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# Unlocking the Power of Acyl Fluorides: A Comprehensive Guide to Synthesis and Properties.

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**Abstract:** Acyl fluorides have emerged as versatile reagents in various synthetic endeavors, offering a range of advantages over their counterparts, acyl chlorides. This study delves into the properties and reactivity of acyl fluorides, particularly their reaction with amines and alcohols, to elucidate their distinct characteristics. We also introduce a facile and practical synthesis of acyl fluorides from a stable solution of  $\text{CF}_3\text{O}^-$  salt. Additionally, we establish an efficient one-pot process for the direct preparation of amides or esters from corresponding acids and amines or alcohols, showcasing the remarkable efficiency of acyl fluorides in these transformations.

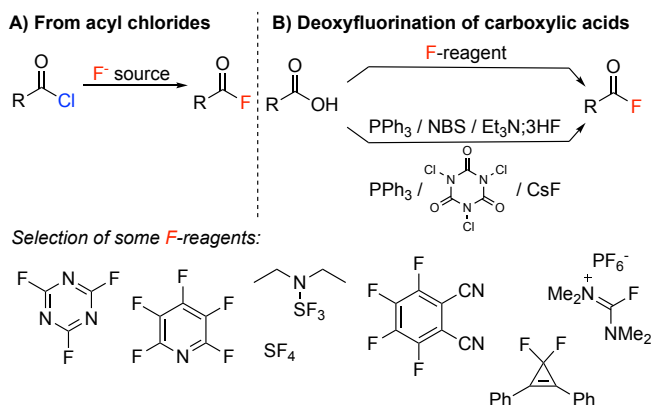
## Introduction

The incorporation of fluorine into molecules imparts remarkable alterations to their properties, leading to a wide array of applications across various fields.<sup>[1]</sup> These modifications include enhanced stability, improved selectivity, and modified biological activities.<sup>[2]</sup> However, the utility of fluorinated molecules extends beyond their final products. They also serve as valuable reagents in the synthesis of various, not exclusively fluorinated, compounds. By leveraging their unique reactivities, fluorinated molecules facilitate the formation of complex molecular structures with tailored properties.<sup>[1a, 3]</sup>

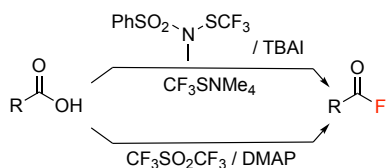
Acyl fluorides, recognized as valuable reagents for amide synthesis several decades ago,<sup>[4]</sup> have witnessed a resurgence of interest in organic chemistry.<sup>[5]</sup>

Our pursuit of a deeper understanding of fluorinated functional groups, spurred by our recent work on carbamoyl fluorides,<sup>[6]</sup> has led us to focus on acyl fluorides.

To facilitate our research, we sought an efficient and rapid method for acyl fluoride synthesis. Literature offers a range of synthetic approaches, extensively reviewed by Paquin et al.<sup>[3c]</sup> (Scheme 1) These methods primarily fall into two categories: (1) fluorine-chlorine exchange from acyl chlorides (Scheme 1A) and (2) dehydroxyfluorination of carboxylic acids (Scheme 1B-C).<sup>[7]</sup> Despite their effectiveness, these well-established methods often involve sensitive substrates (e.g., acyl chlorides) and/or aggressive and expensive reagents (e.g., HF, DAST,  $\text{SF}_4$ , etc.). Recently, a safer and more convenient approach, namely carboxylic acid deoxyfluorination using pentafluoropyridine, has emerged as an alternative.<sup>[8]</sup>

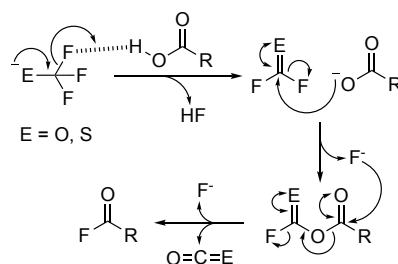


**C) in situ generated difluoro(thio)phosgene from CF<sub>3</sub>E<sup>-</sup> anion (E = O, S)**



**Scheme 1.** Overview of main strategies to obtain acyl fluorides.

The use of simple reagents as difluorophosgene or difluorothiophosgene was also investigated. However, because of the high toxicity of these reagents, their *in situ* generation have been explored. One such approach involves the degradation of CF<sub>3</sub>E<sup>-</sup> anions (E = O, S), to generate the corresponding reactive intermediates (Scheme 1C). Our group demonstrated this concept by reacting carboxylic acids with CF<sub>3</sub>S<sup>-</sup> anions, leading to the formation of acyl fluorides through an addition-elimination mechanism (Scheme 2, E=S).<sup>[9]</sup> In this reaction, CF<sub>3</sub>S<sup>-</sup>, activated by the H<sup>+</sup> of the carboxylic acid, collapses into difluorothiophosgene which then reacts with the carboxylate salt to generate the corresponding fluoromethanethiyl derivative (RC(O)OC(S)F) and release a fluoride anion which can then substitute the OC(S)F group to produce the expected acyl fluoride. Schoenebeck et al. extended this strategy using isolated CF<sub>3</sub>SNMe<sub>4</sub> salts.<sup>[10]</sup> A similar approach was also described by Zhang et al. by using the CF<sub>3</sub>O<sup>-</sup> anion instead of CF<sub>3</sub>S<sup>-</sup> (Scheme 2, E=O).<sup>[11]</sup> In this work, they use CF<sub>3</sub>SO<sub>2</sub>CF<sub>3</sub> (TFMT), well-known to release CF<sub>3</sub>O<sup>-</sup> anion under nucleophilic activation,<sup>[12]</sup> to directly obtain acyl fluorides from carboxylic acids, through an *in situ* sequence CF<sub>3</sub>O<sup>-</sup> release / degradation onto C(O)F<sub>2</sub> / dehydroxyfluorination. However, the volatility of TFMT poses challenges in practical applications.



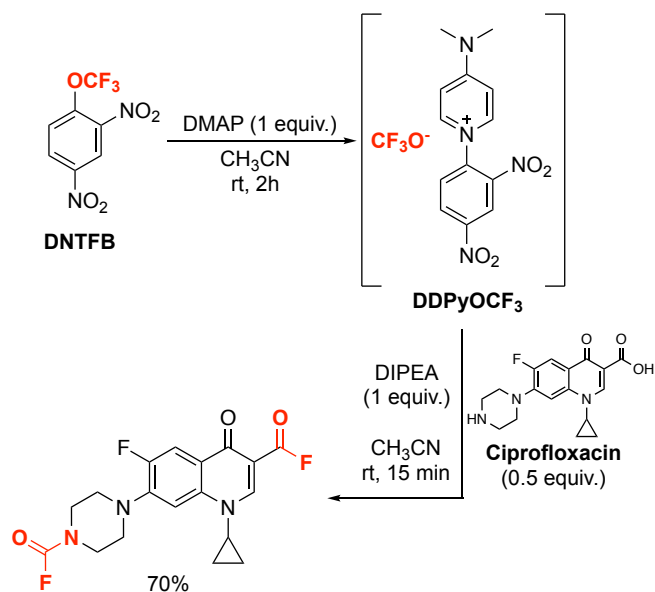
**Scheme 2.** Synthesis of acyl fluorides by using CF<sub>3</sub>E<sup>-</sup> salts.

## Results and Discussion

Despite the availability of several methods for synthesizing acyl fluorides, we decided to focus our interest on an “in house” approach based on our previous research and expertise. We recently reported the synthesis of a stable solution of the CF<sub>3</sub>O<sup>-</sup> salt **DDPyOCF<sub>3</sub>** by reacting 2,4-dinitrotrifluoromethoxybenzene (**DNTFB**) with DMAP.<sup>[13]</sup> The stability of this **DDPyOCF<sub>3</sub>** solution in CH<sub>3</sub>CN has been fully studied and appeared to be stable at least up to 8 days.<sup>[13a]</sup> Recently, we have determined a stability up to 6 weeks. This salt has demonstrated its potential for metal-free trifluoromethoxylation,<sup>[14]</sup> and it also acts as a valuable source of difluorophosgene in the presence of hydrogen-bonding donors. In the presence of amines, we have successfully synthesized carbamoyl fluorides by reacting them with the *in situ* generated difluorophosgene.<sup>[6]</sup>

In the course of this work, we found that reacting ciprofloxacin with two equivalents of **DDPyOCF<sub>3</sub>** yielded the corresponding carbamoyl fluoride with an acyl fluoride function instead of the initial carboxylic acid function (Scheme 3).<sup>[6]</sup>

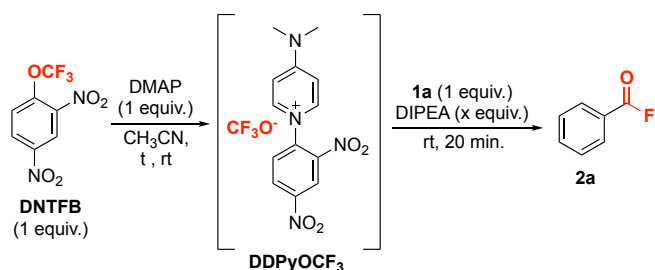
This intriguing result has led us to explore the potential of **DDPyOCF<sub>3</sub>** salt as a valuable reagent for readily synthesizing acyl fluorides.<sup>[15]</sup> Additionally, this approach expands the synthetic range of the **DDPyOCF<sub>3</sub>** salt. Notably, Sanford et al. independently reported a similar approach for acyl fluoride synthesis using similar results.<sup>[16]</sup>



**Scheme 3.** Preliminary results: synthesis of acyl fluoride from ciprofloxacin by using **DDPyOCF<sub>3</sub>**.

Guided by the encouraging results obtained with ciprofloxacin, we conducted a rapid optimization study using benzoic acid (**1a**) as a model substrate to determine the optimal reaction conditions (Table 1).<sup>[15]</sup>

**Table 1.** Reaction of **DDPyOCF<sub>3</sub>** with benzoic acid.



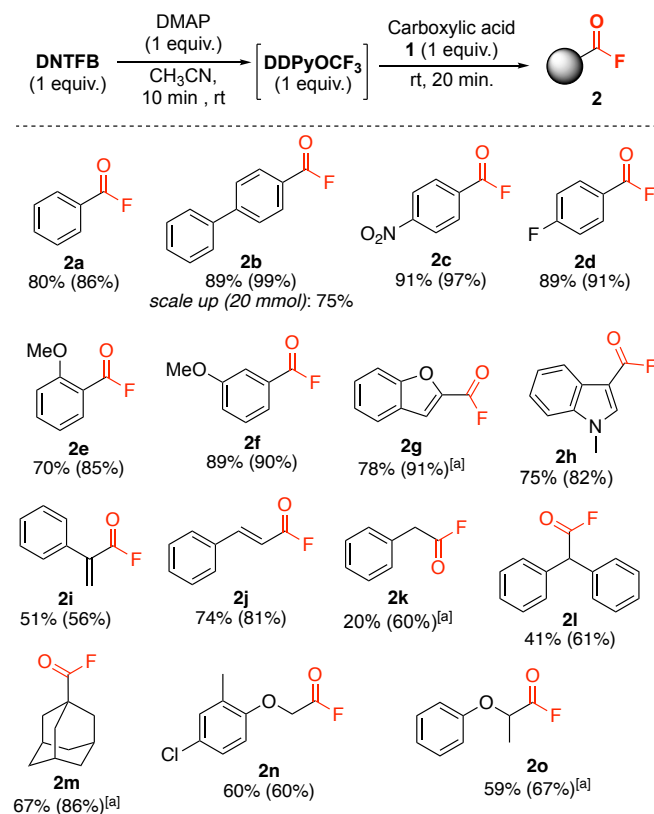
Entry	t (step 1)	DIPEA (equiv.)	<b>2</b> (%) <sup>[a]</sup>
1	2 h	1	85
2	30 min	1	86
3	10 min	1	90
4	10 min	0	86

[a] Yields determined by <sup>19</sup>F NMR spectroscopy with PhCF<sub>3</sub> as internal standard.

We initially employed the reaction conditions used with ciprofloxacin (entry 1). Inspired by our recent comprehensive investigation of the **DDPyOCF<sub>3</sub>** salt,<sup>[14]</sup> we significantly reduced the reaction time for *in situ* preformation to only 10 minutes (entries 2-3). Interestingly, unlike carbamoyl fluoride formation

where the presence of DIPEA facilitated the reaction kinetics,<sup>[6]</sup> its use for acyl fluoride formation appeared to be unnecessary (entry 4).

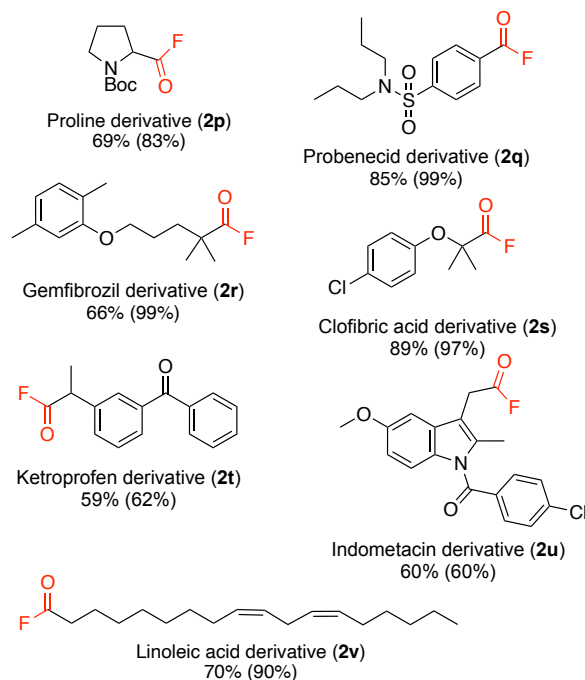
Building upon these optimized conditions, we investigated the scope of this reaction by evaluating its applicability to a variety of substrates (Scheme 4).



**Scheme 4.** Synthesis of acyl fluorides with isolated yields. Yields determined by <sup>19</sup>F NMR spectroscopy with PhOCF<sub>3</sub> as internal standard are given in parentheses. [a] with 2 equiv. of **DDPyOCF<sub>3</sub>**.

Across a range of aromatic substrates, the reaction was unaffected by electronic (**2b-f**) and steric effect (**2e**) of substituents. Similar success was observed with heteroaromatics (**2g-h**). Vinylic (**2i-j**) and benzylic (**2k-l**) acids were also converted with satisfactory to good yields. Finally, aliphatic compounds yielded excellent results (**2m-o**) demonstrating that the reaction is highly tolerant of steric hindrance (**2m**, **2o**). In a few cases, employing two equivalents **DDPyOCF<sub>3</sub>** resulted in improved yields. The reaction was successfully scaled up to 20 mmol with consistent results (**2b**).

Further validation of the method's efficiency was achieved by its application to various bioactive compounds, consistently producing good yields (Figure 1). These results reinforce the remarkable efficacy of this approach for readily converting carboxylic acids to acyl fluorides.

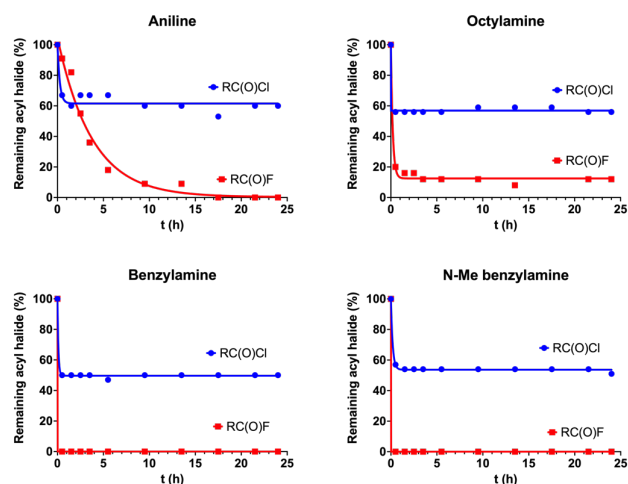


**Figure 1.** Synthesis of acyl fluorides from bioactive carboxylic acids with isolated yields. Yields determined by  $^{19}\text{F}$  NMR spectroscopy with  $\text{PhOCF}_3$  as internal standard are given in parentheses.

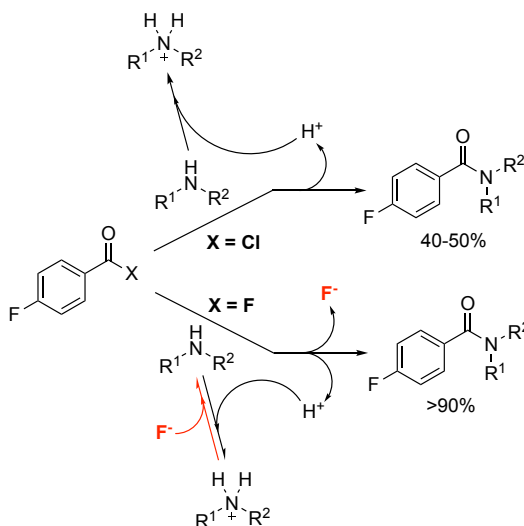
With our efficient method for synthesizing acyl fluorides in hand, we turned our attention to a comparative study of their reactivity and properties. Among their well-established applications, acyl fluorides are renowned for their ability to react with alcohols and amines to form esters and amides, respectively. To delve deeper into this reactivity, we aimed to compare acyl fluorides and chlorides.

We began by examining the amide formation using 4-fluorobenzoyl fluoride (**2d**) and its corresponding acyl chloride as starting material (Figure 2).

Regardless of the type of amine used (aromatic, aliphatic, primary or secondary), acyl chloride conversion was limited to 50-60% while acyl fluoride conversion was consistently complete. This difference can be explained by the protonation of amines by the proton released during amide formation (Scheme 5). In the case of acyl chlorides, this protonation leads to a 50-60% conversion because half of the initial amine is protonated and thus unable to react with the acyl chloride. On the other hand, the fluoride anion released during amide formation from acyl fluorides is sufficiently basic to neutralize the released proton or/and displace the ammonia equilibrium [ammonium  $\rightleftharpoons$  free amine], favoring the nucleophilicity of the amine and promoting complete conversion.

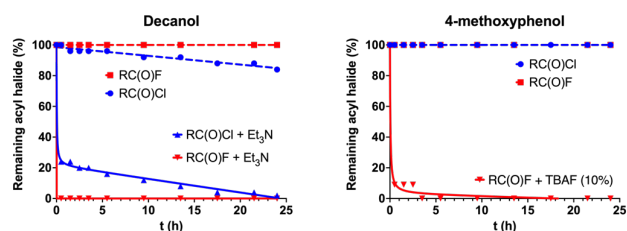


**Figure 2.** Comparative reactivity between 4-fluorobenzoyl fluoride (**2d**) and chloride with various amines. Reaction conditions: acyl halide (0.25 mmol), amine (0.25 mmol),  $\text{CD}_3\text{CN}$  (1 mL), rt. Remaining acyl halides determined by  $^{19}\text{F}$  NMR with  $\text{PhCF}_3$  as internal standard.



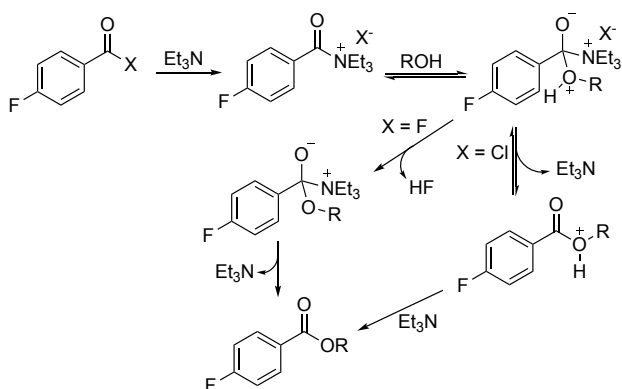
**Scheme 5.** Comparative reaction pathways of acyl fluorides and chlorides with amines.

Interestingly, even with the less nucleophilic aniline, the initial kinetics for the reaction with acyl chloride were higher than those with acyl fluoride ( $k = 3,43 \text{ h}^{-1}$  vs  $0,96 \text{ h}^{-1}$ ). This observation suggests that the protonation of amines, which limits acyl chloride conversion, is not the sole factor determining their reactivity. Similar studies were performed with alcohols (Figure 3).



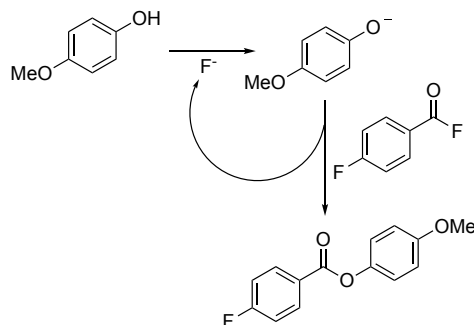
**Figure 3.** Comparative reactivity between 4-fluorobenzoyl fluoride (**2d**) and chloride with various alcohols. Reaction conditions: acyl halide (0.25 mmol), alcohol (0.25 mmol), Et<sub>3</sub>N (0 or 0.25 mmol), TBAF 1M in THF (0 or 25  $\mu$ L), CD<sub>3</sub>CN (1mL), rt. Remaining acyl halides determined by <sup>19</sup>F NMR with PhCF<sub>3</sub> as internal standard.

Without the presence of a base, acyl fluoride **2d** was completely unreactive with any alcohol tested. The corresponding acyl chloride, on the other hand, showed a slow reaction with decanol but not with phenol, aligning with the previously observed observation of the enhanced reactivity of the acyl chloride with aniline. In the presence of triethylamine, decanol reacted with both acyl fluoride and acyl chloride to form the corresponding esters. However, acyl fluoride **2d** exhibited significantly faster kinetics than its chloride counterpart, again hinting at the influence of the basicity of the fluoride anion. This enhanced reactivity is likely attributed to the ability of the fluoride anion to neutralize the proton released during the tetrahedral intermediate formation (Scheme 6).



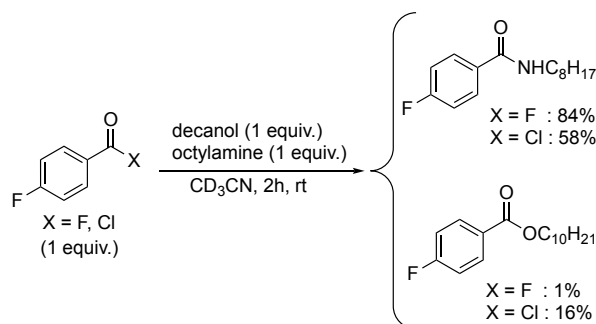
**Scheme 6.** Comparative reaction pathways of acyl fluorides and chlorides with alcohols in the presence of triethylamine.

Intriguingly, the reaction of phenol with acyl fluoride does not necessitate the presence of Et<sub>3</sub>N. Instead, a catalytic quantity of fluoride anion is sufficient to achieve complete conversion. This observation can be attributed to an initial deprotonation of phenol by fluoride anion, forming the more nucleophilic phenolate. This phenolate then attacks the acyl fluoride, yielding the corresponding ester and regenerating a fluoride anion (Scheme 7).



**Scheme 7.** Reaction of a phenol with acyl fluoride catalyzed with fluoride anion.

Buoyed by these results, a competitive reactivity study between amine and alcohol was undertaken (Scheme 8).



**Scheme 8.** Competitive reactivity between alcohol and amine. Yields determined by <sup>19</sup>F NMR spectroscopy with PhOCF<sub>3</sub> as internal standard.

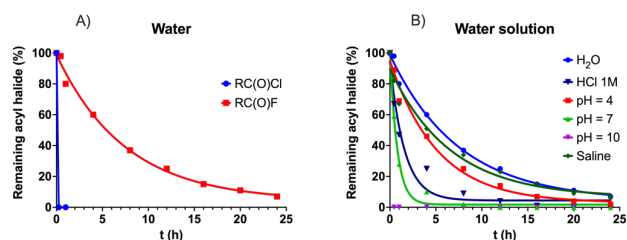
As anticipated from the previous results, acyl fluorides displayed excellent orthogonality, almost exclusively yielding the corresponding amide. In contrast, acyl chlorides produced lower amide yields and poorer selectivity.

The stability towards hydrolysis was also reassessed (Figure 4A). While the hydrolysis of acyl fluoride **2d** proved relatively slow ( $k = 0.13 \text{ h}^{-1}$  and  $t_{1/2} = 5.2 \text{ h}$ ), the corresponding acyl chloride hydrolyzed very rapidly.

A rapid stability study of acyl fluoride **2d** at varying pH values was also conducted (Figure 4B). As expected, the hydrolysis of acyl fluorides accelerates significantly at a pH of 10. Moreover, acyl fluorides exhibit sensitivity to the nucleophilicity of the reaction medium. This is evident from the marked difference in hydrolysis kinetics observed between water ( $k = 0.13 \text{ h}^{-1}$  and  $t_{1/2} = 5.2 \text{ h}$ ) and pH = 7 buffer (Sigma-Aldrich #B4770) containing nucleophilic phosphates and NaN<sub>3</sub> ( $k = 1.26 \text{ h}^{-1}$  and  $t_{1/2} = 0.55 \text{ h}$ ). This enhanced degradation in the pH 7 buffer can be attributed to the presence of nucleophilic species that can effectively attack the acyl fluoride.

A similar effect is observed with hydrochloric acid (HCl) ( $k = 0.64 \text{ h}^{-1}$  and  $t_{1/2} = 1.1 \text{ h}$ ) and saline ( $k = 0.15 \text{ h}^{-1}$  and  $t_{1/2} = 4.6 \text{ h}$ ) where the chloride anions also act as nucleophiles. These observations highlight the sensitivity of acyl fluorides to the nucleophilicity of

the reaction environment, further emphasizing the need for careful control of reaction conditions in acyl fluoride reactions.



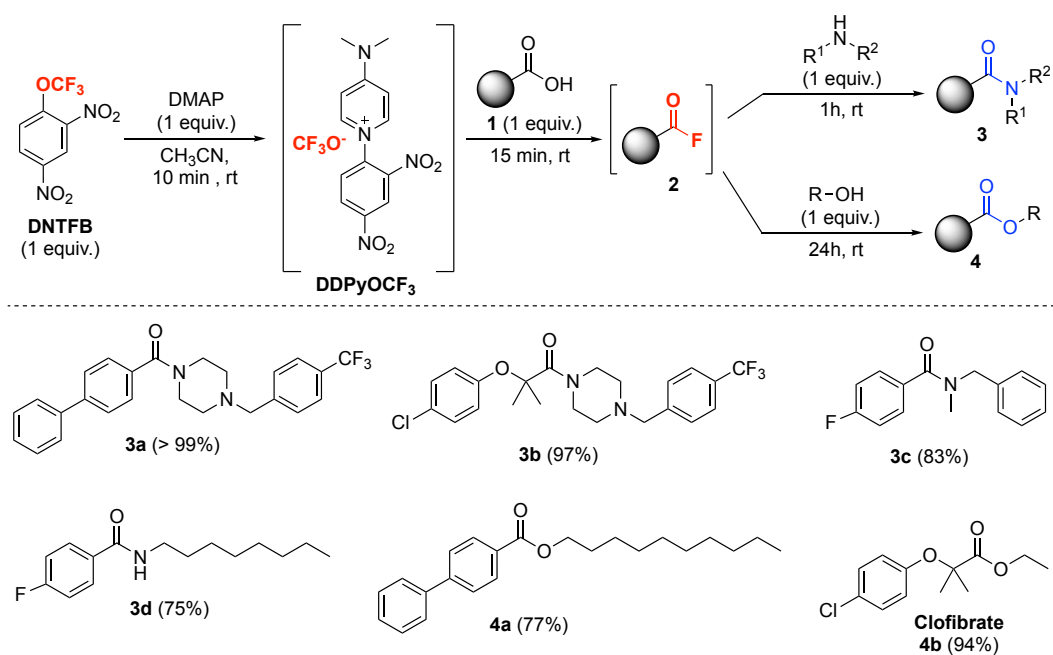
**Figure 4.** Stability of acyl halides in various water media. A) Acyl chloride and acyl fluoride (**2b**) in water. B) Acyl fluoride (**2b**) in various water solution.

Given the potential challenges associated with acyl fluoride isolation and their remarkable reactivity with amines without base catalysis, we explored a streamlined one-pot, three-step process

that bypassed acyl fluoride isolation (Scheme 9, **3a-d**). This approach yielded consistently excellent results with diverse acid and amine combinations.

While isolated acyl fluorides required a base to react with alcohols, we serendipitously discovered that a one-pot process, without the addition of  $\text{Et}_3\text{N}$ , also facilitated alcoholysis. When acid **1b** and decanol were subjected to this one-pot approach, the conversion of acyl fluoride **2b** reached 60% after 1 h, 71% after 4 h and 82% after 24 h. This surprising finding, in contrast to the behavior of isolated acyl fluorides (Figure 3), can be attributed to the slow release of DMAP from  $\text{DDPyOCF}_3$  due to the attack of fluoride anions present in the reaction medium. This DMAP released acts as catalyst, activating the acyl fluorides and enabling alcoholysis. This one-pot reactivity was further demonstrated with several alcohols (Scheme 9, **4a-b**). Notably, the drug clofibrate (**4b**) was obtained in good yields

In most cases, no additional purification was required in this process. A simple extraction was sufficient to isolate the desired amides with good purity, further simplifying this overall procedure.



**Scheme 9.** One-pot synthesis of amides and esters. Isolated yields.

## Conclusion

In conclusion, we have developed a facile and efficient method for the preparation of acyl fluorides, expanding the synthetic toolkit with a versatile reagent. Our reactivity studies with acyl fluorides demonstrate their significance in organic synthesis and provide valuable insights into their utilization.

Moreover, these findings underscore the versatility of the  $\text{DDPyOCF}_3$  salt (easily formed from **DNTFB** and **DMAP**), showcasing its ability to generate *in situ* difluorophosgene, opening avenues for accessing valuable fluorinated compounds.

## Supporting Information

The authors have cited additional references within the Supporting Information.<sup>[4c, 10, 17]</sup>

## Acknowledgements

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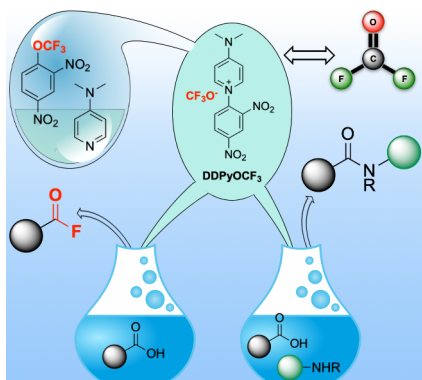
**Keywords:** Acyl fluoride • Amide • Trifluoromethoxide • Acyl chloride • 2,4-dinitrotrifluoromethoxybenzene

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## Entry for the Table of Contents



The facile and safe synthesis of acyl fluorides, under metal-free and cost-effective conditions, presents a remarkable advance in organic synthesis. These versatile reagents, endowed with distinct reactivity owing to the fluorine atom, offer a wealth of possibilities for further utilization.

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