Organic Chemistry

80th International Scientific Conference of the University of Latvia 2022

Report of Contributions

Contribution ID: **1** Type: **Oral presentation**

SYNTHETIC APPROACH TOWARDS ENANTIOPURE CYCLIC SULFINAMIDES

Friday, 11 February 2022 09:40 (20 minutes)

N-Alkylation of readily accessible Ellman's sulfinamide derivatives has become a routine step in preparation of enantiopure amines. On the other hand, rarely exploited nucleophilic character of the *S*-atom in *tert*-butyl sulfinamides can be revealed in a serendipitously discovered intramolecular alkylation. High regio- and stereoselectivity of this transformation allows for facile preparation of diverse cyclic sulfinamides. The latter are convenient enantiopure building blocks for medicinal chemistry owing to ample opportunities for diversification at the asymmetric *S*-atom and at the olefin site.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **2** Type: **Oral presentation**

SYNTHESIS OF 2-AMINOQUINAZOLINES AND INDAZOLES FROM 2-FORMYLPHENYLBORONIC ACIDS

Friday, 11 February 2022 10:00 (20 minutes)

New method for the synthesis of substituted indazoles and 2-aminoquinazolines has been studied and developed. Using invented technique, 2-formylphenylboronic acids can be converted to the target heterocycles in a mild conditions.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **3** Type: **Oral presentation**

DEVELOPMENT OF SYNTHESIS PATHWAYS FOR THE LIMONOID OCTAHYDRO-1H-2,4-METHANOINDENE SCAFFOLD

Friday, 11 February 2022 10:40 (20 minutes)

The octahydro-1H-2,4-methanoindene scaffold is present in various limonoid natural products, such as phragmalin, xyloccensins and others. Limonoid natural products exhibit a wide range of pharmacological properties, including anti-HIV, antibiotic, anti-cancer, anti-malarial, and anti-viral activities, therefore, are of high synthetic interest.

In this work, we explore a pathway for a stereodefined assembly of the scaffold with a substitution pattern beneficial for further functionalisation. The synthesis pathway involves the modification of the Hajos-Parrish ketol to obtain compounds, which after being subjected to Aldol/Claisen type condensations, yield the octahydro-1H-2,4-methanoindene scaffold.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **4** Type: **Oral presentation**

A MECHANISTICAL STUDY OF LEWIS BASE CATALYZED CYANOHYDRIN SYTHESIS

Friday, 11 February 2022 10:20 (20 minutes)

Enantiopure cyanohydrins are valuable building blocks in organic and medicinal chemistry [1]. Both functional groups of cyanohydrins (nitrile and hydroxy group) can be easily modified giving access to a variety of valuable organic compounds such as α-amino acids, α-hydroxy acids and aziridines.
Herein we present chiral Lewis base-catalyzed synthesis of enantioenriched cyanohydrins (enantioselectivity up to 65:35 er) from aliphatic and aromatic aldehydes. In order to understand and improve the stereoselectivity, the mechanism of the reaction was investigated. Two potential reaction paths were identified and explored - first through the formation of a cyanohydrin anion and second through the formation of a hemiaminal intermediate.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **5** Type: **Oral presentation**

COBALT-CATALYZED AMINO ACID C(sp2)-H BOND FUNCTIONALIZATION USING ORGANIC ISOCYANIDES

Friday, 11 February 2022 11:00 (20 minutes)

Over the last decade, high-valent cobalt catalysis has earned a place in the spotlight as a valuable tool for C-H activation and functionalization. The use of cobalt (II) salt catalysts in combination with bidentate directing groups has been proven to be an effective strategy for various C-H bond transformations. Not only cobalt is less expensive alternative to third row noble metals, but also displays similar reactivity and regioselectivity
Very recently, our group has developed a methodology for cobalt-catalyzed carbonylation of phenyl alanine derivatives employing picolinamide (PA) as a traceless directing group. We have further developed this methodology by introducing isocyanides as C-H functionalization reagents. Herein we report a novel and efficient picolinamide directed method for the synthesis of 1,2-dihydroisoquinolines via Co-catalyzed C-H functionalization of amino acid derivatives using organic isocyanides.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **6** Type: **Oral presentation**

COPPER(I) CATALYZED AZIDE-ALKYNE CYCLOADDITION IN IONIC LIQUIDS

Friday, 11 February 2022 14:20 (20 minutes)

Since 2002 when Meldal [1] and Sharpless [2] independently discovered a copper effect on azide-alkyne cycloaddition (Huisgen reaction), the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction has gained a popularity and attention from scientists in various fields. CuAAC can be carried out in a variety of molecular solvents ranging from the nonpolar toluene and dichloromethane, to the polar acetonitrile and N,N-dimethylformamide, and even in aqueous solutions.
We have extended the scope of the CuAAC reaction by using ionic liquids (ILs) as reaction media. In this work the impact of IL structure and composition on benzylazide-phenylacetylene CuAAC reaction kinetics was investigated. Kinetic data were acquired by 1H NMR spectroscopy. The effects of coordinating and non-coordinating IL anions regarding CuAAC reaction kinetics were tested. The importance of water content in this system is demonstrated by remarkable changes in reaction kinetic curves.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **7** Type: **Oral presentation**

SYNTHESIS OF 2-AMINOQUINAZOLIN-4(3H)-ONE BASED PLASMEPSIN INHIBITORS

Friday, 11 February 2022 15:40 (20 minutes)

Malaria is a deadly parasitic infection caused by Plasmodium parasites. The widespread resistance against available antimalarial drugs motivates scientists to develop new therapeutic agents targeting the life cycle of the parasite by novel mechanisms of action.
Plasmepsins (plm) are malarial aspartic proteases which have been proposed as appropriate antimalarial drug targets. It is important to design potent plm inhibitors, which do not inhibit other aspartic proteases like human cathepsin D. This can be achieved with nonpeptidomimetic inhibitors (e.g. 2-aminoquinazolin-4(3H)-ones1) that bind to the open-flap conformation of the pathogen enzyme.2 Detailed structural and dynamic studies of mobile aspartic protease flap loop are required to develop more active and effective plm inhibitors. The effect of inhibitor on binding mode and conformation of the flap pocket can be studied using inhibitors with different flap pocket substituents and testing their activity against plasmepsins.
Here we present the synthesis of 2-aminoquinazolin-4(3H)-ones with different flap pocket substituents and their activities against plasmepsins.
Target molecules 3 were synthesized from building block 2 using Sonogashira reaction with alkynes or Suzuki-Miyaura reaction with vinyl, alkyl or aryl dioxaborolanes with subsequent saturation of unsaturated bonds in substituent and benzoyl group cleavage.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **8** Type: **Oral presentation**

THIAZOLINE CARBENE-Cu(I)-CARBAZOLIDE COMPLEXES AS LUMINESCENT TADF MATERIALS

Friday, 11 February 2022 15:00 (20 minutes)

Highly luminescent two coordinate linear carbene-metal-amide (CMA, metal= Cu, Ag, Au) complexes with short radiative lifetimes have emerged as a highly promising direction towards TADF materials [1,2]. However, structural diversity of CMAs with potential OLED application is still limited to a handful of N-heterocyclic carbene (NHC) structures. In this report we demonstrate luminescent CMAs based on 1,3-thiazoline NHC fragment.
A series of complexes **1-8** composed of thiazoline carbene-Cu(I)-carbazolides was synthesized. In PMMA matrix complexes exhibit sky-blue to bluish green emission (λmax=471-509 nm) with TADF emissive properties and Φpl reaching 0.86 for compound **8**. Radiative rates in the range of 2.8-7.2×10^5 s^-1 were attained. An increase of the of emissive rates was observed with the introduction of sterically demanding substituents at both the carbazole (1,8-dimethly- groups, compounds **2**, **4**, **6** and **8**) and thiazoline (4-phenyl- group, compounds **5-8**). The interactions of the bulky groups induces sterical locking, which increases coplanarity of carbazolide and thiazoline ligands. Emitter **7** was successfully integrated in vacuum-deposited OLEDs with external quantum efficiency reaching 16.5 %.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **9** Type: **Oral presentation**

C-H ACTIVATION OF LUPANE TYPE TRITERPENOIDS

Friday, 11 February 2022 11:40 (20 minutes)

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **10** Type: **Oral presentation**

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

Friday, 11 February 2022 13:40 (20 minutes)

Azido groups in nitrogen heterocycles, if adjacent to annular nitrogen, can spontaneously cyclize to fused tetrazole or at least persist in azide-tetrazole equilibrium [1]. Azide-tetrazole valance tautomerism is considered as a reversible intramolecular 1,5-dipolar cycloaddition with azide tautomer being thermodynamically more stable. However, azide formation is endothermic process, thus azide tautomer is favored at higher temperatures and tetrazole in lower temperatures. The main tautomeric form and equilibrium constant essentially depends on substituents, temperature and solvent polarity. Thus, one can steer azide-tetrazole equilibrium with careful choice of reaction conditions.

While tetrazole tautomer as a fused cycle is unreactive, the open chain azido tautomer can be functionalized as a classical azide. This concept can be used for masking azido functional group [2] and regioselectivity induction in compounds with more than one tautomeric azide [3].

The present study discusses regioselectivity of azido group functionalization in 2,4-diazidopyrido[2,3-d]pyrimidine, reactivity of substituted tetrazolo[1,5-a]pyrido[3,2-e]pyrimidine and equilibrium constants thereof.

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **11** Type: **Oral presentation**

Synthesis of beta-adrenergic receptor agonists for the treatment of obesity

Friday, 11 February 2022 15:20 (20 minutes)

The abstract is in the attachment.

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Presenter: BAZULIS, Maris (Latvian Institute of Organic Synthesis)

Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **12** Type: **Oral presentation**

NEW SYNTHETIC APPROACH FOR THE SYNTHESIS OF SUBSTITUTED 7-ARYLPURINES

Friday, 11 February 2022 11:20 (20 minutes)

Alkylation and arylation on the purine ring usually proceeds almost selectively at N(9) position. While there are some simple pathways to introduce alkyl substituents at N(7) [1], the same is not true for introduction of aryl groups. The most commonly used Cu catalyzed Chan-Lam reaction [2] and arylation with iodanes [3] selectively give N(9) product. The few existing methods for purine N(7) arylation still provide a mixture of two isomers and are substrate dependent [4]. Hence, we decided to test various pathways towards 7-arylpurines starting from substituted pyrimidines.
We have achieved the best results with the following synthetic pathway starting from compound 1: arylation was performed using diaryliodane in the presence of Cu catalyst, giving 5-arylamino substituted pyrimidine 2. Next, in SNAr reaction under optimized conditions only one chlorine atom was substituted. Finally 7-arylpurine was obtained in a ring closing reaction with orthoester under acidic conditions. Modifications of starting material 1, diaryliodane reagent and ring closing reagent can be made to achieve differently substituted 7-arylpurines of type 4.

Primary author: SEBRIS, Armands

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Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **13** Type: **Oral presentation**

SYNTHESIS OF BICYCLIC PROLINE ANALOGUES

Friday, 11 February 2022 14:40 (20 minutes)

α – Amino acids are widely used in drug design and peptide chain synthesis. Proline is the only cyclic natural amino acid, therefore its conformational rigidity plays an important role in protein secondary structures, such as alpha helices.
Herein we report the synthesis of previously unreported bicyclic amino acid derivatives 4 substituted at bridgehead positions. These amino acids are even more conformationally rigid than proline, thereby ensuring that substituents are at fixed positions relative to one another.
The key intermediate that is used for synthesis of amino acid 4 is TBS protected amino alcohol 2, which is obtained by α – lithiation of N-Boc protected bicycle 1. The next lithiation step allows convenient functionalization of the other bridgehead position. Diversity of derivatives 3 can be achieved using transmetallation of organolithium intermediate with CuCN·2LiCl complex, which allows the use of a broad scope of electrophiles R-X.

Amino acid precursors 3 are deprotected and oxidized to give bicyclic α – amino acids 4.

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Presenter: MEIBERGA, Mērija Agnese

Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **14** Type: **Plenary lecture**

SCALE-UP DEVELOPMENT OF AGGARWAL ENAL BICYCLIC INTERMEDIATE – TOWARDS MODERN MANUFACTURING OF PROSTAGLANDIN DRUGS

Friday, 11 February 2022 13:00 (40 minutes)

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Prostanoids are important class of potent lipid mediators that are involved in the regulation of many biological processes such as inflammation, pain response and fever. This class of compounds has found wide-spread use as pharmaceuticals for the treatment of several diseases including pulmonary arterial hypertension and glaucoma (4.5 billion EUR global market). Recently a multitude of modern and short syntheses of various prostanoids were reported, rejuvenating this historically rich synthesis field. Remarkably short seven step synthesis of PGF2α reported by Aggarwal group in 2012 has good potential for industrialization [1].
Herein, we report the results of scale-up investigation of enantioselective two step route to Aggarwal enal bicyclic intermediate using extensively reoptimized reaction conditions [2]. Kilogram scale synthesis of succinaldehyde starting material was developed. Safety assessment of this volatile, unstable and polymerization prone compound was performed revealing recommended handling guidelines. Challenging organocatalytic dimerization of succinaldehyde was achieved on hectogram scale. The transfer from magnetically stirred small scale reactions to mechanically stirred large scale reactions in reactor required the finding of appropriate proline catalyst crystalline form [3].

References:
[1] Coulthard, G.; Erb, W.; Aggarwal, V. K. Nature, 2012, 489, 278–281.
[2] Pelšs, A.; Gandhamsetty, N.; Smith, J. R.; Mailhol, D.; Silvi, M.; Watson, A.; Perez-Powell, I.; Prévost, S.; Schützenmeister, N.; Moore, P.; Aggarwal, V. K. Chem. Eur. J. 2018, 24, 9542–9545.
[3] Pelšs, A.; Shubin, K. Org. Process Res. Dev. 2022, accepted, in revision.

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Presenter: Dr PELŠS, Andrejs (Latvian Institute of Organic Synthesis)

Session Classification: Plenary Lecture

Track Classification: Organic Chemistry: Plenary Lectures

Contribution ID: **15** Type: **Oral presentation**

SYNTHESIS OF PURINE-THIAZOLOPYRIMIDINE CONJUGATES

Friday, 11 February 2022 14:00 (20 minutes)

Purine derivatives have been studied not only as biologically active compounds but also as scaffolds for OLED materials. Recently, purine based derivatives have shown promising results as TADF (thermally activated delayed fluorescence) materials [1].
In this study we have designed new purine-thiazolopyrimidine conjugates A and E containing phenylanthracene moiety, later to be studied as TADF materials [2,3]. Firstly, Negishi cross-coupling between thiazolopyrimide C and purine D and subsequent SNAr reaction with NaN3 will provide compound B. Then CuAAC reaction between B and phenylanthracenyl moiety containing alkyne will provide target derivative A. On the other hand, Stille cross-coupling between purine H and 9-bromo-10-phenylanthracene, and following Negishi cross-coupling with thiazolopyrimidine F will be used for the synthesis of conjugate E. The progress towards conjugates A and E will be discussed.

Scheme 1. Retrosynthetic analysis of target compounds A and E

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Presenter: KRIĶIS, Kārlis (Student)

Session Classification: Oral Presentations

Track Classification: Organic Chemistry: Oral Presentation

Contribution ID: **16** Type: **Plenary lecture**

ELECTROCHEMICAL GENERATION OF HYPERVALENT BROMINE(III) COMPOUNDS

Friday, 11 February 2022 09:00 (40 minutes)

The chemistry of hypervalent halogen species has experienced enormous progress in the last decades, and hypervalent iodine (III) compounds have become common reagents in modern organic synthesis. In sharp contrast, the chemistry of isoelectronic bromine (III) compounds occur to be notably less advanced to date. This dramatic difference obviously is to be connected with the relatively low stability and the high oxidizing power of bromine (III) reagents, which results in a difficult-to-control reactivity. Furthermore, there is a clear deficit of simple protocol for the synthesis of bromine (III) species, but known methods often require a handling of the highly toxic and corrosive BrF3 precursor. In this context, we present a straightforward and scalable method for preparation of a benchtop-stabile λ3-bromanes by anodic oxidation of corresponding aryl bromides with two stabilizing hexafluoro-2-hydroxypropanyl groups. The synthetic use of the generated λ3-bromane is demonstrated by oxidative C-C, C-N, and C-O bond formation reactions [1].

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Presenter: Dr SOKOLOVS, Igors (Latvian Institute of Organic Synthesis)

Session Classification: Plenary Lecture

Track Classification: Organic Chemistry: Plenary Lectures