Tytuł projektu

Organokatalityczna strategia syntetyczna prowadząca do reakcji kaskadowych/domino poprzez aktywację grupy karbonylowej acylowymi enolanami.

Project title

Organocatalytic synthetic strategy leading to the domino/cascade reactions via acyl enolate activation of the carbonyl group

Dyscyplina /Area of science

Nauki chemiczne

PROJECT DESCRIPTION

Project goals

The aim of the project is the exploration of important and challenging NHC-catalyzed enantioselective reactions. Special attention will be focused on the domino processes and the generation of multiple stereogenic centers.

- Stereoselective formation of pyrazolones through NHC-catalyzed dipolar cycloaddition of hydrazoyl chlorides with *α,β*-enals,
- Stereoselective annulation of enals with hydroxy 2,2,2-trifluoroacetophenones *via* cascade reactions for the construction of functionalized dihydrocoumarines,
- Enantioselective synthesis of benzothiazines *via* a formal asymmetric [4+2] cycloadditions of acyl homoenolates with benzo[e][1,2]thiazin-4-one 1,1-dioxide derivatives.

Outline and work plan

Over the last decade asymmetric organocatalysis has grown rapidly to become a very powerful strategy for the synthesis of enantiomerically enriched compounds. It represents an attractive alternative to metal catalysis, and in some cases, offers unparalleled transformations. Despite unquestioned advantages of this methodology, there are still many limitations related to substrates reactivity and catalyst activity.

Based on these strategies, in this PhD project, methodologies for the synthesis of new chiral heterocyclic compounds derived flavone, pyrazolone, benzothiazine and pyridinone skeletons will be developed. These structural motifs are present in a variety of biologically active natural products and numerous pharmaceuticals. The project will result in the development of new efficient organocatalytic processes *via* carbene catalysis, expanding the scope of asymmetric synthesis and opening new applications.

Within the realm of organic chemistry, the identification of new synthetic methodologies leading to the bioinspired targets constitutes a very important and rapidly developing field of

research. The asymmetric synthesis of such compounds is particularly important as their biological activity is directly correlated with the spatial arrangement of the substituents in the chiral molecule. 3,4-Dihydrocoumarin derivatives occupy a prominent position among biologically active molecules and constitute core structures of various natural products and biologically active molecules. Given the significance, these studies will be focused on highly innovative hetero-Diels-Alder-like annulation involving reactions between acyl enolates (from α,β-unsaturated aldehydes or saturated aldehydes with the leaving group in α-position) and selected trifluoroacetyl phenols.

Benzothiazine derivatives are known to possess versatile biological activities. Among them, 1,2-benzothiazine-3-carboxamide-1,1-dioxide derivatives such as piroxicam, ampiroxicam and meloxicam are promising anti-inflammatory agents used worldwide as non-steroidal anti-inflammatory drugs (NSAIDs). Recent findings proved that the 1,2-benzothiazine 1,1-dioxide derivatives as excellent antibacterial, antifungal, anticancer, antioxidant agents and 11*β*-HSD1 inhibitors. Therefore, our efforts will be focused on annulation reactions involving the use of acyl enolate intermediates generated from α,β-unsaturated enals with benzothiazine derivatives. This approach is attractive due to the potential utilization value of the products in molecular biology and pharmacy.

Other type of cycloaddition reaction will also be examined is 1,3-dipolar cycloaddition between hydrazonoyl chlorides and α,β-unsaturated aldehydes *via in situ* formed dipolar nitrile imine. Cascade and one-pot stereoselective strategies have been receiving increasing attention in recent years. Pyrazolone derivatives characterized as a five-membered-ring lactam are important frameworks which exhibit a variety of applications as pharmaceutical candidates and biologically important structural components. For example, analgin is used for the treatment of pains of different origin and variable intensity. The development of asymmetric methods for the efficient preparation of chiral heterocycles containing a pyrazolone ring is an interesting challenge. Importantly, synthetic strategies leading to targets possessing such structural features remain limited.

The project is part of research funded by the National Science Center as part of the Sonata Bis program

Literature

Flanigan D. M., et al., *Chem. Rev.* **2015**, *115*, 9307
Rafiński Z., Kozakiewicz A., Rafińska K. *ACS Catalysis*, **2014**, *4,* 1404
Rafiński Z., Kozakiewicz A., Rafińska K. *Tetrahedron*, **2014**, *70*, 5739
Rafiński Z., Kozakiewicz A. *J. Org. Chem.* **2015**, *80*, 7468.
Rafiński Z**.** *Tetrahedron*, **2016**, *72*, 1860.
Rafiński Z. *ChemCatChem*, **2016**, *8*, 2599.
Dzieszkowski K., Rafiński Z. *Catalysts*, **2018**, *8*, 549.
Rafiński Z. *Catalysts*, **2019**, *9*, 192.

Required initial knowledge and skills of the PhD candidate

- ➔ Good knowledge of organic chemistry
- ➔ Predispositions and strong motivation for scientific work (regularity and timeliness)
- ➔ Independence in achieving the set research goals, at the same time the ability to work in a group.)

Zgłaszający projekt/ Author of the project	
dr hab. Marek P. Krzemiński stopień/tytuł, imię, nazwisko	mkrzem@chem.umk.pl e-mail
	Wydział Chemii UMK jednostka organizacyjna
Proponowani promotorzy i mentorzy/prospective supervisors	
1) promotor główny/ main supervisior	
dr hab. Marek P. Krzemiński	e-mail : mkrzem@chem.umk.pl
	Wydział Chemii UMK jednostka organizacyjna
2) promotor pomocniczy / co-supervisor	
Dr Zbigniew Rafiński	