benzyl mercaptan and benzenethiol. We have developed 4-trimethylsilylphenylmethanethiol (TMSBM, **3**) [2] and 4-trimethylsilylbenzenethiol (TMSBT, **4**) [2] as the odorless alternatives for benzyl mercaptan and benzenethiol, respectively. Protodesilylation made it possible to introduce benzylthio and phenylthio groups into substrates without malodorous smell.

Odorless Sulfide



The dodecyl methyl sulfide (Dod-SMe, **5**) [3] was also found to be odorless, which has given *new odorless protocol for the Corey-Kim oxidation* of alcohols with excellent yields of the products. The corresponding sulfoxide **6** [3] were also utilized to the *odorless Swern oxidation*.[3)]

Ref. [1] *Tetrahedron Lett.* **2001***, 42*, 9207. [2] *Tetrahedron Lett.* **2002***, 43*, 8569.
[3] *Tetrahedron Lett.* **2002***, 43*, 5177.

A SOLUTION OF THE "INTRINSIC PROBLEM" OF DIASTEREOMER METHOD FOR CHIRAL DISCRIMINATION ; RENAISSANCE OF CHIRAL DISCRIMINATION

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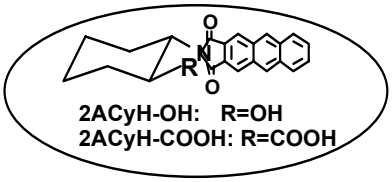
The most widely used diastereomer method for discrimination of enantiomer has a critical problem that it is very difficult or impossible to discriminate the derived diastereomers having chiral centers separated more than four bonds. The problem has been taken to be "intrinsic " to the diastereomer method and left unsolved.

To solve the problem a new principle of chiral discromination was proposed. Based on the principle, multi-functional fluorescent chiral deriving agent **2A1P-OTf(or -OH)**,**1A2P-OTf(or-OH)** (first generation), and **2AcyH-OH** (second generation) were developed for discrimination of enantiomers of methyl branched chiral fatty acids. These reagents have enabled us to discriminate the enantiomers up to 26 th methyl branching by HPLC. **2AcyH-COOH** was also developed for discrimination of chiral alcohols. It has enabled us to discrimoinate the enantiomers of methyl branched fatty alcohols, secondary alcohols having carbon chains different by only one carbon and all four isomers of secondary alcohols having another chirality by an additional methyl branching.



Reference: H.Ohrui, H.Terashima, K.Imaizumi, and K. Akasaka, *Proc. Japan Acad.*, 78, Ser B, 69-72(2002)

TOPOISOMERASE I INHIBITION BY ISOAUROSTATIN DERIVATIVES AND THEIR STRUCTURE-ACTIVITY RELATIONSHIP

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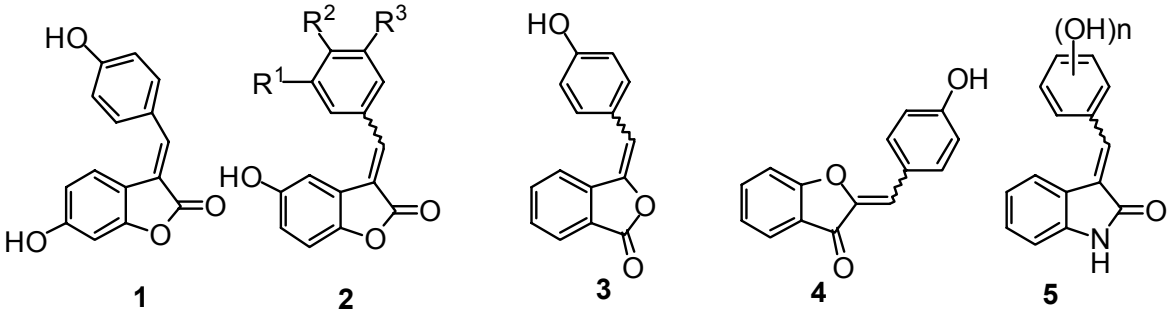
Isoaurostatin (**1**) isolated from *Thermomonospora alba* was modified to the derivatives (**2-5**) showing more potent topoisomerase I inhibitory activities. Their structure-activity realtionship was examined.



Isoaurostatin (**1**) was reported to be an inhibitor of cleavable complex-nonforming type which does not inhibit topoisomerase I by stabilizing the cleavable complex with DNA [1]. To enhance their inhibitory activity we tried to prepare modified compounds and to study on structure-activity realtionship. Each compound with a mixture of *E* and *Z* form is able to vary their ratio by visible light. The ratio gave effect on their inhibitory activities. The *E* : *Z* ratio of compounds **2** and **5** were determined with N.O.E spectra. Compounds with high *E* ratio gave more potent activities.

IC_{50} value was measured with densitometer using topoisomerase I from calf thymus gland and pBR 322 DNA.

Improvement of the IC_{50} value from 67 μM to 3 μM was detected upon change of isoaurostatin (**1**) to benzofuranone (**2**) (R^1=R^2=R^3=OH) . As substituents R^1, R^2, and R^3 on compound **2** OH, OCH_3, NO_2, COOH, OCH_2COOEt, and halogen were used. Consequently compound **2** and indolone **5** with three hydroxyl groups were most potent. Structural isomers, coumaranone **3** and phthalide **4** had no activities.

The cell cycle for potent compounds was measured in *Hela* cell with a cytophotometry. Inhibition of S and G2M phases was observed to depend on substituends.

Inhibitory activities on cancer cell line were also measured.

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SYNTHESIS OF THE SOME NEW 2-AMINO-5-THIAZOLYL-1,3,4-Δ_2-OXADIAZOLINES

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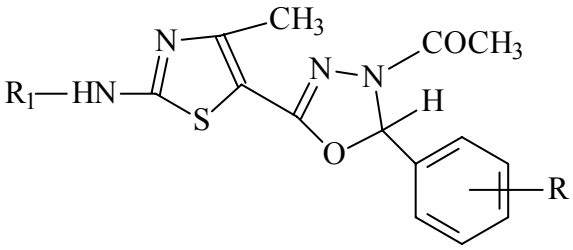
Following our study concerning the synthesis of some thiazolil-oxadiazolines, in this work we proposed the synthesis and characterisation of some 2-amino-5-thiazolyl-1,3,4-Δ_2- oxadiazolines with the general structure:



R_1 =H, AcO, Ar-CH=;
R= Cl, Br, F, NO_2

The chemical structure of the compounds was confirmed by the structural analysis: IR, ^{1}H-NMR and mass-spectra.

FORMAL SYNTHESIS OF γ–LYCORANE.

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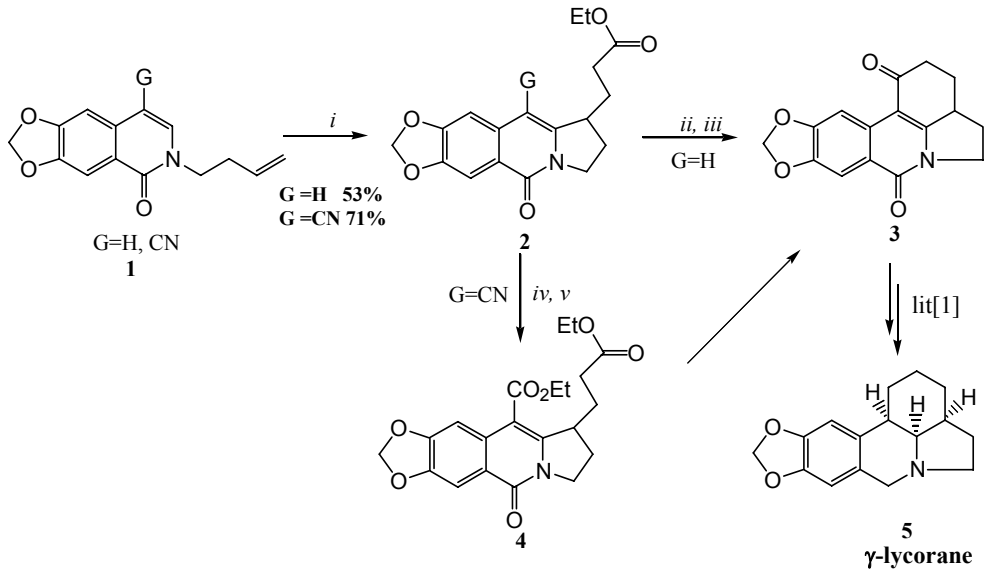
Lycorane (*Amarylidacea* alkaloids) and derivatives have been the subject of several total synthesis and pharmacological studies. We have long been interested in the intramolecular oxidative radical addition onto heteroaromatic compounds as a powerful method for the rapid construction of synthetic intermediates. Here we describe an approach towards an intermediate keto-lactam **3** precursor of γ-licorane **5** using the radical chemistry of dithiocarbonates (xanthates). The key step in the synthesis is an addition/cyclization process of the xanthate **6** and the isoquinolone **1,** which affords the conveniently functionalized derivative **2**. Thus, the tetracyclic system **3** was constructed from **2** by either a Friedel-Crafts acylation (G = H) or a Dieckmann cyclization-decarboxylation process (G = CN).



Reagents and conditions: (i) $EtOCS_2CH_2CO_2Et$ (**6**), DLP, DCE, reflux; (ii) NaOH 40% MeOH, reflux; (iii) HCl (excess of a 5M aqueous solution); (iv) KOH (26 mol equiv), H_2O-MeOH, reflux, 20h then aq. HCl; (v) MeONa, Toluene, then HCl, AcOH.

[1]. Hideo Iida.; Sakae Aoyagi.; Chihiro Kibayashi., *J.C.S., Perkin I*, **1975**, 2502.

REGIOSPECIFIC REACTION OF o-DIAMINO ARENES AND HETARENES WITH POLYCARBONYL PYRROLE DERIVATIVES

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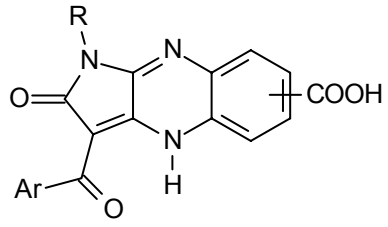
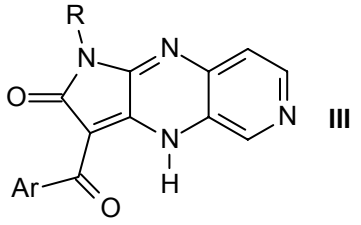
Arenes and hetarenes, *o*-diamino substituted, are useful in the synthesis of fused heterocyclic compounds, especially pyrazine derivatives such as naturally occurring quinoxalines or pteridines, and pyrido[2,3-*b*]pyrazine, pyrido[3,4-*b*]pyrazine systems not appearing in nature [1,2].

We previously described the regiospecific syntheses of new pyrrolo[2,3-*b*]quinoxaline and 1,4,8,9- and 1,4,5,9-tetraaza-cyclopenta[*b*]naphtalene [3,4]. As a continuation we are presenting now the condensation of 3,4-diaminobenzoic acid and 3,4-diaminopyridine with *N*-alkyl or -aryl substituted pyrrolidine-2,3,5-trione derivatives. In all cases the formation of regioisomers have been observed. The synthesis, resolution and NMR structural assignment of respective pairs of isomers (I,II or III, IV) will be presented.

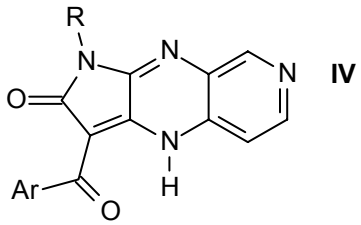
Advances in the synthesis of further derivatives will be discussed.



I, II



III



IV

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[3] K. Ostrowska, M. Żylewski, K. Walocha; *Heterocycles*, **2002**, *57*, 8, 1413-1421.
[4] K. Ostrowska, S. Bugajska, K. Klimczyk; 9th BDSHC, Tatranská Lomnica, Slovak Republic, 2002, PO- 98.

SYNTHESIS OF 2-(2-SUBST.PHENYL)-1H-IMIDAZOLE DERIVATIVES

Patrik Pařík, Vladislav Formánek, Sylva Šenauerová, Vlasta Lišková, Miroslav Ludwig, Oldřich Pytela and Jiří Kulhánek

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We have chosen 2'-substituted 2-phenyl-1*H*-imidazole as a model skeleton for potential ligands. Therefore, the serie of 2-(2-alkoxyphenyl)-1*H*-imidazolines has been prepared [1] by reaction of methyl 2-hydroxybenzoate with ethane-1,2-diamine followed by alkylation with alkylhalogenides [2]. Several oxidation and dehydrogenation reactions have been investigated for testing of imidazoline ring transformation into imidazole. Dehydrogenation on palladium/carbon in toluene [3] has been occured as a best synthetic way. New 2-(2-alkoxyphenyl)-1*H*-imidazoles have been prepared by this way, their structures have been confirmed by elemental analysis and NMR spectroscopy.
Derivatives of 2-(2-aminophenyl)-1*H*-imidazole and 2-(2-dialkylaminophenyl)-1*H*-imidazoles have been also studied. 2-(2-aminophenyl)-1*H*-imidazoline in very low yield 4 %, and 2-(2-dimethylaminophenyl)-1*H*-imidazoline in good yield 60 % have been prepared, as published previously [1]. Dehydrogenation of 2-(2-dimethylaminophenyl)-1*H*-imidazoline into imidazole has been successfully realized. Preparation of 2-(2-nitrophenyl)-1*H*-imidazole has been studied with the idea of its transformation into corresponding amino derivative. Reaction product of methyl 2-nitrobenzoate with ethane-1,2-diamine, 2-nitro-*N*1-(2-aminoethyl)benzamide, has been prepared and its dehydration into corresponding imidazoline has been optimized. 2-(2-nitrophenyl)-1*H*-imidazole has been prepared from 2-nitrobenzaldehyde with glyoxal trimeric dihydrate and ammonium acetate [4]. Similar way using ethyl 2-nitrobenzimidate and aminoacetaldehyde dimethyl acetal has been also investigated [5].

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Authors thank to Grant Agency of Czech Republic for financial support (grant No. 203/02/0750).

NEW FLAVONE DERIVATIVES CONTAINING PYRIMIDINE MOIETIES

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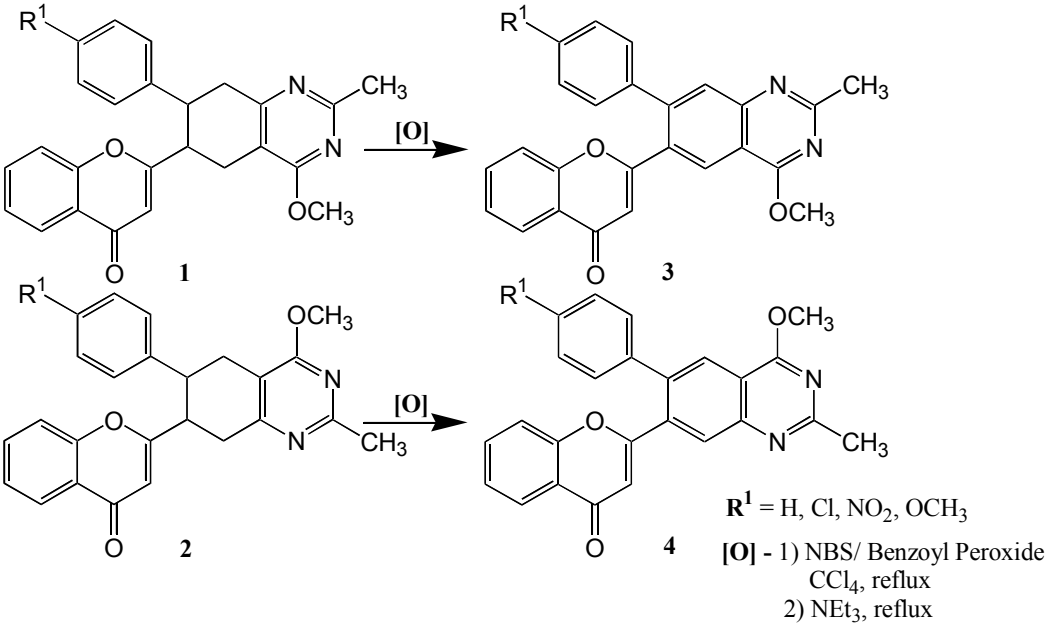
Flavones are an important group of natural products widely occurring in the plant kingdom. Several natural and synthetic flavone derivatives have shown important biocidal, pharmacological and antioxidant activities [1]. During the last years we have studied the synthesis and transformations of 2-styrylchromones.

As a part of this laboratory program we have been developing a synthetic route for new flavone derivatives bearing pyrimidine moieties, starting with 2-styrylchromones. The synthesis of chromones **1** and **2** is achieved from the Diels-Alder reaction of 2-styrylchromones with the 2-methyl-4-methoxypyrimidine-*ortho*-quinodimethane [2].

In this communication we report the aromatization of these adducts **1** and **2** by bromination and elimination of bromic acid obtaining new flavone derivatives, the quinazolylchromones **3** and **4**. The experimental results and structural characterization of all synthesized compounds will be presented and discussed in this communication.



Acknowledgements: Thanks are due to University of Aveiro and FCT-Lisbon, for funding the organic chemistry research unit. One of us (D. T. Patoilo) is also grateful to the FCT/PRAXIS XXI for the award of a student's grant (BD/21362/99).

[1] *The Flavonoids - Advances in Research Since 1986*, Ed. J. B. Harborne, Chapman and Hall, London, **1994**.

[2] D. T. Patoilo, D. C. G. A. Pinto, A. M. S. Silva, A. C. Tomé, J. A. S. Cavaleiro, *The 12th European Symposium on Organic Chemistry*, Groningen, Netherlands, **2001**, Communication P2-100.

N'''-(2-CYANOPHENYL)BENZENECARBOXIMIDOYL ISOTHIOCYANATE - EFFICIENT EDUCT FOR DOMINO-SYNTHESES OF HETEROCYCLES [1]

Pavel Pazdera[a] and Walid Fathalla[b]

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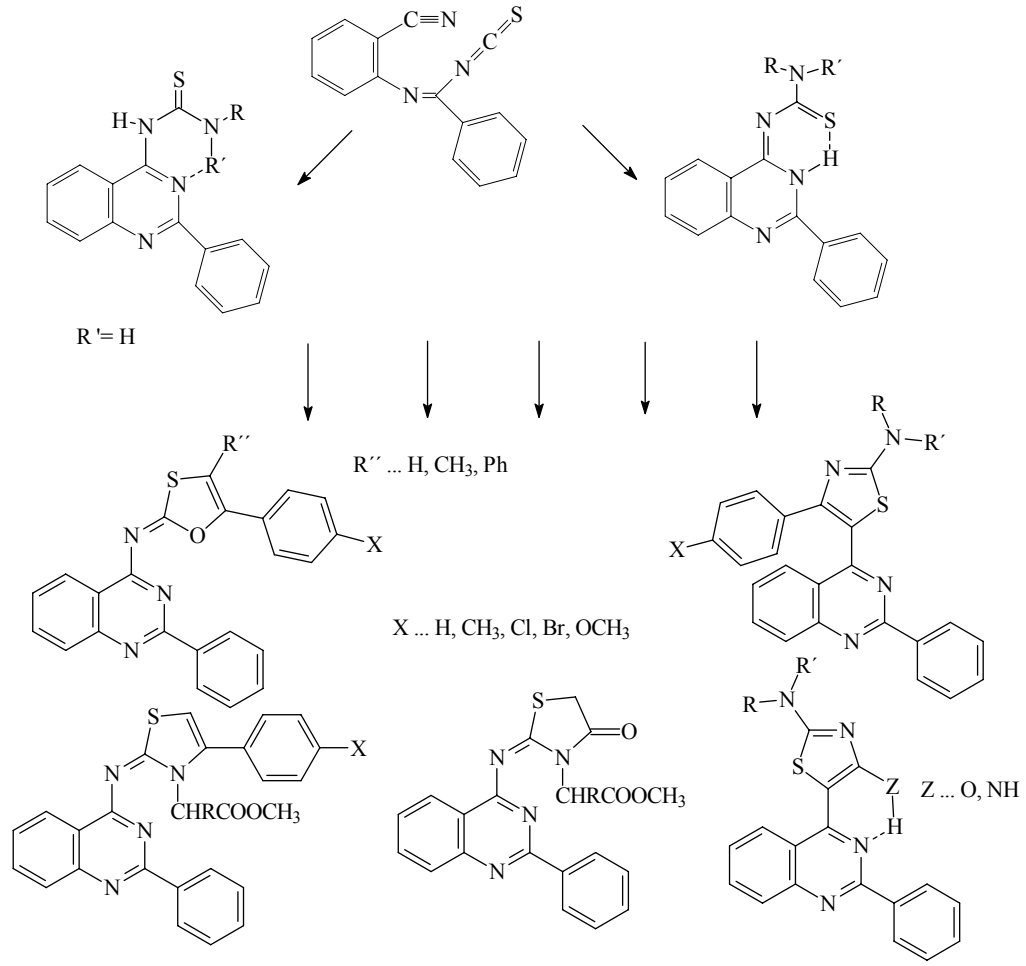
[b]Department of Chemistry, Faculty of Engineer, Suez Canal University, Port Said, Egypt. walid@chemi.muni.cz

Applications of *N*'''-(2-cyanophenyl)benzenecarboximidoyl isothiocyanate for domino-syntheses of quinazolines linked with different substituted oxathioles and thiazoles [2] will be discussed.



[1] Supported by the grant of Ministry of Education of the Czech Republic (Grant No. CEZ: J07/98: 143100011) and Grant Agency of the Czech Republic (Grant No. 203/01/1333).

[2] Fathalla, W., Marek, J. and Pazdera, P., *Molecules* 2001, 6, 588; Fathalla, W., Marek, J. and Pazdera, P., *Molecules* 2001, 6, 574; Fathalla, W., and Pazdera, P., *ARKIVOC* 2002, 1, 7; Fathalla, W., Marek, J., and Pazdera, P., *J. Heterocyclic Chem*. 2002, 1139.

ORTHO-DIRECTED SUZUKI COUPLING REACTIONS ON DIBROMOTHIOPHENES

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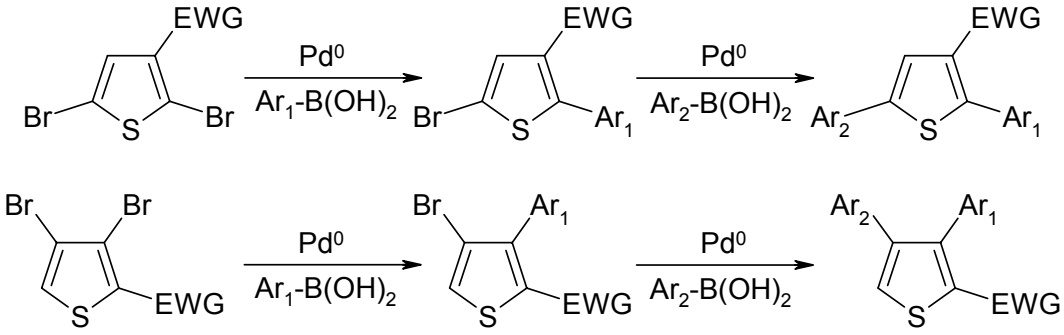
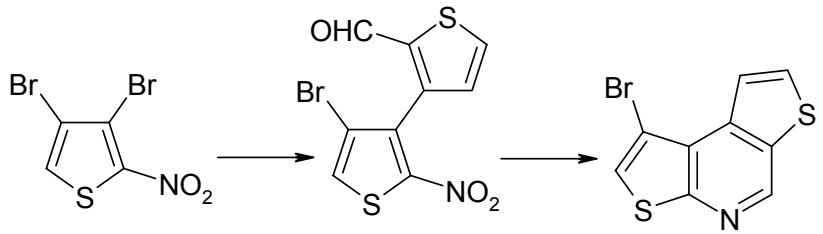
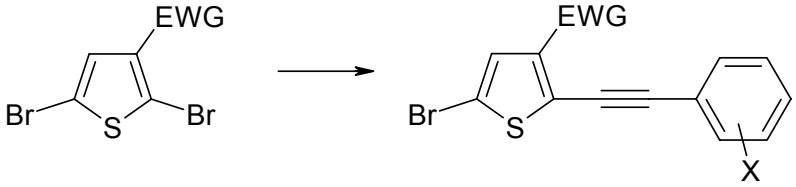
The Suzuki reaction provides a powerful tool in the synthesis of biaryl compounds[1]. Its advantages are the low toxicity, the stability of the arylboronic acids, the compatibility with many functional groups and that no anhydrous conditions are required.
In our research we studied the influence of functional groups ortho to one of the halides in dibromothiophenes. Substituents such as formyl, nitro and nitrile groups exhibited high selectivity and yielded exclusively ortho-mono-arylated products. Esters and oxazolines proved some ortho directing ability and thus produced isomeric mixtures.



Introduction of o-formyl boronic acids during the selective coupling reactions into nitrothiophenes followed by reductive cyclisation gave access to phenantridine analogues:



Moreover, the concept of selective Pd(0) induced coupling reactions was successfully expanded to the Sonogashira protocol:



The selectivity, the influence of the reaction conditions on yield and the formation of by-products will be discussed.

1: Miyaura,M; Yanagi,T; Suzuki,A, Synth. Commun., 1981, 11, 513

ORTHOGONALLY PROTECTED 3,8-DIAZABICYCLO[3.2.1]OCTANE-2-CARBOXYLIC ACID

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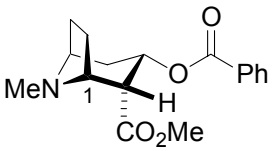
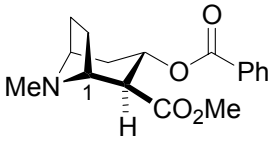
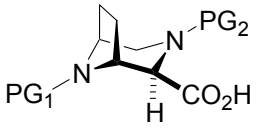
An eight step synthesis of an orthogonally protected 3,8-diaza-bicyclo[3.2.1]octane derivative (**1**) starting from pyroglutamic acid will be described. The target compound serves as a versatile building block for combinatorial synthesis of pharmacologically useful compounds and features α, β, δ and ε amino acid partial structures. Additionally it leads to a novel class of cocaine analogues.



Cocain



Pseudococain



1

VERSATILE SYNTHONS AND MICROWAVE DIELECTRIC HEATING: A COMBINATION THAT REDUCES SUBSTANCE PRODUCTION TIME

Jacob Westman*, Kristina Orrling, Anders Franzén, Ronny Lundin, Maria Östbye, Adam Hurynowicz, Pino Pilotti

Personal Chemistdry, Kungsgatan 76, 753 18 Uppsala, Sweden
*Actar AB, Franzéngatan 6, 112 51 Stockholm, Sweden

The bottleneck in going from biology to clinical trials is believed to be the chemistry development. It is believed that this bottleneck is a bit broadened by the use of microwave dielectric heating. The technology has been proven to reduce reaction times and often ameliorate the yields. There is a risk however, that the time gain of the microwave assisted reaction step drowns in other time-consuming procedures such as preparation of starting materials and reagents and purification of intermediates and final products.

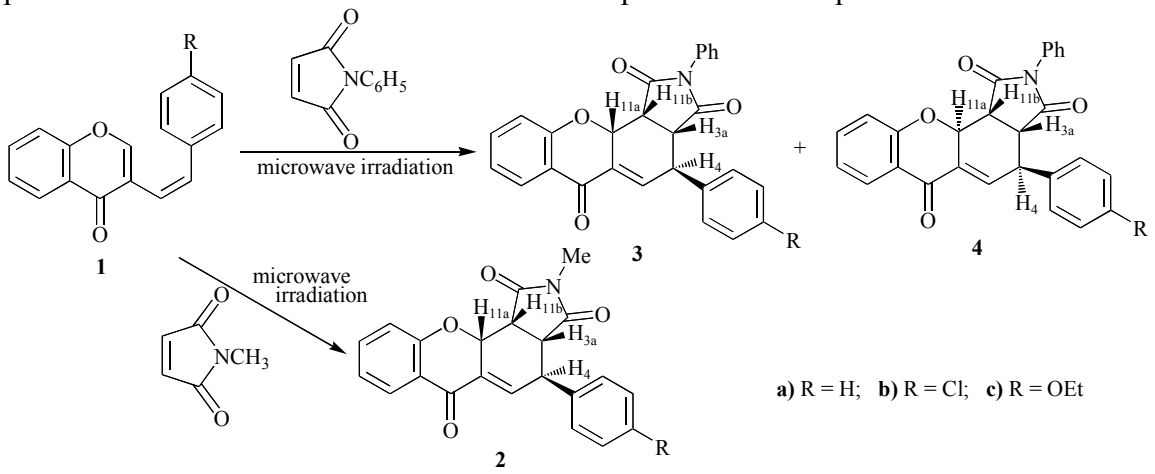
In organic chemistry and in medicinal chemistry in particular, the use of versatile synthons and scaffolds that trigger cascade or domino reactions are of great interest. They introduce high diversity the minimal effort as the need for work-up and purification between the different reaction steps is eliminated. Three such synthons are triphenylphosphorane ethenone, *N,N*-dimenthylformamide diethylacetal and isatoic anhydride.

DIELS-ALDER REACTIONS OF 3-STYRYLCHROMONES WITH N-SUBSTITUTED MALEIMIDES UNDER MICROWAVE IRRADIATION

Diana C. G. A. Pinto[a], Lúcia M. P. M. Almeida[a], Artur M. S. Silva[a], José R. Carrillo[b], Angel Díaz-Ortiz,[b] António de la Hoz[b], and José A. S. Cavaleiro[a]

[a]Departamento de Química, Universidade de Aveiro, 3810-193 Aveiro, Portugal
[b]Facultad de Químicas, Universidad de Castilla-La Mancha, 13071 – Ciudad Real, Spain

Styrylchromones are a small group of heterocyclic compounds; some of their derivatives have shown cytotoxic, anti-allergic and antitumor activities [1]. The synthesis and transformation of 2-styrylchromones have been widely studied, whereas to our knowledge the synthesis of 3-styrylchromones are not abundant and there are no studies on their transformation into other heterocyclic compounds. Following our interest on the transformation of chromone derivatives and knowing that microwave radiation is an alternative to conventional heating and has proved to be efficient in cycloaddition reactions [2], we studied the reactivity of (*Z*)-3-styrylchromones **1** as dienes in Diels-Alder reaction, under microwave irradiation, with *N*-phenyl- and *N*-methylmaleimide. Experimental procedures and structural characterisation of all products will be presented and discussed.



Acknowledgements: Thanks are due to the University of Aveiro, Universidad de Castilla-La Mancha, FCT and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. Financial support from the Spanish DGESIC (Project BQU2001-1095) and from the Consejería de Ciencia y Tecnología JCCM (Project PAI-02-019) is gratefully acknowledged. One of us (D. C. G. A. P.) is also grateful to FCT and FSE, for a Sabbatical grant.

[1] e.g. (a) Doria, G.; Romeo, C.; Forgione, A.; Sberze, P.; Tibolla, N.; Corno, M. L.; Cruzzola, G.; Cadelli, G. *Eur. J. Med. Chem. - Chim. Ther.* **1979**, *14*, 347-351; (b) Brion, J. D.; Le Baut, G.; Zammattio, F.; Pierre, A.; Atassi, G.; Belachmi, L. *Eur. Pat. Appl.* EP 454,587, **1991**.
[2] A. de la Hoz, A. Díaz-Ortis, A. Moreno, F. Langa, *Eur. J. Org. Chem.*, **2000**, 3659.

SYNTHESIS AND TRANSFORMATIONS OF SOME 3-(DIMETHYLAMINO)METHYLIDENE TETRAMIC ACIDS

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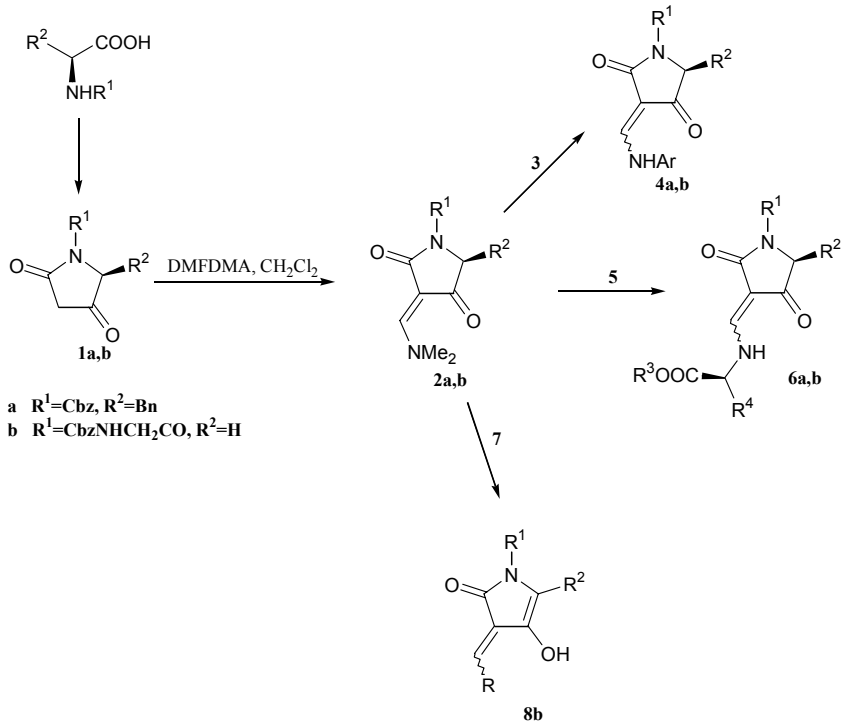
Tetramic acids (pyrrolidine-2,4-diones) have proven to be very useful in the synthesis of various biologically active compounds (statine [1], some HIV protease inhibitors [2], peptidomimetics [3]) Tetramic acid motif is also commonly found in many natural products (vancoresmycin [4], janulosimide [5]).

We prepared two new 3-(dimethylamino)methylidene derivatives of *N*-protected tetramic acids **1a** and **1b**, derived from *N*-Cbz-Phe-OH and *N*-Cbz-Gly-Gly-OH respectively. These compounds were then used in a series of reactions with various *N*-nucleophiles (aryl and heteroaryl amines **3**, amino acid esters **5**) and *C*-nucleophiles such as Grignard reagents **7**.



[1] P. Jouin, B. Castro, D. Nisato, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1177-1182.
[2] J. Courcambeck, F. Bihel, C. De Michelis, G. Quelévér, J. L. Kraus, *J. Chem. Soc., Perkin Trans. 1,* 2001, 1421-1430.
[3] W. Wang, J. Yang, J. Ying, C. Xiong, J. Zhang, C. Cai, V. J. Hruby, *J. Org. Chem,* 2002, **67**, 6353-6360.
[4] C. Hopmann, M. Kurz, M. Brönstrup, J. Wink, D. LeBeller, *Tetrahedron Lett.*, 2002, **43**, 435-438.
[5] S. Yamada, S. Yaguchi, K. Matsuda, *Tetrahedron Lett.,* 2002, **43**, 647-651.

EFFECT OF 2-TRIFLUOROMETHYL GROUP ON THE PICTET-GAMS CYCLIZATION

László Poszávácz and Gyula Simig

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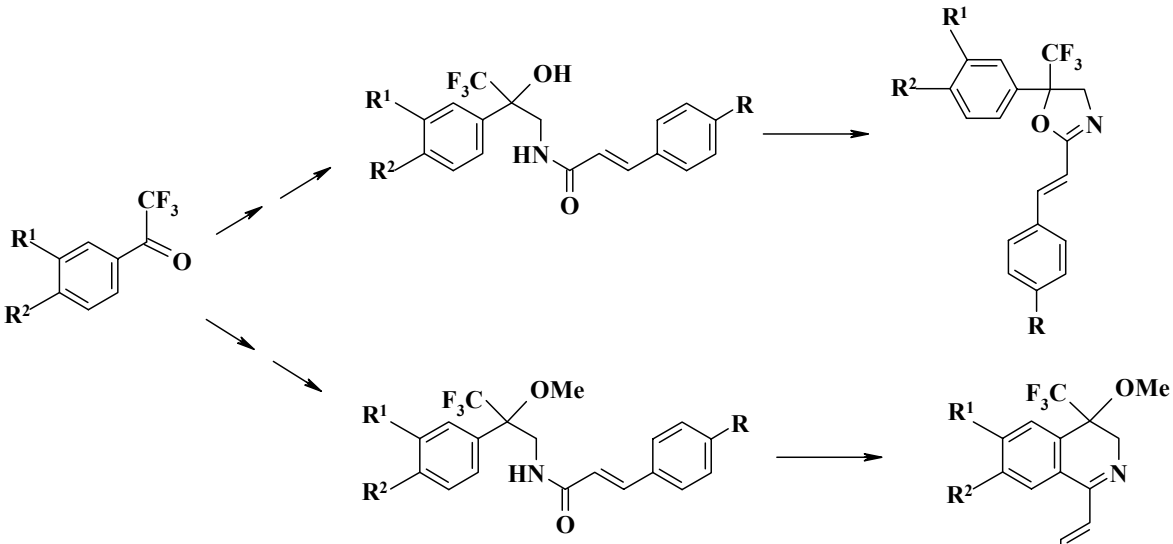
P.O. Box 100, H-1475 Budapest, Hungary

Derivatives of 1-styrylisoquinolines, in particular 1-(4-trifluoromethyl-styryl)-6,7-(methylenedioxy)isoquinoline display remarkable anxiolytic activity without sedative side-effects. Within the framework of our systematic structure activity relationship studies we became interested in the synthesis of related 4-(trifluoromethyl)isoquinoline derivatives. The presence of the trifluoromethyl group has changed the course of the classical Pictet-Gams isoquinoline synthesis. Cyclization of *N*-acyl-2-hydroxy-2-(trifluoromethyl)-arylethylamines under Pictet-Gams conditions afforded 2-oxazolines instead of the expected isoquinolines [1]. However, similar cyclization of the corresponding 2-methoxy derivatives gave 4-methoxy-4-trifluoromethyl-3,4-dihydroisoquinolines [2]. The effect of trifluoromethyl group on these reactions will be discussed.



R	H	F	CF_3	NO_2	CF_3
R^1	OCH_3	OCH_3	OCH_3	OCH_3	O
R^2	H	H	H	H	O

[1] Poszávácz, L.; Simig, Gy. *J. Heterocyclic Chem.,* **2000**, *37*, 343.
[2] Poszávácz, L.; Simig, Gy. *Tetrahedron,* **2001**, *57*, 8573.

SYNTHESIS OF 1,2-DIHYDRO-2-(5-SUBSTITUTED-1,2,4-TRIAZOL-3-YL)-ISOQUINOLINES

Ibolya Prauda and József Reiter

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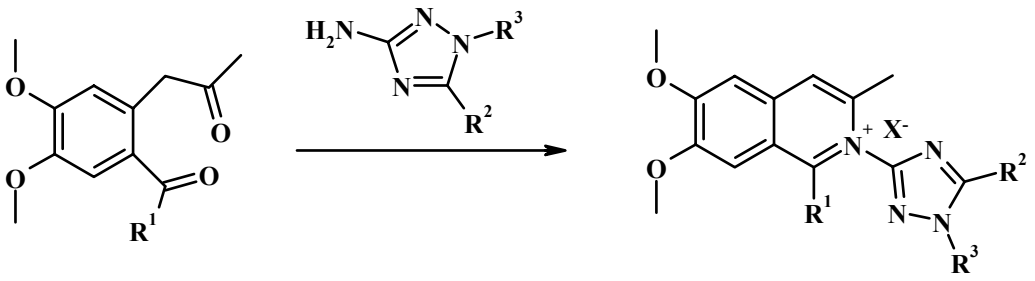
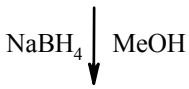
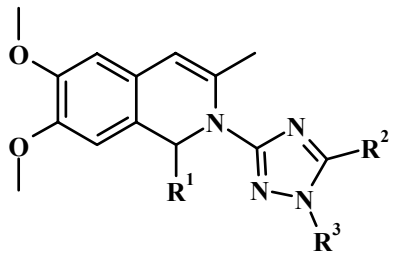
P.O. Box 100, H-1475 Budapest, Hungary

Reaction of ortho-acylarylacetones **1** with 5-amino-3-substituted-1*H*-1,2,4-triazoles afforded isoquinolinium salts **2** [1]. Sodium borohydride reduction of compounds **2** in methanol led to 1,2-dihydro-2-(5-substituted-1,2,4-triazol-3-yl)isoquinolines **3**.



1 **2**





3

R^1 : aryl
R^2 : H, alkyl
R^3 : alkylthio, substituted amino

Earlier reports [2] suggest that treatment of isoquinolinium salts with sodium borohydride in protic solvents give rise to 1,2,3,4-tetrahydroisoquinolines. The unexpected formation of 1,2-dihydroisoquinolines will be discussed.

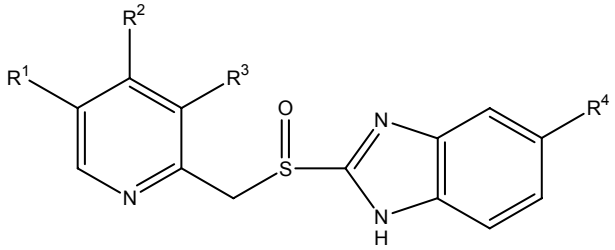
[1] Prauda, I.; Kövesdi, I.; Trinka, P.; Reiter, J. *J Heterocyclic Chem.* **2001**, *38*, 403.
[2] Keay, J. G. *"Partial and Complete Reduction of Pyridines and their Benzo Analogs"* in *Comprehensive Organic Synthesis,* Vol. **8**, 579 (1991) Edited by Trost, B.M.; Fleming, I.

SYNTHETIC STUDIES CONNECTED WITH THE DEVELOPMENT OF GENERIC PRAZOLES

Stanislav Rádl, Ondřej Klecán, Jan Stach

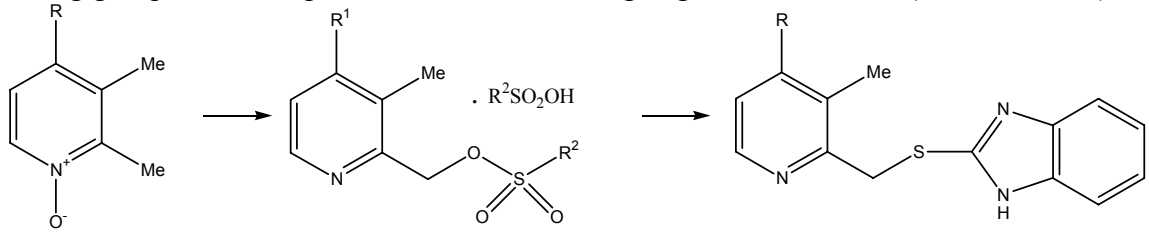
Research Institute for Pharmacy and Biochemistry, Dolní Měcholupy, 102 01 Prague, Czech Republic; e-mail:radl@vufb.cz

Modern antiulcer drugs of the 2-(pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole group called prazoles, such as omeprazole (**1a**), pantoprazole (**1b**), lansoprazole (**1c**), and rabeprazole (**1d**), have been found to be powerful therapeutic agents for treating gastric and duodenal ulcer disease.



1	Drug name	R^1	R^2	R^3	R^4
a	omeprazole	Me	MeO	Me	MeO
b	pantoprazole	H	MeO	MeO	CHF_2O
c	lansoprazole	H	CF_3CH_2O	Me	H
d	rabeprazole	H	$MeO(CH_2)_3O$	Me	H

During our development of generic prazoles we have encountered some interesting possibilities generally applicable in heterocyclic chemistry, e.g. rearrangement of *N*-oxides **2** into the corresponding sulfonates **3,** in which the sulfonyl group can serve as a good leaving group for nucleophilic substitution leading, e.g., to thioethers **4 (**scheme below).



2a; R = NO_2
2b; R = Cl

3a; R^1 = NO_2, R^2 = Me
3b; R^1 = NO_2, R^2 = 4-MeC_6H_4
3c; R^1 = Cl, R^2 = Me
3d; R^1 = Cl_2, R^2 = 4-MeC_6H_4

4c; R = NO_2
4d; R = Cl

Other synthetic examples, as well as synthesis of some impurities of this class of drugs will be also discussed.

NEW SAPONIN'S AGLYCONES: FUNCTIONALISATION OF UNACTIVATED CARBONS

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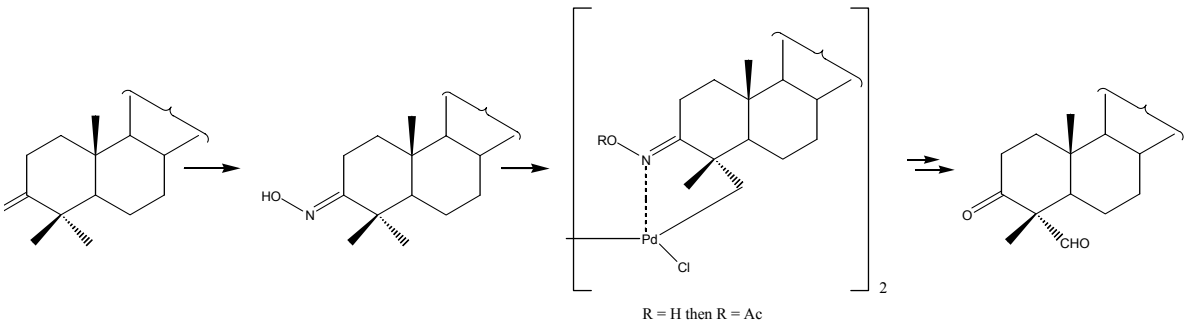
[a] Instituto Nacional de Engenharia e Tecnologia Industrial (INETI)
Estrada Paço do Lumiar, 22, 1649-038 Lisboa, Portugal
[b] University College of London (UCL)
Department of Chemistry, Christopher Ingold Laboratories, 20 Gordon Street, London, WC1H 0AJ, UK

Saponins comprise a diverse class of plant glycosides containing either steroidal or triterpene aglycones linked to carbohydrate chains and they possess a broad range of interesting applications. Their immune stimulating properties, including adjuvant activity, make these compounds an important target for the vaccine industry [1]. Our interest on the synthesis of new terpene aglycones is related with the difficult availability and high complexity of isolation from natural sources.

It seems that an aldehyde group at C-4 is crucial for the activity of the aglycone [2]. The functionalisation of the hindered C-4 equatorial methyl group is possible through the Baldwin's chemistry which involves a cyclopalladation of the referred methyl group from a 3-one oxime functionality [3].

We report the synthesis of new steroid and triterpene derivatives with an aldehyde functionality at C-4.



R = H then R = Ac

Further studies on the biological activity of new aglycones, with and without an aldehyde group at C-4, will allow the elucidation of the importance of this functionality.

Acknowledgement:
Thanks are due to FCT (Fundação para a Ciência e a Tecnologia) for financial support (SFRH/BD/1237/2000)

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[1] Rouhi, A. M. *Chem. Eng. News* **1995**, *73*, 28; [2] Press, J. B.; Reynolds, R. C.; May, R. D.; Marciani, D. J. *Studies in Nat. Prod. Chem.* **2000**, *24*, 131; [3] Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699.

ELECTROCHEMICAL AND SONOELECTROCHEMICAL STUDIES OF HALOGENATED BENZOTHIOPHENES

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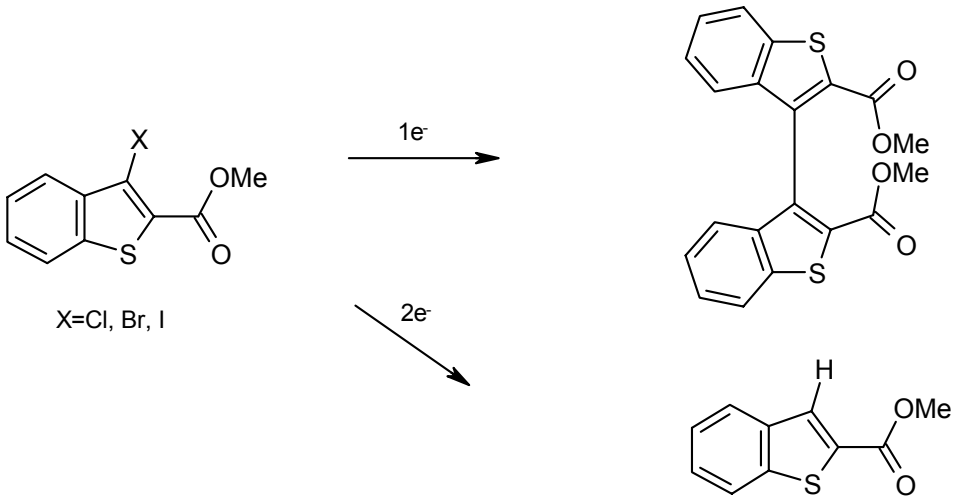
[b]J. Heyrovský Institute of Physical Chemistry, Academy of Science of the Czech Republic, Dolejškova 3, 182 23 Prague 8, Czech Republic

Axially chiral 3,3´-bi(benzothiophene) derivatives are promising intermediates for design of new chiral auxiliaries for enantioselective syntheses and for new liquid crystalline materials [1,2]. In order to explore new synthetic ways leading to the 3,3´-bi(benzothiophene)s, electrochemical behaviour of methyl 3-halobenzo[b]thiophene-2-carboxylates at platinum and mercury electrode was investigated. The influence of ultrasound on the process was also studied.



The first two-electron reduction process corresponding to the splitting off of the halogen is strongly material electrode dependent – electrolysis at platinum electrode is hindered by electrode passivation with the formed by-products. Irradiation by power of ultrasound (sonication) can reactivate the surface of the electrode and enables the preparative electrodimerization. Nevertheless the desired 3,3´-bi(benzothiophene) derivative has not been obtained yet.

Financial support of the grant Agency of Czech Republic (project No. 202/02/0840) and Ministry of Education, Youth and Sports (project No. MSM 223100001) of the Czech Republic is gratefully acknowledged.

[1] Bennincori T., Brenna E., Sannicolo F., Trimarco L., Antognazza P., Cesarotti E., Demartin F., Pilati T.: *J. Org. Chem.* **1996**, *61*, 6244.
[2] Mézlová M., Petříčková H., Maloň P., Svoboda J.: *Collect. Czech. Chem. Commun.* **2003**, *68*, 1020.

SYNTHESIS OF 3,7,9-TRIHETEROBICYCLO[3.3.2]DECANES AND DERIVATIVES

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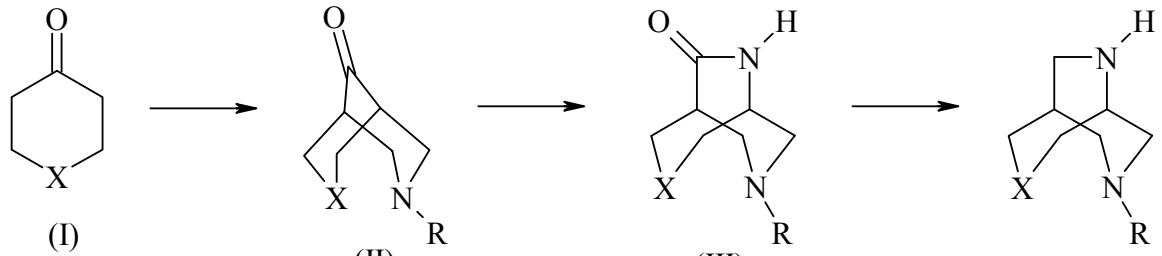
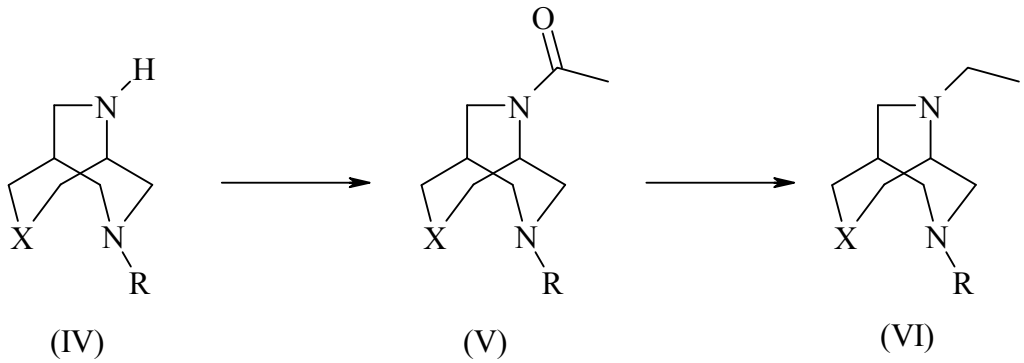
The synthesis of 3,7,9-triheterobicyclo[3.3.2]decanes (IV) is described, which serve as precursors for a series of modified bicyclic bases.



X = S, NR
R = -CH_3, -CH_2Ph

Type (IV) was easily accessible starting from (I) through Mannich condensation (II), Schmidt-rearrangement (III) and subsequent reduction with Red-Al [1, 2].
We also accomplished the successful synthesis of ethyl-derivatives of (IV) *via* acetylation (V) and reduction to (VI) in good yields.



X = S, NR
R = -CH_2Ph

Moreover, several pathways for N-debenzylation of (IV) are discussed and the obtained results are presented.

[1]M. Kozich, PhD-thesis, TU-Vienna,1993
[2]Gregory L. Garrison et al., J. Org. Chem. 1993, 58, 7670-7678

SYNTHESIS OF OF THE ANTICANCER AGENT BAZETOXIFENE

Dirk Röseling[a] , Ving J. Lee[b] , and Ulrich Jordis[a]

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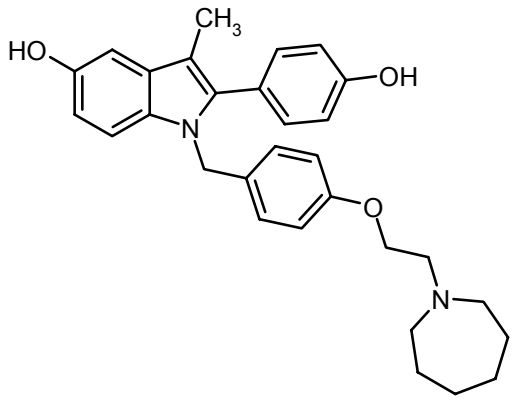
Within the large family of estrogens are tissue-selective estrogens that have been classified as selective estrogen receptor modulators (SERMs). These compds. are characterized by the fact that they exhibit both estrogen agonist and antagonist activity dependent upon the gene promoter and target tissue being examd. SERMs have been intensively studied over the past decade, esp. since one, raloxifene, has been approved for the prevention and treatment of postmenopausal osteoporosis. In order to develop an improved SERM, a stringent screening process was described to select compounds that did not stimulate the uterus or breast. Under these strict conditions, bazedoxifene (WAY-140424) was developed and is presently in phase I and II trials. [1,2].
We will report an optimized synthesis of bazedoxifene that we developed in the context of the collaboration with the DrugMatrix program [3], the world's largest chemogenomics reference database and informatics system.



Leading references: [1] Developing a SERM: Stringent preclinical selection criteria leading to an acceptable candidate (WAY-140424) for clinical evaluation. Komm, Barry S.; Lyttle, C. Richard. Women's Health Research Institute, Wyeth-Ayerst Research, Collegeville, PA, USA. Annals of the New York Academy of Sciences (2001), 949(Selective Estrogen Receptor Modulators (SERMs)), 317-326. CAN 136:256748
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ENANTIODIVERGENT BAEYER-VILLIGER OXIDATION OF FUNCTIONALIZED PROCHIRAL CYCLOHEXANONE AND BICYCLO[3.3.0]KETONE DERIVATIVES UTILIZING RECOMBINANT CELLS

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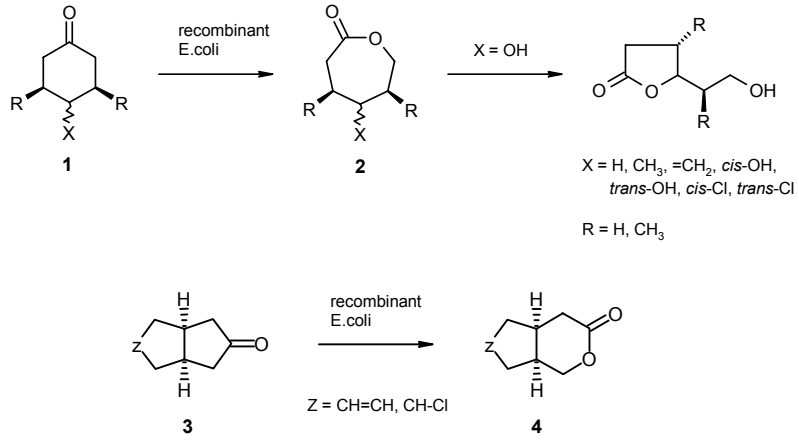
Beside the enantioselective organo-metal catalyzed Baeyer-Villiger oxidation[1] the microbial Baeyer-Villiger oxidation[2] has become a powerful tool to synthesize asymmetric lactones as interesting intermediates in organic chemistry and frequently encountered precursors in enantioselective synthesis. The importance of enantioselective microbial reactions has grown in recent years due to an increased need for "green chemistry" approaches in industrial synthesis. Especially the field of chiral Baeyer-Villiger oxidations is one of the representative domains for biocatalysis.

In this study we present whole-cell mediated Baeyer-Villiger reactions on preparative scale using recombinant organisms as facile tools for organic chemists. Four expression systems for flavin dependent monooxygenases from *Acinetobacter sp.*, *Comamonas sp*., and *Brevibacterium sp*. (I+II) were investigated for their substrate acceptance on prochiral 3,4,5- functionalized carbocyclic (**1**) and bicyclo[3.3.0]ketones (**3**).



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

In this poster we present the results of the microbial Baeyer-Villiger oxidation of compounds **1** and **3** which lead to lactones **2** and **4** in high optical purities and distinguished enantiodivergence. The influence of substrate polarity and sterical aspects of substituents R, X, and Z will be discussed in detail. The enantioselectivity of the enzymatic transformation will be compared with protein sequence analysis of all four different expression systems.

A diastereoselective synthetic route to compounds **1** will be outlined together with potential applications of product lactones **2** and **4** in natural product and bioactive compound synthesis.

[1] Bolm, C. *Peroxide Chemistry* **2000**, 494-510
[2] Mihovilovic, M.D.; Müller, B.; Stanetty, P. *Eur. J. Org. Chem*. **2002**, 3711-3730

CLOROTRIMETHYLSILANE AS A PROSPECTIVE CONDENSING AGENT FOR BIGINELLI REACTION

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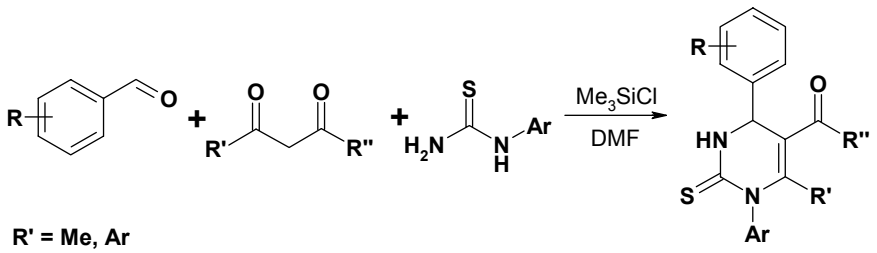
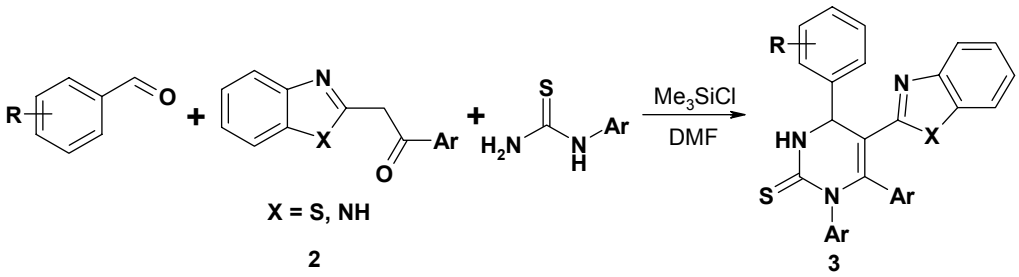
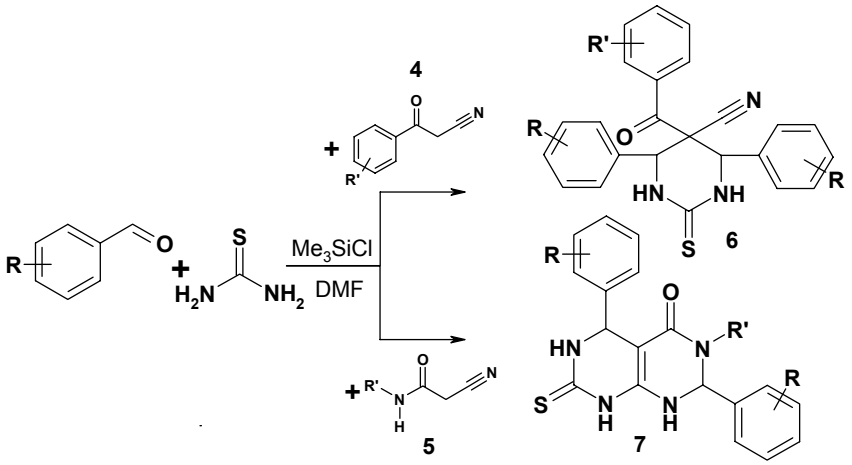
Various aldehydes, 1,3-dioxocompounds and N-arylthioureas were easily condensed into dihydropyrimidines **1** using clorotrimethylsilane as dehydrating agent. This is a first successful example of Biginelli reaction with N-arylthioureas.



Hetarylacetophenones **2** were also used as oxomethylenes, that allowed to obtain dihydropyrimidines **3**.



Furthermore, different active methylene nitriles **4**,**5** were examined in the reaction. In this case the reaction pathway was found to depend on the nature of the nitrile. Thus, starting from benzoylacetonitriles **4** compounds **6**[1] were obtained, while cyanoacetic acid amides **5** yielded hitherto unknown pyrimidopyrimidines **7**.



[1] Kambe S., Saito K., Hirose M., Sakurai, A., Midorikawa H. *Synthesis*; **1984**; *10*; 860-862.

ADDITION OF ORGANOMETALLIC REAGENTS TO CHIRAL (Z)-1,3-DIPHENYL-3-(2-PHENYLIMIDAZO[1,2-A]PYRIDIN-3-YL) PROP-2-EN-1-ON

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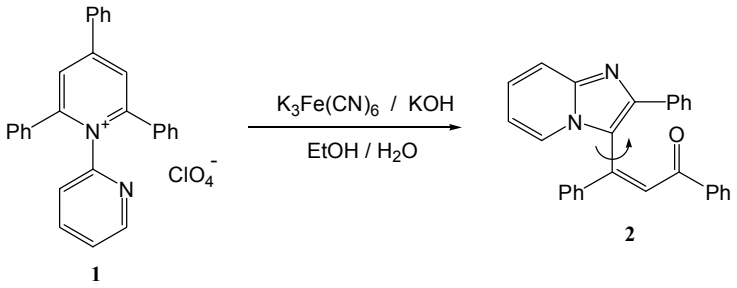
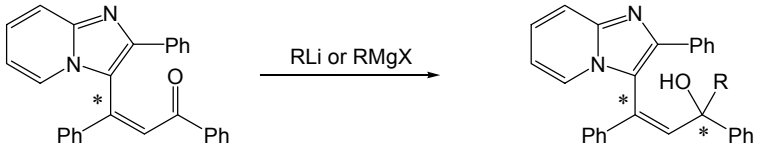
(*Z*)-1,3-diphenyl-3-(2-phenylimidazo[1,2-a]pyridin-3-yl)prop-2-en-1-on **2** is quite easily accessible via ferricyanide oxidation of 2,4,6-triphenyl-1-(pyridin-2-yl)pyridinium perchlorate **1** [1].



1 **2**

Restricted rotation around carbon – carbon bond connecting the heteroaromatic ring with the propenone chain causes an axial chirality of compound **2**. This was proved by ^{1}H NMR measurement in the presence of a chiral shift reagent and by diastereoselective borohydride reduction of the prochiral carbonyl group some time ago [2].

We wanted to determine the regioselectivity and diastereoselectivity of organometallic addition reaction to enone **2**. Thus we carried out a series of experiments with selected organolithium as well as Grignard reagents in various solvents and obtained 1,2-addition products exclusively in all cases.



2 **3**

Tertiary alcohols **3** were isolated as diastereoisomeric mixtures; single racemic isomers could not be separated because of the too low rotational barriers. These were calculated using semi empirical PM3 method and a procedure, which was successfully used [3] for this purpose before. The kinetics of the diastereoisomerization reaction was also monitored by ^{1}H NMR and one of the rotational barriers was thereof specified using Eyring equation.

[1] Böhm S., Kubík R., Novotný J., Ondráček J., Kratochvíl B., Kuthan J.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 2326.
[2] Kubík R., Böhm S., Kuthan J.: *Collect. Czech. Chem. Commun.* **1996**, *61*, 1018.
[3] Böhm S., Pohl R., Kuthan J.: *Collect. Czech. Chem. Commun.* **1999**, *64*, 1761.

EFFICIENT SYNTHESIS OF 2,2'-BIPYRIDINE-BASED CYCLOPHANES VIA RING-CLOSING METATHESIS

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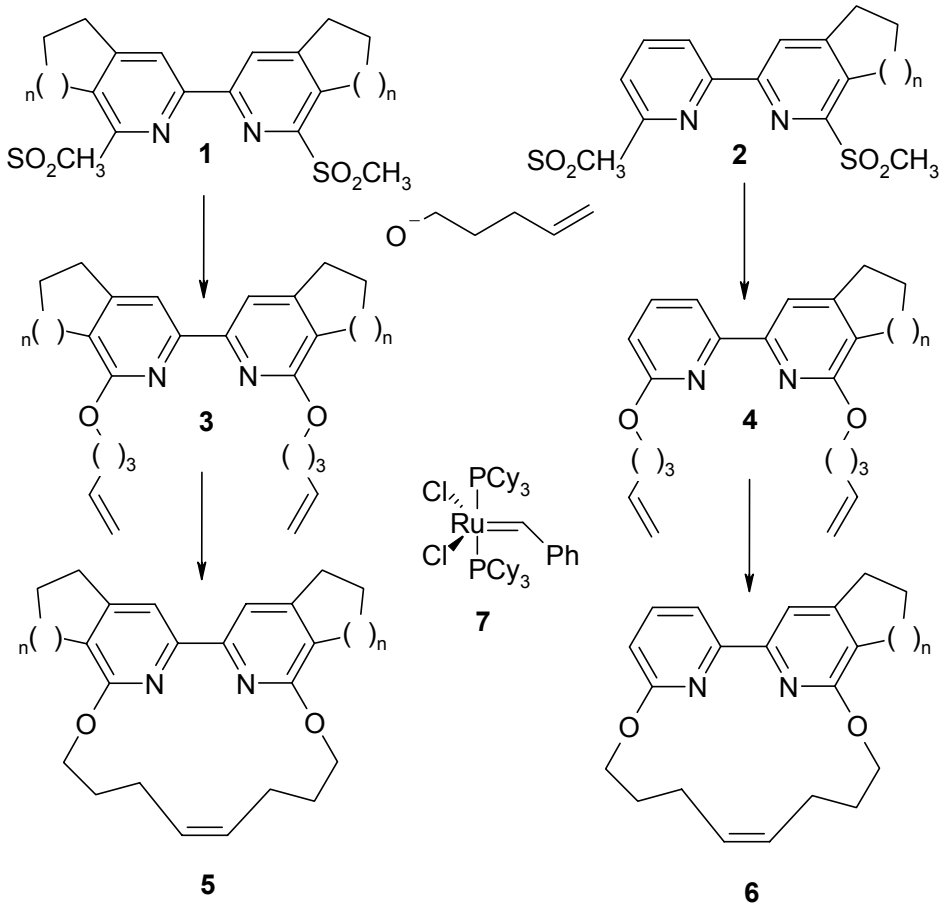
The preparation of cyclophanes and their heterocyclic analogues is still of the major importance in organic synthesis in view of their numerous applications in supramolecular and materials chemistry [1]. We describe herein an efficient synthesis of symmetrical and unsymmetrical cyclophanes, comprising the cycloalkeno[c]fused 2,2'-bipyridines, [2] and a polyether tether connected at the 6,6'-positions, based on the ring-closing metathesis of the corresponding alkenyl ethers **3** and **4**. The general approach is outlined in Scheme.



All alkenyl ethers were reacted under the identical conditions with 25 mol% Grubbs' catalyst **7** in refluxing dichloromethane solution (0.01M concentration). (EE) Stereochemistry of **5** and **6** was confirmed by ^{1}H NMR data and X-ray. Double bond of compounds **5** and **6** can be reduced (10% Pd-C, H_2, 1atm, CH_2Cl_2 25°C) to give the corresponding saturated derivatives.

[1] Tsui, T; Ohkita, M.; Kawai, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 415 and references therein.
[2] For the synthesis of cycloalkeno[c]fused 2,2'-bipyridines see: Branowska, D. and Rykowski, A. *Synlett*, **2002**, 1892.

GROUP 15 HETEROARENES, STABILITY AND AROMATICITY.

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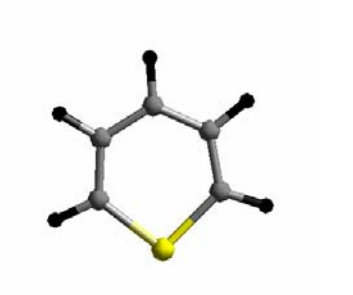
The ambiguous nature of the group 15 heteroarenes C6H5G (G= N, P, As, Sb, Bi) is studied on the base of theoretical calculations (Gaussian98 and Jaguar). The stability, coordination capability and aromaticity change with the presence of a pnicogen atom. The nature of the frontier molecular orbitals in each case seems to be fundamental to find an explanation about the different behavior in this family of compounds. This feature and a reactivity prediction is discussed in this study.



m-HYDROBENZOIN DERIVATIVES AS POWERFUL POLYMER SUPPORTED CHIRAL AUXILIARIES FOR GENERATING LIBRARIES OF ENANTIOPURE α-HYDROXY ACIDS AND 1,2-DIOLS

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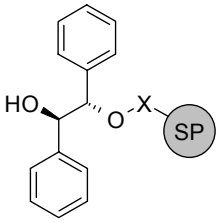
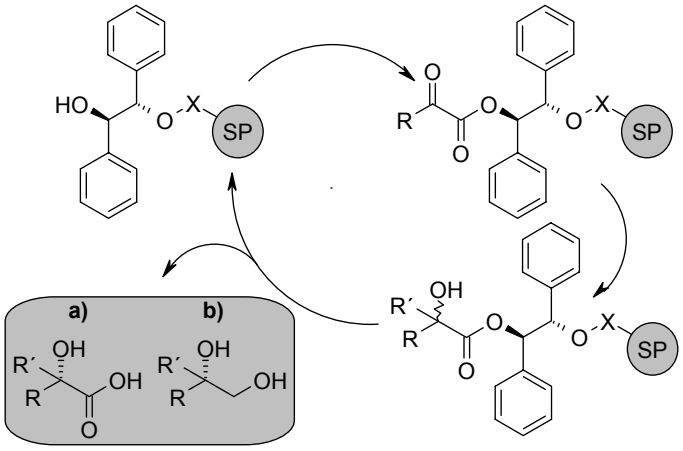
Solid phase synthesis methods have regained much influence in recent years, in particular for the preparation of compound libraries for drug development programs.

As hydrobenzoin derivatives are already known as chiral auxiliaries [1], which possess structural subunits very similar to benzyl ethers like many commercially available linkers, we tested hydrobenzoins as dual chiral auxiliaries and linkers for stereoselective solid phase organic chemistry.



In order to optimize the influence of sublinking units X various model structures derived from *m*-hydrobenzoin, which had easily been desymmetrized by reaction with Noe´s anhydrodilactol [2], bearing different ether substituents symbolising the site of linkage X to a solid support were synthesized and tested as chiral auxiliaries in the reduction [1c, e] of and the addition of organozinc reagents [3] to their benzoylformates, resp., using convenient solution chemistry.



Diastereoselectivities up to 98 % depending on steric and coordinative properties of ether substituents X will be presented.

Results of the stereoselective syntheses of small libraries of chiral α-hydroxy acids and 1,2-diols using the optimized auxiliary bound to commercially available Wang resin and additional recyclability experiments will be presented as well.

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[2] (a) Noe, C. R., Knollmüller, M., Steinbauer, G., Völlenkle, H.; *Chem. Ber.* **1985**, 118, 4453-4458. (b) Noe, C. R., Knollmüller, M., Steinbauer, G., Jangg, E., Völlenkle, H.; *Chem. Ber.* **1988**, 121, 1231-1239.

[3] Boireau, G., Deberly, A., Abenhaim, D.; *Tetrahedron* **1989**, 45, 5837-5844.

2,6-BIS(4-ISOPROPYL-4-METHYL-4,5-DIHYDRO-1H-IMIDAZOL-5-ON-2-YL)PYRIDINES: NEW CHIRAL LIGANDS AND THEIR METAL COMPLEXES

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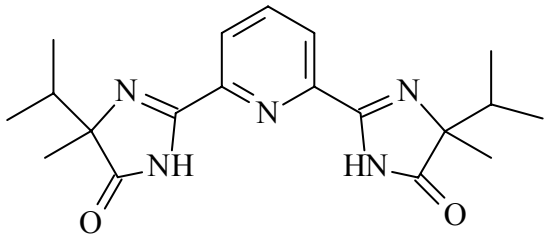
At present, one of the intensively developed fields of heterocyclic chemistry is the synthesis and characterisation of new systems that form coordination compounds with metals. The new complex heterocyclic compounds are widely applicable. If the ligand molecule includes a stereogeneous centre, then such ligands can be utilised as homogenous catalysts in asymmetrical synthesis [1]. In a number of published papers we described syntheses and NMR spectra of substituted 4,4-dialkyl-4,5-dihydro-2-phenyl-1*H*-imidazol-5-ones [2]. Now we designed new 2,6-bis(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridines formally similar to the well-known oxazoline derivatives ("Pyboxes") and terpyridines ("Terpes"). Target 2,6-bis(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridines:(*R,R*): $[\alpha_D^{20} = +32°]$; and (*S,S*): $[\alpha_D^{20} = -33°]$ we obtained by the cyclisation reaction of acylated corresponding butanamides. Acylated butanamides we prepared by reaction of (*R*)-2-amino-2,3-dimethylbutanamide and (*S*)-2-amino-2,3-dimethylbutanamide with dichloride of pyridine-2,6-dicarboxylic acid. *Meso*-form of 2,6-bis(4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-on-2-yl)pyridine (*R,S*) we obtained by crystallisation of racemic mixture.



Our prepared ligands were characterised by ^{1}H, ^{13}C NMR spectroscopy and X-ray diffraction. Further we prepared complexes of our ligands with cobalt and rhodium as a potential catalysts for enantioselective reactions. The mono-dentate complexes with coordination-covalent bonding are characterised by charge transfer between the ligand (electron donor) and the metal (electron acceptor) with subsequent back donation.

The authors thank to Ministry of Education, Youth and Sports of the Czech Republic (Project CI MSM 253 100 001) for the financial support.

[1] Ojima I.Ed.; In *Catalytic Asymetric Synthesis;* VCH Publishers Ltd. 1993.
[2] Sedlák M., Halama A., Mitaš P.,Kaválek J.,Macháček V.: *J.Heterocyclic. Chem.* **1997**, *34*, 1227.

SYNTHESIS OF A NEW SPIRO-BRIDGED HETEROBICYCLIC RINGSYSTEM

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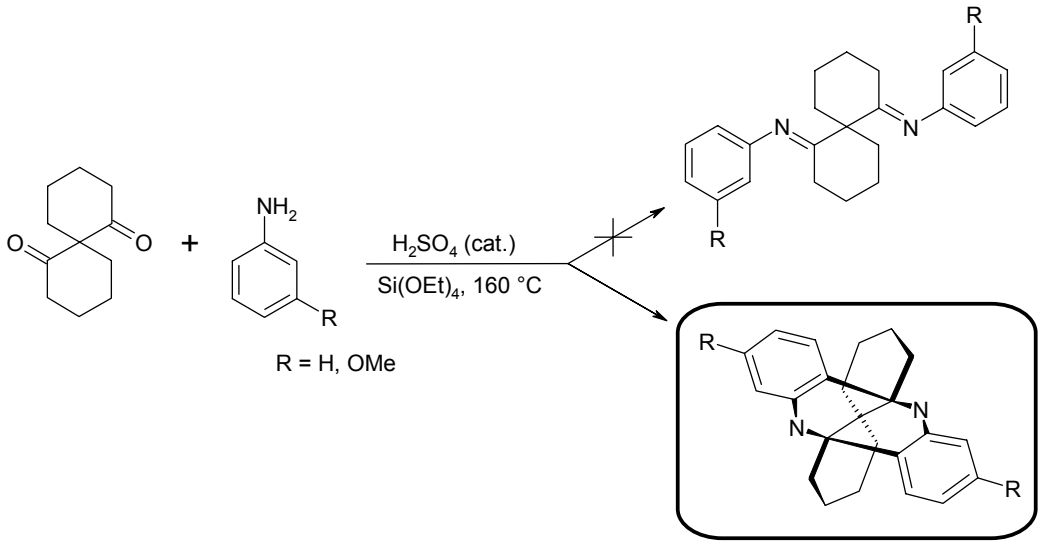
In the course of our research project on functionalised spiro[5.5]undecanes as potential ligands in metal-organic chemistry, we discovered an unusual cyclisation in the course of a reaction originally aiming at the synthesis of sterically hindered imines[1]:



Further experiments with non-spiro 1,3-diketones under the same conditions resulted in corresponding imine-products: this proves that a rigidized diketo-structure is required as a prerequisite for the formation of the isolated bicyclic parent system.

The synthetic strategy in combination with corresponding spectroscopic and crystallographic data of the new compounds will be presented and the obtained results are discussed.

[1] B. E. Love, J. Ren, *J. Org. Chem.* **1993**, 58(20), 5556-5557

PHOTOCHEMISTRY AND PHOTOPHYSICS OF HETEROCYCLIC KETONES

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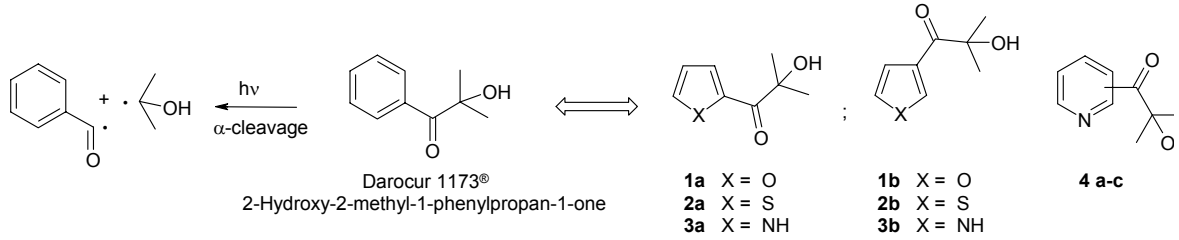
Among the large group of photoinitiator (PI) structures, hydroxyalkylphenones e.g. Darocur 1173 (Scheme 1) have gained much interest for radical polymerization processes in the past decade due to their high reactivity and universal applicability [1]. Many modifications of this hydroxyalkylphenone structure on the α-carbon atom and at the *para*-position of the phenyl moiety have been investigated in the past, since the chemical environment has an enormous influence on the photochemistry of those systems. Since the phenyl moiety was not exchanged by heterocyclic structures until now, it was of interest for us to prepare PIs **1-4** [2]. It could be expected that different substitution patterns give varying photochemical and -physical properties.



Scheme 1: α-Cleavage of hydroxyalkylphenones and products (**1-3**)

All initiators were characterized by UV-VIS absorption spectroscopy. Rates of polymerization and double bond conversion were measured by Photo-DSC. To identify cleavage mechanism and products photolysis experiments were carried out using TEMPO as stable radical for quenching reactions. It has been found that this chromophore is replaceable by electron-poor heterocyclic structures such as pyridines (**4**), which exhibit similar activity under nitrogen atmosphere compared to the highly efficient benzo-aromatic hydroxyalkylphenones. Photo-DSC measurements under air revealed significantly improved reactivity compared to the commercially available initiator [3]. By Laser Flash Photolysis experiments under aerobic conditions decreased oxygen quenching reactions of the formed pyridine carbonyl radical was detected.

[1] H. F. Gruber; *Prog. Polym. Sci.* 1992, **17**, 953.
[2] R. Liska; *Heterocycles*, 2001, **55**, 1475-1486.
[3] R. Liska, D. Herzog; *J. Polym. Sci.* 2003 (in press)

A NOVEL SYNTHETIC ROUTE TO NEW SUBSTITUTED -7H-[1, 2,4]TRIAZOLO[4,3-B][1,2,4]TRIAZOL-1-IUM SALTS

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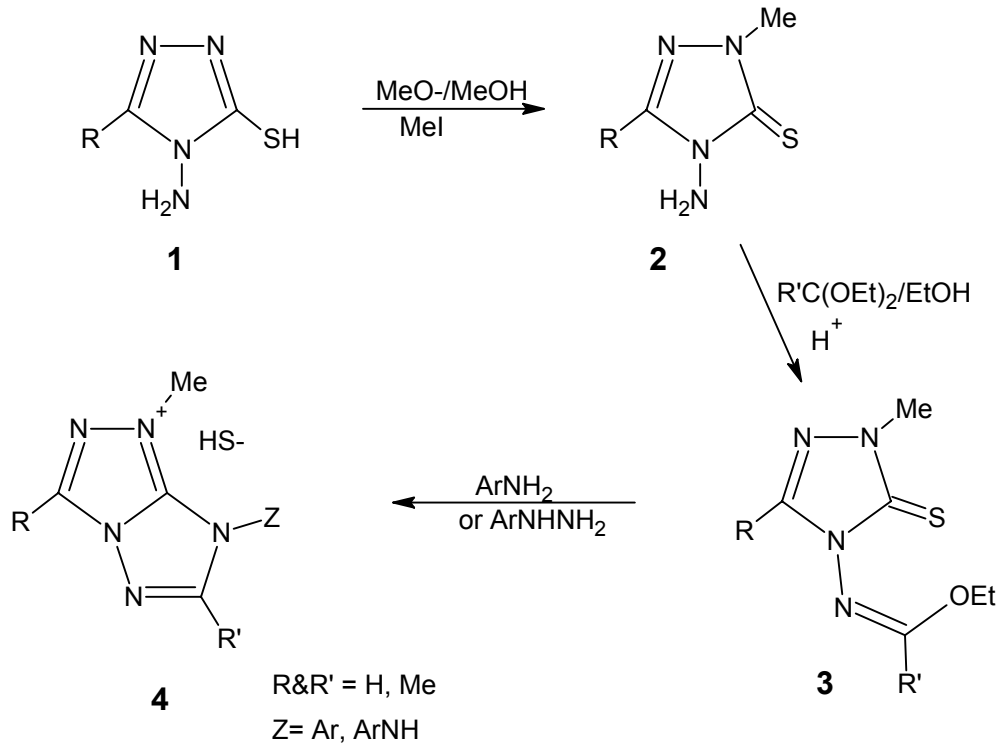
Alkylation of 4-amino-5-methyl-4H-1,2,4-triazole-3-thiols **1** with methyl iodide in the presence of sodium methoxide in methanol gave a rather unexpected N-methylated products **2**. Acid catalyzed condensation of these compounds with triethyl orthoformate or orthoacetate afforded the corresponding ethyl -*N*-(substituted -5-thioxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)ethanimidoate derivatives **3**. These derivatives on treatment with arylamines or arylhydrazines in the presence of triethylamine at reflux underwent substitution and heterocyclisation simulataneously to give the new substituted-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-1-ium salts **4**.



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

Scheme

ALLYL-PHENOTHIAZINES: SYNTHESIS, REARRANGEMENTS, REACTIVITY

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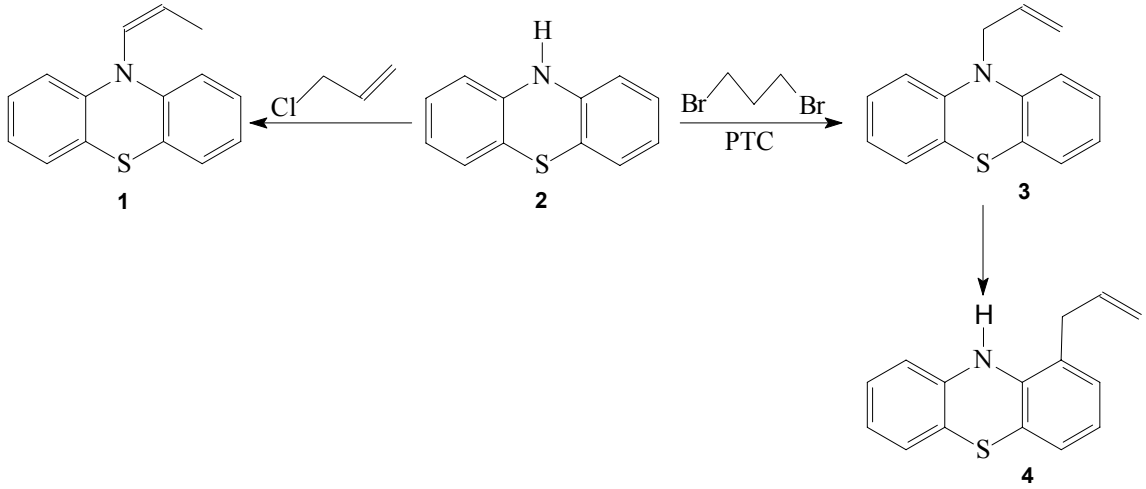
The synthesis of phenothiazines substituted at nitrogen with unsaturated side-chains is a rather controversial subject. The reaction of propargyl bromide with phenothiazine yields the propynyl derivative instead of 10-propargyl phenothiazine[1], clearly indicating the preference for SN' type reactions. Allyl-phenothiazine is mentioned in ref.[2]; the authors claim the preparation of 10-allyl-phenothiazine **3** by the reaction of phenothiazine **2** with allylbromide, a surprising *ipso*-substitution occuring. The conversion of **3** to the ethenyl isomer **1** was observed[3]. The reaction of allylcarbonates with **2** and the stereochemistry of the products was recently studied[4].



We obtained 10-allyl-phenothiazine **3** in good yield, by a very convenient procedure, excluding the formation of **1**, while treating **2** with 1,3-dibromopropane under PTC conditions, when N-substitution is accompanied by dehydrobromination.It was noted that **3** undergoes very easily rearrangements, the amino-Claisen transposition, yielding 1-allyl-phenothiazine **4**, practically unavailable by other routes, being among the observed processes. By repeating the N-substitution under similar conditions, disubstituted derivatives were obtained, both with saturated and unsaturated structures. The paper explores the perspectives of using these new allyl-phenothiazines as starting matter for obtaining electron-exchanging polymers and macrocycles.

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DIELS-ALDER REACTION OF 2- AND 3-STYRYLCHROMONES WITH DMAD UNDER MICROWAVE IRRADIATION

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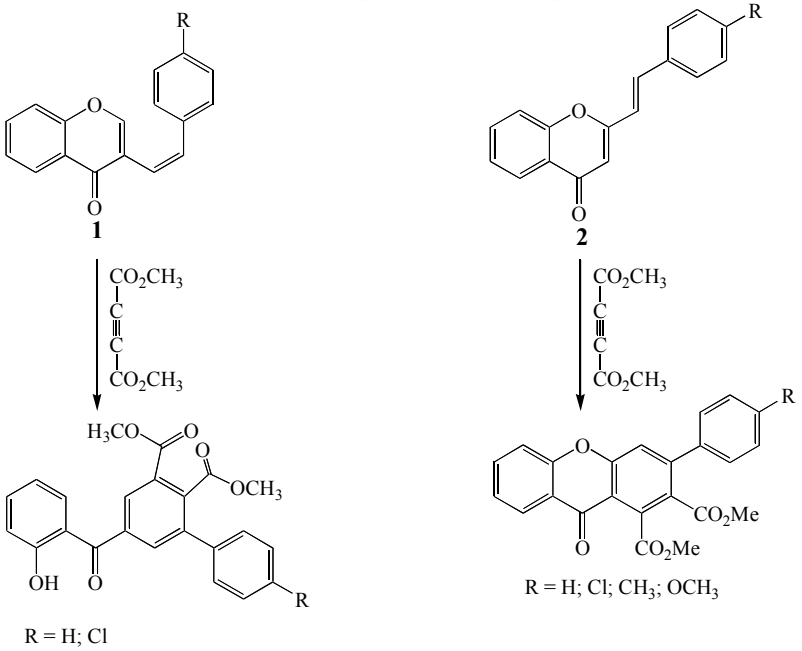
Diels-Alder reactions of 2-styrylchromones, as dienes, with electron poor dienophiles (maleic anhydride and N-arylmaleimides) and electron rich dienophiles (pyrrolidine enamines) have been widely studied [1]. The correct structures of the obtained cycloadducts - xanthones derivatives - have been established only in the 90s [2]. For the 3-Styrylchromone analogues their reactivity in Diels-Alder reactions started to be performed by our group. Following our interest on the transformation of chromones and knowing that microwave radiation is an alternative to conventional heating and has proved to be efficient in cycloaddition reactions [3], we studied the reactivity of 3-styrylchromones **1** and 2-styrylchromones **2** as dienes in Diels-Alder reaction, under microwave irradiation. We report our results when DMAD (dimethyl acetylenedicarboxylate) was used as dienophile. Experimental procedures and structural characterisation of all the synthesised compounds will be presented and discussed.



Acknowledgements: Thanks are due to the University of Aveiro, Universidad de Castilla-La Mancha, FCT and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. Financial support from the Spanish DGESIC (Project BQU2001-1095) and from the Consejería de Ciencia y Tecnología JCCM (Project PAI-02-019) is gratefully acknowledged. One of us (D. C. G. A. P.) is also grateful to FCT and FSE, for a Sabbatical grant.

[1] If you need to include references, please put them into square brackets
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SYNTHESIS OF NEW 4-STYRYL-3-(2-HYDROXYPHENYL) PYRAZOLES

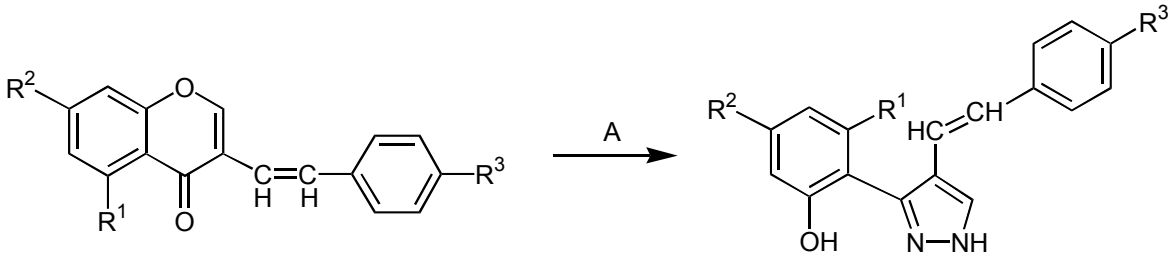
Vera L. M. Silva, Artur M. S. Silva, Diana C. G. A. Pinto and José A. S. Cavaleiro

Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

Synthetic routes leading to pyrazoles have been extensively studied [1, 2]. This has been stimulated by the biological activities associated with the pyrazole nucleus, and the promising applications of such compounds in medicine [2], for instance, as analgesics, anxiolitics, antipsychotics and chemotherapeutic agents.

We report here the synthesis of 4-styryl-3-(2-hydroxyphenyl)pyrazoles **2** by the reactions of *(E)* and *(Z)* 3-styrylchromones with hydrazine hydrate. These 3-styrylchromones **1** have been prepared from the reaction of 3-formylchromone with benzylic ylides.

Experimental procedures and structural characterisation of all synthesised compounds will be presented and discussed in this communication.



(E) and (Z) *(E) and (Z)*

1a R^1=H, R^2=H, R^3=H
1b R^1=OCH_3, R^2=H, R^3=H
1c R^1=H, R^2=OCH_3, R^3=H
1d R^1=OCH_3, R^2=OCH_3, R^3=H
1e R^1=H, R^2=H, R^3=Cl
1f R^1=OCH_3, R=H, R^3=Cl
1g R^1=H, R^2=OCH_3, R^3=Cl

2a R^1=H, R^2=H, R^3=H
2b R^1=OCH_3, R^2=H, R^3=H
2c R^1=H, R^2=OCH_3, R^3=H
2d R^1=OCH_3, R^2=OCH_3, R^3=H
2e R^1=H, R^2=H, R^3=Cl
2f R^1=OCH_3, R=H, R^3=Cl
2g R^1=H, R^2=OCH_3, R^3=Cl

A: $NH_2NH_2.H_2O$, MeOH, under N_2, room temperature

Acknowledgements: Thanks are due to University of Aveiro and FCT-Lisbon, for funding the organic chemistry research unit. One of us (V. L. M. Silva) is also grateful to FCT/POCTI for the award of a student's grant (BD/6647/2001).

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REACTION OF N-CHLOROACETYL DERIVATIVES OF ELECTRON-ENRICHED (HETERO)AROMATIC AMINES WITH PHENOLES AND 2-BENZOXAZOLETHIOLES

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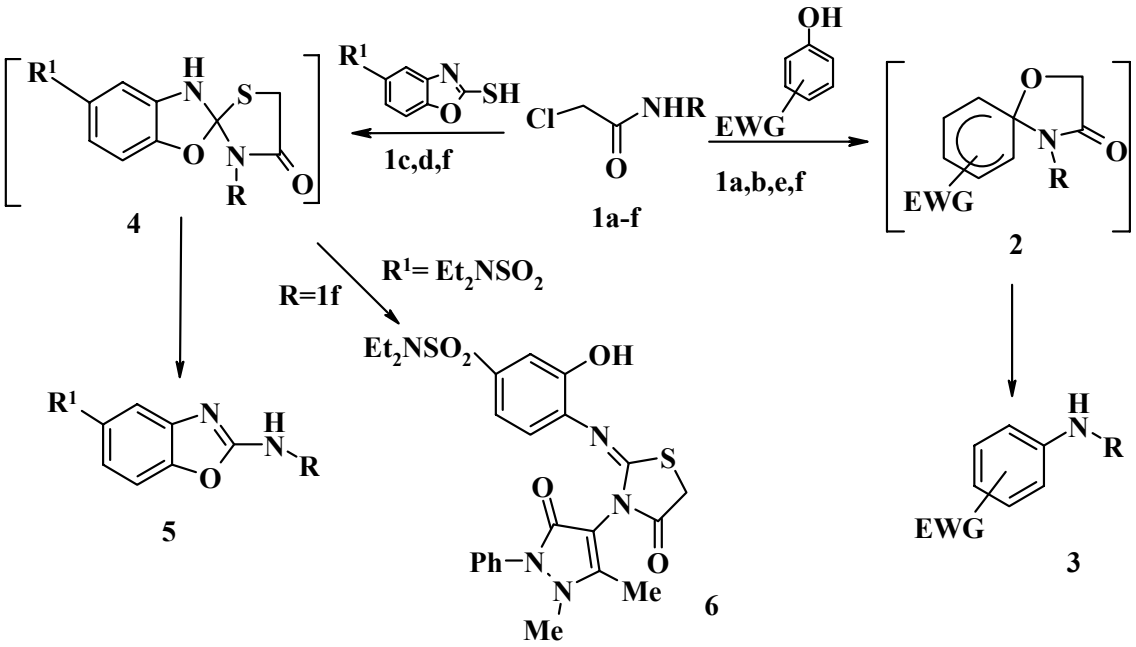
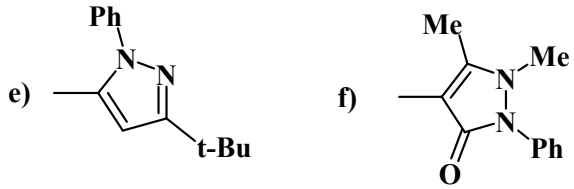
Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033, Kiev , Ukraine;
e-mail:dsinchuk@ukr.net



R = a) 4-(Me_2N)C_6H_4, b) 4-(morpholino)C_6H_4, c) 3-$MeOC_6H_4$, d) 2-MeO-5-ClC_6H_3



The alkylation of phenoles bearing electron-withdrawing substituents with the title chloroacetyl derivatives unexpectedly resulted in the arylamines **3** formation. Probably, the reaction occurs via initial O-alkylation of the phenole with further formation of the intermediate of type 2, which undergoes glycolic acid elimination yielding the product **3**.
2-Benzoxazolethioles were found to react similarly, but with the elimination of mercaptoacetic acid. Moreover, in this case the product of an alternative intermediate **4** transformation, namely the compound **6**, could be isolated, thus proving assumed reaction pathway. The structure of compound **6** was unambiguously confirmed by X-ray crystallographic study.

THE SYNTHESIS OF BIS PHENOL THIOPHENE DERIVATIVES BY USING STILLE COUPLING METHODE WITH PALLADIUM CATALYST

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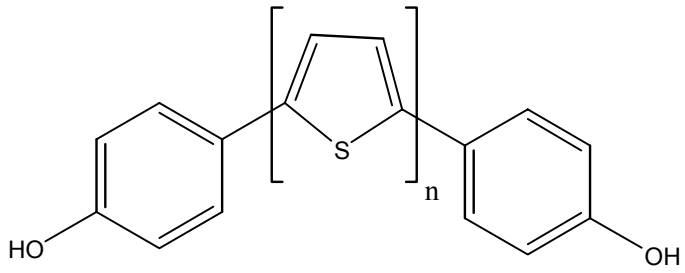
Istanbul Technical University, Faculty of Science, Dept. of Chemistry,
Maslak- 34469-Istanbul-Turkey
sirkeci@itu.edu.tr

The preparation of polyfunctionalized heterocyclic compounds [1] is of interest in research fields as diverse as natural product synthesis, drug design, molecular recognition and material science like polymer chemistry. Therefore, mono and multi thiophenic phenol compounds are using in higher technologic polymer synthesis of a monomer. For all that reason, the synthesized of polyfunctionalized heterocyclic compounds like bis phenol thiophene are very important. In this study , we are going to use Stille coupling methods to produce bis fenol thiophene derivatives in good and effective ways.



n= 1,2 and 3

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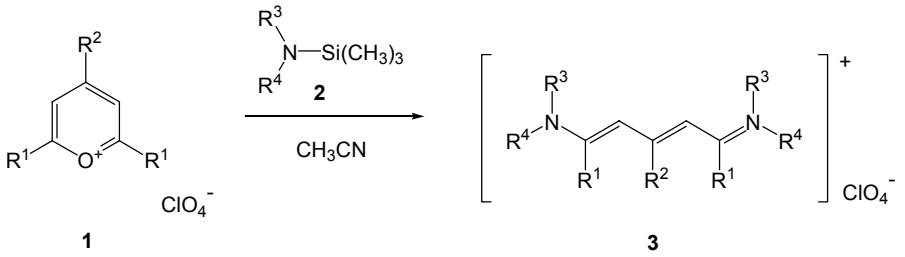
NOVEL SYNTHESIS AND REACTIONS OF PENTAMETHINIUM DYES WITH AROMATIC SUBSTITUENTS IN 1,3 AND 5 OR 1 AND 5 POSITIONS

Markéta Skalická, Stanislav Böhm

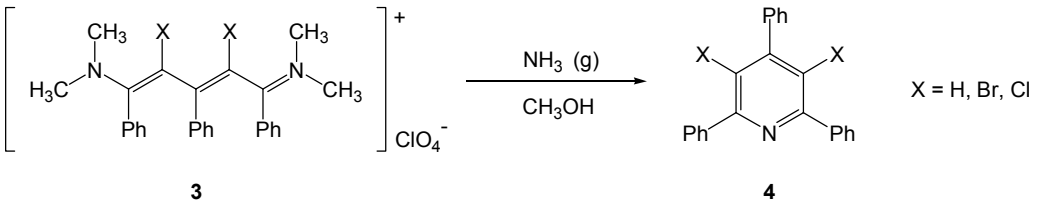
Department of Organic Chemistry, Institute of Chemical Technology, Prague
Technická 5, 166 28 Prague 6, Czech Republic

So far only one reaction leading to 1,5-bis(dialkylamino)-1,3,5-triphenylpentamethinium salts has been reported [1]. Our improved synthetic approach is based on the reaction of appropriate pyrylium perchlorates with N,N-dialkyltrimethylsilylamines.



R^1 = phenyl, biphenyl-4-yl, 2-naphthyl
R^2 = phenyl, H
R^3, R^4 = CH_3, CH_2CH_3, $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$, CH_2Ph

The reaction proceeds smoothly with commercially or quite easy available educts **2** with good yields of perchlorates **3**. A series of pentamethinium dyes was synthesized in this manner. Dependence of the UV-VIS absorption maximum of **3** on the substitution (varying R^1, R^2, R^3 and R^4) was studied.
Bromination and chlorination of selected compounds **3** was carried out yielding halogenated derivatives with significant bathochromic shifts of absorption maxima.
In comparison with other pentamethinium salts [2], 1,5-bis(dimethylamino)-1,3,5-triphenylpentamethinium-perchlorate and its analogues undergo cyclization reaction with ammonia very easily, perhaps due to an increased steric hindrance resulting into a "bent" conformation. Hardly accessible pyridine derivatives **4** were prepared in this fashion.



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[2] Jutz C. et. al: *Justus Liebigs Ann. Chem.* **1975**, 874.

SYNTHESIS OF ASSEMBLY INTERMEDIATE IN DECARESTRICTINE BIOSYNTHESIS

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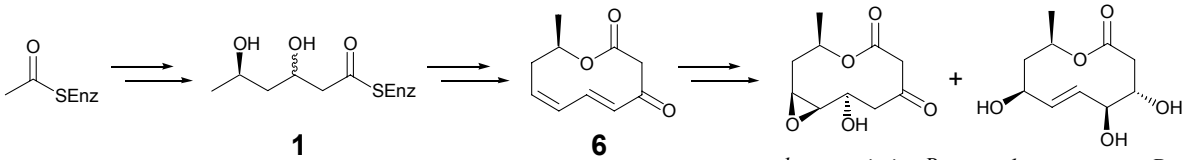
School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK

Decarestrictines, polyketide derived fungal metabolites isolated from *Penicillium simplicissimum*, are active 10-membered ring macrolides and include decarestrictine B and decarestrictine D, as well as a number of other minor components [1, 2]. They are potent inhibitors of cholesterol biosynthesis.



Proposed biosynthetic pathway to the decarestrictines

My research project involves the synthesis of putative intermediates required to elucidate the biosynthetic pathway of the decarestrictines. The synthesis of both diastereomers of the putative intermediate diol **1** in the form of their analogous acids (**2** and **3**) and *N*-acetylcysteamine thioesters (**4** and **5)** is required to provide standards and for feeding studies to determine the stereochemistry of **1** in the biosynthetic pathway.

2 R=OH

4 R=$S(CH_2)_2NHCOCH_3$

3 R=OH

5 R=$S(CH_2)_2NHCOCH_3$

It has been proposed that various decarestrictines may be derived biosynthetically from a common intermediate **6**, however **6** has not been detected in extracts from *P. simplicissimum* [2]. The synthesis of this 10-membered ring lactone will allow the development of a specific assay for the isolation of the protein responsible for the biosynthesis of the intermediate **6**. Progress towards the synthesis of the putative intermediates (**2**-**6**) will be described.

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SYNTHESIS OF DERIVATIVES OF BIS (3-HYDROXY-4(1H)-QUINOLINONE-2-YL)BENZENE

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Department of Organic Chemistry, Palacky University, Czech Republic
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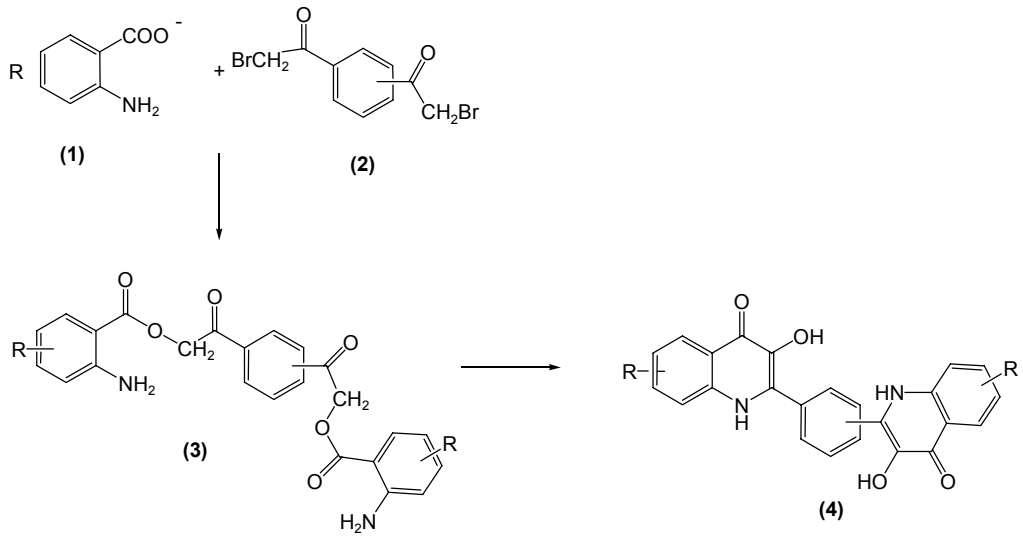
In accordance to preliminary cytostatic screening derivatives of 2-phenyl-3-hydroxy-4(1H)-quinolinones seem to be perspective compounds possessing an interesting biological activity [1]. Part of contemporary research is aimed to synthesis of compounds possessing two
3-hydroxy-4(1H)-quinolinone structures in one molecule. The synthesis of these compounds is based on reaction of bis (bromoacetyl)benzene with salt of anthranilic acid derivatives.



R = H, diCl, NO_2, NH_2

Although the preparation of bis (bromacetyl)benzene is described in literature, practical preparation was found to be more complicated. The preparation procedure had to be modified. Dependence of substitution in quinolone skeleton on solubility and biological activity is intensively studied. Because the tuberculostatic activity of fenacylesters of benzoic acid was found [2], also the derivatives **3** are going to be tested.

This work was financially supported by the Grant Agency of the Czech Republic. (Grant No. 203/01/1360)

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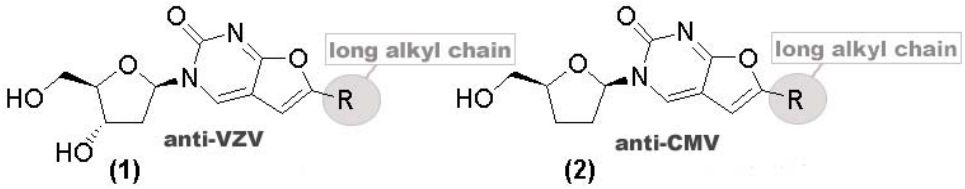
[2] Hradil P., Hlaváč J. : patent PV 2002-3878, applied in Prague, November 25, 2002

DE NOVO SYNTHESIS OF ANTIVIRALLY ACTIVE FUROPYRIMIDINE NUCLEOSIDES FROM FURANS

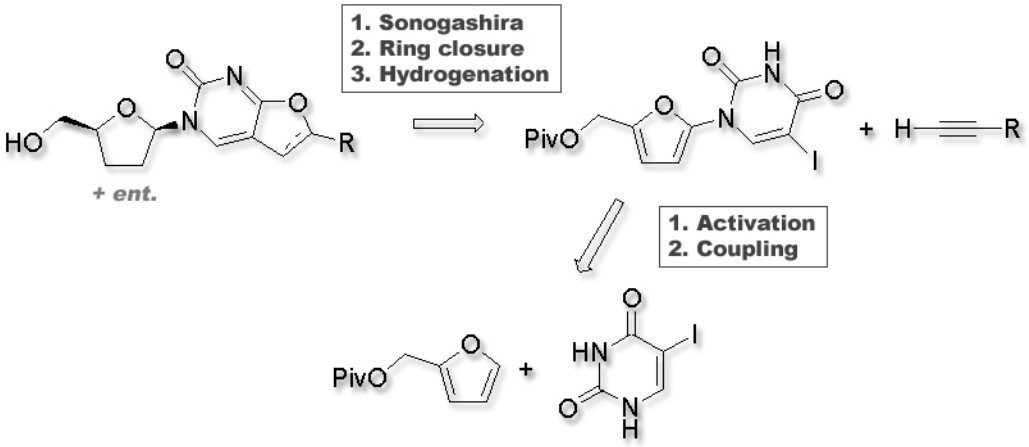
Tanja Sović , Petra Feiertag, Helmut Hönig, and Martin Albert

Institut für Organische Chemie, Technische Universität Graz, A-8010 Graz, Austria

Recently, McGuigan *et al.* disclosed a new, highly potent class of antiviral agents (**1**), which inhibit varicella-zoster virus (VZV) with high selectivity [1]. The characteristic structural element of this new class of nucleoside analogues is determined by an unusual bicyclic furopyrimidine unit with long alkyl chains at the 6-position of the furo ring. The corresponding β-D-2',3'-dideoxynucleosides have been reported to be highly active against cytomegalovirus (CMV) [2].



Based on a synthetic concept, which has been developed in our group [3], we want to report a synthesis of racemic 2',3'-dideoxy furopyrimidine nucleosides starting from 2-substituted furans. The key steps include the fusion of the furan and 5-iodo-uracil, a Sonogashiro-coupling with a terminal alkyne, a copper-catalyzed ring closure and a diastereoselective hydrogenation.



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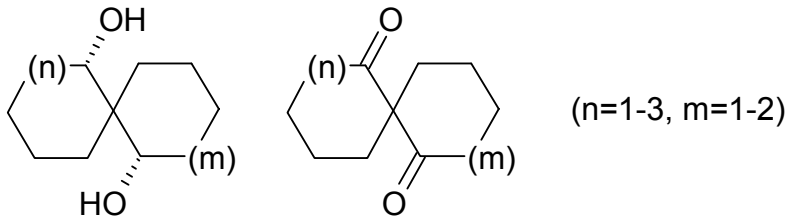
SYNTHESIS AND DERIVATISATION OF (±)-SPIRODIOLS AND –DIONS

Christian Sperger, Thomas Seidel, Christian Hametner and Johannes Fröhlich

Institute of Applied Synthetic Chemistry, Vienna University of Technology, 1060 Vienna, Austria

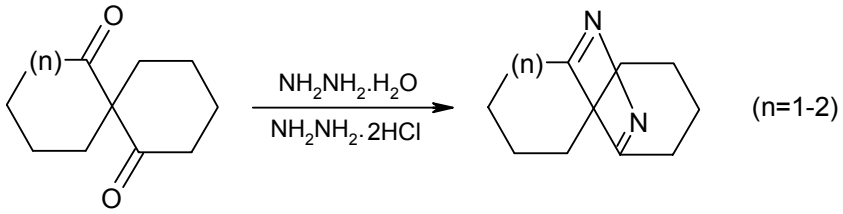
The scope of this work was the synthesis of (±)-Spirocompounds[1] with different ring sizes and variation of the functional groups as shown below.



These spirocompounds were investigated regarding their reactivity towards different reagents. No enantiomerically pure compounds were involved, but the results thus obtained can be used as a blueprint for chiral analogues.

Efforts to di-substitute the synthesized spirodiol led to mono-substituted derivatives only: even using very small-sized halogenated reagents (e.g. methyl iodide) turned out to be not successful. It could be observed, that two isomers were formed in a 2:1 ratio, not depending on the type of reagent used. The substitution at the axial position was preferred over the equatorial position according to NMR-spectroscopy. Only in one single case using an acid chloride, a disubstituted product was isolated with high yield.

Spirodions behaved very similar with monofunctional reagents. However, using a bifunctional reagent like hydrazine led to very interesting new ring systems.



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A CONVENIENT METHOD FOR THE SYNTHESIS OF STERICALLY DEMANDING CARBOCYCLIC AND HETEROCYCLIC ALDEHYDES

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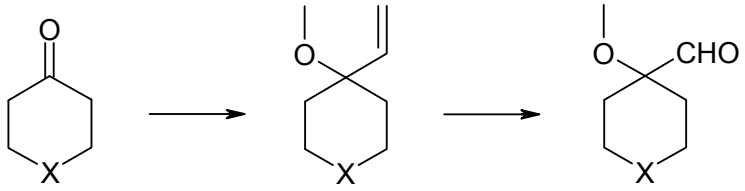
For the synthesis of α-Keto-β-lactames with sterically demanding substituents via Staudinger cyclisation, we required a simple way to prepare aldehydes with a quarternary carbon next to the carbonyl functionality.

In this poster we present convenient method to synthesize aldehydes **3** starting from the corresponding ketones **1**.



1 **2** **3**

X= -CH_2-, -, -$(CH_2)_2$-, -N(BOC)-, -CH(tButyl)-, -N(Tosyl)-, -O-, -N(COOMe)-

The developed methodology involves Grignard – addition of vinylmagnesiumbromide across the keto functionality in **1**, followed by alkylation of the intermediate alcohol.
Oxidative cleavage of the vinyl group to furnish the desired aldehyde was attempted by (a) ozonolysis and (b) diol formation and subsequent Malaprade reaction.

Ozonolysis gave only minimal amounts of aldehydes **3** due to undesired side reactions caused by the adjacent donor group -OMe and the quarternary center.
Access to target compounds **3** was finally achieved using OsO_4/KIO_4 in a single on-pot reaction.

Reaction optimization for both pathways will be discussed in detail.

PREPARATION OF SOME LINEARLY ANNELLATED AZEPINOQUINAZOLINES

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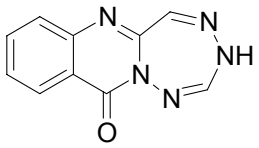
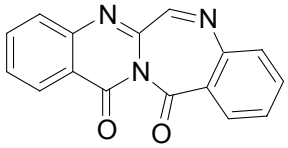
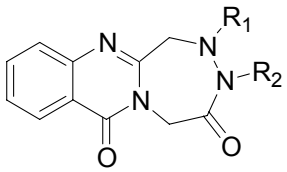
In the continuation of our interest in the synthesis of linearly annellated quinazoline derivatives, among which some compounds with anticancer activities have been found, in the present contribution we wish to report some methods for the preparation of novel tricyclic heterosystem incorporating seven membered nitrogen containing moieties.



I.



II.



III.

The synthesis of I – III was carried out using cyclocondensation reactions. The construction of the shown heterosystems included two till three steps starting from 2-halomethyl- 4*H*-3,1-benzoxazin-4-one.

This work was supported by the Grant Agency of the Slovak Republic No. 1/9254/02 and 1/0058/03.

AZEPINOQUINAZOLINES – ANALOGS OF QUINAZOLINE ALKALOIDS

Štefan Stankovský and Katarína Špirková

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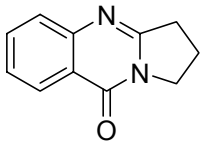
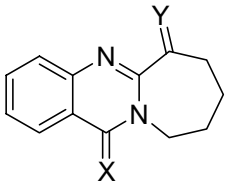
Deoxyvasicinon (2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one), (***I***) was isolated together with other pyrroloquinazolines from the plant *Peganum harmala* in the 60-ties in north China. Its use in popular medicine and later discovered broad spectrum of bioactivity led to syntheses of numerous analogs, characterized either by modified functional groups, or even by changes in the parent heterocyclic skeleton.



I

Deoxavasicinone
2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one



X = O, S

II

7,8,9,10-tetrahydroazepino[2,1-*b*]-quinazolin-12(6H)-one

This contribution presents preparation of selected azepine analogs (***II***) in which oxygen has been replaced by sulfur, and in position 6 of the azepine ring there are functional groups capable of further derivatization.

This work was supported by the Grant Agency of the Slovak Republic No. 1/9254/02 and 1/0058/03.

SYNTHESIS AND PROPERTIES OF SOME 1,2,4-TRISUBSTITUTED PYRROLES

Jarmila Štetinová[a], Viktor Milata[a], Naďa Prónayová[b], Ján Leško[† b], and Ognyan Petrov[c]

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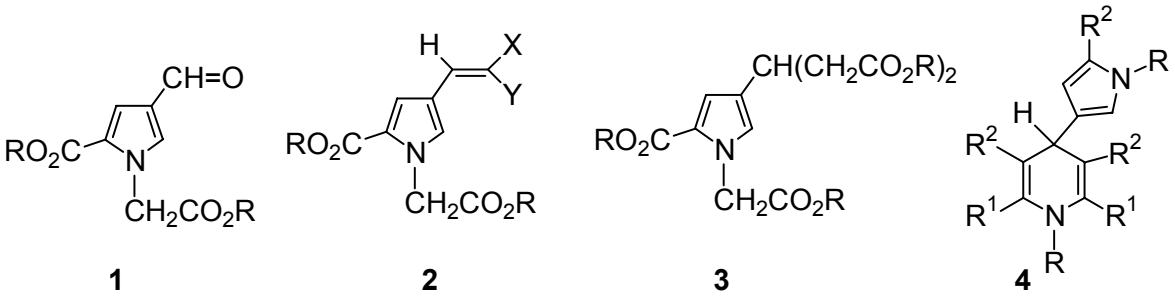
[c]Department of Organic Chemical Technology, Faculty of Chemistry, University of Sofia, BG-1126 Sofia, Bulgaria

The 2-alkoxycarbonylpyrrolyl derivatives display a broad spectrum of biological activities – analgesic, morphine agonist, spasmolytic, antipyretic, and antiinflammatory activities being some of the most important.
We present here the synthesis and some transformations of alkyl (2-alkoxycarbonyl-4-formylpyrrol-1-yl)acetates **1.**These aldehydes, prepared in four steps from pyrrole, were starting materials for substituted 4-pyrrolyl ethylenes **2** and derivatives of glutaric acid **3** (being deaza-analogue of EDTA).



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

1: R = Me, Et; **2**: R = Et; X = CO_2Et, benzazol-2-yl, (benz)azol-2-ylaminocarbonyl; Y = H, CO_2Et, CN; **3**: R = H, Me; **4**: R = H, CH_2CO_2Me; R^1 = Me, R^2 = CO_2Me

Using cyclocondensations reactions or regioselective alkylation in the solid state, we have obtained derivatives **4**, substituted either on nitrogen atom of pyrrole or that of 1,4-dihydropyridine skeleton.

Finantial support for this research by the Slovak Grant Agency (grants no. 1/9254/02 and 1/0058/03) are gratefully acknowledged.

SYNTHESIS OF NOVEL 4-(4-THIAZOLYL)- AND 4-(5-THIAZOLYL)-2-PYRIMIDINAMINES

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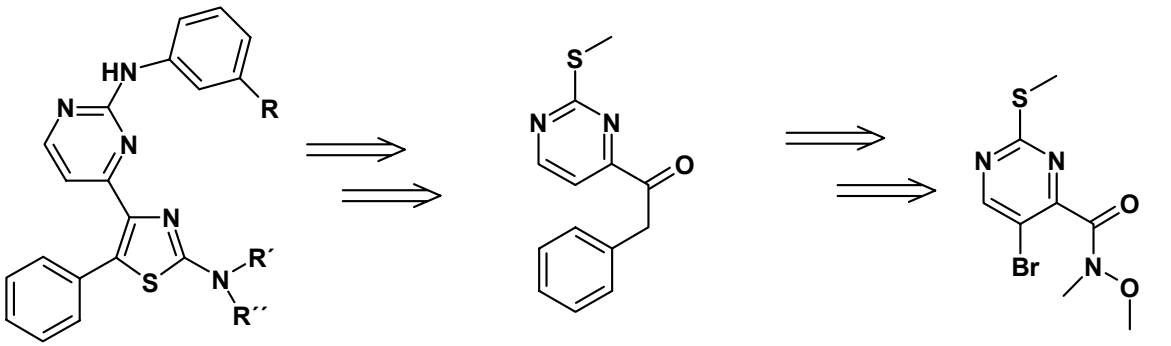
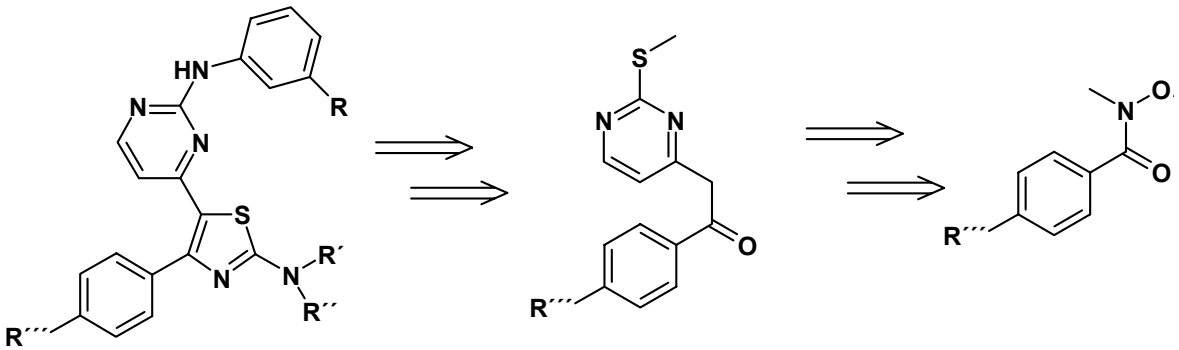
It is known from preliminary results of the biological screening, that the title compounds of the general formulas **I** and **IV** show fungicidal activities and can act as new leads for structural variations hopefully leading to products useful as fungicides in agriculture. As outlined in the retrosynthetic scheme below in both cases suitable phenyl-pyrimidinyl-ethanones were envisaged as key-intermediates. Both of these ethanones were synthesized by exploiting the Weinreb-methodology. Despite of similarities, these ketones showed amazing differences in reactivity which will be discussed along the synthetic pathway. E.g. whereas 1-(2-methylthio-4-pyrimidinyl)-2-phenylethanone (**II**) exist only in the keto-form, the 2-(2-methylthio-4-pyrimidinyl)-1-phenylethanone (**V**) shows a tautomeric equilibrium with variable ratios depending on the substitution pattern as well as the solvent. After bromination, the α-bromoethanones were reacted with selected thioureas affording thiazoles in a classical Hantzsch synthesis. In some cases in the 4-(5-thiazolyl)-2-pyrimidinamine series the cyclization step caused serious problems which will be discussed within the poster presentation.



(I) (II) (III)



(IV) (V) (VI)

R = H, OCH_3, $COCH_3$, $CH(OH)CH_3$
R´, R´´ = H, CH_3
R´´´ = H, OCH_3

THE INVESIGATION OF INTRAMOLECULAR CYCLIZATIONS OF METHYL [(5-NITRO-4-PYRIMIDINYL)AMINO]ACETATES IN BASIC MEDIA

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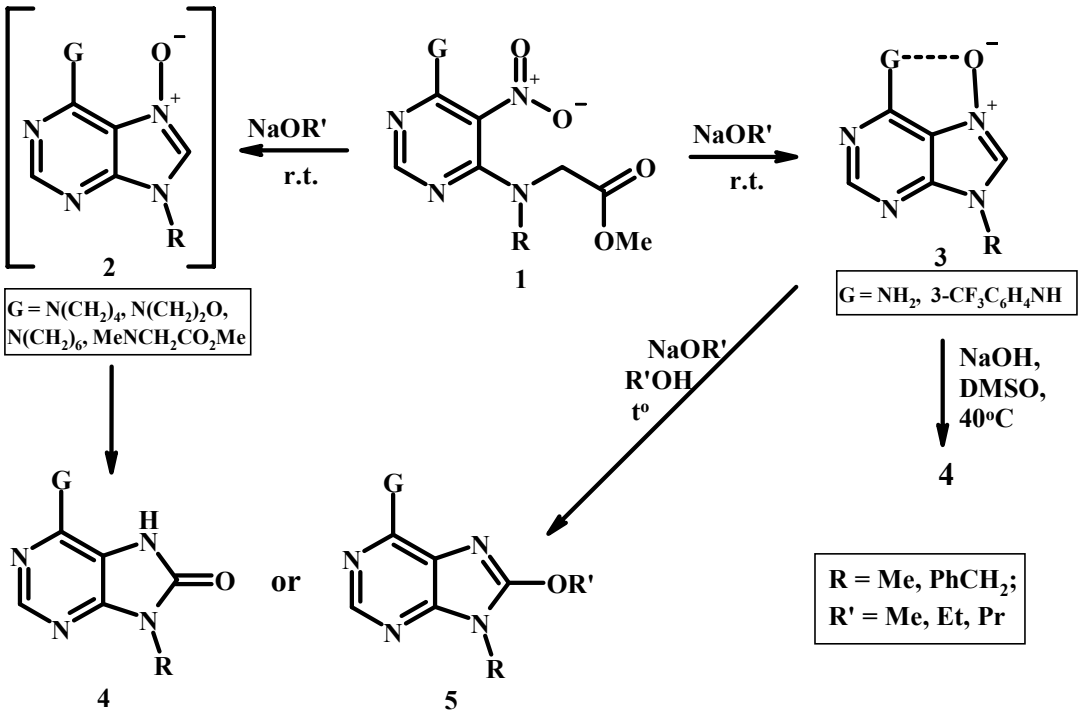
Naugarduko 24, Vilnius 2006, Lithuania

In the course of our investigation in the area of polyfunctional pirimidines and fused heterocycles containing pirimidine ring [(5-nitro-4-pyrimidinyl)amino]acetic acid methyl esters **1** were prepared and their transformations in basic media were carried out. It was found that the title compounds under the treatment by non bulky sodium alcoholates underwent ring closure to give N-oxides **2** and **3**. Unexpectedly, the intermediate **2** turned out very unstable and reacted with nucleophiles - hydroxide anion or methanol presenting in the reaction mixture to give 9H-purine derivatives **4** or **5**. 9*H*-Purine 7-oxides **3** are stabilised by intramolecular hydrogen bond (when substitute G contains NH group) and they were obtained and characterised. Interactions of compounds **3** with some nucleophiles were investigated:



REACTIONS OF 1,4-DINITROPYRAZOLE WITH C-, N- AND O-AMINO COMPOUNDS

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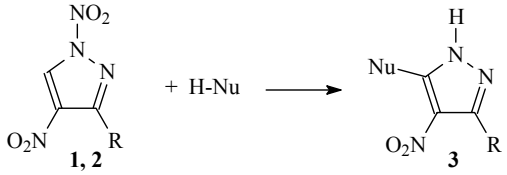
Institute of Organic Chemistry and Technology,Silesian University of Technology, Gliwice, Poland

Known reactions of 3-methyl-1,4-dinitropyrazole (**1**) with nucleophiles occur under very mild conditions, usually in methanol or aqueous methanol solutions at low temperatures. 1,4-Dinitropyrazole (**2**) reacts under similar conditions with 1*H*-azoles. The reactions, which occur according to so-called *cine* nucleophilic substitution mechanism, have found interesting applications in syntheses of 5-substiuted 1*H*-4-nitropyrazoles (**3**). Numbers of *C*-, *N*-, *P*- and *S*- nucleophiles have been used in the reactions with **1**, only azoles in reactions with **2** (Scheme 1). [1]

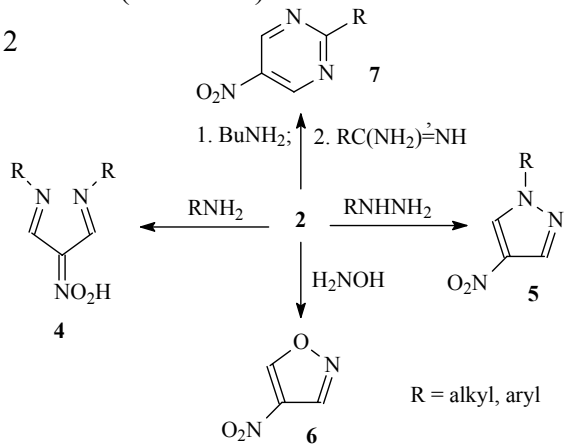
Scheme 1



(**1**) R = Me, (**2**) R=H; H-Nu = a nucleophile or its conjugated acid

In contrast to that, **2** reacts with *C*-, *N*- and *O*-amino compounds like primary amines, hydrazines, hydroxylamine or amidines in methanol solution to afford either ring opening or ring transformation products. The reactions of **2** lead to: linear compounds **4** with primary amines, give *N*-substituted 4-nitropyrazoles **5** with hydrazines, form 4-nitroisoxazole **6** with hydroxylamine and give 4-nitropirymidine derivatives **7** with butyl amine followed by amidine addition (Scheme 2).

Scheme 2



Thus, the behavior of 1,4-dinitropyrazole (**2**) substantially differs from the behavior of its 3-methyl derivative (**1**) towards compounds containing primary amino groups. This can be explained considering that the presence of the methyl group at carbon atom 3 of pyrazole ring decreases susceptibility of this position to a nucleophilic attack.

Ref. 1. J. Suwiński, K. Świerczek, *Tetrahedron*, **57** (2001) 1639-1662 (a review)

CONCERTED VS. NONCONCERTED CYCLOADDITION REACTIONS OF FUSED 2-VINYLTHIOPHENES – A NEW SYNTHETIC ROUTE TO THIALENE DERIVATIVES

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[a]Department of Organic Chemistry,
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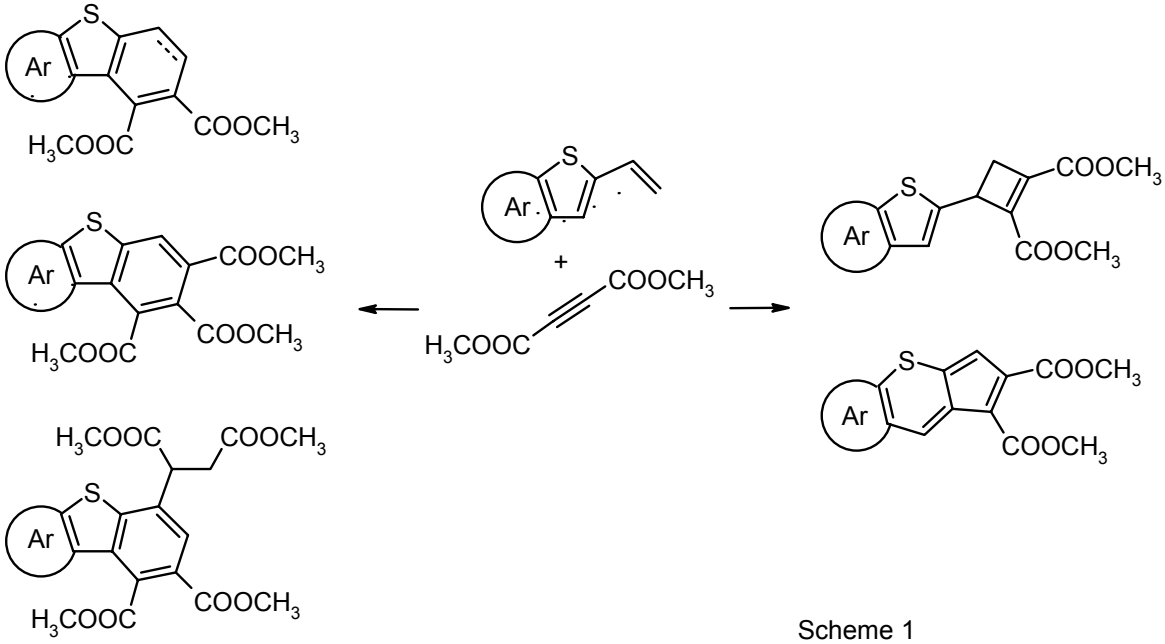
Our interest in the chemistry of 1,4-diheteropentalenes is focused on synthesis, reactivity and material applications of fused thieno[3,2-*b*]furan and thieno[3,2-*b*]thiophene derivatives [1,2]. We also showed that topology of such heterocyclic systems substantially influences their stability and reactivity [3-5].

Herein we report results of the study of cycloaddition reactions of various related 2-vinylthiophene derivatives with dimethyl acetylenedicarboxylate (DMAD). Based on the structure of isolated products and their distribution (only principal products are shown in Scheme 1), two distinct mechanisms of the cycloaddition will be discussed.



Scheme 1

The observed unusal thiophene to thiopyran ring enlargement can be utilized for synthesis of new types of fused thialene systems.

Financial support of Grant Agency (project No. 202/02/0840) and Ministry of Education, Youth and Sports (project No. MSM 223100001) of the Czech Republic is gratefully acknowledged.

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SYNTHESIS OF GYKI-16084 METABOLITES

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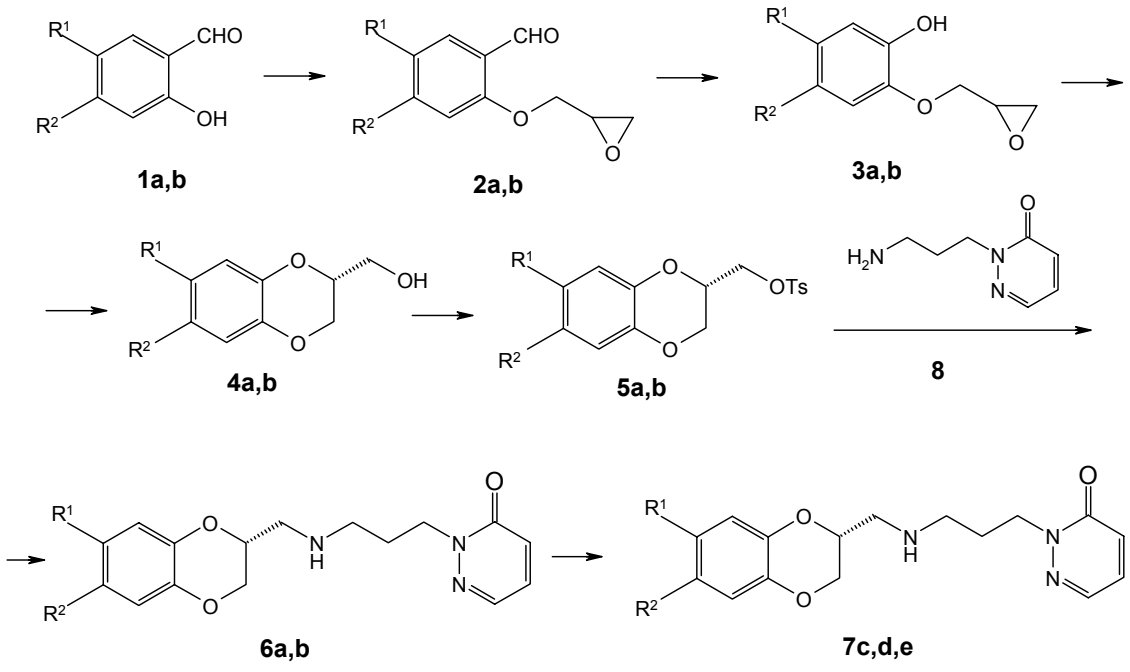
IVAX Drug Research Institute Ltd, Budapest, Hungary

The aim of the present work was to prepare the two regioisomeric (6- and 7-hydroxy, resp.) metabolites of GYKI-16084 [(R)-**7e**, $R^1 = R^2 = H$], a drug candidate for the treatment of benign prostatic hyperplasia.
As the direct substitution of the benzodioxane ring system does not afford the pure 6- or 7-regioisomers, the synthetic route shown below was designed where the desired hydroxy functions were already present (in masked form) in the synthetic intermediates of the benzodioxane moiety.



a $R^1 = H$, $R^2 = MeO$
b $R^1 = MeO$, $R^2 = H$
c $R^1 = H$, $R^2 = OH$
d $R^1 = OH$, $R^2 = H$
e $R^1 = R^2 = H$

The above synthesis was carried out first by using racemic reagents yielding (R,S)-**7c** and (R,S)-**7d** followed by performing the same reaction sequence with (S)-glycidyl tosylate to afford the desired (R)-**7c** and (R)-**7d**.

SYNTHESIS OF NEW 3, 7-DISUBSTITUTED THIAZOLES

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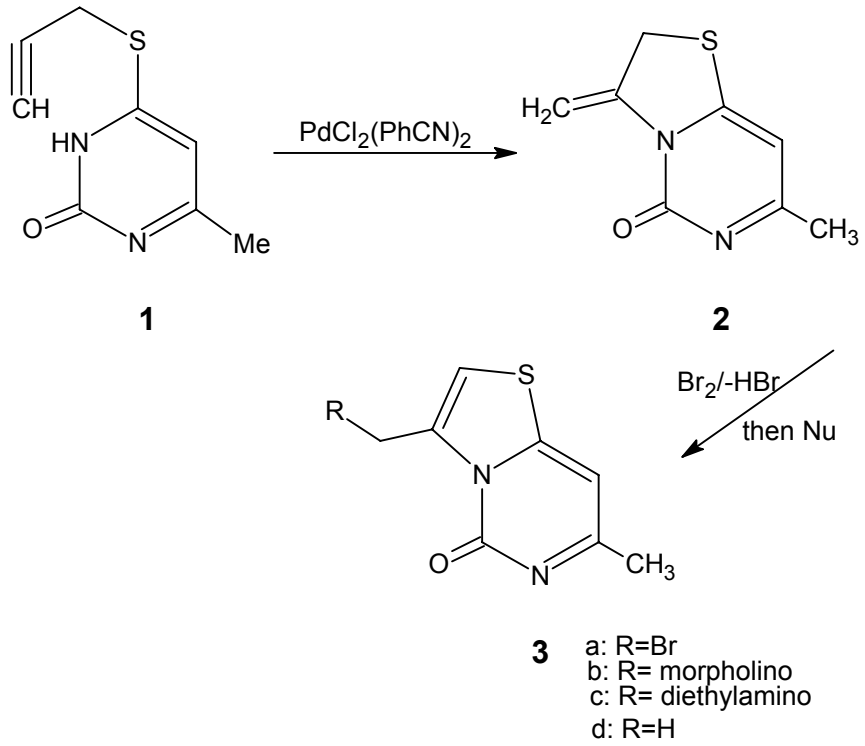
Department of Chemistry, Mazandaran University, Babolsar, Iran

Transformation of 4-propargylmercapto-2(3H)-one **1** to 3-methylene-2, 3-dihydro-5H-thiazolo [3,2-c]pyrimidin-5-one **2** has been performed by the catalytic action of Pd(II) salt. The latter was treated with excess of bromine to afford 3-bromomethyl-7-methythiazolo [3, 2-c] pyrimidin-5-one **3a** which was reacted with nucleophiles such as morpholine and diethylamine to give the corresponding substituted thiazolo[3,2-c]pyrimidine derivatives **3b-c.** One pot cyclization and aromatization of **1** to **3d** by acid catalysis is also described.



1 **2**

3 a: R=Br
b: R= morpholino
c: R= diethylamino
d: R=H

SYNTHESIS OF 2-SPIRONAPHTHO[2,3-B]PYRANOQUINONES

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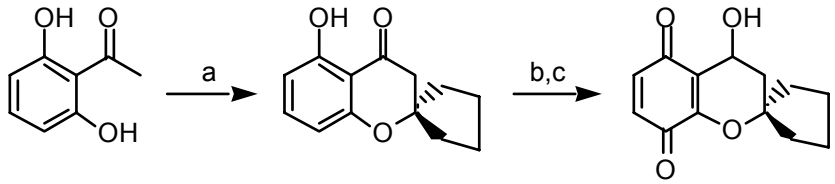
The synthesis of spirocyclic compounds has become an interesting target because a number of pharmacologically relevant natural products having an spiro center exhibit various biological activities. [1]
As part of our continuing interest in the synthesis of naphtho[2,3-b]pyranoquinones with useful biological properties [2] we describe here the preparation of some new derivatives with an spiro center at C-2 of the heterocyclic ring.
Reaction of 2,6-dihydroxyacetophenone (**1**) with cyclopentanone using Kabbe's method [3] afforded 2-spirochromanone **2** in 80% yield. Reduction of ketone **2** with lithium aluminum hydride and oxidation with (diacetoxyiodo)benzene (DAIB) afforded benzopyranoquinone **3** (60%).



1 **2** **3**

a) cyclopentanone, piperidine, 110 ºC; b) $AlLiH_4$, THF; c) DAIB, CH_3CN-H_2O

The Diels-Alder reaction of quinone **3** with 1-(trimethylsilyloxy)-1,3-butadiene, piperylene and 1-methoxy-1,3-cyclohexadiene gave 44-65% yield of the aromatized cycloadducts. The regiochemistry of the cycloadditions will be discussed.

Acknowledgements : This study was supported by FONDECYT, Research Grant 1020874.

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SYNTHESIS OF DIBENZOPHTHALAZINE AND DIBENZOCINNOLINE RING SYSTEMS VIA PALLADIUM CATALYZED CROSS-COUPLING REACTIONS

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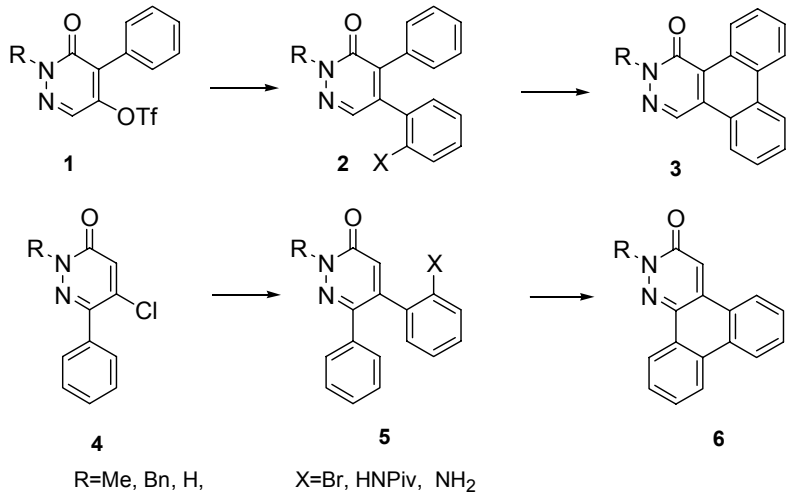
Recently, we have reported on the synthesis of pyridazino-fused tricyclic systems via Suzuki cross-coupling reaction in combination with 'classical' ring closure reactions [1].

In the present work, we describe a novel synthesis of pyridazino-fused tetracycles, in which Suzuki reaction is combined with palladium catalyzed intramolecular arylation or Pschorr reaction. Both approaches afford the dibenzo[*f,h*]phthalazine (**3**) or dibenzo[*f,h*]cinnoline (**4**) ring systems in moderate or good yields.



References:

[1] a) Krajsovszky, G., Mátyus, P., Riedl, Zs., Csányi, D., Hajós, Gy. *Heterocycles* **2001**, *55,* 1105-1111. b) Riedl, Zs., Maes, B.U.W, Monsieurs, K., Lemière G.L.F., Mátyus, P., Hajós, Gy. *Tetrahedron* **2002**, *58,* 5645-5650. c) Maes, B.U.W, Monsieurs, K., Loones K., Lemière G.L.F., Dommisse, R., Mátyus, P., Riedl, Zs., Hajós, Gy. *Tetrahedron* **2002**, *58,* 9713-9721. d) Tapolcsányi, P., Krajsovszky, G., Andó, R., Lipcsey, P., Horváth, Gy., Mátyus, P., Riedl, Zs., Hajós, Gy., Maes, B.U.W., Lemière G.L.F., *Tetrahedron* **2002**, *58,* 10137-10143.

ONE-POT THREE-COMPONENT CONDENSATION REACTIONS IN WATER: AN EFFICENT AND IMPROVED PROCEDURE FOR THE SYNTHESIS OF FURAN ANNULATED HETEROCYCLES

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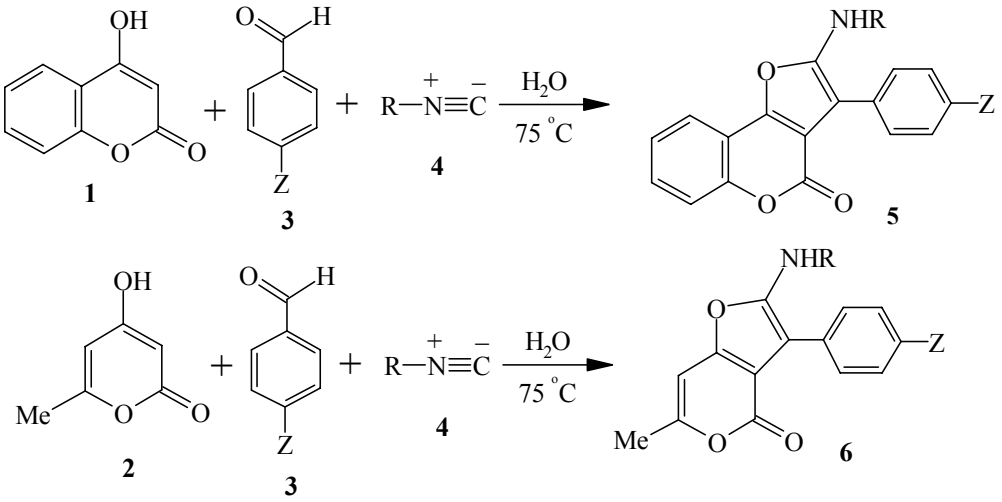
For synthetic chemist, water often appears as a natural enemy to be kept away from the reaction mixture until workup. Nevertheless, in recent years reports have appeared in increasing number describing the deliberate use of water as a solvent for various organic reactions [1]. In 1980, Rideout and Breslow [2], rediscovered a rate increase by a factor of more than 700 when the Diels-Alder reaction is performed in water instead of hydrocarbons. Breslow explains his results on the basis of hydrophobic interaction that induce a favorable aggregation of the apolar components in the polar water [3].
Further reasons that make water as a unique among the other organic solvents are that it is cheap, not inflammable and more importantly, it is not toxic. Choice of solvents is one of the problems to face in order to perform eco-efficient processes.
As a part of our program towards green synthesis [4,5], the environment-friendly of one-pot three-component condensation reactions of 4-hydroxycoumarin (**1**) or 4-hydroxy-6-methylpyrone (**2**), *p*-substituted benzaldehyde (**3**) and alkyl or aryl isocyanides (**4**) to afford furan annulated heterocycles (**5**,**6**) in water, in good yields, after within about one hour at 75 °C are reported.



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SYNTHESIS OF INDAZOLE DERIVATIVES

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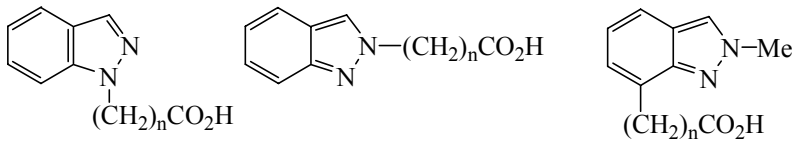
The indazole derivatives are pharmacologically important compounds and the indazole ring system forms the basis of a number of drug molecules, such as granisetron, a 5HT3 receptor antagonist used as an anti-emetic in cancer chemotherapy and benzydamine an anti-inflammatory agent [1]. However, in comparison with other heteroaromatic compounds, such as indole or benzimidazole, indazole chemistry remains less studied.
The indazole ring has two nitrogen atoms and can be funcionalized with high selectivity at different positions. The planarity of the indazole ring and both the length of side chains and their functionalisation and the different positions where it could be bonded, can afford an enormous number of indazole derivatives, presenting a promising field to provide new derivatives with biological/therapeutical properties.
We reporte here the synthesis of indazole substituted at N-1 and N-2 positions, starting from 1H-indazole, to afford a side chain functionalized with carboxylic acid or ester functionalities and the synthesis of indazoles substituted at C-7 position, using chromium tricarbonyl complexes as intermediate, which allow the complete regioselective functionalisation at this position [2].



The crystal structure of 6-indazol-2-yl-hexanoic acid was determined.

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STEREOSPECIFIC SYNTHESIS OF AZETIDINES BY ORGANOSELENIUM CHEMISTRY

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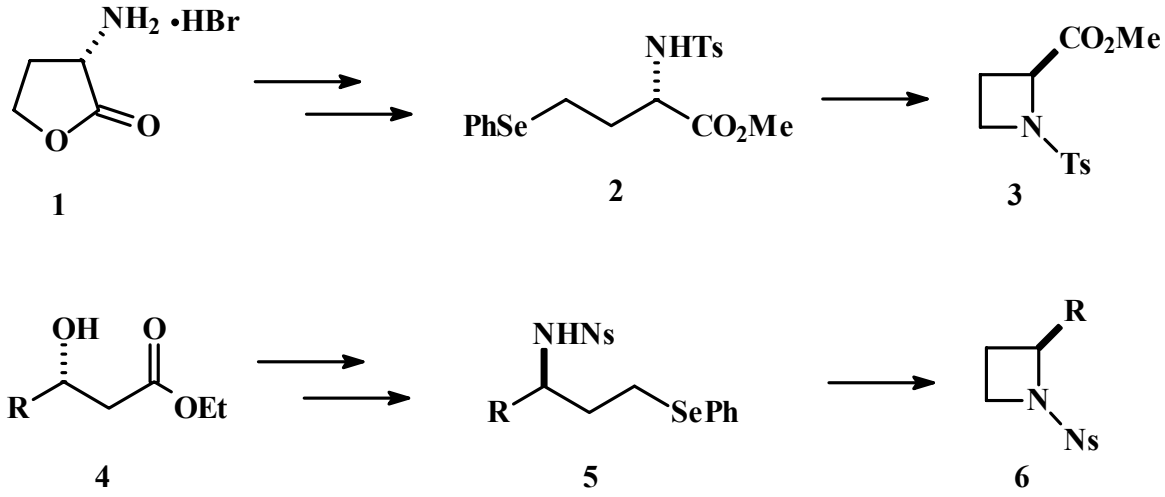
Azetidines are an interesting class of four membered heterocyclic compounds [1] which exhibit various biological activities such as antihypertensive, anti-inflammatory and antidepressant. However, the azetidines skeleton has been one of the most difficult to synthesize. We report herein a general stereospecific synthesis of substituted N-tosyl or N-nosyl azetidines **3** and **6**, respectively, from chiral non-racemic α-amino-γ-lactone **1** and β-hydroxy esters **4**. Thus, **2** and **5** were reacted with *m*-chloroperoxybenzoic acid in THF and in the presence of K_2HPO_4 [2] to obtain the corresponding selenones which after treatment with KOH afford azetidines **3** and **6** as the results of an intramolecular substitution of the phenylselenonyl group by the nitrogen atom.[3]



Thus we have developed a facile and stereoselective synthesis of substituted azetidines from readily chiral non racemic substrates through organoselenium intermediates.

Acknowledgement
Financial support from MIUR, National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" and FIRB Project RBNE01MTYS-007 and from the University of Perugia, Progetti di Ateneo is gratefully acknowledged.

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SYNTHESIS OF PYRROLO[3',4':3,4]PYRIDO[1,2-a]-BENZIMIDAZOLE DERIVATIVES

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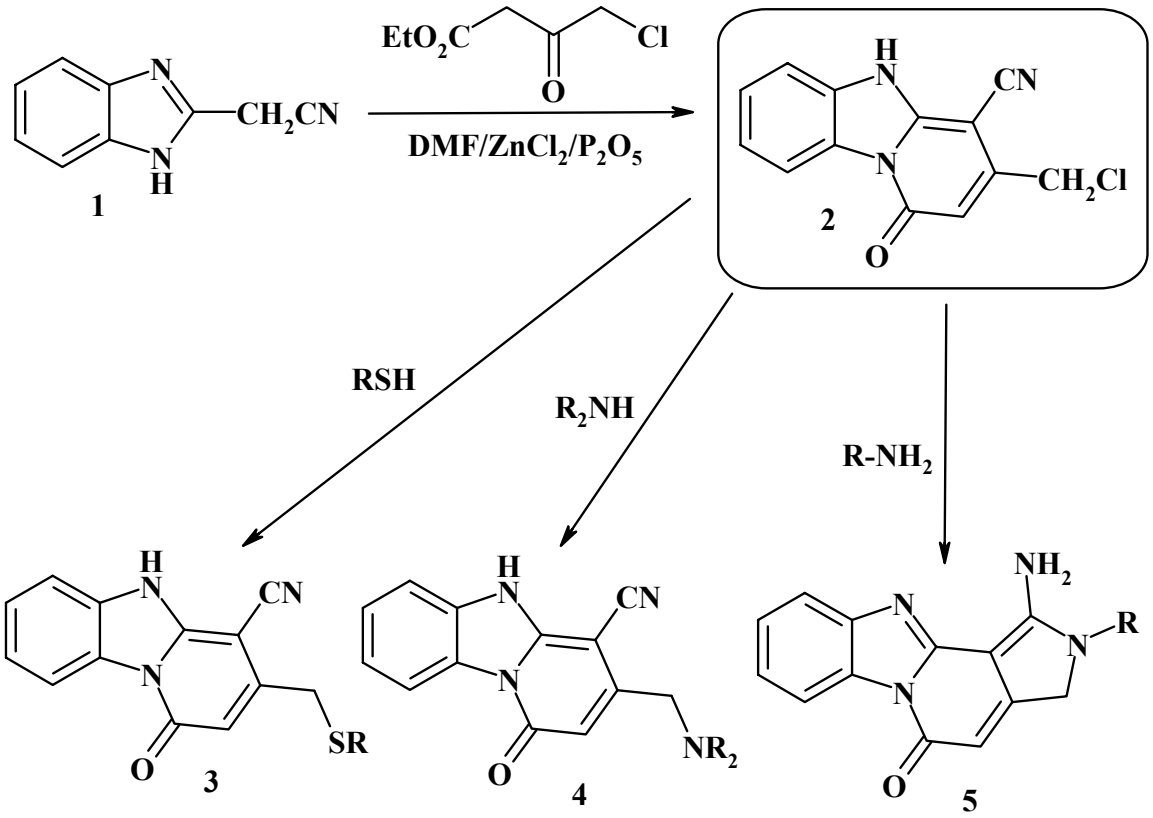
e-mail: atver@mail.univ.kiev.ua



Compounds consisting of 4-halonitrile moiety were shown to be suitable precursors for synthesis of various monocyclic and fused aminopyrrole derivatives. For this reason the preparation of new substances of such structure is of great interest. The condensation of 2-benzimidazoleacetonitrile **1** with ethyl 4-chloroacetoacetate in DMF in presence of $ZnCl_2$ and P_2O_5 allowed to obtain pyrido[1,2-*a*]benzimidazole derivative **2** bearing the target chloronitrile moiety. Compound **2** reacts smoothly with S- and N-nucleophiles yielding substitution products **3,4**. With primary amines the substitution reaction is accompanied with intramolecular addition to the nitrile triple bond leading to the title derivatives **5**. The latter are representatives of a novel heterocyclic system. The structures of all prepared compounds were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy data.

THE SYNTHESIS AND THE STUDY OF THE ANTIMICROBIAL ACTIVITY OF SOME CROMANON-OXYMETHYL-Δ_2-1,3,4 – OXADIAZOLINE

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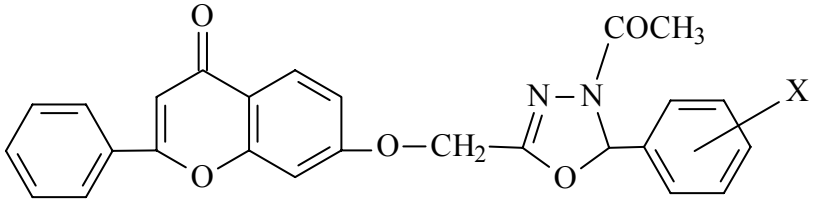
[a] Faculty of Pharmacy, University of Medecine and Pharmacy Cluj-Napoca, Romania
[b] Institut of Molecular and Isotopic Technology Cluj-Napoca, Romania

Following our study concerning the synthesis and biological activity of some isolated poliheterocyclic systems, in the present work we presented the synthesis and physicochemical analysis of the some 2-(2'-phenyl-7'-oxymethyl-croman-4'-on)-4-N-acetyl-5-phenyl-Δ_2-1,3,4-oxadiazolines with general structure:



X = Cl, Br, F, $OCOCH_3$, OCH_3 (o, m, p)

We evaluated the antimicrobials potential of the synthesized compounds using the difusimetric test.

"REDUCTIVE" HECK REACTION OF HALOPURINES

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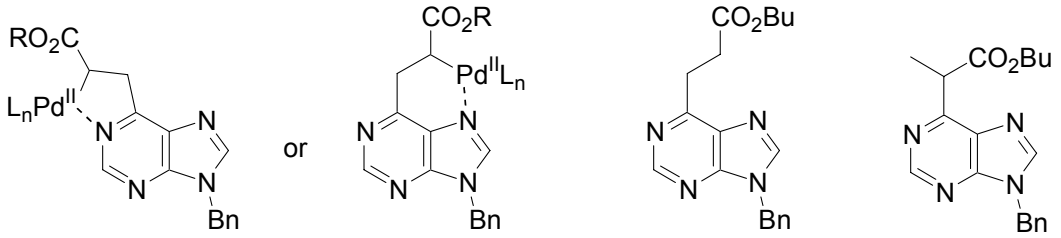
Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, Prague, Czech Republic

Purine derivatives bearing unsaturated chain at position 6 like trans-Zeatin, trans-6-(2-phenyl)ethenylpurine or 6-phenylethynylpurine exhibit cytokinine activity. Palladium catalysed coupling reactions of 6-halopurines are generally used for the introduction of unsaturated side chain into the position 6 of purine. This reactions include Stille, Suyuki-Miyaura, Sonogashira reactions and some others [1]. Surprisingly, the Heck reaction which is commonly used for the arylation of alkenes has not been successfully used for the modification of the position 6 of purine. To the best of our knowledge, the only reported example of the Heck reaction on purine derivative is the reaction of 8-bromocaffeine with *tert*-butyl acrylate, which afforded the desired product in a moderate yield [2]. Our recent attempts to introduce an unsaturated side chain into the position 6 of purine using Heck reaction have failed. N^1-substituted hypoxanthine derivative was obtained, instead of expected product, when the reaction was run in the presence of TlOAc [3]. We suppose, that this lack of reactivity might be a result of the a formation of a stable chelate (**1** or **2**) upon oxidative addition and insertion steps. Cleavage of such a chelate with appropriate reagent would enable the catalytic process to proceed. In fact, when the Heck reaction of 9-benzyl-6-iodopurine with butyl acrylate was accomplished in the presence of triethylammonium formate, a mixture of 6-substituted purines **3** and **4** in 1 : 2.5 ratio was obtained in 75% overall yield. This result is somewhat surprising, since acrylates are known to form β-substituted products like **3** with high selectivity. The origin of this unusual selectivity as well as the reaction of 6-halo-9-substituted purines with other substrates under the above conditions will be discussed.



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

[1] Microreview: M. Hocek Eur. J. Org. Chem. 2003, 245-254

[2] K. A. Jacobson, D. Shi, C. Gallo-Rodriguez, M. Manning, C. Müller, J. W. Daly, J. L. Meumayer, L. Kiriasis, W. Pfeiderer, J. Med. Chem. 1993, 36, 2639-2644

[3] M. Havelková, M. Studenovský, D. Dvořák, Collect. Czech. Chem. Commun. 2000, 65, 797-804

A NOVEL ROUTE TO 1,2,3-THIADIAZOL, 1,2,4-THIADIAZINE AND 1,2,5-TRIAZEPINE DERIVATIVES

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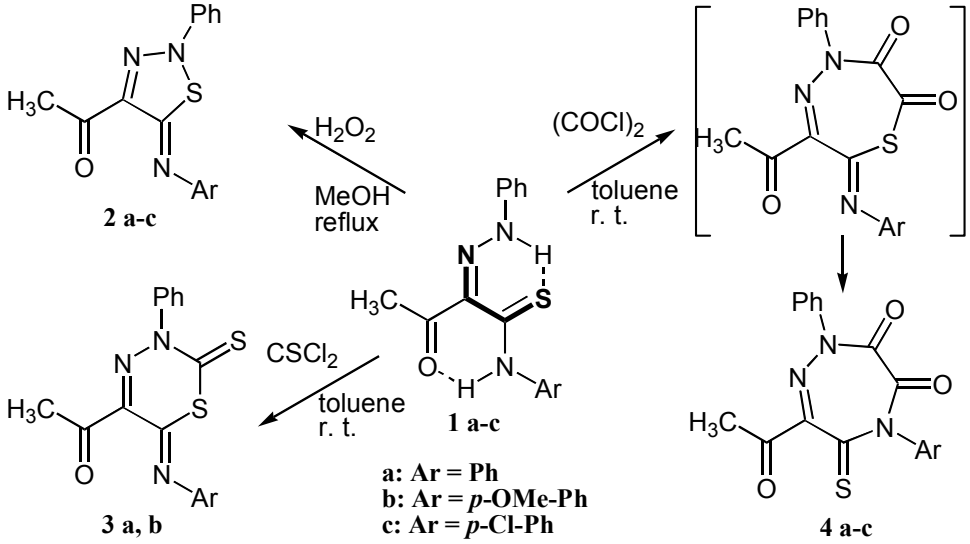
Recently we have reported [1, 2] the synthesis of 1,3- and 1,4-diazines that used thioanilides of 2-anilino-2-methoxy-3-oxobutanoic acid [3] in heterocyclization reactions with various diamines. We have found that good leaving groups at C-2 of these thioanilides offer an entry to formation of six- and seven-member rings by the treatment with binucleophiles.

In order to develop synthetic applications of anilides of 3-oxothiobutanoic acid in closing heterocyclic rings we have transformed them into phenylhydrazones **1a-c** by treatment with phenylhydrazine.

Phenylhydrazones **1a-c** appear only in one stereoisomeric form corresponding to (Z)-configuration of the 1-thia-4-aza-1,3-butadiene system. This conclusion is based on ^{1}H and ^{13}C NMR evidences as well as X-ray analysis. The defined (Z)-configuration incorpo-rates the structural requirements for the construction of heterocyclic rings. (Scheme 1)



Scheme 1

Oxidative heterocyclisation of hydrazones **1a-c**, by treatment with H_2O_2, exclusively produced 1,2,3-thiadiazole derivatives **2a-c**.

The reaction of **1a, b** with thiophosgene led to the formation of six-member rings of 1,3,4-thiadiazine derivatives **3a, b**.

Diacylation of **1a-c** with oxalyl chloride at room temperature in toluene, afforded 1,2,5-triazepine derivatives **4a-c** with high to excellent yields.

[1] Zaleska, B.; Bazanek, T.; Socha, R.; Karelus, M.; Grochowski, J.; Serda, P. *J. Org. Chem.* **2002**, *67*, 4526.
[2] Zaleska, B.; Socha, R.; Karelus, M.; Szneler, E.; Grochowski, J.; Serda, P. *J. Org. Chem.* **2003**, *68*, 2334.
[3] Zaleska, B.; Socha, R.; Ciechanowicz-Rutkowska, M.; Pilati, T. *Monatsh. Chem.* **2000**, *131*, 1158.

2-(BENZO)THIAZOLEACETONITRILES IN HETEROCYCLIC SYNTHESIS

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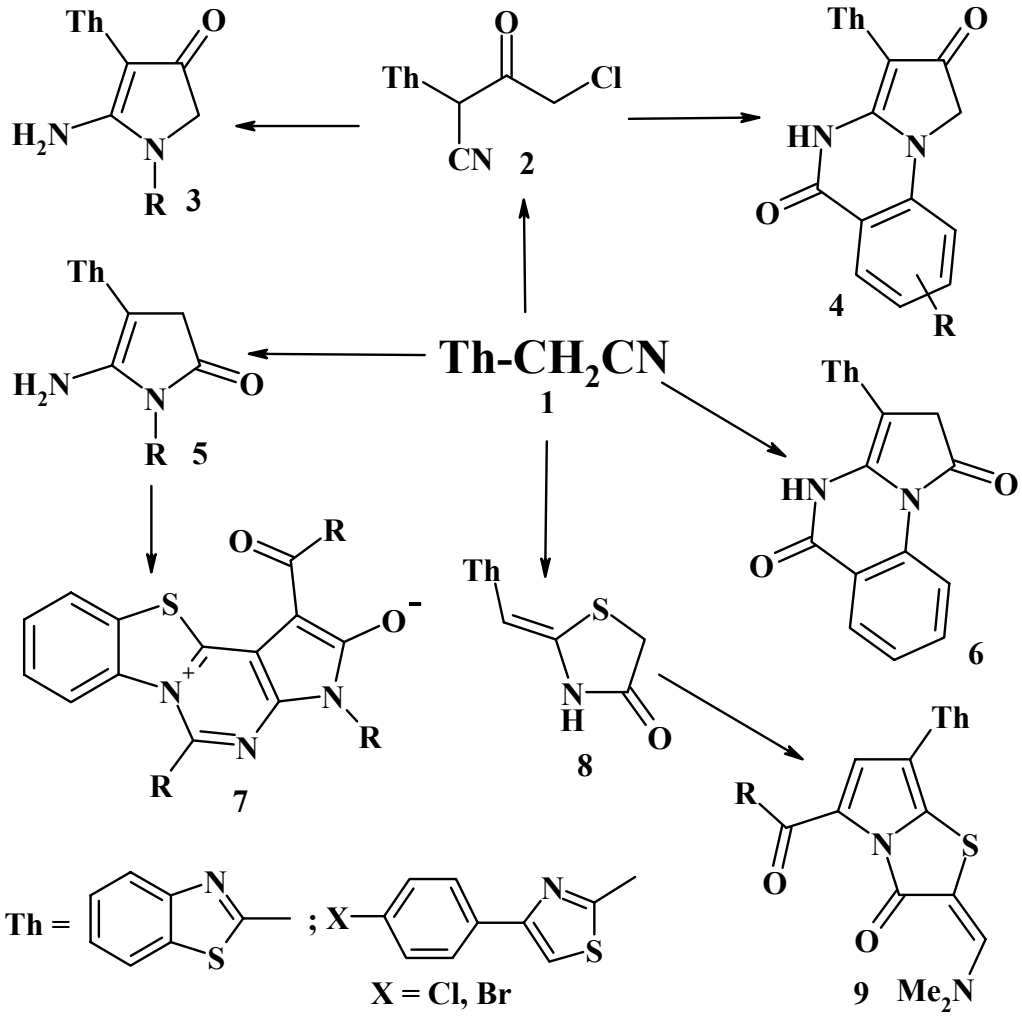
Kiev National Taras Shevchenko University, Volodimirska str. 62, 01033, Kiev, Ukraine; e-mail: atver@mail.univ.kiev.ua



The thiazoleacetonitriles **1** were shown to be suitable precursors for synthesis of various pyrrole-containing compounds **3-7,9**. Thus, acylation of the nitriles **1** with chloroacetyl chloride led to the derivatives **2**. Their amination with primary amines or hydrazine derivatives yielded pyrrolones **3**, whereas with 2-aminobenzoic acid derivatives compounds **4** were obtained. Alkylation of the nitriles **1** with N-substituted 2-chloroacetamides allowed to prepare compounds **5,6** with isomeric oxomethylene moiety topology. The comparative study of the spectral and chemical behavior of the isomeric pyrroles **3** and **5** was carried out. In particular, the acylation of benzothiazole substituted derivatives **5** with acid chlorides was found to give the betainic derivatives of novel heterocyclic system **7**. Finally, upon heating with mercaptoacetic acid the nitriles **1** yielded thiazolones **8**, which were converted into pyrrolo[2,1-*b*]thiazoles **9** in two steps.

INTERESTING MCR 3 REACTION LEADING TO A NOVEL ZWITTERIONIC STRUCTURE; PYRIDINIUM-PYRAZOL-3-OLATE INNER SALT

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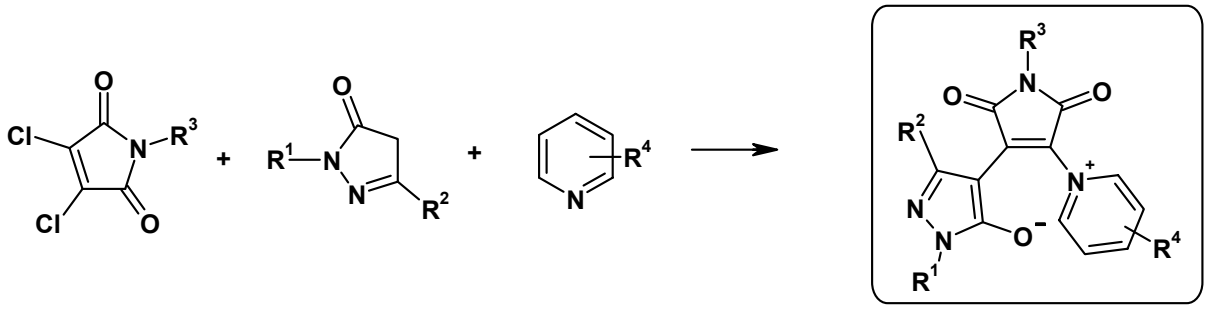
Comgenex Inc., 33-34 Bem rkp., Budapest, Hungary

The fragment based library design approach is based on information-rich building blocks (templates). Decreased size (typically less than 200) and complexity of the molecules (fragments) enables the structure's relative contribution to binding interactions to be identified, even if these fragments show low activity. The fragmental library design approach results in lead-like structures that are typically smaller and less hydrophobic than the drug-like compounds, as defined by Lipinski's rule of 5.

In principal high-affinity ligands and inhibitors can be obtained by assembling several low-



affinity fragments into one unit in a combinatorial manner.

In this presentation we describe a novel multicomponent reaction approach for one-step assembly of different diverse building blocks into one lead-like combinatorial library.

NOVEL SYNTHESIS OF 3a,4-DIHYDRO-3H-BENZO[5,6]-CHROMENO[4,3-c]ISOXAZOLES VIA INTRAMOLECULAR [3+2] NITRILE OXIDE CYCLOADDITIONS

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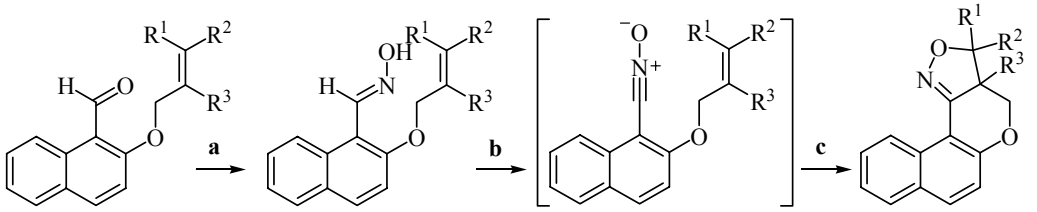
Intramolecular nitrile oxide cycloaddition is the key step in the novel synthesis of 3a,4-dihydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazoles.

Intramolecular 1,3-dipolar cycloaddition in aromatic rings ortho substituted with nitrile oxide and alkene or alkyne functional groups is a powerful tool in the preparation of isoxazole fused heterocycles[1]. Nitrile oxides are usually prepared *in situ* and are rarely isolated. General methods used for their preparation are dehydrochlorination of hydroximoyl chlorides and triethylamine[2a], dehydration of primary nitro compounds with aryl isocyanate[2b] and the oxidation of aldoximes[2c].

In the course of our research on the synthesis of novel heterocycles from oximes of 2-hydroxynaphthaldehyde[3], we became interested in investigating the potential of the intramolecular nitrile oxide cycloaddition with ethylenic dipolarophiles. Our targeted compounds, 3a,4-dihydro-3*H*-benzo[5,6]chromeno[4,3-*c*]isoxazoles **4a-f** were obtained by the intramolecular cycloaddition of 1,3-dipoles **3a-f**, generated *in situ* from dipolarophile "tethered" naphthaldehyde oximes **2a-f**. In the first step alkylation of 2-hydroxynaphthaldehyde with allyl bromide, crotyl chloride, 4-bromo-2-methyl-2-butene, cinnamyl bromide, 3-chloro-2-methyl-1-propene or 2,3-dichloro-1-propene in refluxing acetone containing potassium carbonate gave ethylenyl derivatives **1a-f**. Condensation of **1a-f** with hydroxylamine hydrochloride in refluxing ethanol containing sodium carbonate and acetic acid afforded **2a-f**. Oxidation of **2a-f** with aqueous sodium hypochlorite (5%) or manganese dioxide gave the corresponding heterocycles **4a-f** in good yields.



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

(a) $R^1 = R^2 = R^3 = H$, (b) $R^1 = R^3 = H$, $R^2 = Me$, (c) $R^1 = R^2 = Me$, $R^3 = H$, (d) $R^1 = R^3 = H$, $R^2 = Ph$, (e) $R^1 = R^2 = H$, $R^3 = Me$, (f) $R^1 = R^2 = H$, $R^3 = Cl$. Reagents: (a) acetone, K_2CO_3, Δ, (b) $HCl.H_2NOH$, EtOH, Na_2CO_3, $MeCO_2H$, Δ, (c) NaOCl, Et_3N, CH_2Cl_2, 0°C or MnO_2, CH_2Cl_2, 0°C.

[1] Wade, P. A. In Comprehensive organic Synthesis, B. M. Trost and I. Fleming, Eds., Pergamon, Oxford, 1991, vol. 4, p. 1111.
[2] (a) Gi, H.-J.; Xiang, Y.; Shinazi, R. F.; Zhao, K. *J. Org. Chem*. **1997**, *62*, 88, (b) Sharma, S. C.; Torsell, K. B. G. *Acta. Chem. Scand*., **1979**, *B33*, 379, (d) Kiegiel, J.; Poplawska, M.; Jóźwik, J.; Kosior, M.; Jurczak, J. *Tetrahedron Lett*. **1999**, *40*, 5605.
[3] Supsana, P.; Tsoungas, P. G.; Aubry, A.; Skoulika, S.; Varvounis, G. *Tetrahedron* **2001**, *57*, 3445.

ORGANIC CONDUCTORS BASED ON 2,5-DIAMINO-3,4-DICYANO-THIOPHENE AND DIAMINOMALEONITRILE

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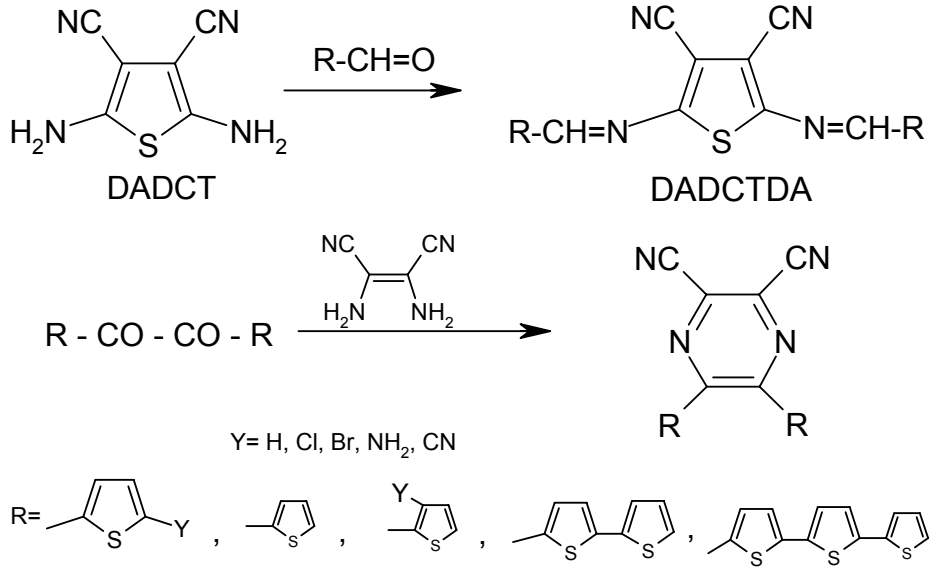
[b] Department of Chemical Physics, Slovak University of Technology, Radlinského 9, SK - 812 37 Bratislava, SR.
[c] VUCHT a.s. Bratislava, SR
[d]Institut für Physikalische Chemie, Universität Wien, 1090 Wien, Austria

In recent years there has been enormous interest in the area of conducting polymers, which display a wide range of electrical conductivities.[1]

Several new derivatives of 2,5-diamino-4,5-dicyanothiophene (DADCTDA) as well as of the new cyclisation product of diaminomaleonitrile with thenils were prepared. The prepared DADCTDA- and 2,3-dicyano-5,6-substituted pyrazine derivatives seem to be suitable candidates for the subsequent preparation of the phthalocyanine like electro-optical materials.



The identification of prepared compounds was based on their ^{1}H and ^{13}C NMR, IR and UV spectra.

[1] Mullen K., Wegner G.: *Electronic Materials., The Oligomer Approach,* Wiley-VCH, 1998.

This work was supported by the Slovak Ministry of Education Grants N°: 1/8109/01; 1/7355/20; 1/9255/02 and the Austrian Ministry of Education, Science and Culture Grant bm:bwk (Ost-West-Kooperation-H,GZ.45.452).

BIFUNCTIONAL AMIDINIUM CARBOXYLATES – A NEW TYPE OF NON-COVALENT MACROHETEROCYCLES

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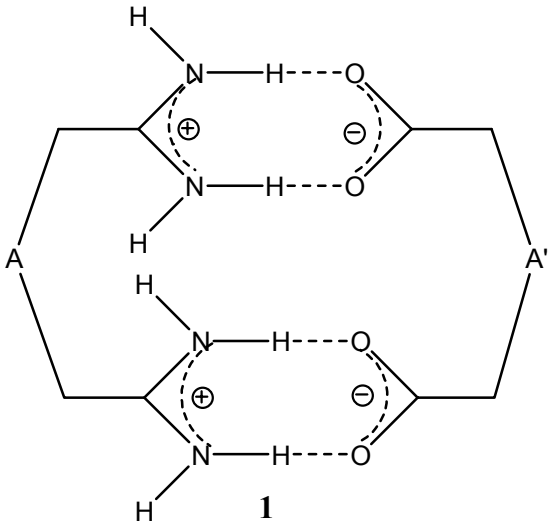
Department of Organic Chemistry, Institute of Chemical Technology, Prague
Technická 5, 166 28 Prague 6, Czech Republic

Amidinium groups combine hydrogen bonds and electrostatic interaction to bind anions. Their complementarity to oxo-anions such as carboxylates, phosphates and sulfates is well known. Therefore many amidinium receptors designed to interact with carboxylates have been described [1]. Simple amidinium-carboxylates X-C(=NH)NH_2*HO(O=C)C-Y, where X = H, CH_3, OCH_3, $NHCH_3$, SCH_3, C_6H_5, subst. phenyl; Y = H, CH_3, CF_3, $COCH_3$, C_6H_5, subst. phenyl, were synthesized in our laboratory some time ago [2]. The substitution effect transfer between amidinium and carboxylate part of the molecule via hydrogen bonds has been proven. Owing to partially covalent character of this interaction and suitable physico-chemical properties including good solubility with negligible dissociation in aprotic solvents, these structures may be of great importance when forming macrocyclic complexes. Bifunctional cyclic amidinium carboxylates **1** (A,A´ = alkanediyl-, arenediyl- or heteroarenediyl-) as interesting molecules in the field of supramolecular chemistry are target compounds in the present work.



1

[1] Sebo L., Schweitzer B., Diederich F.: *Helv. Chim. Acta* **2000**, *83*, 80, and references cited therein.
[2] Krechl J., Böhm S., Smrčková S., Kuthan J.: *Collect. Czech. Chem. Commun.* **1989**, *54*, 673; Krechl J., Smrčková S., Pavlíková F., Kuthan J.: *Collect. Czech. Chem. Commun.* **1989**, *54*, 2415; Krechl J., Smrčková S., Kuthan J.: *Collect. Czech. Chem. Commun.* **1990**, *55*, 460; Krechl J., Smrčková S., Ludwig M., Kuthan J.: *Collect. Czech. Chem. Commun.* **1990**, *55*, 469.

QUANTUM CHEMICAL STUDY OF 1,3-DIPOLAR CYCLOADDITIONS OF FREE AND COORDINATED NITRILES

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[a]Chemistry, University of Surrey, Guildford, Surrey, GU2 7XH, United Kingdom.
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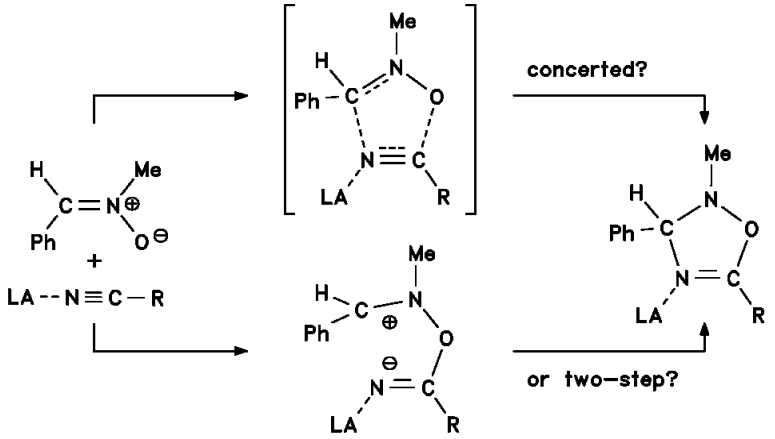
[c] Institut für Chemie, Karl-Franzens-Universität Graz, Heinrichstrasse 28, A-8010 Graz, Austria.

Nitriles, although promising starting materials for the synthesis of heterocycles, are only rarely used in cycloaddition reactions due to their low reactivity towards most dipolar reagents. However, it was found that platinum- or palladium-coordinated nitriles undergo cycloaddition with nitrones under mild conditions to give stable Δ^4-1,2,4-oxadiazoline complexes from which the newly formed ligand can be released and isolated.[1] In bifunctional compounds such as *E*-cinnamonitrile, the presence of the metal switches the selectivity from C=C attack to an exclusive reaction at the nitrile.[2] Thus, the metal mediated reaction allows for transformations that are not feasible in purely organic chemistry.



In order to understand the effect of the Lewis acidic metal on these reactions, we undertook a quantum chemical study on HF/6-31G* and B3LYP/6-31G* level of theory. Analysis of reagents, products, transition states and intrinsic reaction pathways gave insight into the differences in the mechanism of the reactions, the influence of the nitrile substituent, solvent and Lewis acid coordination on the reactivity and selectivity, and the type of activation the metal center exhibits.[3,4] Quantum chemical calculations were also applied to other cycloadditions of free or Lewis acid coordinated nitriles, with the aim to predict new reactions.[5]

[1] G. Wagner, M. Haukka, *J. Chem. Soc., Dalton Trans.* 2001, 2690-2697. [2] B. Desai, T. N. Danks, G. Wagner, *J. Chem. Soc., Dalton Trans.*, accepted. [3] G. Wagner, *Chem. Eur. J.*, 2003, **9**, 1503-1510. [4] B. Desai, T. N. Danks, G. Wagner, manuscript in preparation. [5] V. Vullo, T. N. Danks, G. Wagner, manuscript in preparation.

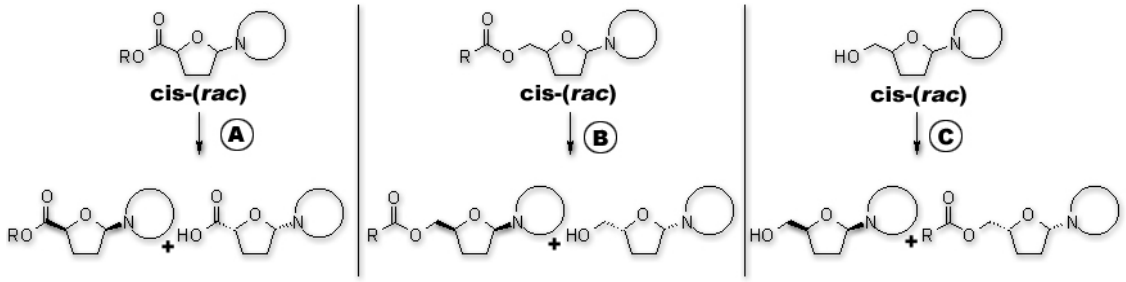
KINETIC ENZYMATIC RESOLUTION OF RACEMIC 2',3'-DIDEOXYNUCLEOSIDES

Kerstin Waich, Petra Feiertag, Helmut Hönig, and Martin Albert

Institut für Organische Chemie, Technische Universität Graz, A-8010 Graz, Austria

Recently, we reported a short synthesis of 2',3'-dideoxynucleosides starting from 2-substituted furans [1]. The reaction sequence consists of a coupling reaction of a silylated *N*-heterocycle with an activated furan, a subsequent elimination to planar furyl nucleosides and a final diastereoselective hydrogenation, which produces a racemic mixture of 2',3'-dideoxynucleosides.

The use of esterases and lipases for the kinetic resolution of racemic esters is well established [1]. For the enzymatic resolution of racemic 2',3'-dideoxynucleosides by means of lipases or esterases the following possibilities exist: hydrolysis of furoic acid derivatives (path **A**); hydrolysis of an acyl-protected furfurol derivative (path **B**); and acyl-transfer to unprotected furfurols (path **C**). The results we obtained for a series of different 2',3'-dideoxynucleosides will be presented.



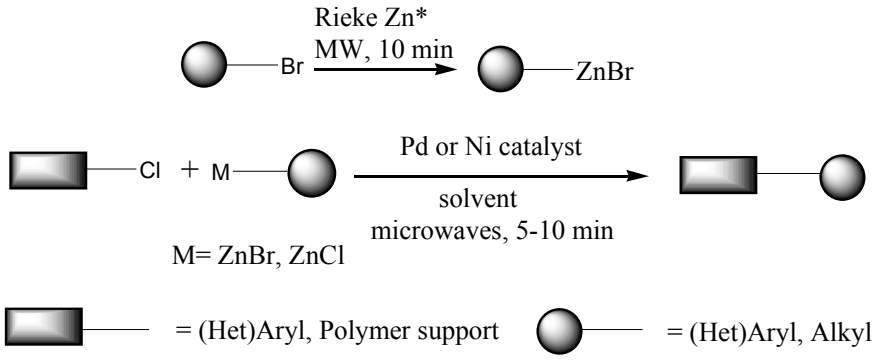
[1] Albert, M.; De Souza, D.; Feiertag, P.; Hönig, H. *Org. Lett.* **2002**, *4*, 3251-3254.
[2] Faber, K. *Biotransformations in Organic Chemistry*, Springer-Verlag, Berlin, Heidelberg, 1992.

MICROWAVE-PROMOTED HIGH-SPEED NEGISHI CROSS COUPLING REACTIONS AS A POWERFUL TOOL FOR ORGANIC SYNTHESIS

Peter Walla and C. Oliver Kappe

Institute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria.
Email: peter.walla@uni-graz.at, oliver.kappe@uni-graz.at

The palladium and nickel-catalyzed cross-coupling of aryl halides with organozinc reagents (Negishi reaction) [1] represents a powerful method leading to synthetically important compounds such as styrene derivatives and biaryls [2,3]. The ready availability and the functional group compatibility of organozinc reagents [4] significantly enhances the utility of this cross-coupling process. There have been limited reports [5] on Negishi cross-couplings promoted under microwave conditions. In our studies, we have extended microwave assisted Negishi cross-coupling reactions (see Scheme 1) utilizing solution and solid phase methods with chloro-substituted scaffolds. Typically, we have been investigating synthetic strategies to involve halogen-substituted heterocyclic moieties for cross coupling with the organozinc reagents. The synthesis of organozinc reagents for the coupling reactions has been successfully conducted under microwave conditions (see Scheme 1).



Scheme 1

We have been looking in this area attempting to extend Negishi couplings with a combinatorial synthetic approach. In our preliminary studies under microwave conditions, we have observed improvement in coupling reactions using Nickel catalysts, in addition, use of Palladium catalysts have been found favorable for bromo-substituted scaffolds. We are currently investigating the scope of this reaction employing different types of halo-substituted scaffolds and optimizing reaction conditions.

[1] For a review, see: Negishi, E.-i. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 1.
[2] For example, see: *Step Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symp. Ser. 624; American Chemical Society: Washington, D.C., 1996.
[3] For example, see: A review of vancomycin antibiotics: Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096-2152.
[4] *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999.
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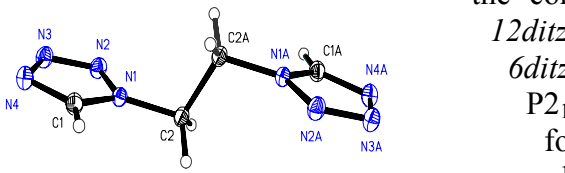
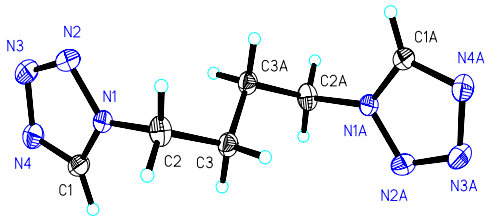
SYNTHESIS AND CHARACTERISATION OF α,ω-BIS(TETRAZOL-1-YL)ALKANES

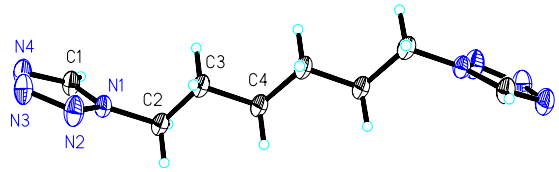
Peter Weinberger[a], Matthias Grunert[a],Kurt Mereiter[b] and Wolfgang Linert[a]

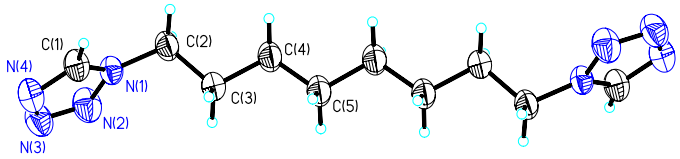
[a]Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-AC, A-1060 Vienna, Austria
[b]Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/164-SC, A-1060 Vienna, Austria

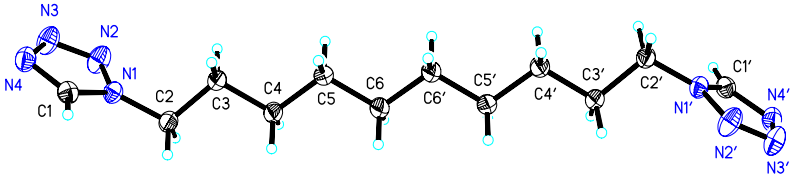
New tetrazole compounds were synthesized and characterized by NMR and FTIR spectroscopy as well as by single crystal X-ray diffraction. One useful tool for the purifications was the deep-temperature re-crystallisation, which was helpful especially for the compounds with longer alkyl chains (*10ditz* and *12ditz*), because of its softness at room temperature. *6ditz*, *8ditz* and *12ditz* crystallise in the space group $P2_1/n$ except the space group $C2_1/c$, which can be found for *10ditz*. They represent a versatile class of building blocks on the way to fascinating supramolecular structures with various transition metals. In the special case of iron(II) these bridging ligands form indispensable brick stones for the design of 3D mutually interpenetrating polynuclear spin crossover complexes [1].

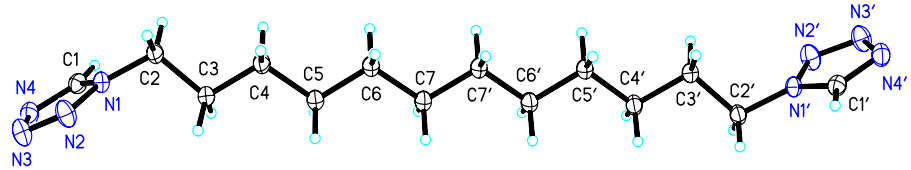












Acknowledgements: Thanks for financial support are due to the "Fonds zur Förderung der Wissenschaftlichen Forschung in Österreich" (project 15874-N03), the Training and Mobility of Researchers Network (TMR) project "Thermal and Optical Spin State Switching" (TOSS) supported by the European Community under the contract number ERB-FMRX-CT98-0199 and to the European Science Foundation under the project "Molecular Magnets".

[1] M. Grunert, J. Schweifer, P. Weinberger, K. Mereiter, M. Boca, G. Hilscher, P.J. van Koningsbruggen and W. Linert, *Inorg. Chem. accepted June 2003*

BIS(1,3,4-THIADIAZOLO)-1,3,5-TRIAZINIUM HALIDES: ACCESS TO A NEW CLASS OF GUANIDINYLATION REAGENTS

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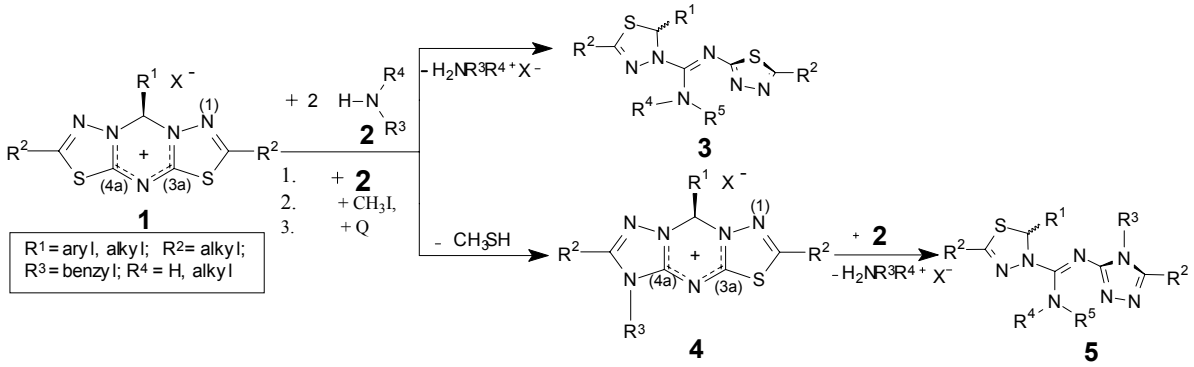
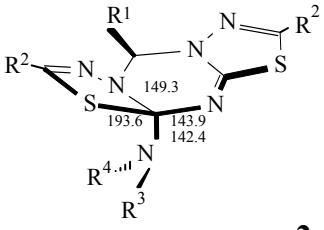
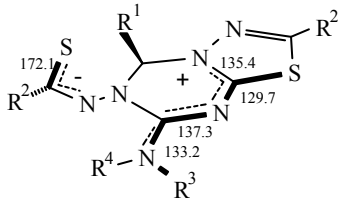
There are only few reports on the preparation of guanidine derivatives containing three different nitrogen heterocycles directly integrated within the guanidine unit. Since the guanidine functionality repeatedly occurs in numerous natural compounds exhibiting significant biological activity, the number of reagents for their preparation is increasing. Recently, guanidines have been employed as potential chiral auxiliaries in asymmetric syntheses.



In this report we show an interesting application of our novel 5/6/5 nitrogen-sulfur heterocycles **1** [1]. The reaction of **1** and primary or secondary (also heterocyclic) amines **2** is accompanied by ring transformation which leads to the formation of interesting polysubstituted guanidines **3** in high yields [2,3,4,5]. These products are generated in the course of multi-step cascade reactions in which, after the initial amine attack, specific bond breaking and bond forming processes occur. This is similar to the way novel heterocycles **4** (triazolo-thiadiazolo-triazinium compounds) and amines **2** react to give the new type of guanidines **5.**



***Intermediate after addition of* 2**



***Triazinium-Imidothioate Zwitterion* 6**

We discuss the mechanism of these ring transformations (**S_N(ANRORC) reactions**) considering the fact that the imidothioate intermediates **6** can be experimentally isolated and detected *via* their characteristic NMR signals. High-level DFT explain the reaction pathways which lead via **6** to e.g. **3** or **4.**

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SYNTHETIC STUDY FOR 6-ACYLDIHYDROPTERIN: THE SITE SPECIFIC OXIDATION OF 6-HYDROXYALKYLPTERIN

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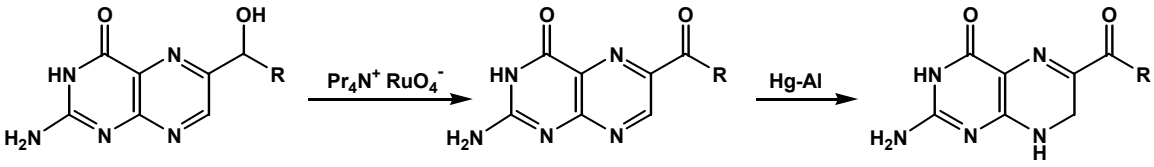
Graduate School of Environmental Studies,
Nagoya University
Nagoya, JP464-8601 Japan

Hydrogenated 6-acylpterins, such as sepiapterin and pyruvoyltetrahydropterin, are known as important metabolic intermediates in tetrahydrobiopterin biosynthesis. Although biological and biochemical characters of these pterins have been well understood, studies for pharmaceutical and medical application of such derivatives do not proceed. As the major reason of the difficulty, we can point out that efficient chemical synthetic procedures of 6-acylpterins and their hydrogenated derivatives have not been established. In this paper, we would like to present a novel chemoselective oxidation of 6-hydoxyalkylpterin to 6-acylpterin and its application to deoxysepiapterin synthesis.

Protected 6-1'-hydroxyethyl-, -propyl-, and -butylpterins were synthesized by regioselective condensation of 4-butoxy-2,5,6-triaminopyrimidine with 2,3-epoxybutanal -pentanal, and -hexanal, respectively. Catalytic oxidation of those 6-1'-hydroxyalkylpterin derivatives by the ruthenium complex (Pr_4N^+ RuO_4^-) afforded the corresponding 4-butoxy-6-acylpterins in 35—65% yields. Alkaline hydrolysis followed by partial reduction (Al—Hg) of 4-butoxy-6-propionylpterin yielded deoxysepiapterin in 32% yield.



MICROWAVE-ASSISTED THREE-COMPONENT ONE-POT SYNTHESIS OF MULTIFUNCTIONALIZED PYRIDIN-2-ONES

Nikolay Yu. Gorobets,[1] Behrooz H. Yousefi,[2] and C. Oliver Kappe[3*]

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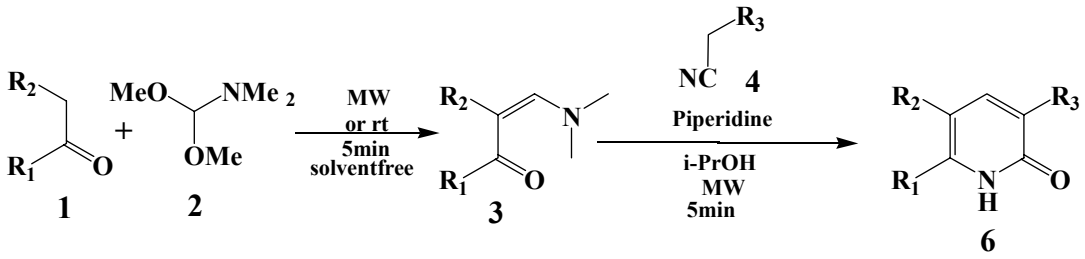
[3] oliver.kappe@uni-graz.at

Pyridone and quinolone analogous are known as biologically active heterocycles, e.g. inotropic and antitumor agents [1, 2]. In this work we report on the rapid microwave (MW) assisted synthesis of 3,5,6-substituted pyridine-2-ones **6** including fused analogous, by three-component condensation of CH-acidic carbonyl compounds, N,N–dimethylforamide dimethyl acetal (DMFDMA) and methylene active nitriles.



Using automated microwave-assisted protocols a library of pyridones **6** was generated. All compounds were isolated in moderate to good yield in high purity, and fully characterized by spectroscopic techniques.

The mechanism of this multi-component reaction and the structures of some isolated intermediates will be discussed.

[1] P. Fossa, R. Boggia, E. Lo Presti, P. Dorigo, M. Floreani and L. Mosti *Farmaco*, **1997**, *52*, 523-530.
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COBALT PHTHALOCYANINES AS BIS-DIENOPHILES FOR DIELS-ALDER REACTION

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A series of bisadduct cobalt phthalocyanine systems having furopyridine-type ring has been synthesized through the Diels-Alder reaction [1] between CoPc **Ia,b** as bisdienophile and series of pyridine N-oxides **IIa-f** as dienes . This work describes the result of the inverse-type cycloaddtion of some electron-deficient pyridine N-oxides **IIa-f** [2]with1,4-epoxy-1,4-dihydronaphthalene ring [3] of the cobalt phthalocyanines **Ia,b**. (Scheme 1). In these reactions, the bisadducts **IIIa-f** formed from the 1,5-sigmatropic rearrangment also the monoadduct is accesssible.
The bisadducts **IIIa-f** were isolated, purified by column chromatography and charcterized with several spectrometrical methods in addition to ESR spectroscopy. (Figure 1).

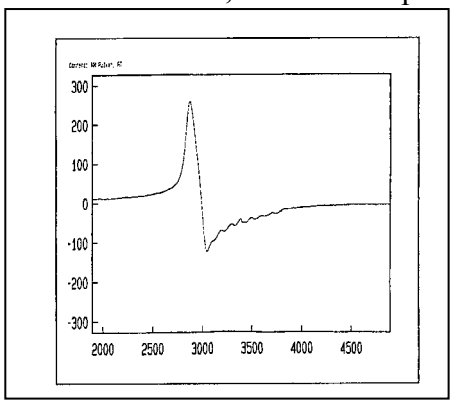
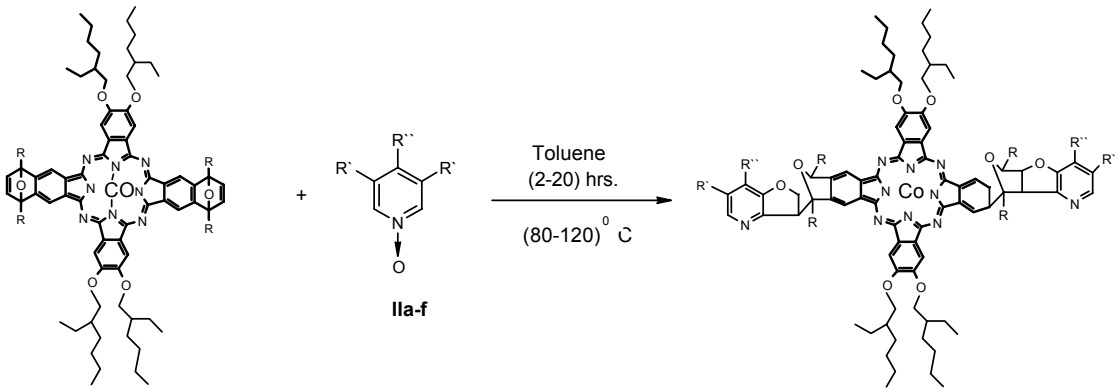


Fig. 1. ESR spectra of **IIIa**



Scheme 1 .Preparation of Cobalt phthalocyanine bisadducts IIIa-f

References

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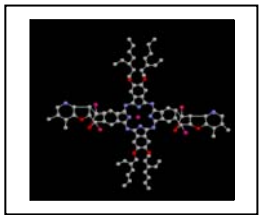
[2] T. Hisano, K. Harano, T. Matsuoka, T. Suzuki and Y.Murayama, Chem. Pharm. Bull. 1990, 38, 605.
[3] D. H. Ruff, S.Fiedler and M. Hanack, Synth. Met. 1995, 69, 579.



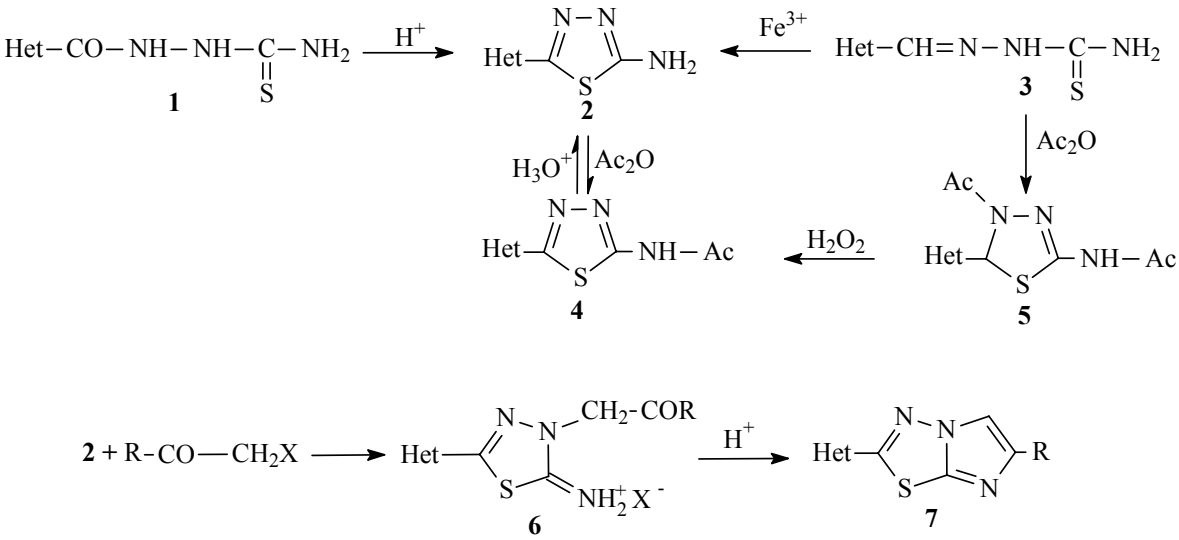
OBTAINMENT AND BEHAVIOUR OF SOME 2-AMINO-5-THIAZOLYL-[1,3,4]-THIADIAZOLES

V. Zaharia[a], D. Ghereg[a], Ileana Chitoc[b], Daniela Zaharia[a], Alina Elena Pârvu[a]

[a] "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania
[b] Research and Development National Institute of Isotopic and Molecular Technologies, Cluj-Napoca, Romania

In previous papers we have presented the obtainment of some thiazolyl-mercapto-[1,2,4]-triazoles by cyclization of some thiazolyl-carbonylthiosemicarbazide in alkaline solution.

Starting from the same precursors - acylthiosemicarbazides **1**, under the action of concentrated H_2SO_4, aminothiadiazoles **2** have been obtained. Compounds **2** have also been obtained by cyclization of tiosemicarbazones **3** under the action of $FeCl_3$. N-Acetyl derivatives **4**, obtained by the successive action of acetic anhydride and hydrogen peroxide on compounds **3,** have been transformed in aminothiadiazoles **2**, by hydrolysis.
In order to obtain imidazo[2,1-b][1,3,4]thiadiazoles **7**, compounds **2** have been condensed with a series of α-halocarbonyls.



Het = 2-phenyl-thiazol-4-yl; 4-methyl-2-phenyl-thiazol-5-yl.

Ac = CH_3—CO ; **R** = CH_3 ; C_6H_5

In a test performed on Wistar-Bratislava male rats, aminothiadiazoles and their precursors proved to have a good anti-inflammatory effect by reducing of the phagocytic activity and by inhibiting the acute phase bone marrow response.

SYNTHESIS AND STEREOCHEMISTRY OF SATURATED 3,1,2-BENZOXAZAPHOSPHORINANES

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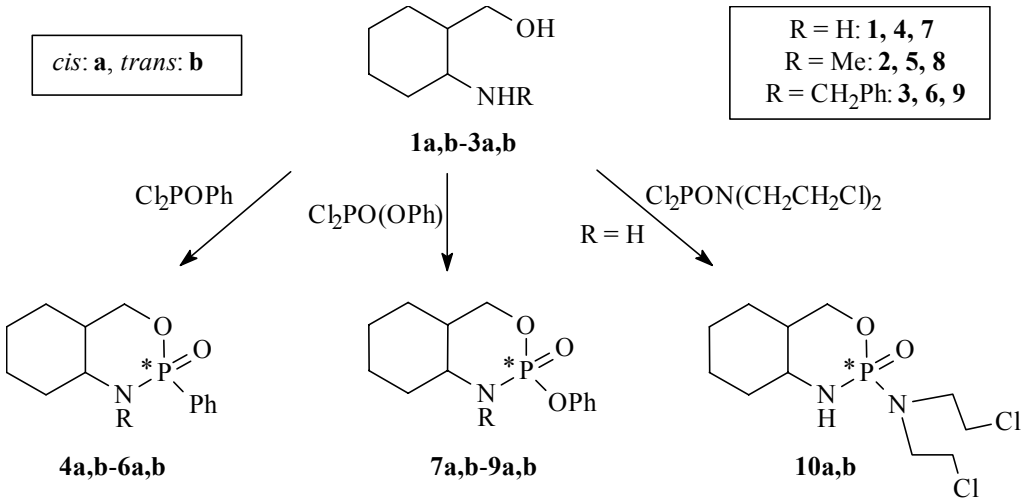
The syntheses and transformations of 1,3,2-oxazaphosphorinane 2-oxides have been thoroughly studied in recent decades, in consequence of the wide synthetic applicability and therapeutic importance of this type of compound. However, the syntheses and conformational behaviour of the cycloalkane-condensed 1,3,2-oxazaphosphorinanes have been studied less extensively. The substituents on the nitrogen proved to have a great influence on the conformational equilibria of perhydro-2-[bis(2-chloroethyl)amino]-1,3,2-benzoxazaphosphorinane 2-oxides [1].



Our present aim was to synthesize the regioisomers of the previously investigated 1,3,2-benzoxazaphosphorinane analogues. Ring closures of amino alcohols **1-3** with phenylphosphonyl dichloride, phenyl dichlorophosphate and bis(2-chloroethyl)-phosphoramidic dichloride resulted in P-2 epimeric diastereomers (**a** and **b**) of *cis*- and *trans*-perhydro-3,1,2-benzoxazaphosphorinanes (**4-10**), which were separated by column chromatography. The configuration and the substituent effects on the predominant conformation of the synthesized compounds were determined by NMR spectroscopy.

[1] Viljanen, T.; Tähtinen, P.; Pihlaja, K.; Fülöp, F. *J. Org. Chem.* **1998**, *63*, 618.

REACTIONS OF MALEISOIMIDES WITH AMINES AND ALCOHOLS

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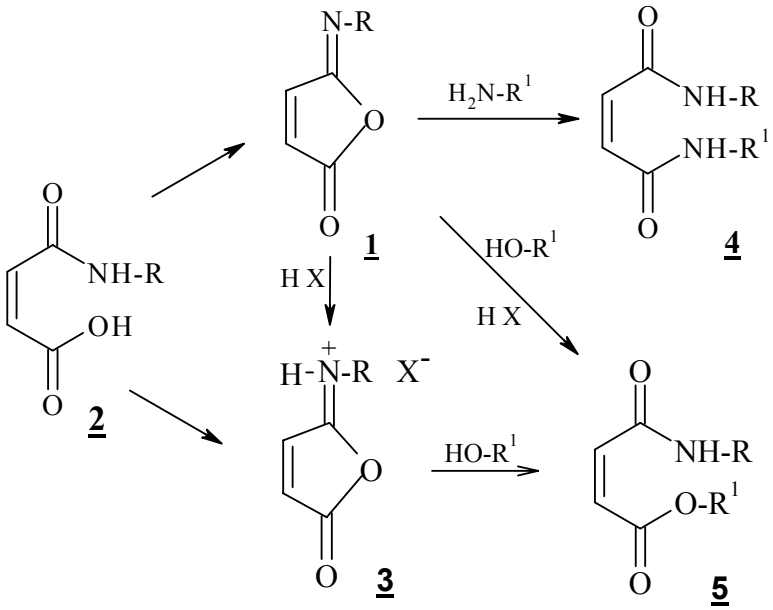
Maleisoimides (MII, **1**) are easily available precursors for syntheses of various maleic acid derivatives, cyclisation reactions of maleic acid hemiamides (HA, **2**) in presence of dehydrating reagents and at reduced temperature providing preparative yields of **1**. MII (**1**) are quite stable substances to be handled without special precaution. Their structures confirm NMR, IR and MS data. GC method can be successfully used for MII analyses.



MII form corresponding maleisoimidium salts (**3**) with acids, the salts with strong acids (perchloric acid, trifluoroacetic acid, a.o.) being stable solids. These salts can be obtained also from HA and acids in the presence of dehydrating agents, e.g., with $HClO_4$ in acetic anhydride medium.

Reactions of MII (**1**) with nucleophilic reagents - amines or alcohols - allow preparing a set of corresponding maleic diamides (MD, **4**) or amidesters (AE, maleamates, **5**). Because of high reactivity, MII (**1**) or their salts (**3**) can be even regarded as activated forms of HA (**2**). Reactions of MII with amines take place without any catalyst, but reactions with alcohols need acid catalysis or exploitation of MII salts (**3**). Yields of **4** and **5** are high, and these maleic acid derivatives are mainly stable solids. They contain hydrophobic substitutes (R) at nitrogen, hydrophilic substitutes (R^1) at other nitrogen or in the ester group, and easily polymerizable C=C double bond. The last allows exploitation of **4** and **5** in copolymerization reactions with acrylic or vinyl monomers to obtain copolymers modified with surfactants, e.g., styrene or butyl methacrylate latexes with covalently bond surfactants on their surface.

SYNTHESIS OF PYRROLIZIDINES USING 1,2-OXAZINES AS STARTING MATERIAL

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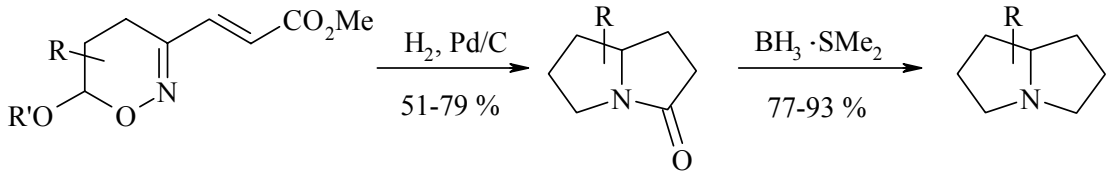
e-mail: rzimmer@chemie.fu-berlin.de

1,2-Oxazines are versatile building blocks in organic synthesis.[1] Their ring cleavage and ring transformation reactions can be used for the synthesis of a variety of nitrogen-containing heterocycles, e.g. pyrroles, proline derivatives, pyridines or indolizines.[2] We describe in the presented contribution an efficient synthesis of pyrrolizidines starting from the precursor **3** (R = H) and derivatives thereof.
1,2-Oxazines **3** with an exocyclic C,C double bond at position 3 can easily be prepared by hetero-Diels-Alder reaction of an electron-rich olefin **1** with the α-nitroso alkene **2** generated in situ from methyl (*E*)-5-bromo-4-hydroximino-2-pentenoate and base.[3]

1 **2** **3**

The synthesis of pyrrolizidines could be achieved in a two step procedure from 1,2-oxazines **3**. In the first step hydrogenolysis of different substituted 1,2-oxazines **3** with H_2/palladium on charcoal leads to the formation of pyrrolizidinone derivatives **4**. Subsequent treatment of intermediates **4** with borane dimethylsulfide complex at room temperature furnished the expected pyrrolizines **5** in good yields.[4]



3 **4** **5**

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INVESTIGATION OF HETEROCYCLIZATION OF ACETYLENYLARENES AND –HETARENES WITH VICINAL CONTAINING BIFUNCTIONAL GROUPS

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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*-bifunctional groups (COOH, $CONH_2$, $CONHNH_2$, CONHOH).

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's atoms of the triple bond.

We have showed that cyclization in benzene and azole 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.

We also investigated influence of different kind of transition metal catalysts other catalysts on the cyclization direction.

Our synthetic studies have allowed us to prepare various condensed benzo- and azolo lactones, -pyrrolidinones, -pyridinones, and -pyridazinones.

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

Fused systems formed by two 5-membered rings were not observed to form for these substrates in the given working conditions. This is correlated with our conclusions in earlier works.

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

This work was supported by grant CRDF REC-008, (2003).

ASYMMETRIC TOTAL SYNTHESIS OF ELISABETHIN A

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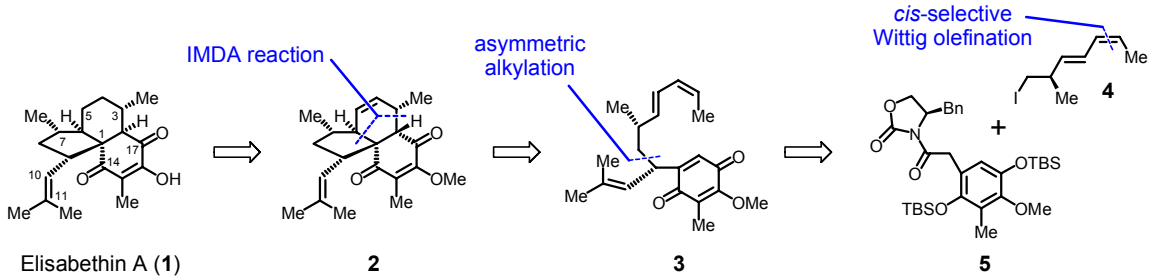
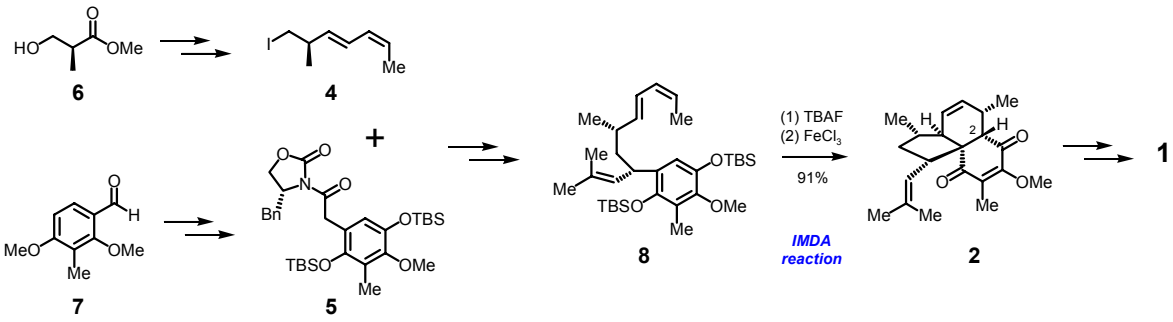
[a]Department of Organic Chemistry, University of Vienna, Austria

In the late nineties the marine diterpenoid elisabethin A (**1**) was isolated from the chemically rich Caribbean gorgonian *Pseudopterogorgia elisabethae* (Octocorallia).[1] It acts as a highly bioactive terpenoid secondary metabolite; natural products of the elisabethane class show significant activity against *Mycobacterium tuberculosis*, as well as in vitro cancer cell cytotoxicity.

According to our retrosynthetic plan (see below) the elisabethane carbon skeleton should be assembled *via* an intramolecular Diels-Alder (IMDA) cyclisation of quinone **3** which is generated by oxidation of the corresponding hydroquinoid precursor. Compound **3** is derived from the α-alkylation of imide **5** with iodide **4**.



The dienyl iodide **4** was synthesised using an eight step sequence (54% overall yield) from chiral ester **6**, while fragment **5** was obtained in nine steps (47% overall yield) from known aldehyde **7**. Alkylation of imide **5** with iodide **4** delivered stereoselectively the desired product in 86% de. Three further routine steps furnished the desired Diels-Alder precursor **8**.



Deprotection of **8** with TBAF and oxidation with aq. $FeCl_3$ resulted in the formation of quinone **3** which cyclised stereoselectively *in situ* to give adduct **2**. Selective hydrogenation of the disubstituted olefin followed by base-catalysed epimerisation at C2 and cleavage of the methyl ether led to elisabethin A (**1**).[2]

In conclusion we have accomplished a convergent and highly stereocontrolled total synthesis of elisabethin A (**1**) in 20 steps and 7% overall yield along the longest linear sequence. The synthesis is flexible and potentially allows the introduction of a variety of non-natural substituents.

[1] A. D. Rodríguez, E. González, S. D. Huang *J. Org. Chem.* **1998**, *63*, 7083-7091.
[2] T. J. Heckrodt, J. Mulzer *J. Am. Chem. Soc.* **2003**, *125*, 4680-4681.

NANOPOROUS NETWORK POLYMERS

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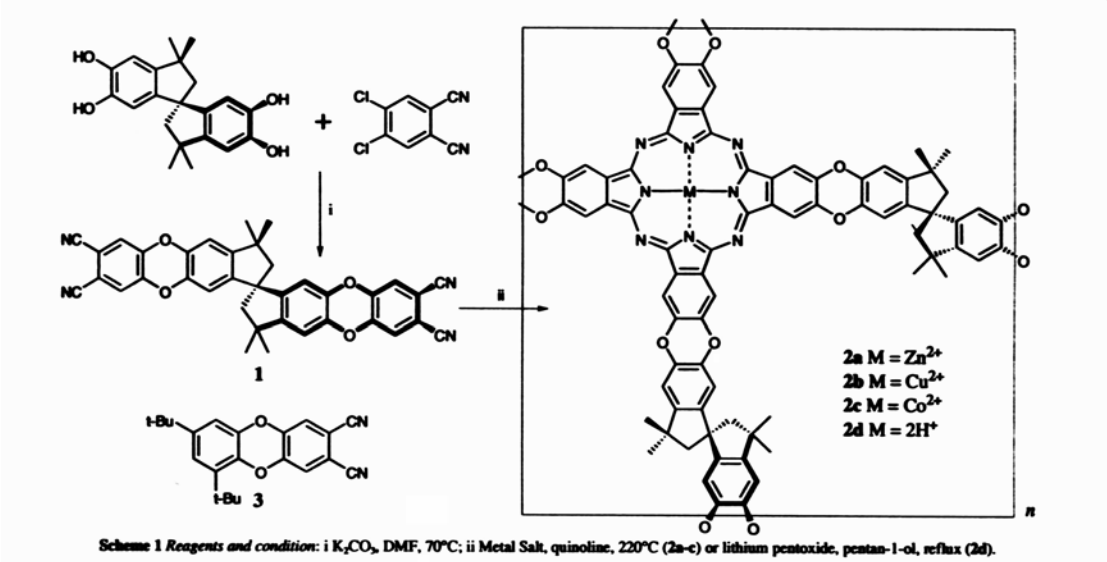
It was anticipitated that a microporous organic material would result from the covalent binding of large planar molecules via rigid spacers that contain a spiro-centre (i.e. an atom which is shared by two ring systems). The spiro-centre would ensure that the adjacent planar components are orthogonal and, therefore, the resulting network polymer should not fill space efficiently. It is important to restrict rotational freedom within the networks to ensure that the void space is not eliminated due to reorientation of the rigid components.

Phthalocyanine is a particularly desirable planar component for evaluating this concept due to its size, rigidity and stability. Also, it can play host to cations derived from over seventy elements and several metal phthalocyanines are well-established catalysts. For example, cobalt phthalocyanine is used as a homogeneous catalyst in the industrial desulfurisation of crude petroleum, a process (*Merox*) that involves the oxidation of thiols under aerobic conditions. In addition, iron phthalocyanine is a useful laboratory catalyst for several oxidation reactions including alkene epoxidation and hydrocarbon oxidations.

The required spiro-containing phthalocyanine network is derived from 5,5`,6,6`-tetrahydroxy-3,3,3`,3`-tetramethyl-1,1`-spirobisindane using the synthetic chemistry shown in figure 1. The network polymers 2 (M= H^+_2, Zn^{2+}, Cu^{2+}, Co^{2+}) are formed by heating 1 in a high-boiling solvent (e.g. quinoline) at temperatures in excess of 200 ^{0}C in the presence of the appropriate metal acetate. Nitogen adsorption measurements give BET surface areas in the range 500-1000 m^2 g^{-1} indicating a nanoporous structure.



Scheme 1 *Reagents and condition*: i K_2CO_3, DMF, 70°C; ii Metal Salt, quinoline, 220°C (2a-c) or lithium pentoxide, pentan-1-ol, reflux (2d).