UNIVERSITY OF SALERNO

DEPARTMENT OF CHEMISTRY AND BIOLOGY

Ph.D. Course in Chemistry - XXXIV Cycle

Ph.D. Thesis in Chemistry

Exploring batch and flow catalytic reactions as valuable tools for safer and greener synthesis of APIs and their fluorine intermediates.

Tutor:
Prof. Alessandra Lattanzi

Co-tutor:
Prof. Maurizio Benaglia
Dott.ssa Sara Meninno

Ph.D. Student:
Francesca Franco

Ph.D. Coordinator:
Prof. Claudio Pellecchia

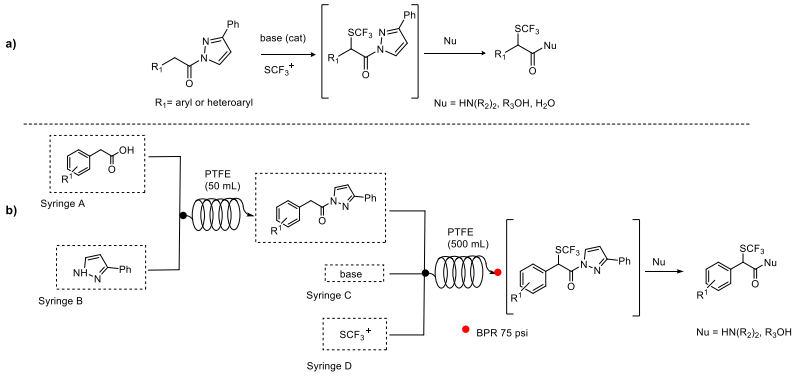
2021-2022

ABSTRACT

The trifluormethylthio (SCF_3) group assume a key role in the field of drug discovery thank to its unique properties. The high electron-withdrawing and lipophilic character made advantageous its incorporation in biologically active molecules. Different methods for the introduction of this group at the α-position of carbonyl compounds have been intensively investigated, achieving important results for ketones, aldehydes and 1,3-dicarbonyl compounds both under batch and flow conditions. However, few methods have been reported for the α-trifluoromethylthiolation of carboxylic acid derivatives.

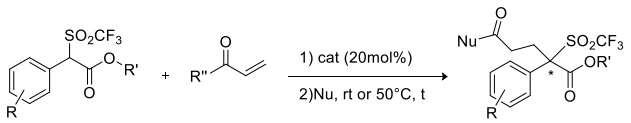
In this industrial doctoral work, in collaboration with Laboratori Alchemia firstly a convenient metal-free and catalytic one-pot route for the introduction of SCF_3 group at α-position of carboxylic acid derivatives via *N*-acyl pyrazoles as surrogates was developed, amenable to mild conditions for enolate formation and simple transformation in one-pot fashion, into amides, esters, or carboxylic acids (Scheme Ia).

Furthermore, with the attempt to develop more convenient synthesis also suitable for industrial applications, a telescopic synthesis of the same products, starting directly from commercial sources by exploiting the flow chemistry technology, has been developed. With this strategy, the environmental footprint and the reaction time of the one-pot process are considerably reduced, minimizing the waste production and avoiding purification of the intermediates (Scheme Ib).



Scheme I a) Organocatalytic one-pot α-trifluoromethylthiolation of carboxylic acid derivatives. b) Telescopic flow synthesis.

The last part of this doctoral thesis has been focused on the asymmetric organocatalytic synthesis of trifluoromethyl-substituted compounds bearing a quaternary stereocenter (Scheme II).



Scheme II Organocatalytic enantioselective one-pot Michael addition.

A first one-pot enantioselective organocatalytic Michael reaction to prepare highly enantioenriched triflones bearing a quaternary stereocenter has been developed, starting from easily enolizable aryl acetic triflone esters and acryloyl pyrazole. The one-pot methodology enables to obtain a variety of aryl-substituted triflones working under mild reaction conditions.

Finally, during the period spent in Laboratori Alchemia an intensive study on the *related substances* of Metaraminol, an API synthesized by Laboratori Alchemia through a new synthetic pathway, was performed

with the aim to identify these byproducts and allow to Laboratori Alchemia to declare the purity of Metaraminol.