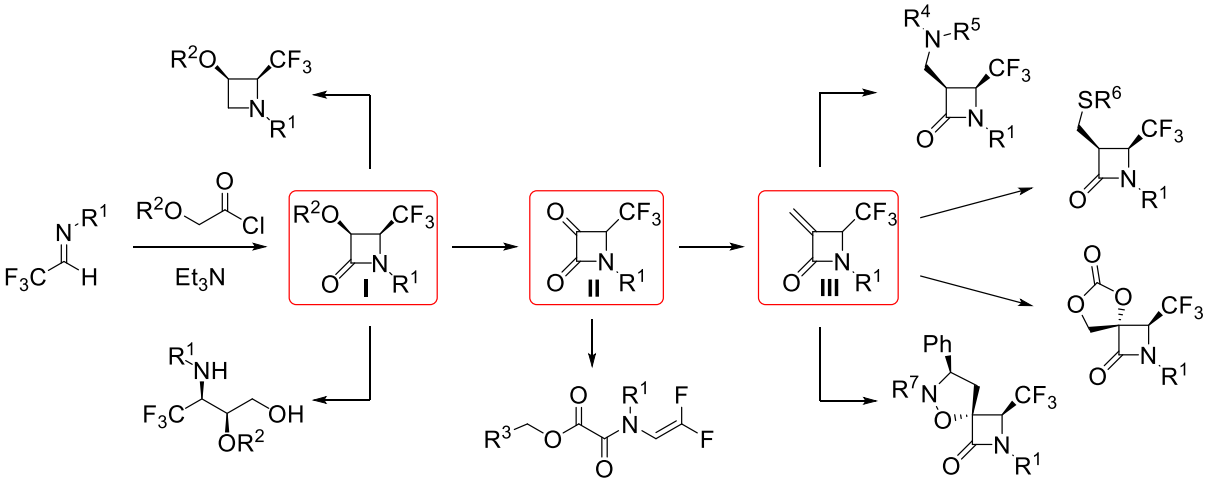
Synthesis of 4-(trifluoromethyl)azetidin-2-one building blocks and transformations into novel CF_3-substituted amines and heterocyclic systems

Hang Dao Thi,[1,2] Tuyen Van Nguyen [2] and Matthias D'hooghe[*1]*

[1] *SynBioC Research Group, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

[2] *Institute of Chemistry, Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, CauGiay, Hanoi, Vietnam*

During the past decades, organofluorine compounds have attracted a lot of attention in the field of organic and medicinal chemistry due to the profound effect of fluorine on bioactive molecules. Azetidin-2-ones or β-lactams are very important compounds in organic synthesis due to their high ring strain energy, which allows for further elaboration toward a variety of nitrogen-containing acyclic and heterocyclic target compounds. In light of the beneficial effects of fluorine introduction, β-lactams bearing a trifluoromethyl group comprise interesting entities for the construction of novel targets with promising bioactivities. Consequently, the preparation and deployment of CF_3-substituted azetidin-2-one building blocks **I**, **II**, **III** toward a diverse set of functionalized CF_3-amines and CF_3-azaheterocycles was demonstrated.



In the first part, 4-CF_3-azetidin-2-ones **I** were successfully prepared, and their synthetic potential as eligible new building blocks for the construction of CF_3-containing azetidines, diaminopropanes, aminopropanol derivatives, 1,3-oxazinanes and 1,3-oxazinan-2-ones was evaluated.[1] In the second part, 4-trifluoromethyl-3-oxo-β-lactams **II** were synthesized from substrates **I** and unexpectedly transformed into 2-[(2,2-difluorovinyl)amino]-2-oxoacetates as major products, accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates. This peculiar reactivity was investigated in-depth from both an experimental and a computational point of view, in order to shed light on the underlying reaction mechanism.[2] In the final part, 3-methylene-4-(trifluoromethyl)azetidin-2ones **III** were efficiently prepared from 3-oxo-β-lactams **II** and successfully evaluated as novel substrates in organic synthesis. In particular, Michael additions, electrophilic additions and cycloadditions were applied to allow an easy access to a broad variety of stereodefined mono- and spirocyclic 4-CF_3-β-lactams.[3] This β-lactam building block approach has thus been shown to provide a convenient new entry into trifluoromethylated scaffolds as useful synthetic intermediates *en route* to a variety of functionalized target structures.

(1) Dao Thi, H., Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. *Synlett* **2016**, *27*, 1100.

(2) Unpublished results.

(3) Dao Thi, H.; Danneels, B.; Desmet, T.; Van Hecke, K.; Van Nguyen, T.; D'hooghe, M. *Asian J. Org. Chem.* **2016**, *5*, 1480.