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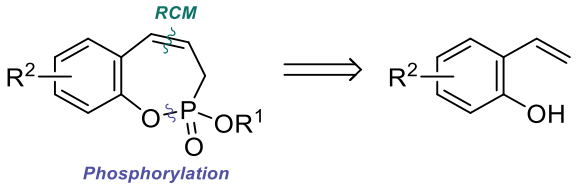
DEVELOPMENT OF BENZOXAPHOSPHEPINE 2-OXIDES AS CARBONIC ANHYDRASE INHIBITORS

Anastasija Balašova[1,2], Raivis Žalubovskis[1,2]

[1]*Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
[2]*Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, Paula Valdena iela 3/7, Riga, Latvia*
e-mail: balasova@osi.lv

Carbonic anhydrases (CA, EC 4.2.1.1) are essential metalloenzymes found across all kingdoms of life. These enzymes are involved in many important physiological processes, as they catalyse the reversible hydration of carbon dioxide [1]. To date, 15 different human CA isoforms have been identified, out of which CA IX and XII isoforms are highly overexpressed in different tumour types and may contribute to the progression of cancer [2]. Therefore, there is a particular need to develop potent and selective CA inhibitors.

Herein we report our results on the development of a new class of CA inhibitors — benzoxaphosphepine 2-oxides. Aforementioned compounds showed a remarkable selectivity and good activity against the tumour-associated isoforms CA IX and XII [3]. Furthermore, these compounds can be used as starting points for the design of more potent CA IX/XII inhibitors.



Acknowledgements

This project has been supported by the European Social Fund within the Project No 8.2.2.0/20/I/008 and by the Latvian Institute of Organic Synthesis under internal student grant IG-2023-09.

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ACRAB-TOLC EFFLUX PUMP INHIBITOR ANALOG SYNTHESIS

Laura Pauniņa[1], Cristina Durante Cruz[2], Marina Madre[1], Tania Szal[3], Päivi Tammela[2], Aigars Jirgensons[1], Björn Windshügel[3], Jānis Veliks[1]

[1]Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia
[2]Drug Research Program, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, Finland P.O. Box 56 (Viikinkaari 5E), FI-00014, Helsinki, Finland
[3]Discovery Research ScreeningPort, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Schnackenburgallee 114, 22525 Hamburg, Germany
e-mail: laura.paunina@osi.lv

Bacterial resistance to the existing classes of antibiotics is one of the most important challenges for the future healthcare system and bacterial cells efflux pumps play an important role for this internal drug resistance. To reduce the ability of the efflux pumps binding to medication substrates, the molecules called efflux pump inhibitors are used to rejuvenate the antibiotics activity by binding to the efflux pump protein [1].

In the framework of the project, it was hypothesized that AcrAB-TolC efflux pump outer membrane protein TolC in Gram-negative E.coli bacteria cells could represent an attractive drug target. Therefore, structure analogs of known clinical candidate compound have been synthesized and identified their structure-activity relationships (SAR) to TolC efflux pump [2].

Acknowledgements

This project was supported under the framework of the JPIAMR – Joint Programming Initiative on Antimicrobial Resistance. B.W. was supported the German Federal Ministry for Education and Research (01KI1827A). A.J. was supported by the state education development agency (1.1.1.5/ERANET/19/03), C.D.C and P.T. were supported by the Academy of Finland (Grant no. 326261).

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SYNTHESIS OF POTENTIAL IRE1A INHIBITORS

Jānis Šadauskis[1,2], Igors Kļimenkovs[2], Edgars Sūna[1]

[1]*Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
[2]*University of Latvia, Faculty of Chemistry, Jelgavas iela 1, Riga, Latvia*
e-mail: janis.sadauskis@lu.lv

Cancer has a major impact on society around the world and it is one of the leading causes of death. IRE1α is an enzyme that plays a part in the development of certain cancers, such as breast cancer, colon cancer, and prostate cancer. IRE1α inhibitors might be used to treat these types of cancer. [1]

The aim of this study was to find IRE1α inhibitors that would have a greater selectivity and bioavailability than the previously discovered ones. Based on computational data about the activity of compound 4f, it was chosen as the model compound for further synthesis.

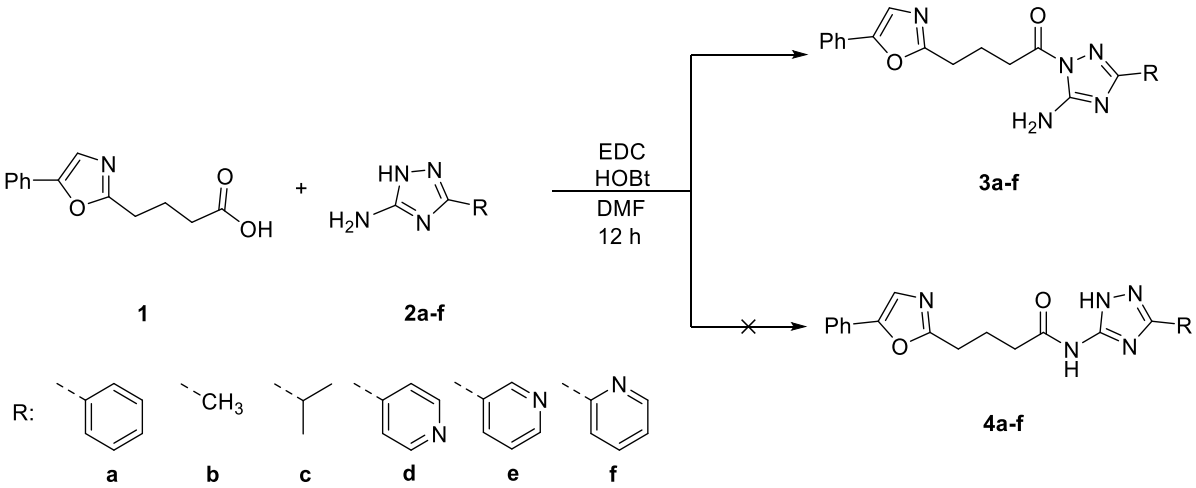

Fig. 1. Synthesis of target compounds **4a-f**.

The reaction used for the synthesis of compound 4f and its analogues was found to yield endocyclically acylated 1,2,4-triazol-5-amines instead of the anticipated exocyclically acylated compounds, but isomerization of endocyclically acylated 1,2,4-triazol-5-amines yielded exocyclically acylated compounds. However, limited hydrolytic stability of compounds 3a-f suggested that the inhibitory activity of these compounds could be mainly due to the presence of compounds 2a-f in solution. Indeed, compound 2f had the greatest ability to inhibit IRE1α out of all the synthesized compounds.

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SYNTHESIS OF QUINAZOLINES AND INDAZOLES FROM

Vitalii Solomin[1,2], Darija Zaharova[2,3]

[1]*Riga Technical University, Paula Valdena iela 3, Riga, Latvia*
[2]*Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
[3]*University of Latvia, Faculty of Chemistry, Jelgavas iela 1, Riga, Latvia*
e-mail: vitalijs.solomins@osi.lv

New mild methods for the synthesis of indazole and quinazoline has been studied and developed. Using novel protocols, 2-formylphenylboronic acids **1** can be converted to the heterocycles of interest in a good yield.

For quinazoline **3** synthesis, guanidines and amidines **2** can be used [1]. Reaction proceeds in alcoholic media with Cu(I) iodide as a catalyst (Chan-Evans-Lam reaction conditions [2]).

With dialkyl azodicarboxylates **4** and dialkyl hydrazinedicarboxylates **5** *N*-protected indazoles **6** can be synthesized [3]. Two-step protocol involves coupling, mediated by Cu(II) acetate, with subsequent one-pot conversion of formed semi-product to indazole in acidic media.

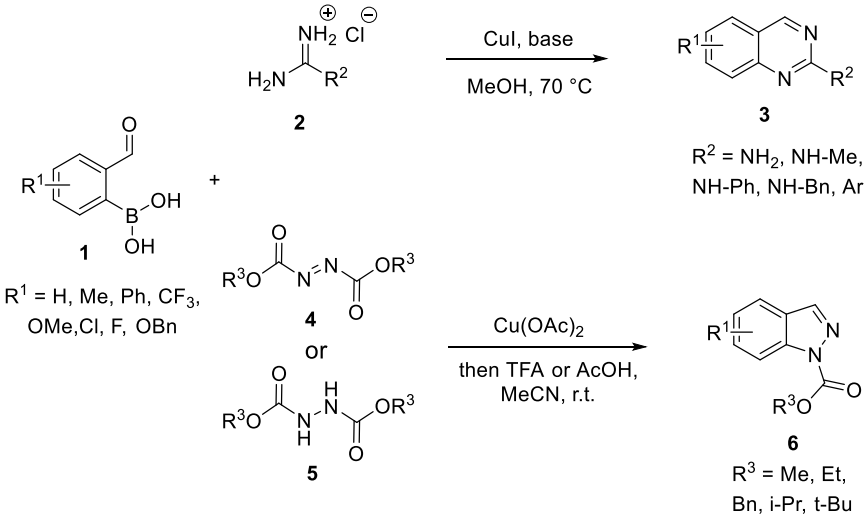

Fig. 1. Synthesis of quinazolines and *N*-protected indazoles.

Present approach suggests 2-formylphenylboronic acids as a multi-purpose building blocks for a convenient access towards fused nitrogen-containing heterocycles.

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AZIDE-TETRAZOLE EQUILIBRIUM IN PYRIDO[3,2-*D*]PYRIMIDINES

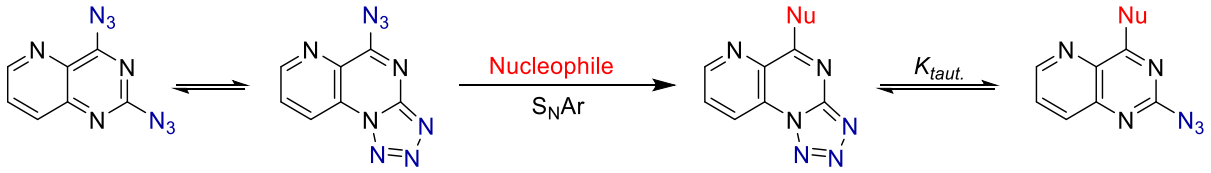
Kristaps Leškovskis[1], Irina Novosjolova[1], Māris Turks[1]

[1]*Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena Str. 3, Riga, LV 1048, Latvia*
e-mail: kristaps.leskovskis@rtu.lv

Heterocycles with an azido-azomethine structural entity are interesting due to their intrinsic dynamic azide-tetrazole tautomeric equilibrium in the solution phase [1] alongside rich azide functional group chemistry [2].

Herein, a method for the synthesis of 5-substituted tetrazolo[1,5-*a*]pyrido[2,3-*e*] pyrimidines from 2,4-diazidopyrido[3,2-*d*]pyrimidine in S_NAr reactions with *N*-, *O*-, and *S*- nucleophiles is presented [3]. The tetrazolo[1,5-*a*]pyrimidine derivatives can be regarded as 2-azidopyrimidines due to present azide-tetrazole valance tautomerism and functionalized in copper(I)-catalyzed azide-alkyne dipolar cycloaddition (CuAAC) and Staudinger reactions.

Equilibrium constants and thermodynamic values were determined using variable temperature ^{1}H NMR and were found to be ΔG_{298} = −3.33 to −7.52 (kJ/mol), ΔH = −19.92 to −48.02 (kJ/mol) and ΔS = −43.74 to −143.27 (J/mol·K). The negative Gibbs free energy values assert tetrazole as the major tautomeric form in solutions. Furthermore, the key starting material 2,4-diazidopyrido[3,2-*d*]pyrimidine shows a high degree of tautomerization in different solvents presenting up to 7 tautomeric forms.



Scheme 1. Azide-tetrazole equilibrium guided S_NAr reaction of azidopyrimidines.

Acknowledgements:

The authors thank the Latvian Council of Science Grant LZP-2020/1-0348 for financial support. K.L. thanks the European Social fund within project Nr. 8.2.2.0/20/I/008.

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SYNTHETHIC pathways TOwards PURINE derivative as a potential MOLECULAR SYSTEM FOR THE PHOTO-CATALYSIS

Aleksejs Burcevs, Irina Novosjolova

Riga Technical University, Faculty of Materials Science and Applied Chemistry, P. Valdena str. 3, Riga, Latvia
e-mail: aleksejs.burcevs@rtu.lv

Fluorescent purine derivatives have a variety of uses in analytics, such as metal ion [1] and pH sensors [2], as well they are used for cell imaging [3] and as photo-catalysts [4].

Target purine compound **2** was designed with an aim to be used as a potential system for photo-catalysis. For the synthesis of **2**, derivatization of *C*(6), *C*(8) and *N*(9) positions of 6-chloropurine (**1**) with **A**, **B** and **C** moieties is required. Several synthetic pathways were designed and have been tested. In the end, target compound **2** was obtained, using the combinations of S_NAr, S_N2, CuAAC, C-C metal catalyzed coupling, alkylation and Mitsunobu reactions and these results will be discussed.

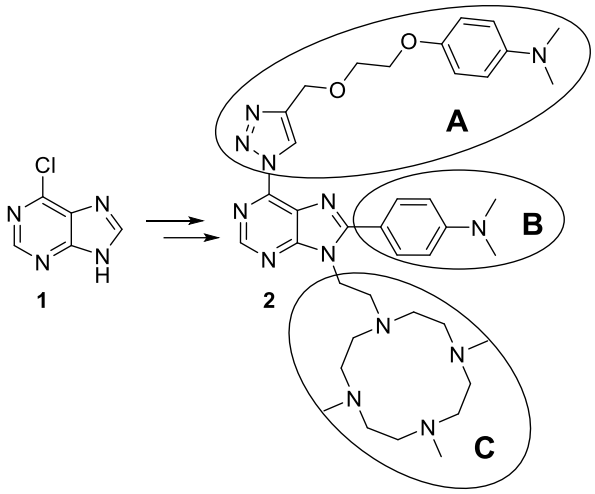

Fig. 1. Starting material **1** and target compound **2**.

Acknowledgements:

The authors thank MEPS co-project LV-LT-TW/2022/9 for financial support.

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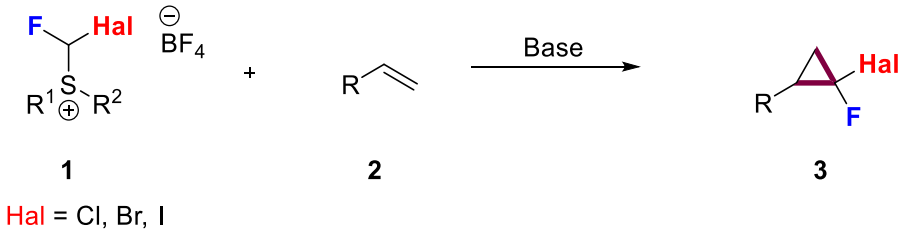
FLUOROHALOMETHYLSULFONIUM SALTS AS A NOVEL FLUOROHALOCARBENE SOURCE

Artūrs Sperga, Jānis Veliks

Latvian Institute of Organic Synthesis, Aizkraukles street, 21, Riga, Latvia
Riga Technical university, Faculty of Materials Science and Applied Chemistry 3/7 Paula Valdena Street, Riga, Latvia
e-mail: arturs.sperga@inbox.lv

Synthesis of fluorine containing molecules is of great interest due to its unique properties and vast application in pharmaceuticals, agrochemicals and materials [1].

Previously in our group we have developed fluoromethylene transfer from fluromethylsulfonium salts [2, 3]. Herein we wish to report preliminary results on synthesis of reagents **1** and its initial application in carbene transfer reaction (Scheme 1).



Scheme 1. Alkene cyclopropanation with fluorohalomethylsulfonium salts.

We have found that functionalized sulfonium salts – fluorohalomethylsulfonium reagents **1** are efficient source of fluorhalocarbene under basic conditions and they undergo unactivated alkene **2** cyclopropanation to deliver fluorohalocyclopropanes **3**.

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DESIGN OF S AND SE CONTAINING NUCLEOPHILIC CATALYSTS

Oto Filipsons[1,2], Artis Kinēns[1,2]

[1]*Latvian institute of organic chemistry, Aizkraukles iela 21, Riga, Latvia*
[2]*University of Latvia, Faculty of Chemistry, Jelgavas iela 1, Riga, Latvia*
e-mail: otofilipsons@osi.lv

Pyridine and its derivatives are often used as effective nucleophilic catalysts for reactions such as *the Baylis-Hillman* reaction, acyl group transfer reactions and others. A noteworthy example is DMAP which is a widely known acylation reaction catalyst. Alcohol acylation reactions can also be catalysed by isochalcogenurea derivatives which exhibit a 1,5-O···Ch interaction in the acylated intermediates [1]. Similar chalcogen bonding interactions haven`t been investigated in DMAP-type catalysts.

In this research chalcogen containing DMAP-type catalysts were synthesized. Activities of the newly obtained catalysts were determined by performing an acylation reaction of a sterically hindered secondary alcohol (Figure 1). Experiments show that introducing a substituent at the C-2 position significantly decreases the catalytic activity which was expected and has been previously reported [2]. Importantly, it was observed that the activity of sulfur-containing catalysts increases with increasing electron donating ability of the C-4 substituent of pyridine, but the opposite trend was observed for selenium-containing catalysts.

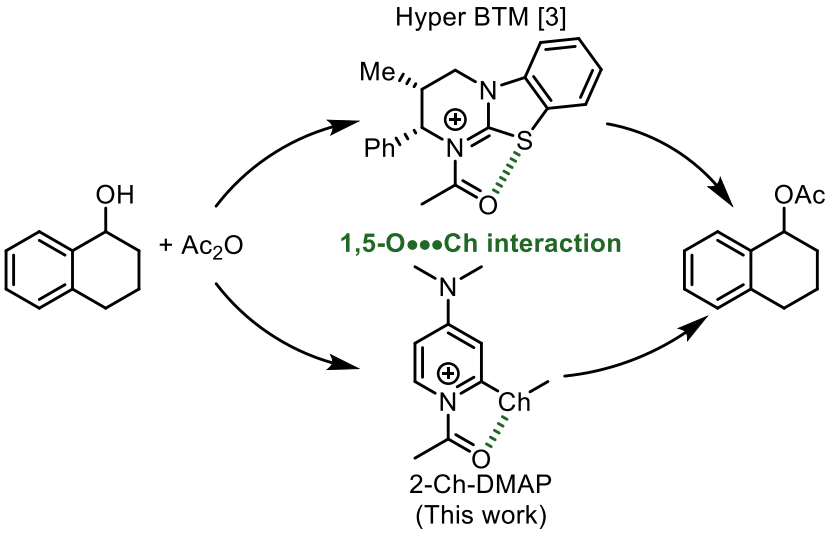

Fig. 1. Acylation of a sterically hindered 2° alcohol using Lewis base catalysis.

References:

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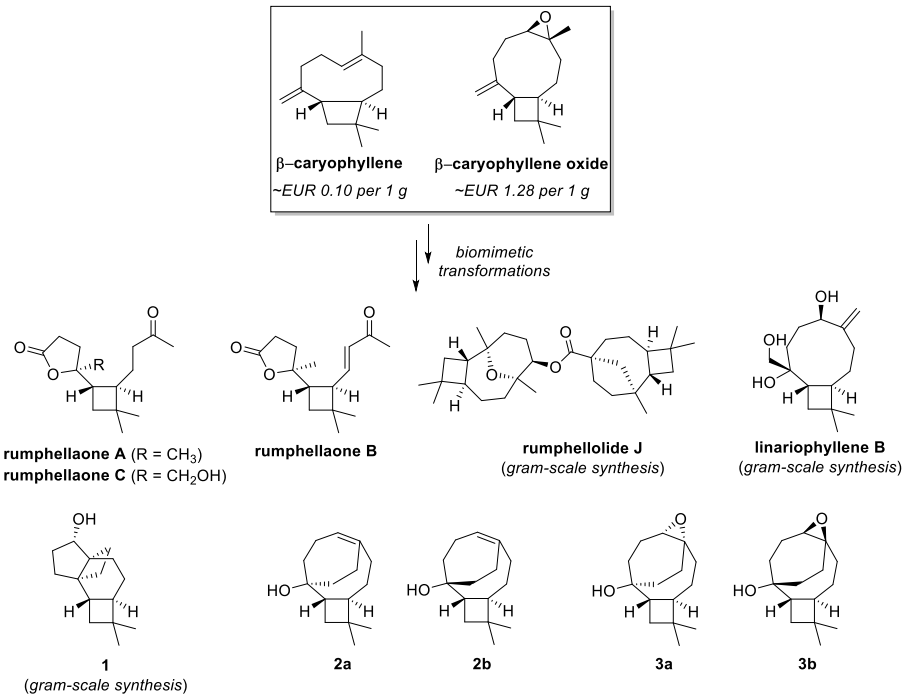
SYNTHESIS OF LOW-ABUNDANCE SESQUITERPENOIDS FROM B-CARYOPHYLLENE

Georgijs Stakanovs[1], Dace Rasiņa[1], Aigars Jirgensons[1]

[1]*Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
e-mail: georgijs.stakanovs@osi.lv

β-Caryophyllene is one of the most abundant sesquiterpenes found in nature, therefore it is available at low price from several commercial sources. The unusual structure of β-caryophyllene with two stereodefined chiral centers renders this terpene an attractive renewable starting material for the access of diverse high value compounds.

We demonstrate that β-caryophyllene and its oxide can be used in synthesis of biologically active sesquiterpene lactones rumphellaones A-C [1], disesquiterpenoid rumphellolide J [2], and linariophyllene B (scheme 1). In our ongoing research we show that rare structural units, such as propellane **1**, bridgehead olefins **2a,b** and epoxides **3a,b** (scheme 1) can be prepared from β-caryophyllene in a stereoselective fashion [3]. Such compounds can serve as reference standards for the analysis of constituents of various plant extracts. The biomimetic transformations employed in several chemical steps elucidate the possible biosynthetic route towards natural sesquiterpenoids. Structures of final products were unambiguously confirmed by single crystal X-ray diffraction analysis.



Scheme 1. Diverse semisynthesis of natural products from β-caryophyllene and its oxide

References:

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[3] Manuscript in preparation

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THE SYNTHESIS OF OCTAHYDROINDOLOQUINOLIZINES VIA IODINE-PROMOTED OXIDATION/BISHLER-NAPIERALSKI CYCLISATION SEQUENCE

Niklāvs Ūdris[1], Gints Šmits[1]

[1]*Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga, Latvia*
e-mail: niklavs@osi.lv

Octahydroindoloquinolizine is a common structural motif in corynanthe-type indole alkaloids. These natural products possess a broad scope of pharmacological activities. Members of this natural product family are known to be α_1-adrenergic and opioid receptor antagonists as well as exhibit cytotoxicity in various cancer cell lines.

Octahydroindoloquinolizines are typically prepared *via* Bishler-Napieralski or Pictet-Spengler cyclization reactions. In course of our studies, we found that these transformations are often low yielding and sluggish on structurally complex substrates and alternative mild protocols are highly desirable. After an extensive screening of reaction conditions, we found that elemental iodine [1] is a good oxidant for the preparation of lactams **3** in good yields starting from the corresponding tertiary amines **1c**. These intermediates **3** were further subjected to mild Bishler-Napieralski cyclization conditions furnishing the target octahydroindoloquinolizines. Interestingly, in the unprotected **1a** or TBS-protected substrates **1b** indole ring tends to oxidize first leading to spirocycles **2**.

The mechanistic aspects of the developed reaction sequence as well as its application in the total syntheses of corynanthe-type indole alkaloids will be presented.

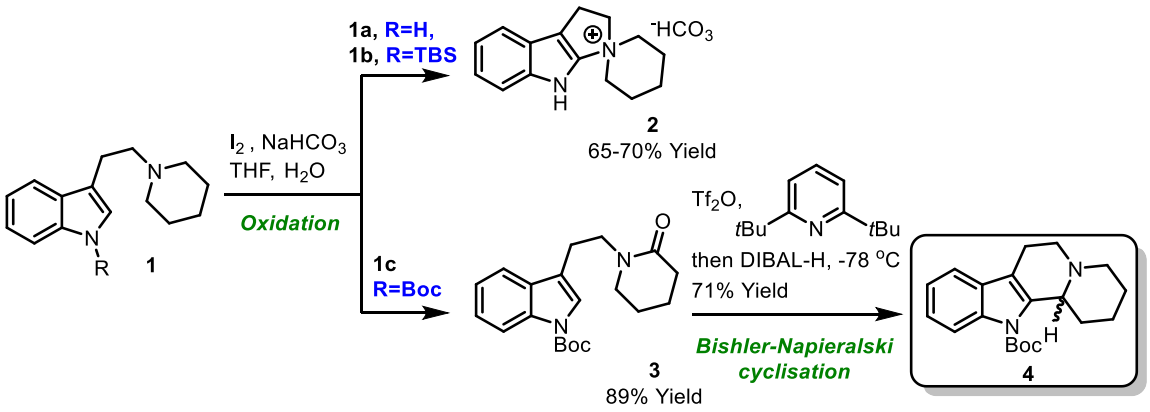

Fig. 1. Octahydroindoloquinolizine preparation *via* iodine-promoted oxidation/ Bishler-Napieralski sequence

Acknowledgements:

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C-H ARYLATION OF PENTACYCLIC TRITERPENOIDS

Vladislavs Kroškins, Jevgeņija Lugiņina, Māris Turks*

Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena str. 3, Riga 1048, Latvia.
e-mail: vladislavs.kroskins@rtu.lv

Naturally abundant pentacyclic triterpenoids are significant secondary metabolites which have aroused huge interest by possessing wide range of remarkable biological activities such as antitumor[1] antidiabetic [2] anti-inflammatory [3] and antiviral activities [4]. Oleanolic, ursolic acids and betulin, are the most recognizable compounds of this branch, which are isolated from various plants. The aim of this work is to obtain novel triterpenoic derivatives by C-H arylation at C(22). For this purpose, precursors bearing picolinic amide directing groups were synthesized.

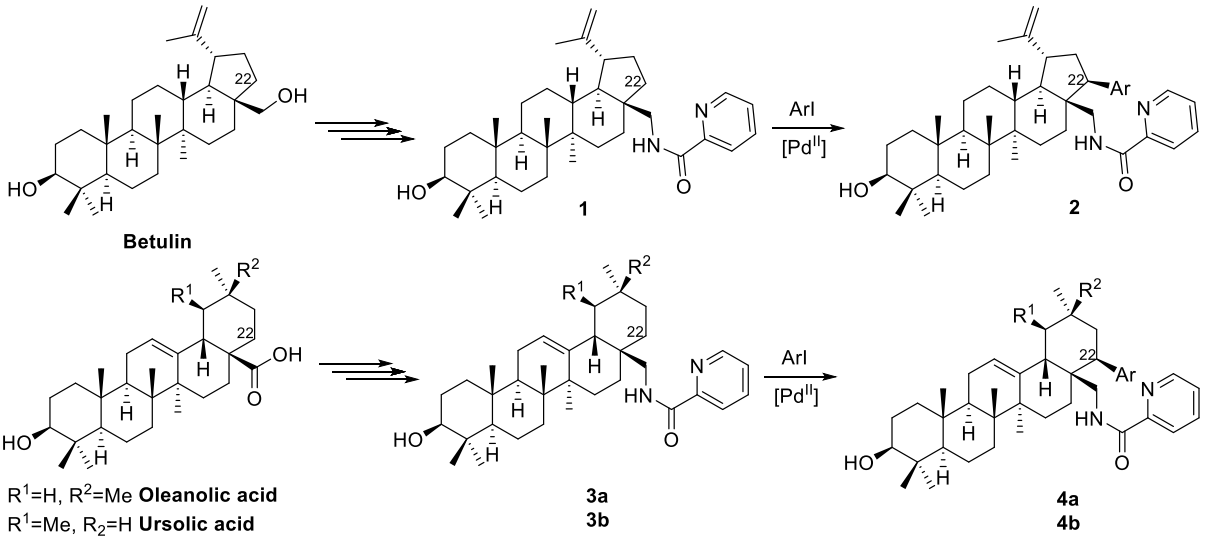

Fig. 1. C-H activation of betulin, oleanolic acid and ursolic acid.

Obtained picolinic amides **1**, **3a**, **3b** were successfully combained with aryl iodides employing Daugulis conditions and C-H arylated products **2**, **4a**, **4b** were obtained [5].

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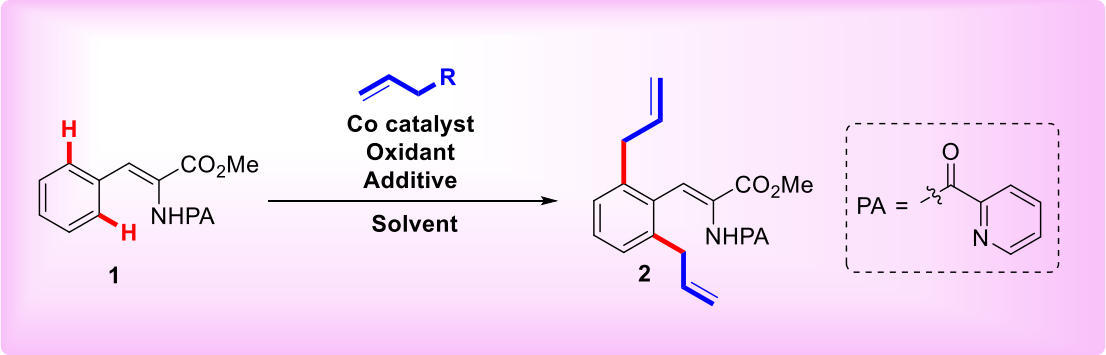
COBALT-CATALYZED C(sp^2)-H BOND ALLYLATION

Emīls Edgars Bašēns, Aleksandrs Čižikovs, Liene Grigorjeva

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia
e-mail: emils.edgars.basens@osi.lv

In the last couple of decades, high-valent cobalt catalysis has been used as a valuable tool for C-H bond activation and functionalization.[1] The use of cobalt(II) salt catalysts in combination with bidentate directing groups has proven to be an effective strategy for various C-H bond transformations.[2,3] With cobalt being less expensive alternative to noble metals, it also displays unique reactivity and regioselectivity.[4]

Allyl- functional groups are important in organic synthesis as they open the door to many further modifications of the substrate. Employing cobalt catalyzed C-H bond allylation on amino acid derivatives **1**, it is possible to utilize cheap reagents to obtain useful building blocks for other synthetic applications. Using optimization of cobalt catalysts, solvents, oxidants, additives and allylation reagents we were able to obtain diallylated phenylalanine derivative **2** in good yield.



Scheme 1. Current work on allylation of phenylalanine derivatives **1**

Acknowledgments:

This research is funded by Latvian Institute of Organic synthesis internal grant Nr. IG-2023-05.

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EXPLORING THE REACTIVITY OF C(sp^2)-H ACTIVATED AMINO ACID COBALT COMPLEXES: A FACILE ROUTE TOWARDS INDOLES

Aleksandrs Čižikovs, Liene Grigorjeva

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia
e-mail: aleksandrs.cizikovs@osi.lv

In the last few decades transition metal-catalyzed direct C-H bond functionalization has served as a valuable tool for the construction of complex molecules from more simple starting materials, mainly due to its atom- and step-economical nature.[1] Nowadays, the field of third row transition metal catalyzed C-H functionalization is being extensively studied as a cheaper and attractive alternative to noble metal catalysts.[2]

Our current work is dedicated to the development of cobalt-catalyzed picolinamide-directed C-H bond functionalization of amino acid derivatives. Starting from α,β-unsaturated amino acids **1** we were able to synthesize different C-H activated Co(III) complexes **2** in very good yields (fig. 1.). Moreover, using *N*-fluorobenzenesulfonimide, indole **3** derivatives can be obtained.

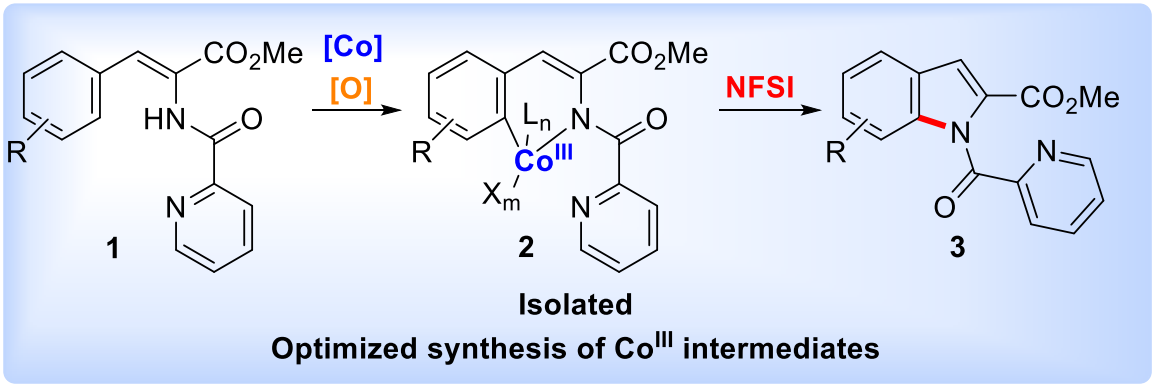

Fig. 1. Cobalt-catalyzed, picolinamide-directed indole **3** synthesis.

Acknowledgments:

This research is funded by Latvian Institute of Organic synthesis internal grant Nr. IG-2023-05.

References:

[1] Gandeepan, P.; Muller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev*. **2019**, *119*(4), 2192.
[2] Lukasevics, L.; Cizikovs, A.; Grigorjeva, L. *Chem. Commun.* **2022**, *58*, 9754-9757.

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USE OF TERMINALLY FUNCTIONALIZED PROPARGYL SILANES FOR THE SYNTHESIS OF VARIOUS 5-MEMBERED HETEROCYCLES VIA 1,2-SILYL MIGRATION

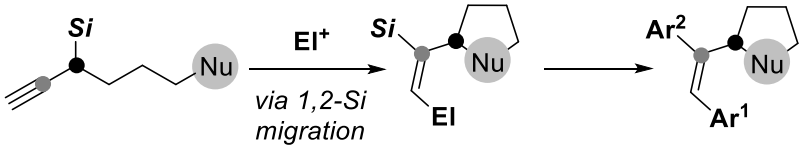
Rasma Kroņkalne, Rūdolfs Beļaunieks, Artjoms Ubaidullajevs, Māris Turks

Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, P.Valdena Str. 3, Riga, LV-1048, Latvia;
e-mail: rasma.kronkalne@rtu.lv

Small heterocycles, particularly those containing a 5-membered cycle, are popular motifs in pharmaceuticals, displaying a broad range of biological properties [1]. A well-established strategy for the synthesis of 5-membered saturated/partially saturated heterocycles involves intramolecular cyclization, made possible by internal nucleophile attack on carbocations.

In this work we investigate the use of electrophile induced 1,2-silyl migration in terminally functionalized propargyl silanes to generate stabilized carbocations, capable of reacting with various internal nucleophiles, forming heterocyclic units (scheme 1). Various nucleophilic species could be utilized, namely alcohols, carboxylic acids, oximes, acyl and sulfonyl amides, carbamates and thioacetates.

The synthetic utility of the cyclization products was demonstrated by difunctionalization of the alkene moiety in cross-coupling reactions to selectively obtain trisubstituted alkenes. The resulting heterocycle derivatives were obtained with a high degree of stereoselectivity and yields up to 82%.



•Multiple electrophilic species:
H^+, Br^+, I^+, $PhSe^+$
•Multiple internal nucleophiles:
-OH, -COOH, -NOH, -NHCOR, -$NHSO_2R$, -SAc
•Site selective alkene functionalization

Scheme 1. Heterocyclization of propargyl silanes.

References:

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USE OF PROPARGYLSILANES FOR THE PREPARATION OF HIGHLY FUNCTIONALIZED ALKENES VIA 1,2-SILYL MIGRATION

Rūdolfs Beļaunieks, Mikus Puriņš, Rebeka Anna Līpiņa, Māris Turks

Faculty of Materials Science and Applied Chemistry, Riga Technical University, P.Valdena iela 3. Rīga, Latvia, LV-1048.
e-mail: rudolfs.belaunieks@rtu.lv

The ease of the unsaturated system reactivity proceeding via β-silyl carbocation ion can be explained by the stabilizing effects of the silicon-carbon bond interaction with carbocation ion - known as β-silicon effect. This can be achieved by either vertical (hyperconjugation) or non-vertical (formation of cyclic silonium ion) stabilization. The formation of the latter, in combination with other stabilizing effects, causes 1,2-silyl migration [1].

Previously, we have reported the use of Brønsted acid to catalyze reactions of propargyl silanes to form various silyl dienes and indenes [2,3]. Herein, we report the expanded use of the concept by using electrophilic bromine to induce the formation of the reactive allylic cation that readily reacts with a variety of nucleophilic solvents like methanol, dimethylformamide, and acetic acid to form allyl functionalized vinyl silanes.

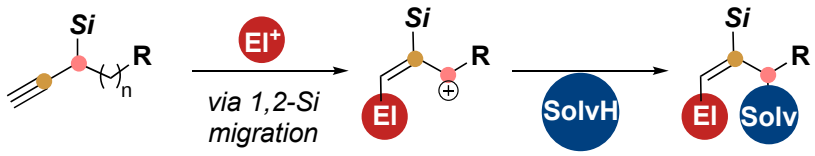

Fig. 1. General scheme of electrophile-induced propargyl silane transformation with solvents.

Use and the functionality of the obtained vinyl silanes are showcased in a variety of transition metal-catalyzed transformations like Suzuki-Miyaura coupling, C-H activation, electrophilic silicon exchange reaction, and Lewis acid-promoted intramolecular cyclization to form indenes.

Acknowledgments:

This work was supported by European social fund within the project Nr. 8.2.2.0/20/I/008 and Riga Technical University doctoral student grant

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ELECTROCHEMICAL DECARBOXYLATION OF *N*-SUBSTITUTED 2-AMINOMALONIC ACID MONOESTERS IN INTERMOLECULAR HOFER-MOEST REACTION

Katrīna Prāne[1,2], Oļesja Koleda[1,2]

[1]*University of Latvia, Faculty of Chemistry, Jelgavas iela 1, Riga, Latvia*
[2]*Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
e-mail: katrina.prane@gmail.com

One of the oldest methods in electroorganic synthesis is Kolbe reaction, where alkyl radical is generated upon anodic decarboxylation [1]. In contrast, Hofer-Moest reaction provides a carbocation after anodic decarboxylation followed by a reaction with a nucleophile [2,3].

Aminomalonic acid derivatives are readily available substrates that can be relatively easily functionalized, e.g. by alkylation reactions. Herein we report a previously unreported intramolecular Hofer-Moest reaction of *N*-substituted 2-aminomalonic acid monoesters. A stabilized cation **2** is formed after anodic decarboxylation of a malonic acid monoester **1** followed by intramolecular cyclization. The developed method allows to obtain new tetrahydrofurane and tetrahydropyrane fragment containing amino acid derivatives **3** in good yields (Fig. 1.).

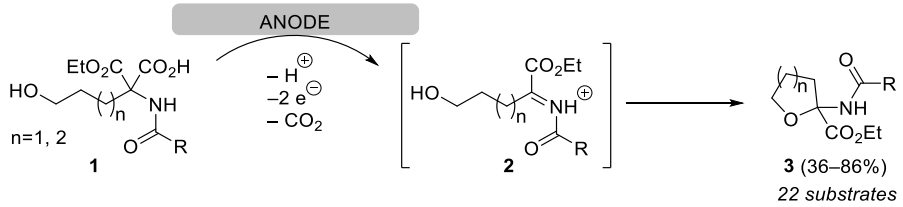

Fig. 1. Intramolecular Hofer-Moest reaction of *N*-substituted 2-aminomalonic acid monoesters

References:

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IMPURITY-INDUCED PHOSPHORESCENCE IN CARBAZOLE DERIVATIVES

Artūrs Mazarevics[1,2], Kaspars Leduskrasts[1], Edgars Suna[1,2]

[1] *Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga, Latvia*
[2] *University of Latvia, Faculty of Chemistry, Jelgavas iela 1, Riga, Latvia*
e-mail: arturs.mazarevics@osi.lv

Phosphorescence is a type of luminescence in which the emission lifetime is longer than 1μs. Usually, phosphorescence is exhibited by metal containing compounds, but the high toxicity and manufacturing costs as well as low stability limits the use of such materials. To overcome these drawbacks purely organic phosphorescent materials recently have become popular because of their biocompatibility, low cost, and limitless design possibilities.[1]

Carbazole **1** subunit is a widely used moiety in the field of purely organic phosphorescence, but in 2021 it was shown that commercially available carbazole has an isomeric impurity – benzo[*f*]indole **2**, which is responsible for the phosphorescence obtained from carbazole containing luminophores.[2] Herein, we report the synthesis of carbazoles **3b**–**7b** in which the carbazole ring was formed through *Clauson-Kaas* cyclization, thus avoiding commercial impurities. Initially, carbazoles **3b**–**7b** showed phosphorescence, however, after laborious purification, it disappeared. This led us to believe, that a byproduct in the *Clauson-Kaas* cyclization was responsible for the phosphorescence. Therefore, we created a series of two component systems, where carbazole derivatives **3b**–**7b** were used as hosts and byproducts **3c**–**7c** and **3d** –**7d** as dopants. The two component systems where the indole derivatives **3c**–**7c** were used as dopants, didn't exhibit phosphorescence. Meanwhile employing benzo[*b*]carbazole derivatives **3d** –**7d** as dopants resulted in an intense phosphorescence.

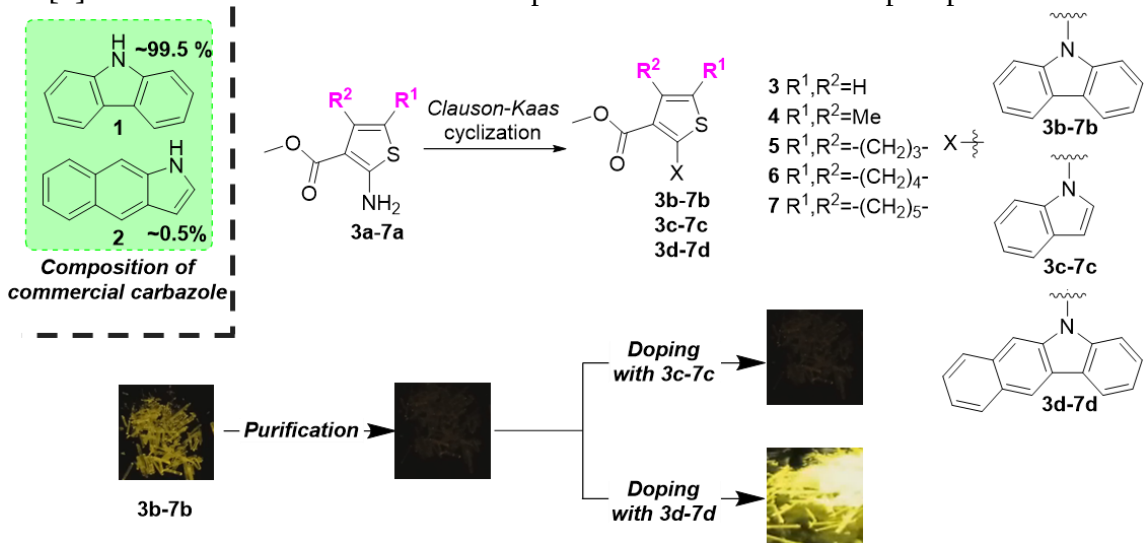

Fig. 1. Impurity-induced phosphorescence in carbazoles **3b**–**7b**

References

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SYNTHESIS AND USE OF NOVEL MOLECULARLY IMPRINTED POLYMERS FOR SELECTIVE EXTRACTION OF CATECHOLAMINES AND THEIR METABOLITES

Artūrs Šilaks, Antons Podjava

Laboratory of Chromatography and Mass Spectrometry, Department of Chemistry, Academic Center of Natural Sciences, University of Latvia, Riga, LV-1004, Latvia
e-mail: asilaks@gmail.com

Catecholamines (CAs) are important hormones and neurotransmitters. Abnormal levels of CAs in bodily fluids can be associated with neurodegenerative diseases as well as adrenogenic tumors. Simultaneous determination of CAs and their metabolites in biological fluids is an efficient way of diagnosis and treatment of the aforementioned diseases. Molecularly imprinted polymers (MIPs) are slowly replacing conventional sorbents used in solid-phase extraction (SPE) to achieve superior selectivity for target analyte isolation from complicated matrices. So far there were no attempts to obtain selective sorbents for simultaneous isolation of CAs and their metabolites except the one made by our group [1].

To provide enhanced aqueous stability for polymer particles and improve molecular recognition for both CAs and their metabolites, the MIP is synthesized using methylenebisacrylamide (MBAA, cross-linker, **4**) with acrylated homovanillic alcohol (HVAAC, **1**), *N*-(4-vinylbenzyl)-*N*-methylamine (NVNM, **2**) and homovanillic acid (HVA, **3**) that act as templates/monomers for CAs and their metabolites, respectively.

MIP sorbents and non-imprinted polymers (NIPs) with varied cross-linker/monomer ratios were prepared and packed into cartridges. Standard analyte mixture was passed through. The imprinting factor (IF), selectivity factor and recovery for each compound were compared to the corresponding NIPs. The preliminary results show that the MIPs have improved retention of CAs compared to NIPs (pH 6). The best-performing MIP will be chosen for further studies.

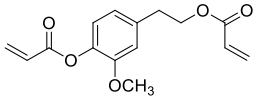
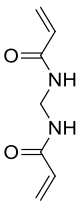
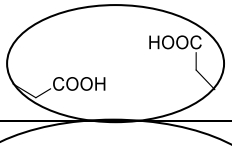
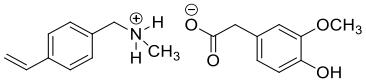
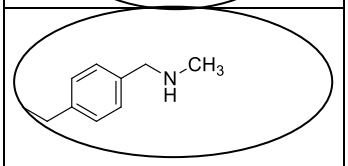
	Combined Functional Monomer/Template	Cross-linker	Binding Site Functionality
CAs, MN and NM	 **1**	 **4**	
HVA and VMA	 **2** **3** (NVNM/HVA salt)		

Table 1. Structural formulas of the compounds chosen for synthesis of the MIPs.

Acknowledgments:

This work is supported by the Fundamental and Applied Research Project lzp-2022/1-0141.

References:

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