

Development of a telescoped continuous flow methodology for the synthesis of carbamates and primary amines from esters

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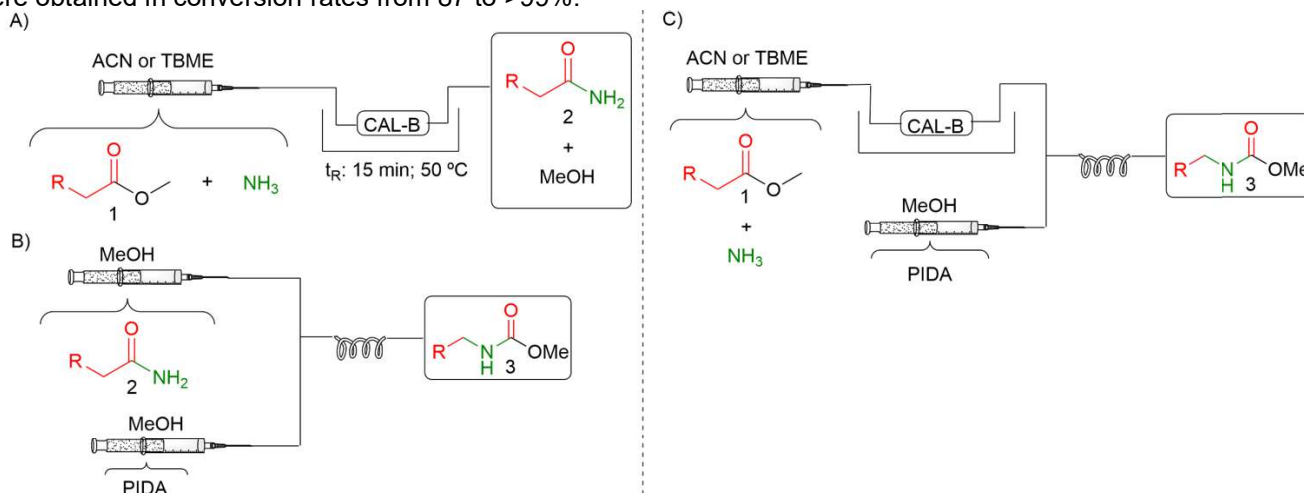
Palavras-Chave: Continuous flow, Carbamates, Primary amines, Ester, Lipase, Organic synthesis.

Highlights

Novel integrated methodology, continuous flow methodology, synthesis of carbamates and primary amines from esters, hypervalent iodine chemistry, efficient enzymatic reaction.

Resumo/Abstract

Amides, carbamates, and amines are compounds with great applications in biochemistry, pharmacy, medicine, and materials, which makes them interesting targets for their synthesis¹. With this in mind, we propose a new flow chemistry protocol involving the integration of ammonolysis reaction of esters catalyzed by lipase (**1**) and the Hofmann rearrangement of amides (**2**) to directly produce carbamates (**3**) (Scheme 1) and, indirectly, primary amines after a quick deprotection step. For the first step, ammonolysis reaction of esters² catalyzed by lipase B from *Candida antarctica* (CAL-B) afforded amides in excellent conversion rates (up to >99%). For the second step, we choose a methodology using (diacetoxyiodo)benzene (PIDA)³. Initially, under batch reactions, some reactions parameters were optimized, including temperature, concentration, stoichiometry, solvent, time and the presence of bases. Performing the Hofmann rearrangement of amides (**2**) under continuous flow conditions, the carbamates were obtained in conversion rates from 87 to >99%.



Scheme 1: A) Ammonolysis of esters. B) Hofmann rearrangement of amides. C) Integration of ammonolysis and Hofmann rearrangement for carbamate synthesis.

Chemical compatibility of the two reactions were evaluated. Some solvent modifications were needed, and our initial experiments simulating the telescoped system using TBME as solvent showed conversion rates of 40-43% for the carbamate and 48-53% for the intermediate. Studies on optimization and scope expansion are still ongoing.

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