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Continuous flow multistep synthesis of α-functionalized esters via lithium enolate intermediates

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ABSTRACT

This manuscript describes a continuous flow protocol for the α-alkylation of esters. The method is based on the generation of lithium enolate intermediates from the esters and in situ delivered LDA. The process is then integrated with the electrophilic addition step and a quench in line. A series of α-functionalized ester have been prepared using this procedure with moderate to good yields. Key reaction parameters such as temperature and residence time and their influence on the reaction outcome are discussed in detail.

1. Introduction

Lithium enolates are among the most important and commonly used intermediates for the α-functionalization of carbonyl compounds.[1] The construction of C-C bonds adjacent to carbonyl groups via enolate intermediates has attracted particular attention over the past decades (Fig. 1).[2] A plethora of methods for the α-alkylation and arylation of ketones, esters, and carboxylic acids, including asymmetric C-C bond formation methods have been developed and are nowadays fundamental techniques in organic synthesis.[1,2]

Lithium diisopropylamide (LDA) is arguably the most commonly used base for the quantitative formation of enolates. Since the publication of the seminal work of Hamell and Levine over 6 decades ago,[3] organic chemists have benefited from its high regioselectivity and fast and complete enolate formation. Although LDA is commercially available as solution in THF/hexanes or other nonpolar organic solvents, it is commonly prepared in situ from diisopropylamine and n-butyl lithium (^{n}BuLi).[4] Generation of LDA from ^{n}BuLi is more cost effective, reliable, and ^{n}BuLi solutions are typically more stable over prolonged periods. In rare instances, significant differences in reactivity between commercial and in situ generated LDA have been reported – and ascribed to the presence of LiCl in the commercial reagent.[5–7] The reaction between ^{n}BuLi and diisopropylamine is very exothermic, and cryogenic conditions (−78 °C) are usually employed.[1,2,4] On large scale production this is an important drawback. To control the exotherm produced during the LDA generation and potentially enable its safe production and in situ utilization on large scale, several research groups have developed continuous flow strategies.[8–12] Thus, solutions of ^{n}BuLi and diisopropylamine are pumped and mixed using a micromixer. The enhanced mass transfer characteristic of a microreactor allows safe generation of LDA at much higher temperatures (−10 °C, 0 °C or even room temperature[10]).

Certain enolate transformations are very difficult or impossible to perform due to the high reactivity of the carbonyl moiety towards the ensuing carbanion or the instability of the enolate itself. Undesired self-condensations or polyalkylations often occur, especially in the case of enolates derived from ketones and aldehydes. In this context, continuous flow and microreactor technology offers unique opportunities to improve the efficiency and selectivity of enolate-based alkylations. The exquisite mixing and residence time control achieved in a microreactor enables very accurate reaction times, if required in the order of second or even milliseconds.[12,13] Thus, a continuous flow LDA generator can be

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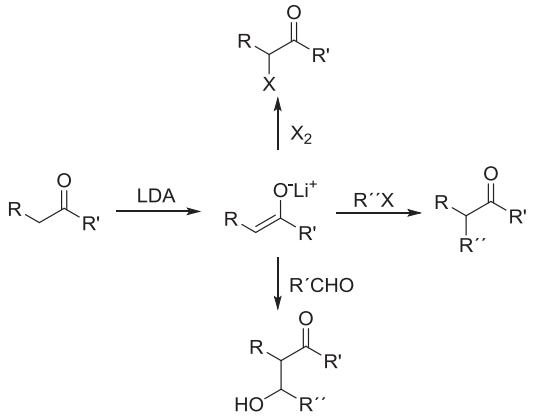


Fig. 1. Typical α-functionalization reactions of carbonyl compounds via lithium enolate intermediates.

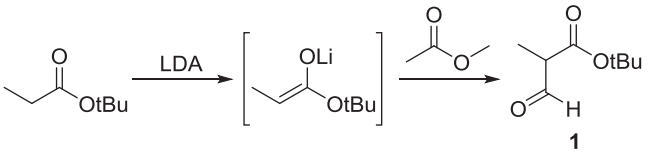
coupled with a stream containing the carbonyl substrate to generate the enolate intermediate. After an optimal contact time, the generated enolate can be mixed with a suitable electrophile minimizing side reactions.

In this manuscript, we present our results on the development of a continuous flow multistep α-alkylation of esters. The sequential process includes in situ generation of LDA, its reaction with the ester to form an unstable lithium enolate intermediate, and subsequent reaction with a suitable electrophile. Effect of temperature, residence time, and other parameters on the yield and selectivity for the key reaction steps are described in detail.

2. Results and discussion

The reaction conditions for the continuous flow multistep LDA generation, lithium enolate formation and reaction with an electrophile were optimized using the coupling of t-butyl propionate with methyl formate, providing α-formyl ester **1**, as model reaction (Scheme 1). This reaction is typically performed in batch at −78 °C.[14] The ester is mixed with an LDA solution and reacted for 30 min before adding the methyl formate. The ensuing α-formyl esters are useful scaffolds for the preparation of thymine derivatives,[15,16] or coumarins,[17] among other compounds.

The continuous flow setup consisted of 4 reaction zones (i.e. LDA generation, enolate formation, electrophilic addition and quench) (Fig. 2) and a total of 5 separate feeds, one for each of the reactants involved and a quench feed. All reagents solutions were introduced using commercially available peristaltic pumps (Vapourtec V-3 and SF-10 pumps). The reactors were made of PFA tubing (i.d. 0.8 mL for the LDA generation and 1.6 mm for all other reaction zones) and the reagents were sequentially mixed using Teflon T-mixers (1.6 mm i.d.). Clogging of the system occurred in some cases after enolate formation during the reaction with the electrophile. To avoid clogging the electrophilic addition reaction zone, including the T-mixers, was immersed in an ultrasound bath. Sonication of tubing and chips is often used in continuous flow chemistry to avoid clogging when formation of solids is expected, as well as to enhance



Scheme 1. LDA mediated coupling of t-butyl propionate with methyl formate.

mass transfer in biphasic reaction systems.[18,19] The reaction mixture was quenched in-line with a feed of distilled water at room temperature, usually producing a biphasic mixture which separated by gravity in the collection flask. The system was pressurized using a back-pressure regulator at 5 bar. Due to the high reactivity of the reagents and intermediates generated, strictly anhydrous conditions were required for all experiments. Owing to the undesired presence of moisture in some reagents, the amount of LDA generated and utilized, with respect to the ester, was set to ca. 2 equivalents to ensure reproducible results. Higher amounts of LDA did not lead to significantly improved results.

As generation of LDA for its direct use in continuous flow is a well-known procedure,[8–12] we focused our study on the conditions for the generation of the lithium enolate intermediate and its reaction with electrophiles. Evaluation of the reaction kinetics of the enolate formation after addition of t-butyl propionate to a freshly prepared solution of LDA was initially attempted in batch. The reaction was monitored by FTIR using a ReactIR probe (Mettler-Toledo), which was immersed into the reaction mixture. Notably, the deprotonation of the ester by LDA proved to be very fast, faster than the typical instrument measuring time (15 s) even at −78 °C. We then decided to directly optimize the residence time in the continuous flow reactor. By using tubular reactors of different internal volumes for the enolate formation reaction zone (and keeping all other reaction parameters constant) a set of reactions with variable residence time was obtained (Table 1). For each experiment the reactor was run for several minutes until steady-state conditions were assured. Then, aliquots of the crude reaction mixture from the reactor output were collected and analyzed by GC-FID after acidification to pH 2 and separation of the organic phase. A comparatively long residence time of 5 min for the electrophilic addition step was used in all cases. The GC yield achieved increased from 1 s reaction time to 5 s (entries 1–3).

Further improvement in the GC yield was not observed when the reaction time was increased to 10 s (entry 4). Cryogenic conditions were not needed for this reaction in continuous flow. Thus, analogous results were achieved at −78 °C and 0 °C, including comparable isolated yields (entries 5–7). Variable amounts of the undesired homo-Claisen condensation product were observed in all cases, reducing the yield of the reaction. It should be noted, however, that similar results were also obtained in batch on small scale for this substrate (ca. 1 mmol). The small volumes involved likely allow good heat transfer to the cooling medium thus keeping the selectivity high (this would most probably not be the case for larger scale experiments, where temperature overshoots are difficult to control).

The residence time for the electrophilic addition of the lithium enolate to methyl formate was evaluated in a second set of experiments (Table 2). These experiments, executed using a small scale batch procedure, showed the high reactivity of the lithium enolate towards methyl formate. After 30 s the reaction was essentially completed with a GC yield of 90% (Table 2, entry 1). Increased reaction times, up to 30 min (entries 2–5) provided identical results, indicating that the resulting α-formyl ester is stable under the reaction conditions and side reactions do not occur (i.e. multiple alkylation). Unfortunately the observed reaction times could not be reproduced in a fully continuous setup with pre-cooling of the methyl formate solution stream. A residence time of 1–2 min was required. We ascribe this variation to the effect of adding a room temperature reagent solution vs a precooled stream.

As mentioned above, the water stream used to quench the reaction in-line produced a biphasic mixture that separated by gravity in the collection flask. Acidification of the aqueous layer with 2 M HCl to pH 2 under stirring permitted a simple workup procedure by extraction of the product to the organic phase.