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A Novel and Efficient Continuous-Flow Route To Prepare Trifluoromethylated *N*-Fused Heterocycles for Drug Discovery and Pharmaceutical Manufacturing

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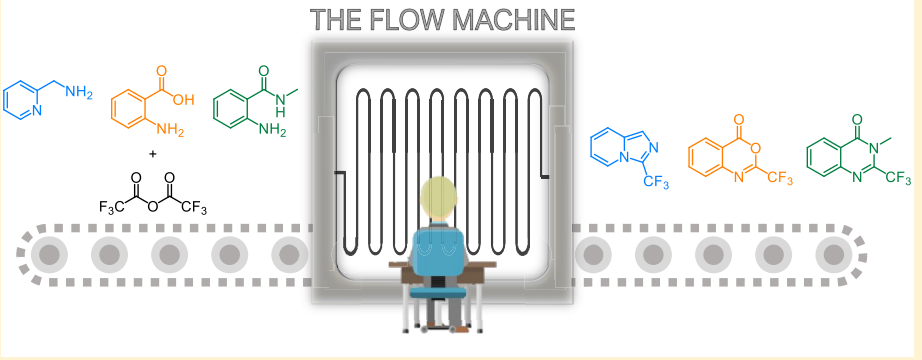
Supporting Information



ABSTRACT: Continuous-flow processing has become one of the fastest-growing research areas in chemistry in the last 10 years. Herein we disclose an automated and scalable continuous-flow route for the quick introduction of trifluoromethyl groups on a variety of heterocycles, with application in drug discovery and manufacturing. This involves the direct alkylation-cyclization of amines in the presence of trifluoroacetic acid or anhydride, cheap and readily available CF_3-containing building blocks. Compared to traditional batch reactions involving an intermediate purification step, the continuous-flow reactions occurred quickly and at mild conditions, with high yield and broad functional-group tolerance. The practical utility of the method was demonstrated by a gram-scale synthesis and by the estimation of modern green metrics.

1. INTRODUCTION

Flow chemistry (also referred to as continuous manufacturing) represents an emerging chemical technology with the potential to revolutionize the pharmaceutical industry.[1,2] Benefits of flow chemistry are seen throughout all areas of the pharmaceutical pipeline, from library synthesis in discovery[3] to rapid optimization of multistep reactions in chemical development.[4,5] More recently, there has been an interest in using continuous processes for drug delivery, due to the possibility of preparing extremely reproducible nanoparticles using continuous reactors.[6] When compared with traditional batch technologies, continuous manufacturing offers maximized reaction yields, reduced solvent consumption, minimal waste generation, and lower production costs.[7] In addition, because of the superior control over heat and mass transfer, it leads to increased safety margins, which is particularly important when working with energetic or highly corrosive reagents.[8] Therefore, there is a wide interest from academia and industry to translate batch chemistries to scalable continuous-flow methods.[9−12]

The synthesis of heterocycles is among the most relevant reactions in pharmaceutical practice. Heterocycles are often-encountered motifs in many drugs, as they provide improved protein interaction and enable the modulation of physico-chemical properties.[13,14] Imidazopyridines, benzoxazinone, and quinazolinone (Figure 1) are privileged scaffolds. Despite being so critical, methods to prepare heterocycles often rely on long reaction times, high temperatures, and low isolated yields.[15] Moreover, scientific challenges may arise during the drug discovery process, as heterocycles are prone to enzymatic metabolism in the position adjacent to the heteroatom (i.e., nitrogen, oxygen, and in some cases sulfur).[16] Therefore, strategies to reduce metabolism of these rings are often applied, and these include blockage of the site of metabolism and/or alteration of the electronic properties of the compound. Among those, the incorporation of electron-withdrawing

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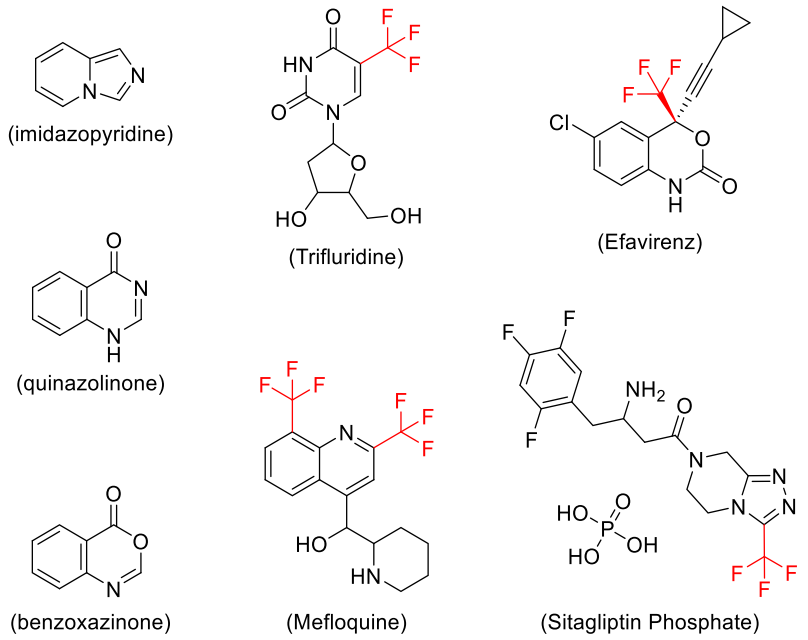
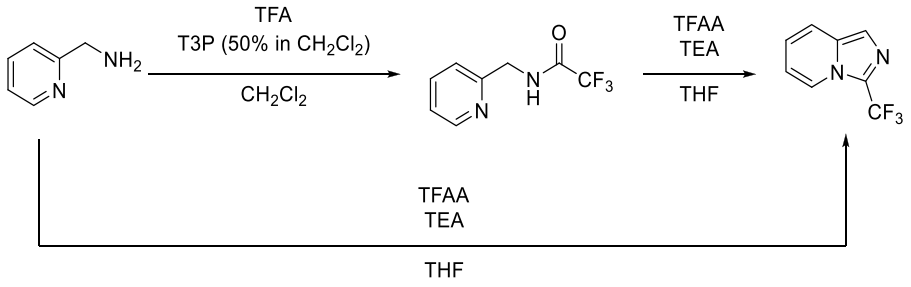


Figure 1. Common heterocycles in pharmaceuticals and a selection of drugs featuring trifluoromethyl groups.

Scheme 1. Summary of Two Novel Synthetic Strategies to Prepare Trifluoromethylated Heterocycles[23,24]



functionalities, such as trifluoromethyl groups, into the drug candidate is a widely employed synthetic artifice to protect against in vitro and in vivo metabolism (Figure 1).[17,18]

To incorporate a CF_3 group on a heterocycle, researchers have disclosed a variety of methods in the past using nucleophilic, electrophilic, or radical reagents, although most of these procedures are not industrially viable due to the high cost of the starting materials and poor atom economy.[18−24] Therefore, CF_3-containing arenes are still prepared today by converting trichloromethylated compounds into their fluorinated derivatives, using HF or SbF_3/SbF_5 at high temperature.

The recent disclosure of two reactions for the industrial synthesis of trifluoromethylated *N*-heterocycles from amines has attracted a wide interest in the field, due to its operational simplicity and the use of inexpensive building blocks (Scheme 1).[23,24] The reaction, in particular, proceeded either via amide bond formation on primary amines using trifluoroacetic acid (TFA) and propylphosphonic anhydride (T3P), followed by dehydrative cyclization in the presence of T3P or trifluoroacetic anhydride (TFAA) to give a trifluoromethylated heterocycle (Scheme 1). Alternatively, the reaction could proceed via one-pot condensation-cyclization of primary amines using TFAA and trimethylamine (TEA) (Scheme 1). These protocols provided for the first time good isolated yields in the synthesis of fluoro-substituted heterocycles, but the presence of strong acids and mild bases in the process hinted to potential thermal safety issues.

Taking inspiration from these two methodologies, we report herein a thermal investigation of the reactions and continuous-flow routes to prepare trifluoromethylated *N*-fused heterocycles. A literature analysis showed that such methods have been never implemented in a continuous-flow reactor, and most of the continuous-flow routes to prepare trifluoromethylated compounds are based on photochemistry, a technology which is not yet mature enough to be scalable.[25−27] All safety aspects related with the exothermic dosage of acids and bases have been controlled by performing the reactions in flow mode. Compared to batch conditions, dosing time was eliminated in the microfluidic pipes of the PFRs, which resulted in a constant mixing, avoiding undesired accumulation of unreacted reagent. Moreover, because of the increased surface-to-volume ratio, heat transfer was quasi-immediate and hotspot formation was minimized. As demonstrated in this work, this guaranteed good temperature control, low by-product formation, high safety margins, improved isolated yields, and higher sustainability values.

2. RESULTS AND DISCUSSION

2.1. Thermal Safety Analysis. We commenced our study by conducting a thermal investigation of the synthetic methods

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reported in Scheme 1.[25,26] In fact, for highly exothermic batch reactions, such as those involving the dosing of acids and bases in a reactive mixture, the risk of a potential loss-of-control is severe and may lead to a temperature increase, triggering a decomposition step and/or a pressure upsurge. Therefore, it is necessary to understand how a certain batch reaction can get out of control and, more generally, how to control such events in continuous mode.

There are specific experimental parameters that can be determined to assess the criticality of a chemical step.[28] In particular, after a cooling failure, the reaction temperature ($T_{reaction}$) increases due to the enthalpy of the reaction if unconverted material is still present. The adiabatic temperature rise (ΔT_{ad}) indicates the temperature increase in the absence of any energy exchange of the system with the surrounding. This depends on the amount of nonreacted material. The maximum temperature of the synthesis reaction (MTSR) is thus the sum of the reaction temperature and the adiabatic temperature rise (MTSR = $T_{reaction}$ + ΔT_{ad}). At this stage, a secondary reaction (typically a decomposition step) can be triggered and the heat produced leads to a further temperature increase. An important safety parameter is the maximum temperature for technical reasons (MTT), which is the maximal technically allowable temperature in the process due to technicality (for instance, the boiling point of the solvent or the temperature limit of the reactor materials). For this reason, MTT can be considered a safety barrier to operation. On the basis of the relative levels of these temperatures, five potential risk scenarios can be identified (Figure S1).

We have conducted a calorimetry analysis to determine the relative level of the temperatures indicated above. For the dosage of TFA and T3P (Table 1), the study showed that the addition of TFA into a reactive mixture was exothermal, with an adiabatic temperature rise above 50 °C, which would correspond to a medium (class 3) severity risk in case of cooling failure. Considering that MTSR > MTT, the reaction would require in batch the installation of technical safety measures, such as the dimensioning of a boiling, and is particularly adapted to flow mode, because of the superior heat dissipation.[29] For the dosage of TEA and TFAA (Table 2), which is needed in the cyclization and one-pot method, the calorimetry showed that the addition of TFAA into TEA is exothermal, with an adiabatic temperature rise largely above 50 °C. Considering its risk class scenario (MTSR > MTT, critical class 4), it is very unlikely that such a method would find application into a batch reactor. Overall, the investigation suggests that the implementation of both the two-step and one-pot reactions in a microfluidic reactor would be favorable for safety reasons.

Table 1. Reaction Calorimetry for the Dosage of TFA and T3P[a]

dosing agent	$T_{reaction}$ (°C)	ΔT_{ad} (°C)	*MTSR* (°C)	*MTT* (°C)
T3P	25	19	44	40
TFA		65	90	

[a]Pyridin-2-ylmethanamine (1 mmol) was dissolved in CH_2Cl_2 (7.5 mL, 0.13 M) and either T3P (50% in CH_2Cl_2, 3 equiv) or TFA (1.3 equiv) was dosed while monitoring the temperature rise. The reagent stoichiometry is based on earlier works.[23,24]

Table 2. Reaction calorimetry for the dosage of TFAA and TEA[a]

dosing agent	$T_{reaction}$ (°C)	ΔT_{ad} (°C)	MTSR (°C)	MTT (°C)
TEA	25	−2	–	39
TFAA		116	141	

[a]Pyridin-2-ylmethanamine (0.13 mmol) was dissolved in THF (2 mL, 0.07 M) and either TEA (2.6 equiv) or TFAA (2.5 mmol) was dosed, while monitoring the temperature rise. The reagent stoichiometry is based on earlier works.[23,24]

2.2. Transfer of the Two-Step Routes from Batch to Flow. We continued our study by exploring the suitability of transferring the synthesis of trifluoromethylated heterocycles (Scheme 1) from batch to flow. There is no standard procedure detailing how to move from a batch to a continuous-flow reactor. However, there are some hints based on reaction thermodynamics and kinetics that can simplify the reactor design.[30] As shown in Scheme 1, the two-step synthesis consisted of a trifluoroacetamide formation and a dehydrative cyclization. The one-pot reaction consisted of the cyclization step only. For these reactions, Table 3 shows the estimated reaction times and recommended reactor type, reactor material, and reagent addition. A commercial flow system satisfying all equipment requirements was chosen. It comprised two dual-piston pumps, a back-flow regulator to prevent backflow, and a back-pressure regulator. As TFA and TFAA are not compatible with many of the ceramic heads in standard pumps, the system was equipped with an autosampler, allowing the solution to be injected through a sample loop. This injection mode bypassed the pump heads and eliminated potential TFA and TFAA pumping issues.

With this in mind, we first analyzed the trifluoroacetamide formation in the presence of TFA and T3P. The reaction was studied in a continuous-flow system consisting of a coil-type tubular reactor of 26 mL internal volume, and the pressure was kept at 6 bar to avoid evaporation of the CH_2Cl_2 solvent (bp: 40 °C at 1 bar) and TFA (bp: 72 °C at 1 bar). The temperature and residence time were varied in a design of experiments (DoE) approach. This is a systematic, rigorous, and analytical method to determine the relationship between factors affecting a process and the output of that process.[31] Ultimately, this results in optimal conditions with a minimal expenditure of runs, time, and resources. A set of 19 experimental points was collected over two different substrates, namely, pyridin-2-ylmethanamine and 2-amino-*N*-methylbenzamide, to obtain, respectively, 2,2,2-trifluoro-*N*-(pyridin-2-ylmethyl)acetamide (data points in green) and *N*-methyl-2-(2,2,2-trifluoroacetamido)benzamide (data points in red). The collected results are summarized in the contour plot in Figure 2. Temperature and residence time in the microreactor were found to have a positive influence on the isolated yield, with residence time effect being more important than temperature effect. The figure depicts that a temperature of 40−60 °C and a residence time of 10−15 min can be selected as optimal.

Upon formation of trifluoroacetamide, the next step was the cyclization of the intermediate to give the trifluoromethylated heterocycle (Scheme 1, top). The optimization turned out to be challenging and it was not easy to adapt the batch experiment, conducted under inert atmosphere at 0 °C and stirring the reaction mixture until full conversion (typically for 24 h), to flow. Moreover, all intermediates from step 1 needed to be purified before being used for the cyclization, because the presence of side products or intermediates from the first step gave a drop of conversion in the second one. Because of the

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Table 3. Estimated Reaction Times and Recommended Reactor Design Parameters for the Trifluoroacetamide Formation and Dehydrative Cyclization in Scheme 1[a]

reaction type	reaction time	reaction phase	reactor type	reactor material	recommended reagent addition
trifluoroacetamide formation	<10 min	1 (liquid)	PFR	Hastelloy or PTFE	entry 1, T3P + TFA; entry 2, benzyl amine
dehydrative cyclization[b]	>10 min	2 (gas–liquid)	PFR	Hastelloy or PTFE	entry 1, TFAA; entry 2, trifluoroacetamide + TEA

[a]The table is based on the reaction/reactor matrix developed by Pouffe et al.[30] [b]This step applies to the one-pot method as well (Scheme 1).

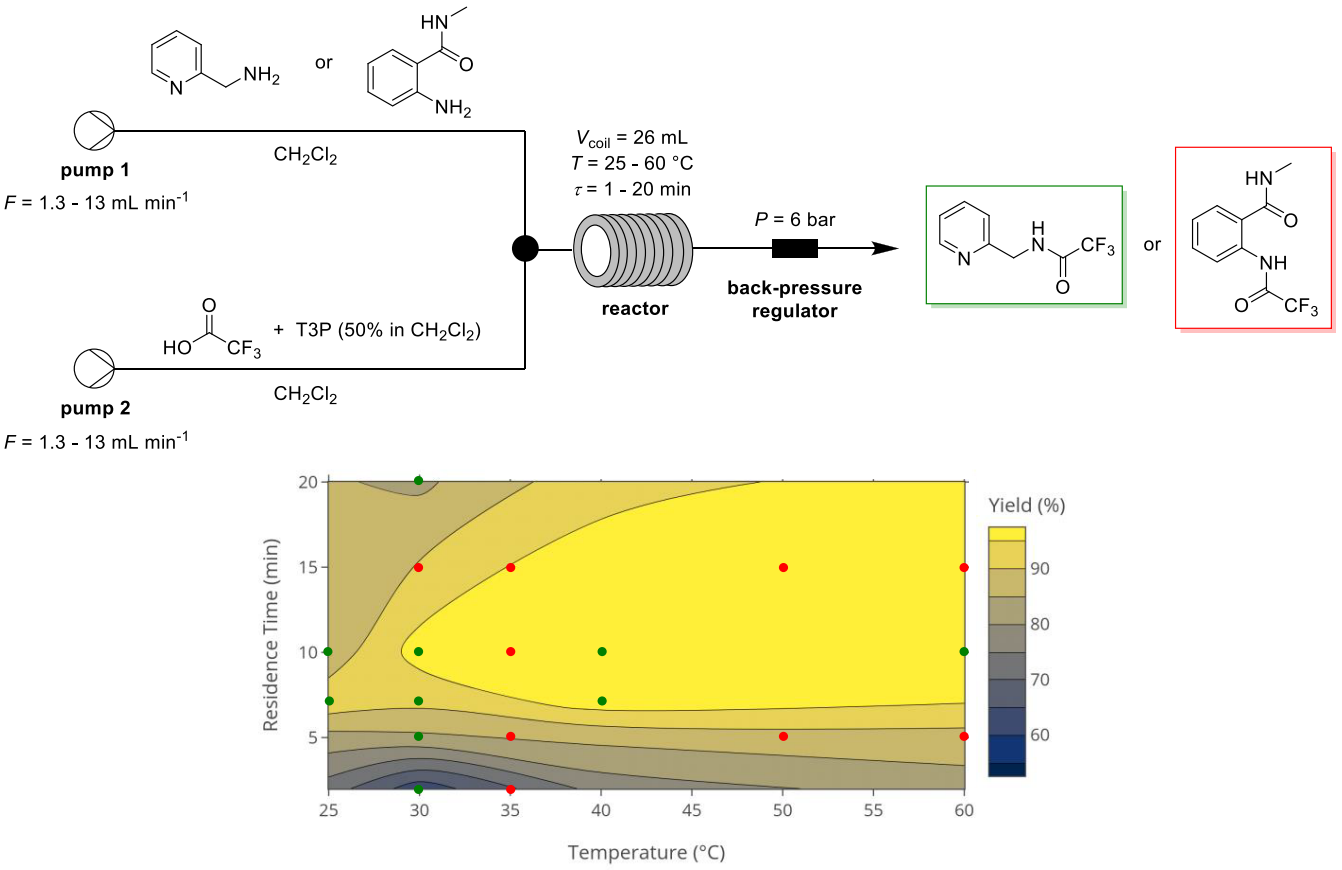

Figure 2. Continuous-flow trifluoroacetamide formation in the presence of TFA and T3P and contour plot depicting the isolated yield of trifluoroacetamide as a function of the reaction temperature and residence time. For the data points in green, pyridin-2-ylmethanamine (1 mmol) was dissolved in CH_2Cl_2 (7.5 mL); furthermore, trifluoroacetic acid (1.3 equiv) was dissolved in CH_2Cl_2 (5.75 mL) and a solution of T3P (50% in CH_2Cl_2, 3 equiv) was added. For the data points in red, 2-amino-*N*-methylbenzamide (1 mmol) was dissolved in CH_2Cl_2 (7.5 mL); furthermore, trifluoroacetic acid (1.3 equiv) was dissolved in CH_2Cl_2 (5.75 mL) and a solution of T3P (50% in CH_2Cl_2, 3 equiv) was added. This reagent stoichiometry was based on earlier works.[23,24] The solutions were pumped separately, mixed using a standard T mixer, and passed through a reaction chamber consisting of a 24 mL Hastelloy coil. As indicated in the contour plot, the reaction was conducted at different temperatures and residence times, keeping the pressure at 6 bar. Yields refer to purified products (see the Experimental Section).

exothermic reaction between TEA and TFAA, these two reagents had to be separated and injected using different entries. It was also decided to mix the starting material with TEA. A new DoE campaign was performed, focusing in particular on the imidazopyridine derivative, exploring a broad temperature range (from −50 to 80 °C), different pressures (1 and 6 bar), and variable TFAA:TEA stoichiometries (1.2:1.3 and 2.4:2.6).

As shown in Figure 3, the yield of the cyclized product increased with the temperature, reaching a maximal value at 80 °C (at 1 bar and TFAA:TFA = 1.2:1.3). On the other hand, we observed that higher pressures and TFAA:TEA amounts would be beneficial for the reaction. In fact, at T = 80 °C, P = 1 bar, and TFAA:TEA = 1.2:1.3, we obtained the trifluoromethylated imidazopyridine with 80% yield. At T = 80 °C, P = 6 bar, and TFAA:TEA = 2.4:2.6, the trifluoromethylated imidazopyridine was prepared with a quantitative (>99%) yield. Overall, a temperature of 80 °C, a pressure of 6 bar, and a TFAA:TEA stoichiometry of 2.4:2.6 were chosen as optimal (at a residence time of 30 min). The fact that the second step required a pressure of 6 bar was considered positive, as this would avoid the evaporation of TFAA (bp: 39 °C at 1 bar) and THF (bp: 66 °C at 1 bar).

With the two steps optimized individually, we performed a broad substrate scope analysis, exploring the suitability of the two methodologies for the synthesis of several trifluoromethylated heterocycles. Table S1 summarizes these results. The isolated yields were moderate-to-good in most cases. The reactivity dropped in the presence of inductive electron withdrawing functional groups, such as halogen atoms. In

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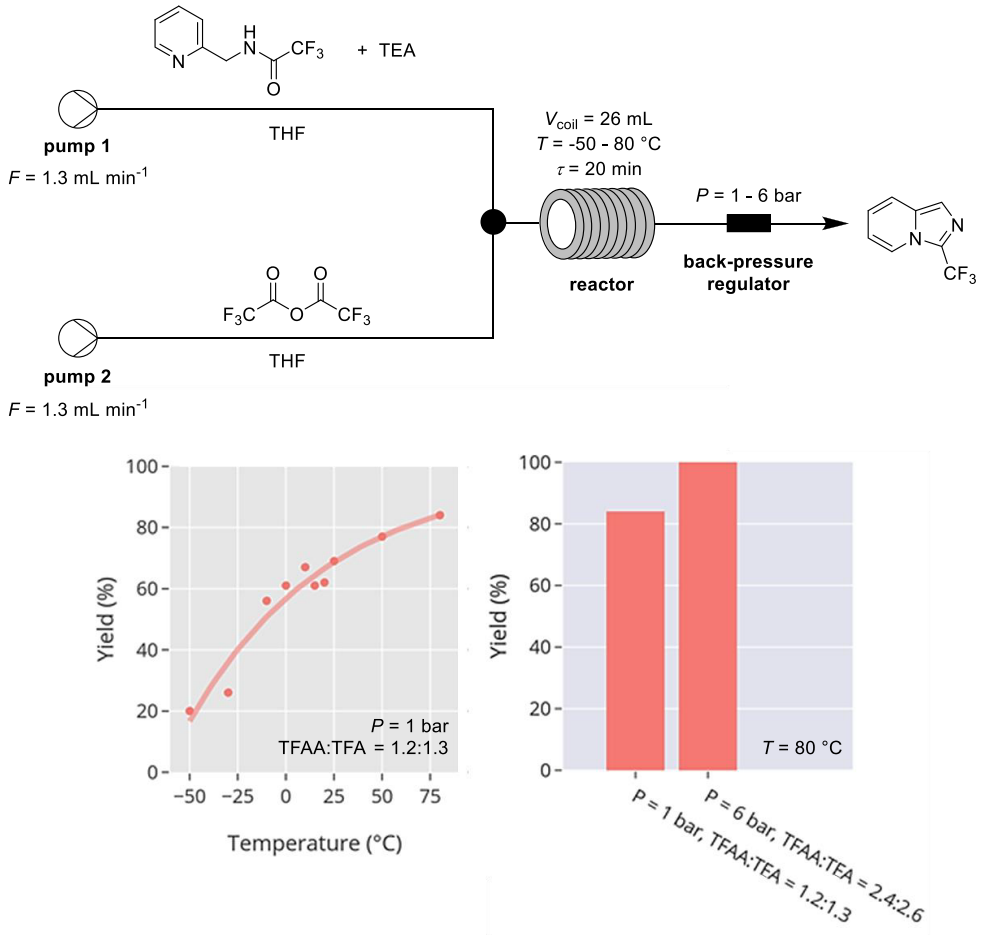

Figure 3. Continuous-flow cyclization of trifluoroacetamide and graphs showing the isolated yield of trifluoromethylated imidazopyridine as a function of the reaction temperature, pressure, and TFAA:TEA stoichiometry. The trifluoroacetamide intermediate (0.15 mmol) was dissolved in THF (2 mL) and TEA (1.2 or 2.4 equiv) was added; furthermore, TFAA (1.3 or 2.6 equiv) was dissolved in THF (2 mL). The reagent stoichiometry is based on earlier works.[23,24] The solutions were pumped separately, mixed using a standard T mixer, and passed through a reaction chamber consisting of a 24 mL Hastelloy coil. The reaction was conducted at different temperatures and pressure. Yields refer to purified products (see the Experimental Section).

addition, compounds with bulky substituents ortho to the heteroatom (i.e., nitrogen or oxygen) of the heterocycle showed lower reactivity compared to its constitutional isomers (para- and meta-substituted). The low selectivity for compound in entry 8 (Table S1) could be explained by the observed cleavage of the *tert*-butyl group in the presence of TFAA. The obtained results proved that it is possible to extrapolate the applicability of the developed two-step continuous-flow conditions to different heterocyclic precursors. It is important to note that, for safety aspects, the two reaction steps could not be integrated into a single, cascade-type process, because we observed that the presence of the first base, acid, and eventual byproducts from step 1 in the reacting mixture prevented the second reaction. The two reaction steps were thus conducted in sequential mode, with the cyclization after acetamide formation and purification.

2.3. Development of a One-Pot Flow Route. In view of a process simplification, avoiding intermediate workup and purification steps, and with the goal of further increasing safety margins, we considered performing the two reactions in a single step and using TFAA as both CF_3-source and dehydrative cyclization agent, as shown in Schäfer et al.[24] We tested our hypothesis on the imidazo[1.5-a]pyridine precursor, using the flow system in Figure 4.

We kept the reaction conditions optimized in Figure 3, slightly increasing the TEA:TFAA ratio to push the reaction to full conversion. Also in this case, TEA was premixed with the starting material and TFAA was injected in a separate line. The initial test showed satisfying conversion levels (80−100%), indicating no need for an additional DoE assessment. The method was thus applied with a broad substrate variation and, as shown in Figure 4, good-to-excellent isolated yields were obtained for a variety of heterocycles, including imidazopyridines (**4a**−**4f**), imidazopyridazine (**4g**), benzoxazinones (**4h**−**4l**), and quinazolinones (**4m**−**4r**). The yields were higher than those reported in Table S1 for the two-step continuous-flow process. The mildness of the reaction conditions could be further demonstrated by the introduction of several sensitive functional groups, such as methoxy (**4e**) or allyl (**4q**). Moreover, some of the scaffolds reported here (**4e**, **4f**, **4i**, **4k**, **4n**, and **4q**) have been never prepared before.

The scalability of the one-pot method was demonstrated for two compounds of interest. In particular, during 8 h continuous operation, we reprepared **4d** with ca. 60% isolated yield (>99% purity by ^{1}H NMR), validating the results

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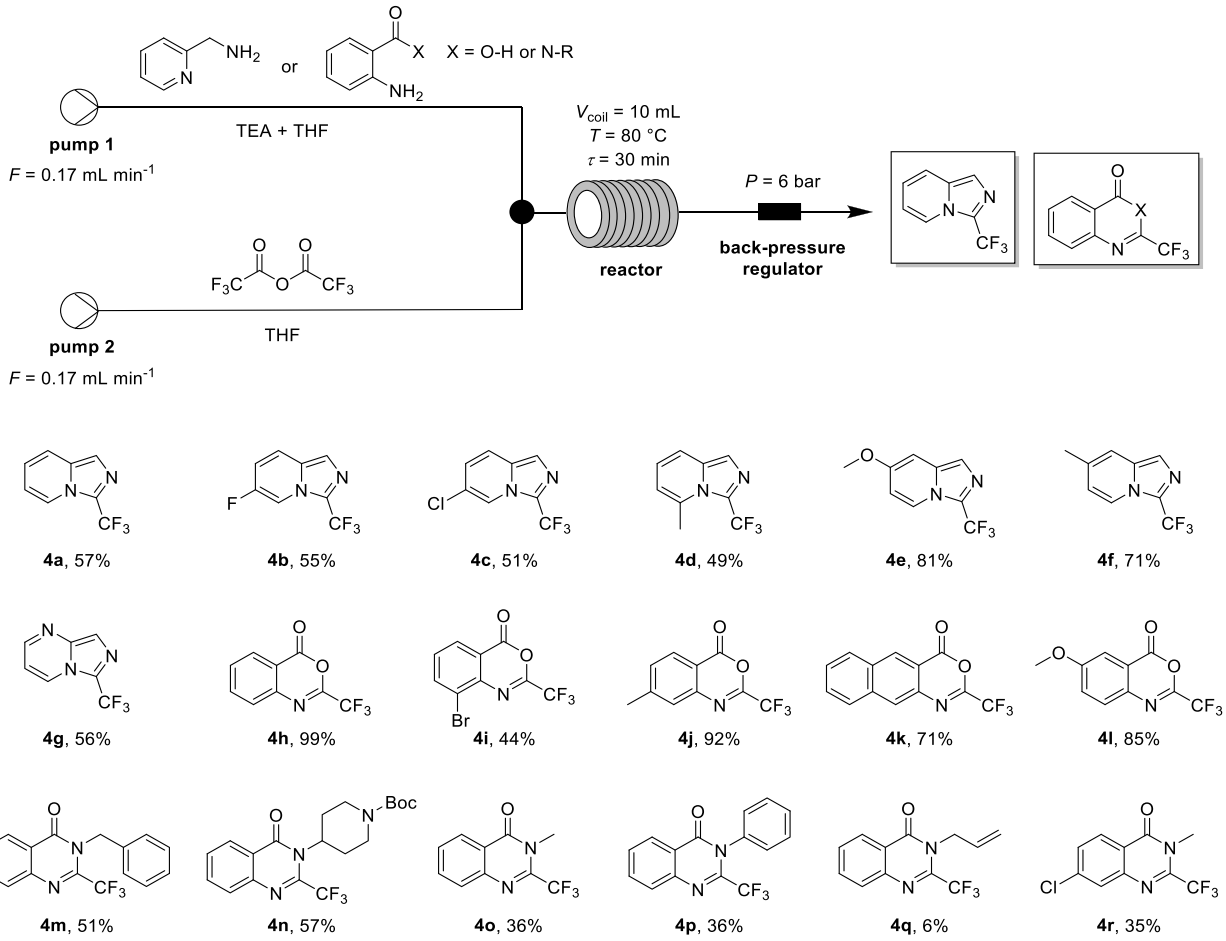

Figure 4. One-pot, continuous-flow synthesis of trifluoromethylated heterocycles. The amine reagent (0.133 mmol, 1 equiv) and TEA (0.43 mmol, 3.2 equiv) were dissolved in THF (2 mL); furthermore, a solution of TFAA (0.37 mmol, 2.8 equiv for compounds **4a**−**4g** and **4m**−**4r**; 0.47 mmol, 3.5 equiv for compounds **4h**−**4l**) was dissolved in THF (2 mL). The solutions were pumped separately, mixed using a standard T mixer, and passed through a reaction chamber consisting of a 10 mL Hastelloy coil, kept at 80 °C and 6 bar. Yields refer to purified products. Details are given in the Supporting Information.

obtaining at small scale, and reaching a productivity of 1 g/h. This productivity level is acceptable for any medicinal chemistry application, as it would enable the quick synthesis of scaffolds in gram quantities. Interestingly, no pumping (or any technical) issues were observed during the scale up experiments, pointing to the robustness of the flow system and method developed.

2.4. Process System Engineering, Green Metrics, and Cost Analysis. Green chemistry is the area of research focusing on the designing of products and processes that minimize the use and/or generation of hazardous substances. Green metrics are therefore an important tool to promote a safe, sustainable, and waste-minimizing chemistry and have demonstrated positive correlation to process economics.[32] For example, lower E-factors are indicative of reduced manufacturing costs, reflecting lower process materials inputs and outputs, reduced costs from hazardous and toxic waste disposal, improved use of manufacturing capacity, and reduced energy demand.[33,34]

To verify that the one-pot method was able to increase the greenness of the reaction compared to the initial two-step process, we have estimated the process mass intensity (PMI), the E-factor (EF), the relative process greenness (RPG), the relative process improvement (RPI), and the overall process improvement (oPI).[34] In addition, we have conducted a cost analysis. All calculation details are given in the Experimental Section. As shown in Table 4, the continuous-flow one-pot method is clearly more sustainable and cost-effective than the two-step reaction, both in batch and flow mode. This improvement is related to the absence of any intermediate workup and purification step in the one-pot method, and in the reduction of the process step complexity through development of a combined synthetic approach, leading to a more efficient and simplified synthesis procedure.

Table 4. Green Metrics and Cost Analysis

metrics	one-pot[a] flow	two-step[a] flow	two-step[a] batch
overall yield (%)	57	51	13
PMI (−)	183	496	1728
EF (−)	182	495	1727
RPG (%)	14[b]	5[c]	–
RPI (−)	9[b]	4[c]	–
oPI (−)	5[b]	2[c]	–
cost (USD/$g_{product}$)	100	591	2355

[a]Synthesis of **4a**. [b]Process improvement compared to the two-step reaction in flow mode. [c]Process improvement compared to the two-step reaction in batch mode.

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3. CONCLUSIONS

Fluorinated organic molecules are highly valuable but are generally challenging to synthesize efficiently. In this work, a novel flow route for the synthesis of trifluoromethylated heterocycles has been developed and presented. The approach constitutes a significant improvement compared to the original batch method, which was based on a two-step reaction and intermediate chromatographic isolation, and to alternative literature procedures based on photochemistry. The use of a continuous-flow microreactor enabled rapid reaction optimization, precise control of the reaction conditions within the small microreactor pipes, avoidance of waste-generating workup and purification procedures, and reduction of all manual handling steps. Coupling of the high-throughput continuous-flow system with modern design of experiments capabilities maximized the productivity of the flow reactor for the screening and optimization of experimental parameters. The obtained one-pot continuous-flow route could be generalized to a variety of building blocks, scaled up to multigram amounts of target heterocycles, and demonstrated to be beneficial in terms of green metrics and cost efficiency. In our view, this one-pot method could find useful applications for the rapid, modular, and automated introduction of halogenated moieties in diverse heterocycles for pharmaceutical and agrochemical sectors.

4. EXPERIMENTAL SECTION

Analytics. All chemicals employed in this study were purchased and used as such, with no further purification. Liquid chromatography−mass spectrometry (LC-MS) analyses to monitor reaction progress were performed on an analytical Agilent G4220A pump coupled with Thermo MSQ Plus mass spectrometer (ionization: ESI+), Dionex DAD-3000RS, evaporative light scattering detector (ELSD) Sedex 90, and using the Water column (2.1 mm × 50 mm, 2.5 μm) from Agilent Technologies. ^{1}H and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker NMR 400 MHz Spectrometer Advance 2 using 5 mm BBO probehead. Chemical shifts (δ) values were reported in parts per million using residual solvent signal ($CHCl_3$ or DMSO) as reference, and the coupling constants (J) were reported in Hertz. High-resolution mass spectrometric (HRMS) measurements were performed on a SYNAPT G2 spectrometer from Waters (ESI). Differential Scanning Calorimetry (DSC) was measured with a Mettler Toledo STARe System, using ceramic sensors and gold crucibles, and ramping the temperature from 20 to 400 °C, with a heating rate of 4 °C per minute. Calorimetric measurements were performed on the EasyMax 402 Heat Flow Calorimetry for Chemical Development and Safety Screening.

Reaction. The flow reactions were carried out on the Vapourtec R2S-Series microreactor, equipped with four pumps (two dual piston pumps and two peristaltic pumps) and an autosampler for automated reagent injection (2 mL loop) and product collection. Prior to each reaction, the system was flushed with the reaction solvent to remove residual moisture. The reacting solutions were pumped at a flow rate F_L, mixed using a standard T mixer, and passed through a reaction chamber consisting of a 10 or 24 mL Hastelloy coil, kept at a fixed temperature T. In particular, cooling was achieved with a cryostat unit and high temperatures were reached by hot air circulation technology. The system was fitted with a back-pressure regulator at the outlet. The product at the outlet of the reactor was quenched at room temperature using MeOH (2 mL).

Purification. The solvent was evaporated under reduced pressure to obtain crude materials. The compounds from DoE investigation were purified by flash chromatography (heptane:EtOAc, from 100:0 to 70:30) on a prepacked silica RediSep columns (120 g) using the Teledyne ISCO CombiFlash RF system. The library compounds in Figure 4 were purified by preparative high-performance liquid chromatography on a Zorbax column using acid conditions. All yields reported in this work refer to purified compounds.

Calculations. The process mass intensity (PMI) was calculated as the ratio between the sum of raw materials, reagents, solvents and water, and the mass of the product obtained in the reaction. The E-factor (EF) was calculated as the ratio between the sum of raw materials, reagents, solvents, product and water, and the mass of the product obtained in the reaction. Therefore, EF = PMI − 1. Although EF is an important parameter to assess the sustainability of a process, the pharmaceutical industry has generally adopted the PMI as a more complete parameter. The relative process greenness (RPG) was calculated as the ratio of the green aspiration level (which was set to 26 kg of water per kg of product)[34] and the EF. The relative process improvement (RPI) is the difference between the RPG of the current process and the RPG of the reference process. The overall process improvement (oPI) was the ratio between the average of RPI and the difference between the numbers of steps in the current and reference processes. The process cost was calculated by summing the cost of raw materials, reagents, solvents, and water.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.iecr.9b01906.

Details on thermal safety and additional experimental and characterization data (PDF)

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Author Contributions

G.V. conceived the work. L.A.R. conducted all experiments. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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