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ABSTRACTS

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## The reaction of 3,4-dihidro-$\beta$-carbolines with nitrile oxides

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The tetrahydro-$\beta$-carboline ring system can be found in numerous natural and synthetic compounds having interesting biological activities. We aimed at the synthesis of novel tetracycles (harmicine-derivatives) containing two or more heteroatoms in the five-membered D ring. The reaction of 3,4-dihydro-$\beta$-carbolines (**1a-e**) with a suitable, *in situ* generated nitrile oxide (**2'**) seemed to be useful to establish the D ring of the tetracycle (**3a-e**) (Fig. 1).

By the reaction of unsubstituted 3,4-dihidro-$\beta$-carboline (**1a**) with 4-fluoro-$N$-hydroxybenzenecarboximidoyl chloride (**2**), the product (**3a**) formed was converted to an isomer (**4**), that decomposed slowly in the presence of water. To avoid this isomerisation, we tried to carry out the reaction with 1-methyl-3,4-dihydro-$\beta$-carboline under the same conditions. In this case, two products were formed, the expected tetracycle (**3b**) and a triazole-$N$-oxide derivative (**6b**). The structure of the isolated products was proved by NMR and mass spectroscopy and single crystal X-ray analysis.

Then, the reaction was carried out with the 1-ethyl-, 1-isopropyl- and 1-phenyl-3,4-dihydro-$\beta$-carbolines (**1c-e**) as well. In each case, the above mentioned types of products (**3c-e**, **6c-e**) were formed.

The summary of the reactions of **1a-e** and **2** is illustrated in Fig. 2.

Using only one equivalent of **2** the formation of the triazole-$N$-oxide (**6a-e**) could be avoided. Instead of this, the harmicine derivative (**3a-e**) was formed in quantitative yield.

Studying the reaction mechanisms, it was found, that it is not an 1,3-dipolar cycloaddition, that is a typical reaction of nitrile oxides, but rather a non concertic stepwise addition. The addition of the first equivalent of the nitril oxide molecule (**2'**) generates the tetracycle (**3a-e**). Another addition of the dipole (**2'**) to the D ring of the tetracycle (**3a-e**) forms the triazole-$N$-oxide derivative **(6b-e**).

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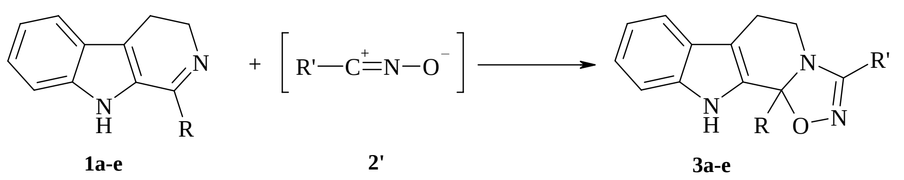
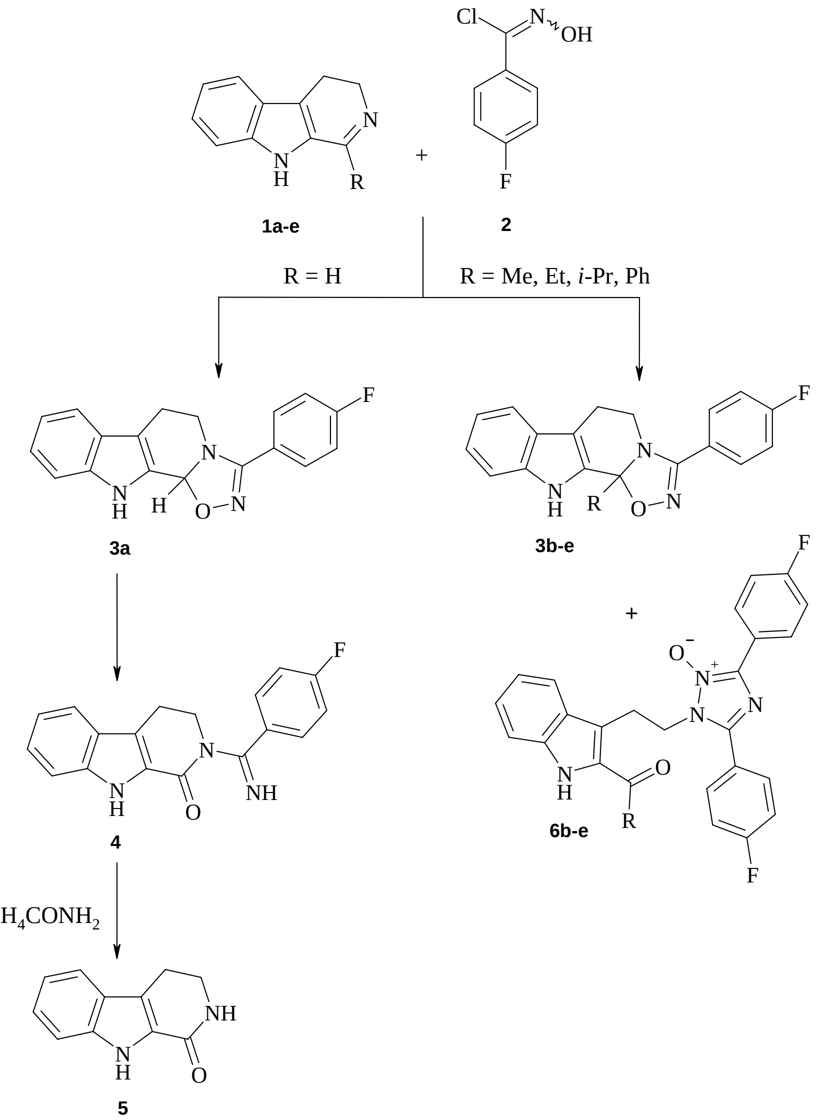
**Fig. 1.** The reaction of 3,4-dihydro-$\beta$-carbolines with the in situ generated nitrile oxide



R = H, alkyl, aryl group
R' = aryl group

**Fig. 2.** The reaction of 3,4-dihydro-$\beta$-carbolines with 4-fluoro-$N$-hydroxyben



## Synthesis of difunctionalised 1-[2-(trifluoromethyl)phenyl]pyrrole derivatives

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In the last decade, synthesis and characterisation of numerous new 1-arylpyrrole derivatives have been accomplished at the Department of Organic Chemistry and Technology.

In the framework of that ongoing project we have developed three new methods for the synthesis of difunctionalised, chiral 1-[2-(trifluoromethyl)phenyl]pyrrole (**1**) derivatives (Fig. 3).

First, a new resolution method was applied for separation of the enantiomers of dicarboxylic acid **2**, then selective transformations of the two carboxylic functions were accomplished. Thus, optically active dimethyl ester was prepared (**3**, R$^3$=R$^4$= COOMe) then the benzoic acid ester function was selectively hydrolyzed. The half ester – half acid derivative (**3**, R$^3$= COOMe, R$^4$= COOH) was transformed into new, optically active aminoalcohol derivatives (**3**, R$^3$= CH$_2$-NR$^5_2$, R$^4$= C(R$^6_2$)OH) via several chemical steps.

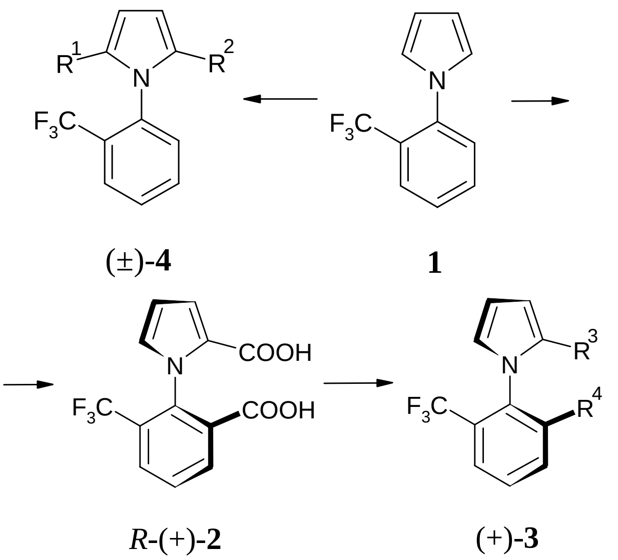

Fig. 3.

Second, brominating agent ($BrCH_2CH_2Br$) was used as electrophilic reagent after dimetalation of **1** for preparation of 2-bromo-[1-(2-bromo-6-trifluoromethyl)phenyl]pyrrole (**3**, $R^3$=$R^4$= Br) which is a versatile intermediate for the preparation of other new chiral 1-arylpyrrole derivatives.

Third, dibromination of compound **1** was carried out and the 2,5-dibromo derivative (**4**, $R^1$=$R^2$= Br) was isolated in high yield. This compound was also transformed into new chiral 1-arylpyrrole derivatives using consecutive bromine/lithium exchange, electrophylic addition reactions. Thus, a new chiral phosphine (**4**, $R^1$= $PPh_2$, $R^2$= Br) was also synthetised.

### Development of flame retardant polymer systems for landfill application produced by up-cycling of polymer waste

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Landfills have to be extended because of high volume of polymers, originated from automotive, electronic industry and household consumption. In Hungary many landfills can not fulfil the requirements and do not correspond neither to the Hungarian nor to the European Union regulation and therefore should be closed. During the planning of landfills, choosing and producing the adequate materials for covering is one of the highest challenges for researchers. Besides the good mechanical, water and gas barrier properties the geomembranes should be flame retarded in order to protect against spontaneous combustion, which can cause huge disasters. These two research areas can be connected by producing polymer elements for landfill application, made of recycled plastic waste, in order to replace as much primary materials as possible. The composition of the plastic waste (originated from automotive industry and separated by density) was analysed by FTIR spectrometry. Rendering the materials flame retarded, intumescent additives were used containing recycled polyurethane waste. Two different test specimens were produced. Recycled basalt fiber and multi-layer-system (sandwich structure) was applied when the mechanical resistance was the most important parameter, while in the case when the flexibility had higher importance, one-layer-system had been developed using recycled ground tyre rubber. The flammability of all systems was significantly reduced, while their mechanical properties were maintained. In case of one-layer-system the ratio of the recycled materials reached 48%, whereas in case of multi-layer-system 81% was also available. Development of functional polymer systems from plastic waste can be one of the solutions for diminishing the amount of the deposited polymer waste.

### Investigation of mineral-type catalyst modified with metal ions in organic syntheses

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In the last decades an important aim in the organic chemical research work is the development of new catalysts or reagents which are more active, selective, recyclable or reusable, and environmentally more benign than the traditional acid-base catalysts. In the recent research activities the different mineral-based catalysts, such as natural and modified clay minerals, zeolites, mixed oxides play the key role.

A research group of the Department of Organic Chemistry and Technology works on the investigation of the applicability of different solid acid and solid base catalysts in organic chemical syntheses for years. During this work a number of methods were elaborated, thus, e.g. a new magnesium-lanthan mixed oxide modified with palladium (Pd/MgLa) was developed and was applied successfully in carbon-carbon coupling reactions (*e.g.* Heck-, Sonogashira-, Suzuki-reactions).

Continuing this work first we tested this Pd/MgLa catalyst in the reaction of amines and aryl halides (Buchwald-reaction).

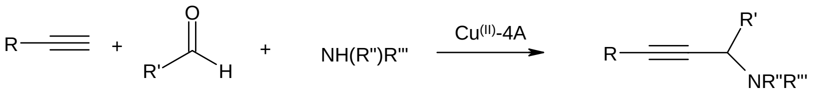

Fig. 4.

We found that under the reaction conditions the amines form a complex with the palladium, thus the catalyst will be inactive in the Buchwald-reaction.

Next we examined other metals on different supports. We found that copper supported on the quite strong base 4 Å molecular sieve is a good catalyst in the coupling of alkynes with amines and aldehydes ($A^3$-coupling, Fig. 4). The reactions were made at room temperature without solvent. Secondary amines gave excellent yield with phenylacetylene and paraformaldehyde, while aromatic amines did not react. Aromatic aldehydes gave moderate yield. The catalyst was easily recoverable and reusable without any significant loss of acitivity.

X-ray fluorescence investigations of the products showed that they do not contain appreciable amount of copper. This is advantageous from environmental point of view, and a proof of a real heterogeneous reaction.

Using ketones such as acetone or acetophenone instead of aldehydes the desired $A^3$-type coupling didn't occurred but we observed a Glaser-type autocoupling of phenylacetlyene.

We tested other supports modified with copper such as more and less acidic clay minerals. We found that these catalysts can be used in the hydroarylation of alkines, but in contrast with the catalysts described in the literature the yield was quite low and the reaction was not regioselective.

## Growth pattern analysis in cell cycle mutants of fission yeast

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In the first half of the $20^{th}$ century yeasts have become model organisms in cell cycle studies. Since the late 1950s *Schizosaccharomyces pombe* (fission yeast) has been spotlighted through its favourable physiological features, for example, its symmetrical division enables good synchronisation techniques. The cylindrically shaped fission yeast cells grow exclusively at their tips almost from birth to division by maintaining a constant diameter, therefore cell length is approximately proportional to cell volume. As a consequence, cell length is an easily measurable parameter, which characterizes cell age. Length growth patterns may therefore indicate connections between volume changes and cell cycle events. The classical method to study the growth of individual cells is time-lapse microphotography; cells are growing on the surface of an agar pad in a thermostated photomicroscope, and later on the growth pattern of cell length can be simply studied by a projector. A size control acts in every cell cycle so that cells have to more or less double their volumes during their cell cycles as to keep the size of the cells constant. With further analyses of growth patterns we are able to estimate the position of this size control.

In different cell types, there is considerable controversy concerning the exact growth profile of size parameters during the cell cycle. Linear, exponential and bilinear (i.e., two linear segments with a Rate Change Point (RCP)) models are commonly considered, and the same model may not apply for all species. Selection of the most adequate model to describe a given data-set requires the use of quantitative model selection criteria, which are suitable for comparing differently parameterized models. Recently, data of length increase from individual fission yeast cells, measured on time-lapse films have been reanalysed using these model selection criteria. A linearised biexponential model (called bilinear) was developed, which makes a smooth, continuously differentiable transition between two linear segments possible.

I have measured the length growth pattern of 120 fission yeast cells, namely 60 *cdc2-3w cdc25*$\Delta$ double mutant and 60 *cdc2-3w cdc25*$\Delta$ *pyp3*$\Delta$ triple mutant ones. The above mentioned model selection criteria were used for discriminating among linear, exponential and bilinear models and selecting the most adequate one in the case of all these cells' length growth patterns. Although relatively small differences were found in several cases, essentially all the quantitative selection criteria considered here indicated that the bilinear model was generally more adequate than either the exponential or the linear ones. At least the half of the cells had a bilinear growth pattern. "Average cells" were also constructed from all the individual cells' data for both strains, whose patterns were definitely found to be bilinear by any criterion used. In these mutants size control seems to act after RCP, in late $G_2$. This is in sharp contrast to wild type cells, but confirms our former results.

## Electrospun nanofibers for pharmaceutical technology

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Nowadays one of the largest challenges in the field of pharmaceutical technology is the enhancement of drug release from orally taken solid dosage forms as most of the recently developed Active Pharmaceutical Ingredients (APIs) have poor water solubility [1]. In the period of nanotechnology there are new possibilities to improve dissolution of these already developed and candidate drug molecules. Electrospinning is a relatively new technique in the field of pharmaceutical technology and it was mainly applied to achieve sustained drug release [2].

In this work DonepezilHCl with good water solubility and Carvedilol with poor water solubility were used as model drugs to investigate the capabilities of electrospun materials to improve the dissolution rate.

Poly(vinyl-alcohol) (PVA) and poly(vinyl-pyrrolidone) (PVP) were dissolved in water or in methanol with the model drugs and these solutions were electrospun onto carriers. Morphology of the samples was investigated by AFM, SEM and optical microscopy. Chemical properties and crystal morphology were characterized by Raman-microscopy, FT-IR, DSC and XRPD. In vitro drug release was followed by UV-VIS spectrometry.

The diameters of obtained fibres were 100-200 nm in the case of PVA, while the drug loaded PVP fibres were somewhat thicker 500-900 nm. The electrospun samples were dissolved by water immediately and drug release time was no more than half minute. Dissolution time of the other “traditional” films was more than half an hour, which is much longer than that of electrospun mats. According to XRPD, Raman-microscopy, FT-IR and DSC investigation the APIs were in amorphous state in the polymer matrix.

This work shows that this technique is able to fabricate mats with ultra-fast drug release from poorly water soluble drug (Carvedilol) and the production in industrial scale is available because it was carried out in the recent years in the textile industry.

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## Structure and bonding in pentacoordinated main group elements

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The relatively high stability of pentacoordinate silicon and phosphorus compounds has a big influence on the reactivity of these elements, providing easier access to e.g. nucleophilic substitution reactions. This different behavior plays an important role in the hydrolysis of polyphosphates in biochemistry, and results even in synthetic chemical applications, such as the fluoride-induced removal of protecting silyl groups. However, despite their importance in the chemistry of third and fourth row elements, no detailed, comprehensive experimental or theoretical study has been published yet.

In this computational approach $EH_4X$ (E: $Si^-$, $Ge^-$, P, As, $S^+$, $Se^+$; X: -H, -F, -OH, $-NH_2$, $-CH_3$) type pentacoordinate compounds have been investigated by density functional (B3LYP, MPW1K, PW91) and perturbation (MP2) methods, to explore the different electronic effects that influence the structure of such compounds.

According to the NBO analysis and the changes in the planarity of the amino group, the energy difference between the equatorially and axially substituted trigonal-bipyramids is highly influenced by the difference in electronegativity between the central atom and the ligand, hyperconjugation, and in case of ligands having a lone electronpair $n \rightarrow \sigma^*$ donation as well.

The ability to form pentacoordinated structures has been evaluated by the energy of the hypothetic hydrogenation of the corresponding tricoordinated derivatives. The reaction energies show that electronegative ligands and electropositive central atoms increase the stability of the compound.

## Is industrial wastewater worth pretreating?

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In order to meet the directives of the EU, our most important duties have been to ensure the treatment of the utmost fraction of our wastewaters as well as the modernization and optimization of existing WWTPs (Wastewater Treatment Plants). Associated is the requirement to achieve the limit values in the sewer system for industrial wastewaters, too. Thus, a lot of industrial plants are forced to build pretreating technologies at high costs, where the addition of e.g. external nitrogen and phosphorous sources is necessary for the appropriate elimination of the carbon sources. This solution, besides the high investment costs, leads to increased operational costs as well. Moreover, due to the varying wastewater quality it often results in overdosing, that has to be eliminated in the subsequent domestic WWTP.

On the other hand, the increase of water prices and the recent economical difficulties led to the decrease of water consumption, and as a result, the residence time of domestic wastewater in the sewer system has increased. Therefore, especially in the summer periods, the readily biodegradable carbon sources may already be eliminated in the sewer system, thus the C:N ratio in the domestic treatment plant influent wastewater tends to be unfavorable, which leads to requirement of dosing high-cost external carbon sources for the appropriate denitrification (the final step of nitrogen elimination, production of nitrogen gas from nitrate).

In the research the possibilities of improving the performance of the Törökbálint WWTP, and in this context, the effects of the wastewater of Eismann Ltd., a firm producing ice cream, have been studied. It has been a common practice to originate the problems of communal WWTPs from the influent industrial wastewater. Thus, the elimination of these industrial inlets is thought to be a solution of the troubles. During the experiments it has been studied, whether in this particular case this assumption is true or not. In order to reveal the causes of the present problems at the plant, review of some former data (01. 2006 – 02. 2009), and on-site concentration-profile measurements to track the ongoing bioreactions have been carried out. Consequently with the help of computer simulations possibilities of enhancing nitrification and denitrification have been examined. Based on the simulation results and the analysis of the data, the following conclusions have been drawn. Although high Dissolved Organic Carbon (DOC) content in the industrial influent may significantly hinder the nitrification process under the present poor aerating conditions, after the installation of a pretreatment plant addition of an external carbon source is needed for the denitrification process. Thus, instead of building of a high-cost pre-teratment facility, the improvement of the domestic WWTP's aeration efficiency and the improvement of the bioreactor-arrangement, requiring only minimal costs, provide the real, cost-effective and long-term reliable solution.