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COMMUNICATIONS

Continuous flow synthesis of Celecoxib from 2-bromo-3,3,3-trifluoropropene

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Abstract

We describe the total flow synthesis of the widely prescribed anti-inflammatory COX-2 inhibitor Celecoxib from 2-bromo-3,3,3-trifluoropropene, as a convenient and available trifluoromethyl building block, to generate trifluoropropynyl lithium and to trap it immediately with an aldehyde. Oxidation of the obtained alcohol into ketone followed by condensation with 4-sulfamidophenylhydrazine afforded the targeted drug with full regioselectivity. It is noteworthy that the quality of these flow reactions (50% overall yield within 1 h cumulated residence time over 3 steps) directly furnished the target API and intermediates with excellent purity.

Keywords Organofluorine chemistry · Active pharmaceutical ingredients · Organolithium chemistry · Oxidation · NSAID

The current situation with the COVID-19 pandemic has revealed the significant limitations of several countries in providing large quantities of active ingredients for the treatment of the pandemic. Indeed, considerable drug shortages were cruelly experienced, jeopardizing the capacity of the public health systems to treat their fellow citizens. Over the last twenty years, the production of intermediates and active pharmaceutical ingredients (API) has been stopped in numerous countries for economic reasons, which is intrinsically linked to the batch method used to produce these active pharmaceutical ingredients. Indeed, the use of batch reactors means that, in order to produce more, their capacity must be increased, leading to high investments. However, over the last several decades new promising technologies have been integrated in organic synthesis, enabling to address some of the challenges and limitations faced by organic practitioners. Namely, continuous flow synthesis can have a number of advantages, including the ability to handle hazardous compounds safely, enhanced heat and mass transfers, improved selectivity of reactions, higher purity of compounds, as well as an accurate control over the residence time and stoichiometry, and even the performance of « batch-hopeless» reactions [1–4].

In the field of API, pharmaceutical industry expresses a strong interest in pyrazole scaffold compounds, since they are linchpins for the treatment of cancer, diabetes, central nervous system and metabolic diseases [5–8]. Among them, Celecoxib (Celebrex™), a NSAID used to treat inflammation and pain in various type of arthritis developed by G. D Searle & company and marketed by Pfizer, is considered as a blockbuster and widely prescribed ($1.129 billion retail sales in 2018) (https://njardarson.lab.arizona.edu/).

Pyrazoles are usually obtained via the cyclo-condensation of hydrazines with 1,3-dicarbonyl compounds. Hence, Penning, Talley and co-workers described the first batch synthesis of Celecoxib along with other 1,5-diarylpyrazoles in 1997 [9]. The authors noticed the exclusive formation of 1,5-regioisomers, when carrying out the condensation of the hydrochloride salt of the phenylhydrazine with 1,3-dicarbonyl compounds in either refluxing ethanol or MTBE. Subsequently, the group of Ley reported a continuous flow synthesis of celecoxib in a modest yield (48%) via the vitamin C-assisted reduction of a diazonium salt followed by hydrolysis and cyclo-condensation at 140 °C (Fig. 1) [10]. Afterwards, a very few Celecoxib continuous

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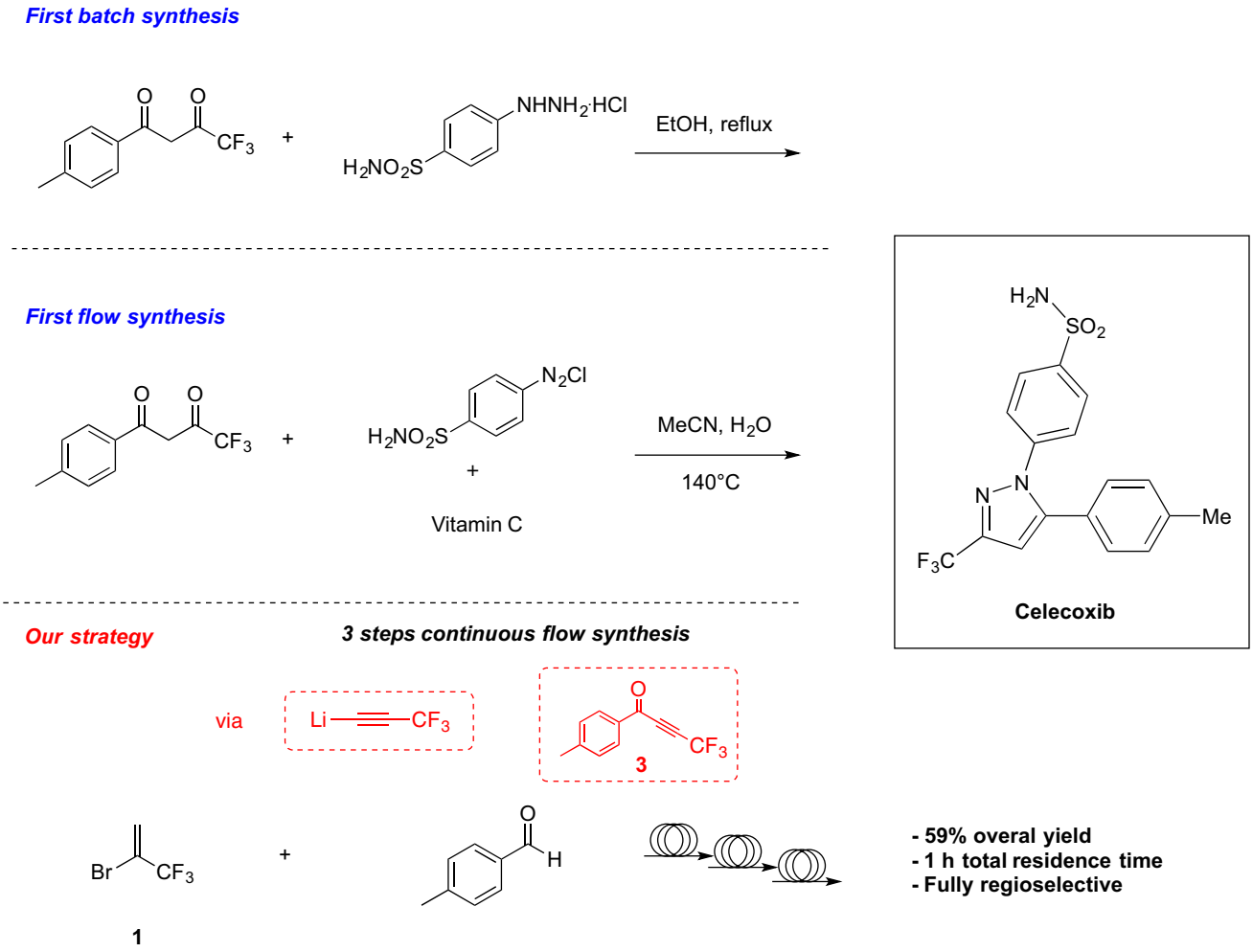

Fig. 1 Selected synthetic pathways to Celecoxib

flow syntheses were depicted, namely a process implying one-step system platform with in-line extraction and separation, based on cyclo-condensation of diketone and hydrazine hydrochloride in an *i*-PrOH/water mixture [11]. In 2020, Sandford described a batch synthesis of the same target through batch deprotonation of 2,3,3,3-tetrafluoropropene [12]. This year, a stepwise flow synthesis of Celecoxib was reported, starting from a Claisen condensation to access 4,4,4-trifluoro-1-(4-methyl-phenyl)-butane-1,3-dione followed by a cyclo-condensation reaction with sulfamidophenylhydrazine hydrochloride [13]. Along these lines, we now describe a simple, safe and time-saving three steps procedure for the preparation of Celecoxib. Starting from the commercially available 2-bromo-3,3,3-trifluoropropene **1**, the transient and difficult-to-handle gaseous 3,3,3-trifluoromethylpropyne was formed and converted into the corresponding lithium alkynyl to trap the appropriate aldehyde, furnishing an alcohol, which was successfully oxidized to a corresponding ketone. The latter was then reacted with 4-sulfamidophenylhydrazine via 1,4-conjugate addition/cyclization reaction with the formation of Celecoxib (Fig. 1).

For all steps in flow, we used the commercially available flow synthesis platform from Vapourtec (R2 and R4 combination). This system incorporates a pumping module (2 pumps) and a reagent module (4 reactors). The proposed synthetic route to the trifluoromethyl butynone is shown in Fig. 1. In this first step of the sequence, we generated the volatile 3,3,3-trifluoromethylpropyne (bp = -48 °C) from the deprotonation of the commercially available 2-bromo 3,3,3-trifluoropropene (BTP, **1**) with lithium diisopropylamide (LDA). A second deprotonation occurred to generate the nucleophilic lithiated alkyne that could react with an appropriate electrophile introduced through a third inlet. Unfortunately, the formation of the ketone **3** by trapping an ester, acyl chloride or Weinreb amide was not observed. However, the trifluoromethyl propynyl lithium reacted with *p*-tolualdehyde to afford the secondary alcohol **2** (Fig. 2).

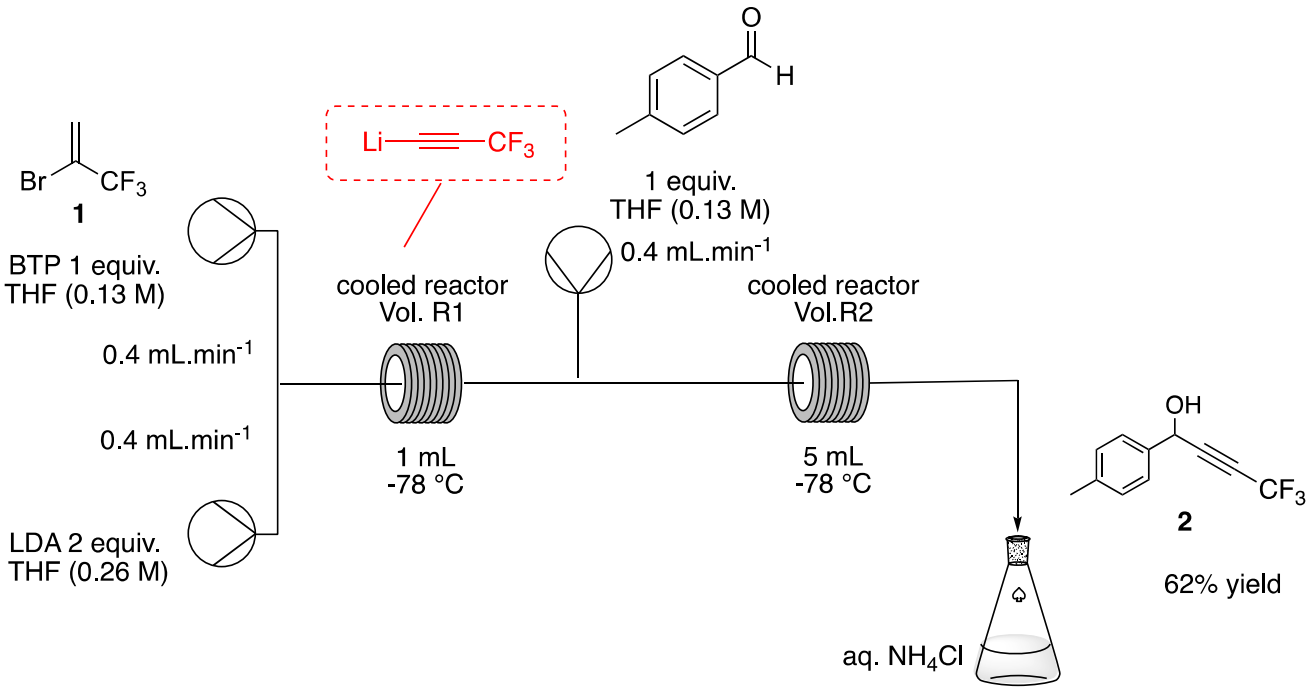

Fig. 2 Flow synthesis of aryl trifluoropropynyl alcohol **2**

Thus, BTP **1** (1 equiv. 0.13 M in THF) and LDA (2 equiv. 0.26 M in THF) were loaded through inlet 1 and 2, respectively, and mixed in a simple T-mixer at -78° C and the combined output was directed into a cooled 1 mL reactor at a total flow rate of 0.8 mL·min^{-1} (0.4 mL· min^{-1}/inlet; PFA tubing with ID = 1.0 mm) to form the lithiated alkyne. The latter was reacted in a second T-mixing piece at -78 °C with the stream of the *p*-tolualdehyde solution (1 equiv. 0.13 M in THF), which was introduced at the same flow rate of 0.4 mL· min^{-1}, using a portable SF-10 Vapourtec pump. The resulting solution passed through a cooled 5 mL reactor and the outlet was quenched with a NH_4Cl aqueous solution into an Erlenmeyer flask. After extraction, alcohol **2** was obtained in good 62% yield and a fairly decent purity to pursue the second step without further purification. Notably, the total residence time of this transformation comes up to only 5 min 25 s. Moreover, flow systems are particularly well suited for such reactions involving significant amounts of pyrophoric lithiated compounds and gaseous intermediates, whereas a batch process would be much more problematic and even dangerous to handle when scaling up. Interestingly, THF could be potentially exchanged for the industrially preferred MTBE, (62% yield in both cases).

Then, we designed the oxidation reaction of the secondary alcohol **2** into the targeted ketone **3** under continuous flow. Even though such transformation is a well-described textbook transformation, those dealing with fluorinated acetylenic alcohols are still underexplored and appeared tricky [14]. Initially, we tested the most common approaches, namely manganese(IV) oxide, IBX, as well as Oppenauer, Swern, Ley-Griffith oxidations, etc…., which were unfortunately inefficient in our hand. We found that the flow reaction with a solution of Dess-Martin periodinane (DMP) with the outlet connected to a short plug of silica allowed in-line removal of the DMP byproducts and gave a purification-free access to the pure ketone **3** (100% ^{1}H NMR yield). Nevertheless, the cost and instability of the DMP reagent hamper its use in large scale and process. Therefore, we continued our investigations, looking for a more suitable alternative. Eventually, we found out that passing a solution of alcohol **2** in DCM (0.2 M) through a packed bed reactor containing a mixture of barium permanganate (15 equiv.) and silica (1 g total) constituted an effective, simple and practical set up for the oxidation reaction (Fig. 3). Delightfully, with an optimized heating at 50 °C (and 6 bar BPR) with a flow rate of 0.1 mL·min^{-1}, a residence time of 10 min gave full conversion of **2** into **3**. The collection of the clean product at the reactor outlet was then easily accomplished, followed by a simple evaporation of the solvent (87% yield, no purification). Alternatively, the reaction could be carried out in acetone to circumvent the use of dichloromethane, without significant loss of the reaction efficiency.

The final step was the reaction between the solution of ketone **3** (0.1 M in EtOH) and the 4-sulfamidophenylhydrazine **4** (0.1 M in EtOH/H_2O, 3:1); the latter was easily prepared in batch via diazotization of amine, followed by the reduction of the N–N triple bond with tin(II) chloride. [15, 16] The condensation of these two reagents **3** and **4** was

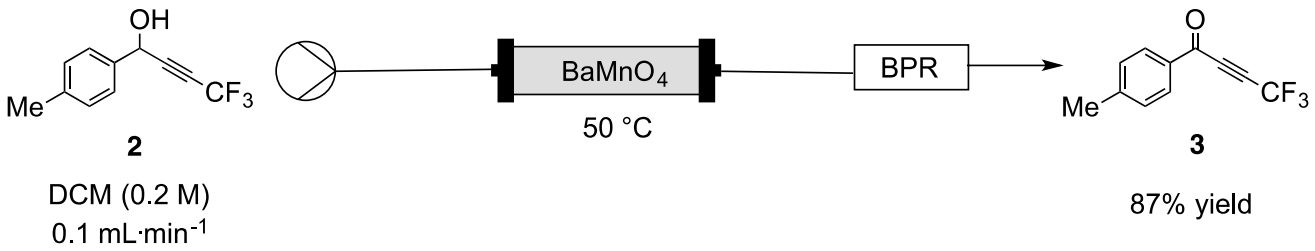

Fig. 3 Oxidation of alcohol **2** into ketone **3** through the $BaMnO_4$ packed bed reactor

performed in a classical flow system equipped with a simple T-mixing piece, a 10 mL tubular reactor (flow rate = 0.1 mL·min^{-1} per inlet) and 6 bar BPR, to allow the heating of the solvent at 100 °C (Fig. 4).

Under these conditions, the desired Celecoxib was obtained. After the evaporation of the solvents, ethanol was added and Celecoxib was fully solubilized, while insoluble byproducts were easily removed by simple filtration. The Celecoxib was then obtained in 90% yield as a pure product without any further purification.

In summary, we have developed the synthesis of the anti-inflammatory COX-2 inhibitor Celecoxib under continuous flow in three steps, starting from 2-bromo-3,3,3-trifluoropropene in a fair 50% overall yield. This novel synthetic pathway goes through the easy generation of trifluoropropynyl lithium and its subsequent trapping with an aldehyde in a single flow set-up, followed by an oxidation in a packed bed reactor (set-up 2) and the final condensation between a ketone and a hydrazine (set-up 3). The sum of these three residence times is close to 1 h and no tedious purification was required at any stage, with an appreciable time saving. Moreover, from a methodological standpoint, the flow chemistry of trifluoropropyne could be further developed and could even offer an access to other CF_3-containing APIs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41981-021-00205-x.

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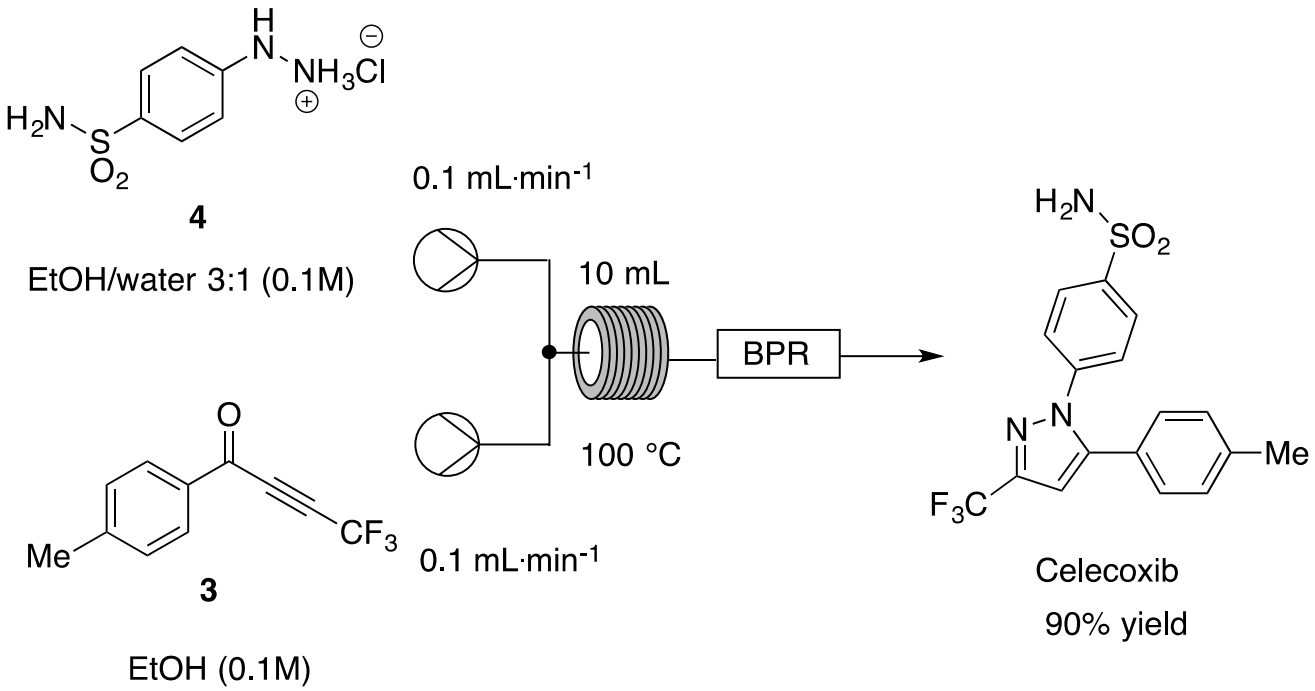

Fig. 4 Access to Celecoxib by condensation between ketone **3** and hydrazine **4**

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest

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