

In-flow generation of thionyl fluoride (SOF₂) enables the rapid and efficient synthesis of acyl fluorides from carboxylic acids

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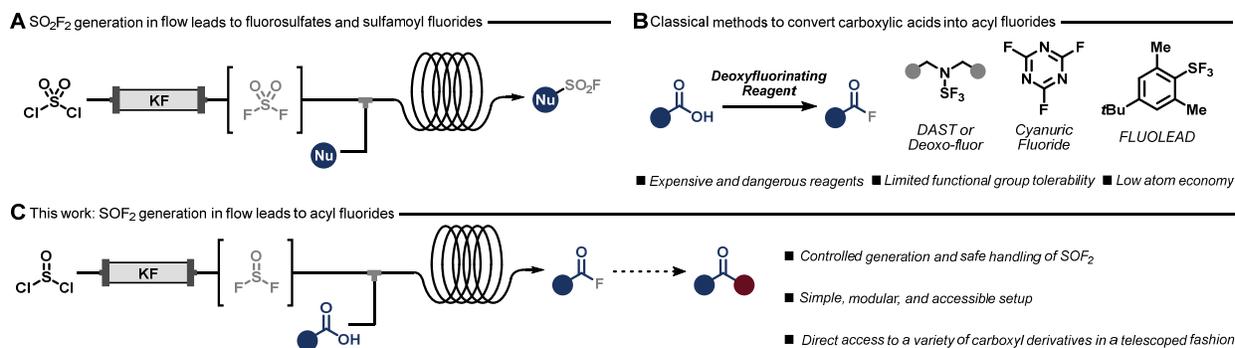
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Herein, we report an approach for generating thionyl fluoride (SOF₂) from the commodity chemicals thionyl chloride (SOCl₂) and potassium fluoride (KF). The methodology relies on a microfluidic device that can efficiently produce and dose this toxic, gaseous reagent under extremely mild and safe conditions. Subsequently, the in situ generated thionyl fluoride is reacted with an array of structurally and electronically differing carboxylic acids, leading to the direct and efficient synthesis of highly sought-after acyl fluorides. Importantly, our investigation also highlights the inherent modularity of this flow-based platform. We demonstrate the adaptability of this approach by not only synthesizing acyl fluorides, but also directly converting carboxylic acids into a diverse array of valuable compounds such as esters, thioesters, amides, and ketones. This versatility showcases the potential of this approach for a wide range of synthetic applications, underscoring its significance in the realm of chemical synthesis.

In contemporary synthetic laboratories, the utilization of toxic and hazardous gaseous compounds is subject to stringent regulations and control measures.^[1] The elusive nature of gases makes handling and dosing of these reagents a formidable challenge when employing traditional batch equipment.^[2] This has prompted the scientific community to devise engineered chemicals that can release *in situ* the desired gases via a chemical reaction.^[3] Alternatively, some solid reagents have been developed to serve as gas surrogates to perform the same types of transformations.^[4] However, these approaches often suffer from inefficiency due to the formation of stoichiometric by-products, and, paradoxically, they frequently necessitate the initial use of the parent gases for the synthesis of the reagents.

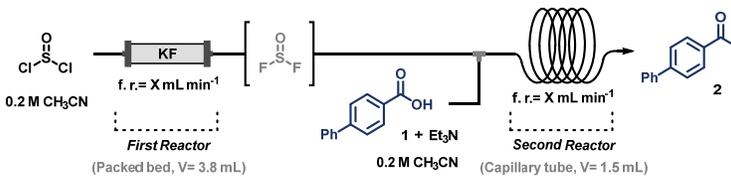
In our laboratory,^[5] we have recently made significant strides in leveraging the power of flow chemistry^[6] to directly harness and manage various gaseous reagents.^[7] Within this research framework, we have unveiled a modular flow platform capable of producing SO_2F_2 from readily available, bench-stable chemicals such as KF and SO_2Cl_2 (Scheme 1A) through a Cl–F exchange process.^[5a] The intrinsic containment properties of this flow system ensure the safe and controlled generation of the gaseous reagent, while also facilitating precise dosing of the reactive gas.^{[7],[8]} This breakthrough has enabled the execution of a diverse range of SuFEx (Sulfur(VI) Fluoride Exchange)^[9] ligations on a wide spectrum of compounds, including small molecules, biorelevant compounds, peptides, and proteins.



Scheme 1. A: In-flow generation of sulfuryl fluoride from sulfuryl chloride enables the rapid and direct synthesis of fluorosulfates and sulfamoyl fluorides. B: Selection of reagents capable of converting carboxylic acids into acyl fluorides. C: In-flow generation of thionyl fluoride allows the rapid and direct synthesis of acyl fluorides.

Recently, we wondered whether we could extend the range of gases generated through this microfluidic device to thionyl fluoride, SOF_2 . This gas has long been overlooked as a deoxyfluorinating reagent due to safety concerns associated with its handling and toxicity. Only recently, work by Sammis and co-workers demonstrated how stock solutions of this gas could be produced through an *ex situ* approach.^[10] However, this strategy requires multiple manipulations due to the batch setup, and forms the undesired F/Cl mixed species SOFCl and stoichiometric amounts of HCl , limiting its practicality and potential applications. Our interest in generating SOF_2 stemmed from its ability to swiftly convert abundant carboxylic acids into acyl fluorides. This stands in stark contrast to the limitations of low atom economy, limited functional group tolerability, and high costs associated with the use of engineered reagents like DAST, cyanuric fluoride, Deoxo-Fluor, or Fluolead, among others (Scheme 1B).^[11] Acyl fluorides are in fact an enticing class of carboxylic acid derivatives known for their synthetic utility as well as their enhanced stability and peculiar reactivity compared to their chloride analogs.^[12] Acyl fluorides are isolable and exhibit increased stability with respect to other acyl halides, and yet require mild reaction conditions to engage in diverse synthetic transformations.^[13] Thus, when reacted with nucleophiles, they offer a straightforward route to a wide range of valuable products such as esters, amides, or thioesters, almost regardless of the steric and electronic properties.^[14]

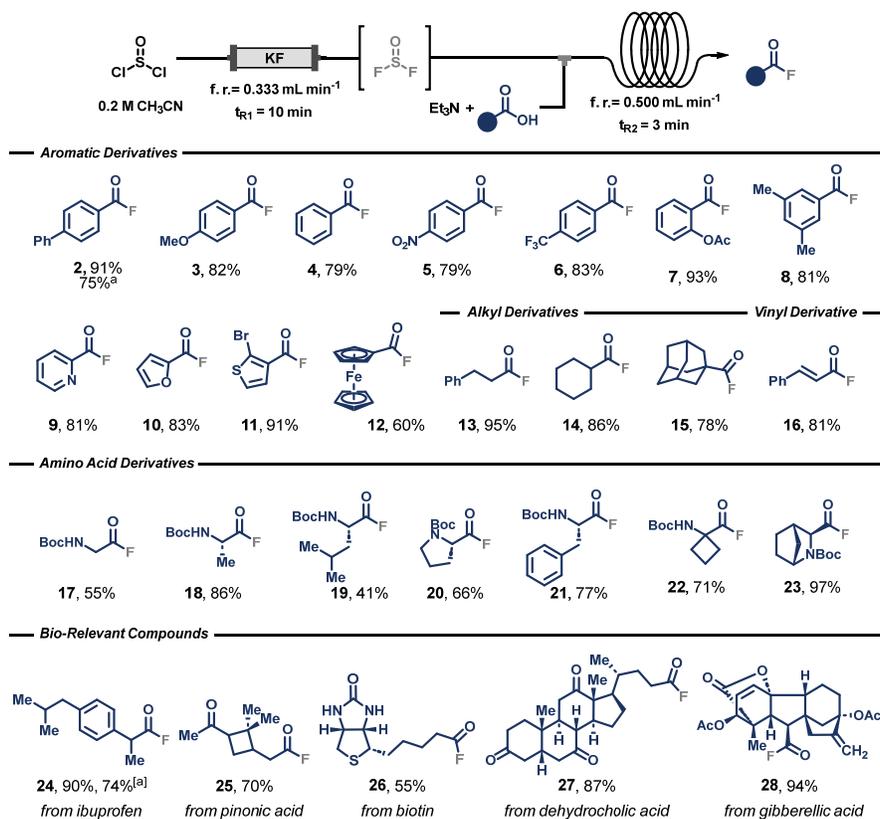
Herein, we report the development of a strategy that harnesses the power of a microfluidic device to form thionyl fluoride and swiftly use it to convert carboxylic acids into acyl fluorides (Scheme 1C). Furthermore, we demonstrate the feasibility of a multistep flow approach^[15] where the carboxylic acids are directly converted into amides, esters, thioesters, and ketones.

Table 1. Optimization of the reaction conditions.^[a]

Entry	Flow rate 1 st reactor	Flow rate 2 nd reactor	SOCl ₂ /acid ratio	Yield (%) ^[b]
1	0.400	0.500	4:1	> 95
2	0.333	0.500	2:1	> 95
3	0.262	0.500	1.1:1	84
4 ^[c]	0.333	0.500	2:1	> 95
5	0.600	1.00	1.5:1	94
6	1.20	2.00	1.5:1	> 95
7	1.50	2.50	1.5:1	92

[a] Reactions performed on a 0.5 mmol scale of carboxylic acid **1**, using 2.5 equivalents of triethylamine and 4-1.1 equivalents of thionyl fluoride. [b] Yields were determined by ¹⁹F NMR analysis, using 1,2-difluorobenzene as internal standard. [c] Reaction performed using 3 equivalents of Et₃N.

Our investigation commenced with an exploration of the feasibility of SOF₂ generation by flowing a solution of SOCl₂ in CH₃CN through a packed bed reactor filled with a 1:1 mixture of KF and glass beads (see the Supporting Information (SI) for details). We observed efficient and consistent formation of the coveted gaseous reagent regardless of the residence time of the solution within the packed bed reactor. Interestingly, the reactor cartridge itself has a reduced lifespan when decreasing residence time of the solution within it (see the SI for details). We reasoned that higher flow rates might lead to the formation of preferred flow channels, which prevent SOCl₂ from reacting with the remaining KF present in the packed bed reactor.^[16] Subsequently, we coupled the thionyl fluoride generator to a stream of CH₃CN solution containing a mixture of model substrate 4-phenylbenzoic acid **1** and Et₃N and studied the influence of the stoichiometry and the flow rates of the different feeding solutions (Table 1).



Scheme 2. Array of acyl fluorides synthesized by means of our device. To facilitate isolation, the solution of the acyl fluoride was treated with 1.05 equivalents of *N*-hydroxyphthalimide and yields (%) refer to the corresponding esters unless otherwise indicated. t_{R1} , t_{R2} : residence times in the first and second reactor, respectively. [a] The acyl fluoride was directly isolated.

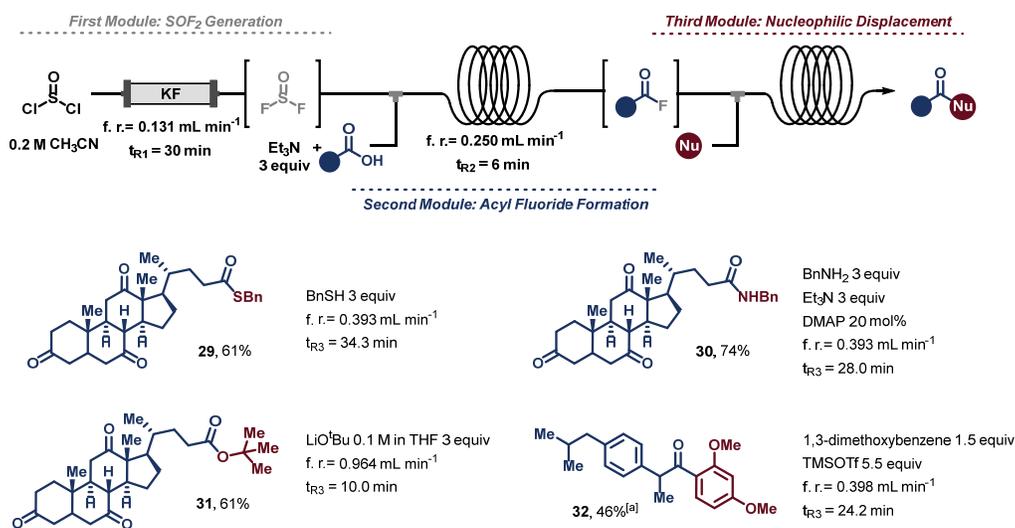
This process demonstrated exceptional efficiency, as the acyl fluoride formation occurred in high yields when employing 4, 2, and 1.1 equivalents of thionyl chloride with respect to the carboxylic acid (entries 1–3). Increasing the amount of the Et_3N did not diminish the acyl fluoride formation (entry 4). Furthermore, the reaction displayed impressive speed, with optimal yields achieved even at reduced residence times in the second reactor of 90, 45, or as little as 36 seconds (entries 5–7). In the case of entry 4, the productivity of this process amounts to 0.792 g h^{-1} and the space-time yield to $149 \text{ g L}^{-1} \text{ h}^{-1}$.

To showcase the robustness and versatility of this process, we selected the conditions detailed in entry 4 and varied the carboxylic acid partner (Scheme 2). We began by examining a wide array of aromatic carboxylic acids. The reaction is insensitive to the electronic nature of the substituents or their position on the aromatic ring. Indeed, electron-rich (2,3), electron-neutral (4) and electron-poor derivatives (5,6), as well as acids with substituents on the ortho (7) and meta (8) positions, were swiftly converted into the corresponding acyl fluorides

(79-93% yields). Moreover, the reaction also took place when heteroaromatic (**9–11**) or ferrocenyl (**12**) derivatives were used (60–91% yields). Subsequently, we assessed the generality of the process in terms of alkyl carboxylic acids. Primary (**13**), secondary (**14**), and tertiary (**15**) carboxylic compounds all yielded the corresponding acyl fluorides in good-to-excellent yields (78–95% yields). Similar success was observed when an α,β -unsaturated carboxylic acid was used (**16**, 81% yield). Moreover, several Boc-protected α -aminoacidic derivatives, such as glycine (**17**), alanine (**18**), leucine (**19**), proline (**20**), and phenylalanine (**21**), as well as non-natural structures such as cyclovaline (**22**) and azabicyclo[2.2.1]heptane-3-carboxylic acid (**23**) were smoothly converted into the targeted acyl fluoride derivatives (41–97% yield) with very little erosion of their enantiopurity (see SI). Finally, we demonstrated how the mild conditions of this approach make it suitable for the functionalization of structurally diverse bio-relevant compounds decorated with various functional groups, such as ibuprofen (**24**), pinonic acid (**25**), biotin (**26**), dehydrocholic acid (**27**), and gibberellic acid (**28**) (55–94% yields). Crucially, this method enables the exclusive formation of the acyl fluoride even in the presence of a ketone functionality (see **25** and **27**), which would be rapidly converted into a difluorinated motif in the presence of other deoxyfluorinating reagents such as DAST or Deoxo-Fluor.^[17]

After having found a set of optimal conditions to promote the formation of acyl fluorides and having assessed the generality of the scope, we embarked upon an endeavor to leverage the full potential of this class of compounds with this microfluidic device. As previously described, acyl fluorides are appealing intermediates to forge new carbon–carbon and carbon–heteroatom bonds. Exploiting the advantages offered by the modular flow chemistry approach, we envisioned a device comprising three sections (Scheme 3): the first module, in which SOCl_2 is converted to SOF_2 through Cl–F exchange; the second, in which the gaseous reagent is reacted with a carboxylic acid to yield the acyl fluoride; and the third, in which the acyl fluoride is finally mixed with a chosen nucleophile to furnish the target compound. This required re-optimization of the procedure (see the SI for details). Crucially, the equivalents of SOF_2 were lowered to 1.1 to avoid subsequent undesired reaction with the nucleophilic component within the third module. This adjustment, in turn, mandated an extension of the residence time within the second module to 6 minutes to ensure optimal acyl fluoride formation. It is worth noting that the productive use of 1.1 equivalents of SOF_2 in batch conditions would be extremely challenging to achieve, as the gas would inevitably evolve towards the headspace of the reactor. Under these finely tuned reaction conditions, our investigation was directed towards the exploration of potential coupling nucleophiles.

As expected, a thiol, an amine, and an alcohol could all be employed to obtain the corresponding thioester (**29**, 61% yield), amide (**30**, 74% yield), and ester (**31**, 61% yield) derivatives of dehydrocholic acid upon acyl substitution. Furthermore, we evaluated the possibility of forging C–C bonds. After a brief optimization of the reaction conditions already present in literature^[18] (see the SI for details), we were able to obtain ketone **32** in 46% yield by employing 1,3-dimethoxybenzene as the nucleophile, TMSOTf as additive, and ibuprofen as the acyl fluoride precursor in a Friedel-Crafts-type acylation reaction.



Scheme 3. Employing the microfluidic setup for the synthesis of various acyl derivatives by fluorine displacement. [a] 3 equivalents of Et₃N were used in the second module for entries **29** and **31**, and 2.5 equivalents for entries **30** and **32**. t_{R1}, t_{R2}, t_{R3}: residence times in the first, second, and third reactor, respectively.

In conclusion, we have developed a microfluidic reactor capable of safely producing SOF₂, an overlooked reagent due to its gaseous and toxic nature, starting from the commodity chemicals SOCl₂ and KF. This gas was generated *in situ* and reacted with a wide variety of carboxylic acids, including aromatic, aliphatic, and α -amino acid derivatives, to yield the corresponding acyl fluorides in a telescoped fashion. Furthermore, this method was capable of converting biorelevant molecules with perfect selectivity and in good chemical yields. Finally, as acyl fluorides are attractive intermediates for the synthesis of other acyl derivatives, we devised a streamlined three-module flow setup where, after the generation of the gas and the acyl fluoride production, the latter is directly reacted with a nucleophile to forge C–S, C–N, C–O, and C–C bonds. Based on these findings, we believe this flow approach makes thionyl fluoride a convenient reagent to convert carboxylic acids into acyl fluorides. Further applications of this strategy are ongoing in our laboratories.

Supporting Information

The authors have cited additional references within the Supporting Information.

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