Selective Decarboxylative Mono- and Difluorination of β-Ketoacids in Continuous Flow Mode

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Introduction

Fluorination, involved in the synthesis of fine chemicals like active pharmaceutical ingredients (**APIs**), represents a useful tool for improving both pharmacodynamics and pharmacokinetics. Fluorine as the most electronegative atom enables precise alteration of nearby functional groups, which can affect the bioavailability of pharmaceutical agents. Their interaction with the active site of their appropriate target protein can be enhanced by fluorine insertion, which alter conformational preferences, thus potentially improving drug efficiency.[1] Several fluorination methods show drawbacks regarding atom economy and efficiency, so there is still a need to develop an **efficient and selective synthesis for fluorinated compounds**.

Approach

We investigated a process which allows a selective mono- or difluorination of the benchmark β-keto acid **1** with an improved synthesis method in continuous flow mode, compared to literature.[2,3]

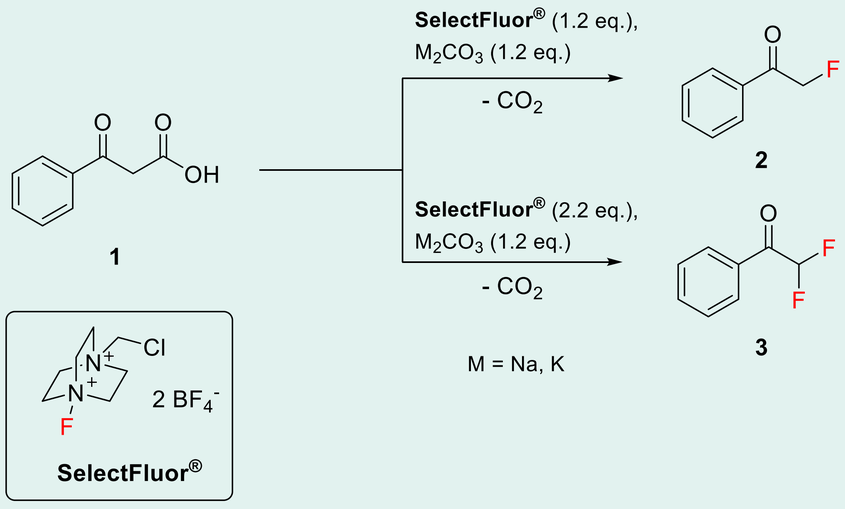


Figure 1: Mono- and difluorination of the benchmark substrate 3-oxo-3-phenyl propionic acid 1 with SelectFluor®.

Influences of different additives on selectivity

We **started** with batch experiments at room temperature, SelectFluor® as source for electrophilic fluorine and different alkaline carbonates as base for deprotonation of the substrate **1**. K_2CO_3 was exposed as the most sufficient reagent. The absence of K_2CO_3 led to the formation of phenacyl difluoride **3**, although 1.2 equivalents of SelectFluor® were used, decreasing the selectivity towards the monofluorinated product **2**.

Under higher temperatures (T = 60 °C), other alkaline carbonates showed similar effects. We investigated that the selectivity of the mono- and difluorination is significantly altered by the presence of certain **anions**. In this case, a **carbonate source** leads to the highest selectivity towards the monofluorination product **2**.

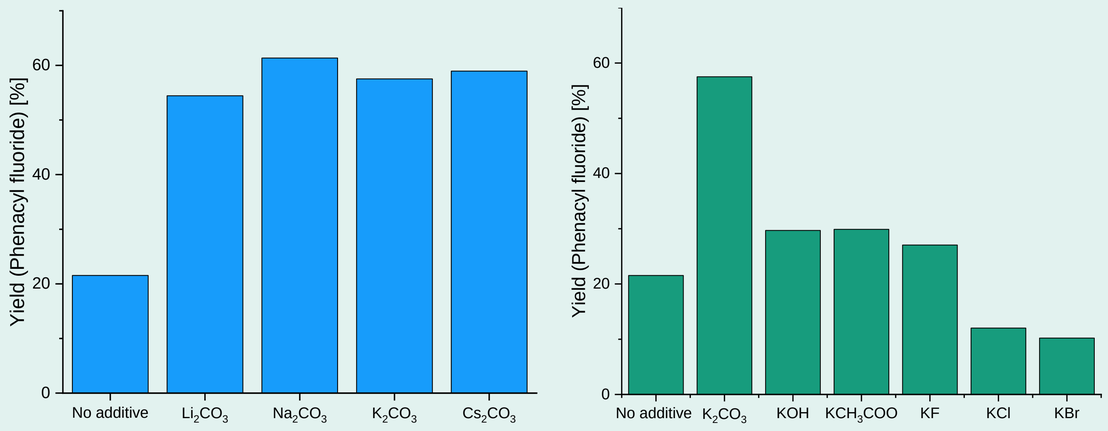


Figure 2: Impact of different additives on monofluorination of 3-oxo-3-phenyl propionic acid 1. Batch conditions: 30 mM substrate (1.0 eq.), 36 mM SelectFluor (1.2 eq.), 36 mM additive (1.2 eq.) in MeOH/water (1:2). T = 60 °C, t = 60 min.

Process development in continuous flow mode

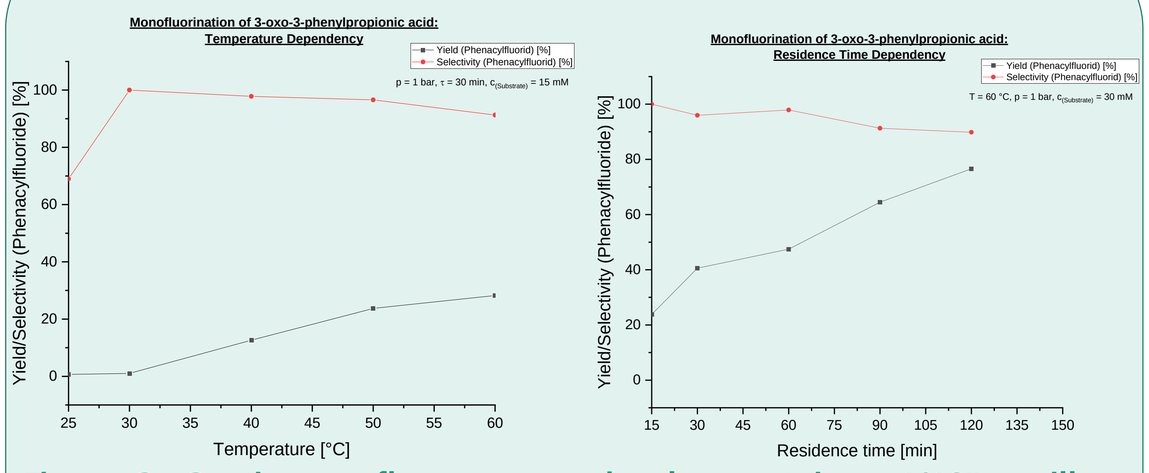
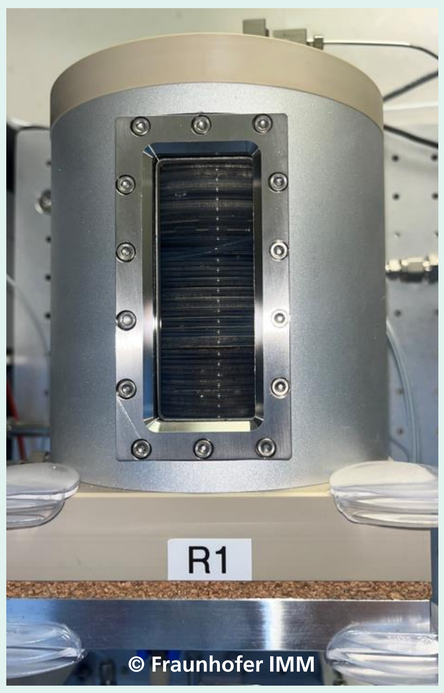


Figure 3: Continuous flow process development in a 1/16" capillary reactor. Temperature (left) and residence time (right) were altered to achieve the best parameters for increased yield and selectivity of phenacyl fluoride 1.



The **transfer from batch to flow conditions**, using a capillary reactor for enabling a continuous processing, showed excellent results after further process development. We are able to perform the **monofluorination with yields up to 72 %** without using any additional phase transfer catalyst[2] and increasing the reaction time from up to 48 hours[2] to only one hour.

Figure 4: Thermal capillary reactor (1/8") for the continuous flow fluorination reactions. Reaction conditions after final process intensification: SelectFluor® (0.36 mM, 1,2 eq.), substrate (0.30 mM, 1.0 eq.) and K_2CO_3 (0.36 mM, 1.2 eq.) in MeOH/water (1:2), T = 60 °C, τ = 60 min

By increasing the equivalents of SelectFluor®, a **difluorination** is also enabled (Yield (isolated): 59%). This allows a heavily improved synthesis method compared to literature, where toxic solvents, e.g. nitro methane and reaction times up to several days are required to sufficiently synthesize the phenacyl difluoride **3**.[3]

Continuous flow two-phase extraction

Due to the intense mixing in the capillary, sufficient extraction of the formed product can be performed during the reaction course by performing two-phase reactions.

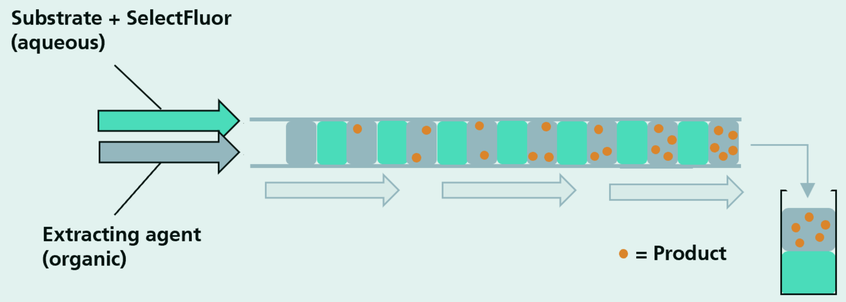


Figure 4: Continuous flow extraction during the synthesis of phenacyl fluoride 1. The aqueous solution, including the substrate, SelectFluor® and K_2CO_3, and the extracting agent were fed into the capillary reactor.

At this point, we plan to use the established continuous flow synthesis plant for additional reactions, performing **multiple-step cascade reactions**.

References

[1] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, "Fluorine in Medicinal Chemistry", *Chemical Society reviews* **2008**, *37*, 320..
[2] J. Li, Y.-L. Li, N. Jin, A.-L. Ma, Y.-N. Huang, J. Deng, „A Practical Synthesis of α-Fluoroketones in Aqueous Media by Decarboxylative Fluorination of β-Ketoacids"*Adv. Synth. Catal.* **2015**, *357*, 2474.
[3] Y.-L. Li, J. Li, J. Deng, „Practical Access to Difluoromethyl Ketones via Straightforward Decarboxylative Difluorination of β-Ketoacids", *Adv. Synth. Catal.* **2017**, *359*, 1407.

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