BALTICUM ORGANICUM SYNTHETICUM 2022

In memory of Prof. Victor Sniečkus

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PROGRAM AND ABSTRACT BOOK

LATE-STAGE OLEFINATION IN PBD NATURAL PRODUCT TOTAL SYNTHESES

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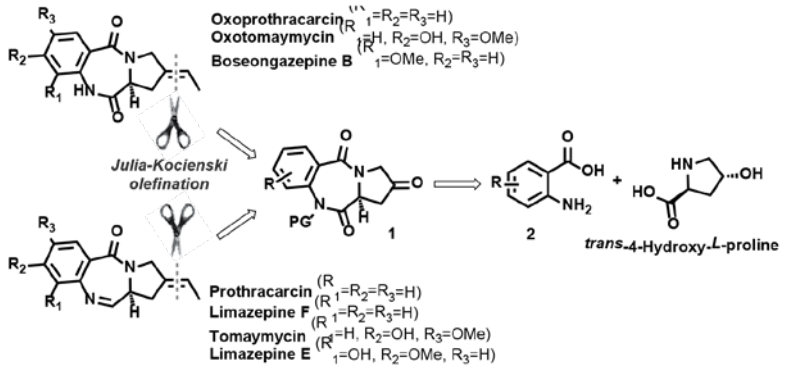
Pyrrolo[1,4]benzodiazepines (PBD) are a broad family of natural products possessing considerable anticancer activity owing to their ability to covalently bind to minor grove of DNA.[1] Several PBD members possess an *E*- configured C2 alkylidene group in the pyrrolidine ring, the configuration of which plays a crucial role in the cytotoxic properties of these compounds.[2] Although several total syntheses of these natural products have been published, a stereoselective introduction of the alkylidene substituent still possesses a considerable challenge. Within our preliminary studies,[3] we have shown that a late-stage olefination is a convenient approach to synthesize these natural products.

Herein we report our studies on the Julia – Kocienski olefination of PBD triones **1**, including the development of novel reagents, optimization of reaction conditions, and determining the olefination stereochemistry determining factors. The necessary triones **1** can be easily accessed starting from readily available *trans*-4-hydroxy-L-proline and the corresponding anthranilic acids **2**.



Scheme 1. *Retrosynthetic analysis of PBD natural products.*

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AZIDOAZOMETHINE-TETRAZOLE TAUTOMERISM IN PYRIDOPYRIMIDINES

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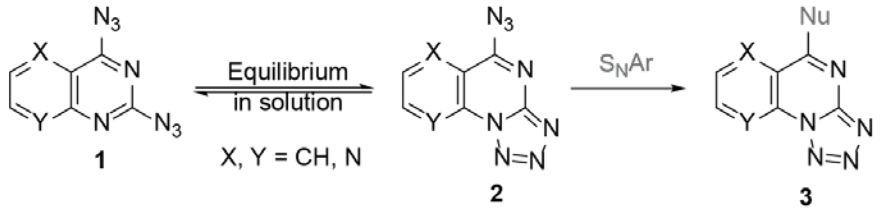
Heterocycles with azido-azomethine structural entity undergo dynamic azide tetrazole equilibrium in solution phase. The equilibrium can be shifted towards one or other tautomer by altering ambient conditions such as solvent polarity and temperature. Thus, azide tetrazole ring-chain tautomerism is known to influence S_NAr reactivity and regioselectivity.

We have synthesized a new class of tetrazolopyridopyrimidines **3** and characterized azidoazomethine-tetrazole tautomerism thereof. FT-IR and X ray analysis of **3** reveals tetrazole to be the major tautomeric form present in the solid state. Thermodynamic heats of tautomerization in solutions were calculated using variable temperature NMR and DFT.



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SYNTHESIS OF OXEPANE DERIVATIVES BASED ON ENOLATE ADDITION TO ALKENE

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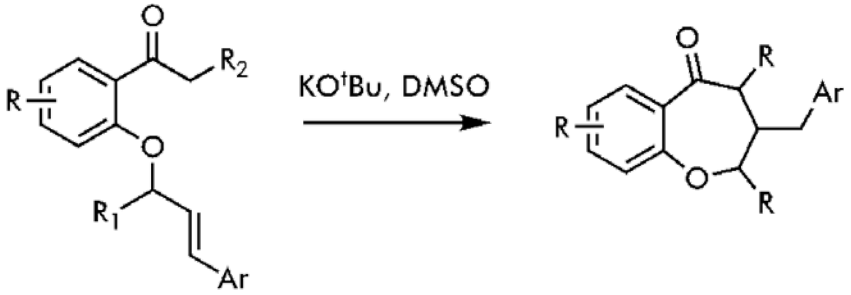
Oxepane heterocyclic system is often found in the structure of many natural products and pharmaceutical agents. The currently known synthetic methods used for the assembly of these seven-membered heterocycles often rely on multi-step procedures, especially in cases of heavily functionalized scaffolds, where multiple stereocenters have to be introduced with high stereoselectivity. Herein we report a novel one-step procedure for the formation of oxygen containing seven-membered rings using enolate addition to non-activated double bonds. The procedure utilizes affordable 2-hydroxyacetophenone derivatives appended with styrene functionalities as starting materials. These reactions proceed under very mild conditions using potassium tert-butoxide as a base, yielding products with good diastereoselectivities and yields.



RING OPENING REACTIONS OF FUSED TETRAZOLOPYRIMIDINES

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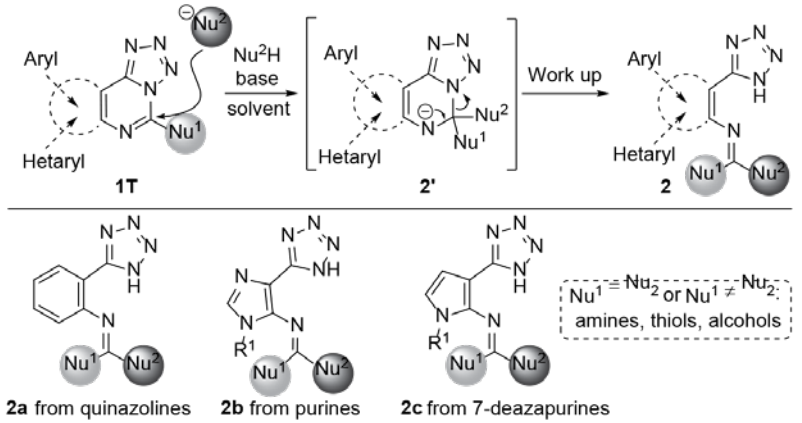
Purine derivatives can be opened at both pyrimidine and imidazole rings.[1] In our research we focused on investigation and optimization of ring opening reactions in fused pyrimidines based on azido-tetrazole equilibrium. Under nucleophile attack the pyrimidine ring opened, forming tetrazolyl derivatives **2a-c**. The structures were proved by X-ray analysis.



Acknowledgements: This work is supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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THE SELENYLATION OF PURINE DERIVATIVES

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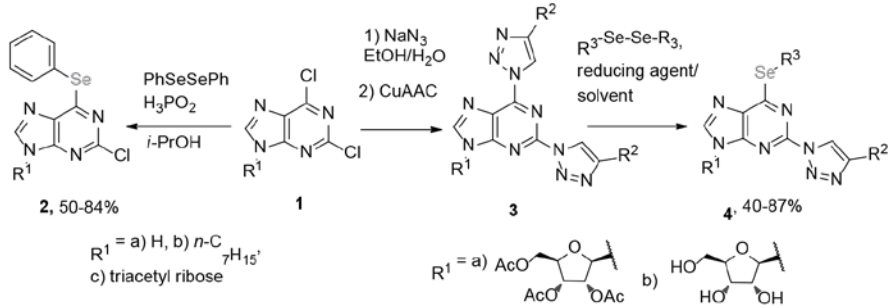
Earlier we demonstrated that 1,2,3-triazole moiety at C(6) position of purine is a good leaving group in S_NAr reactions with *N, S, O, C* and *P*-nucleophiles [1,2]. In this study we extended the range of nucleophiles with selenols. The synthetic routes to 6-selanyl-2-triazolylpurine nucleosides (**4**) and 2-chloro-6-selanylpurines (**2**) were developed and will be discussed.



Acknowledgements: This work was supported by the Latvian Council of Science grant No LZP-2020/1-0348.

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SUSTAINABLE SYNTHESIS OF USEFUL BUILDING BLOCKS ENABLED BY ELECTROLYSIS IN CONTINUOUS-FLOW

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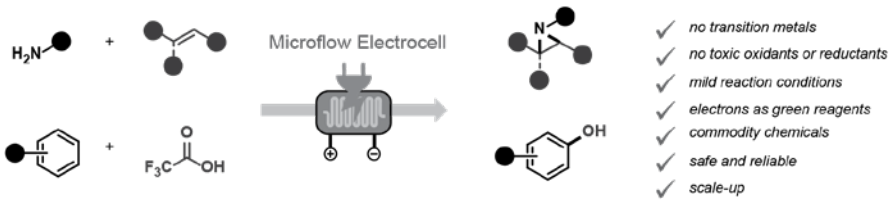
Electrochemistry has recently witnessed a renaissance in modern organic chemistry. This approach uses electrons as traceless and green reagents to generate highly reactive radical species under mild reaction conditions avoiding the utilization of hazardous oxidants or reductants and metal catalysts. Combining electrochemistry with the continuous-flow technology, we managed to obtain highly valuable building block, such as aziridines and electron-rich phenols, starting from common and broadly available starting materials.[1,2] In flow microreactors, high electrode surface-to-volume ratio and effective mixing significantly reduce reaction time, which helps to prevent degradation of sensitive products under the electrochemical conditions and increases reaction selectivity. The continuous nature of the process readily allowed to scale-up the reactions safely and efficiently.



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