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Tertiary-Amine-Initiated Synthesis of Acyl Fluorides from Carboxylic Acids and $CF_3SO_2OCF_3$

Hai-Xia Song,[†,a] Ze-Yu Tian,[†,a] Ji-Chang Xiao,[b] and Cheng-Pan Zhang*[,a]

[a] Hai-Xia Song (co-first author),[†] Ze-Yu Tian (co-first author),[†] Prof. Dr. Cheng-Pan Zhang
School of Chemistry, Chemical Engineering and Life Science
Wuhan University of Technology
205 Luoshi Road, Wuhan 430070, China
E-mail: cpzhang@whut.edu.cn, zhangchengpan1982@hotmail.com.

[b] Prof. Dr. Ji-Chang Xiao
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032, China
E-mail: jchxiao@sioc.ac.cn.

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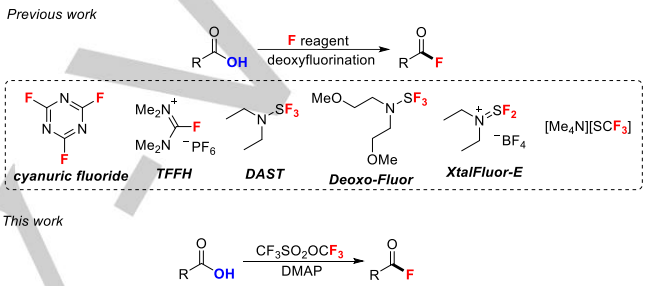
Abstract: A convenient method for deoxyfluorination of aromatic and aliphatic carboxylic acids with $CF_3SO_2OCF_3$ in the presence of a suitable base at room temperature has been developed. The reaction allows a straightforward access to a variety of acyl fluorides and proves that $CF_3SO_2OCF_3$ is an effective deoxyfluorination reagent for carboxylic acids. The method features simplicity, expeditiousness, high efficiency, ease of handling, good functional group tolerance, a wide range of substrates, excellent yields of products, compatibility of many amine initiators, use of environmentally friendly reagents, and effortless removal of byproducts. This reaction represents the first utilization of trifluoromethyl trifluoromethanesulfonate as a fluorination reagent.

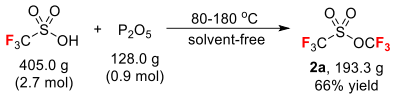
Because of the unique properties imparted by fluorine, fluorinated compounds have attracted great interest in the fields of chemistry, biology, and materials science.[1] Acyl fluorides (RCOF), an intriguing class of carboxylic acid derivatives bearing a fluorocarbonyl group, have played an increasingly important role in organic synthesis.[2] They can be used as versatile "RCO" sources in acylation reactions, "R" sources in decarbonylative coupling reactions, and "F" sources in fluorination reactions. Acyl fluorides possess better stability than the homologous acyl halides but much higher reactivity than the analogous esters and amides, displaying a good balance between stability and reactivity, due to the special electrostatic nature of the C-F bonds.[2] So far methods for the synthesis of acyl fluorides have included deoxyfluorination and halogen-exchange reactions of carboxylic acids or their derivatives with different types of fluorination reagents, e.g., MF (M = H, Na, K, Cs, Bu_4N), KHF_2, KSO_2F, cyanuric fluoride, 2-fluoropyridinium salts, fluoro formamidinium salts (e.g., TFFH), perfluoroalkylamines (e.g., Ishikawa's reagent), BrF_3, SF_4, R_2N-SF_3 (DAST, morpholinosulfur trifluoride and Deoxo-Fluor), $(R_2N{=}SF_2)BF_4$ (XtalFluor), $ArSF_3$, $(Me_4N)SCF_3$, and others (**Scheme 1**).[3-6] These reagents enabled efficient and practical fluorination of various carboxylic acids and their derivatives to the corresponding acyl fluorides in satisfactory yields. Nevertheless, application of many of these reagents was restricted owing to their high toxicity, thermal instability, high cost, air or moisture sensitivity, harsh reaction conditions, difficulty to access or control, and/or release of vast hazardous byproducts.[3-6] In this context, the development of environmental benign reagents for deoxyfluorination of carboxylic acids to acyl fluorides is highly sought after.



Scheme 1. Synthesis of acyl fluorides from carboxylic acids with different fluorination reagents (selected).

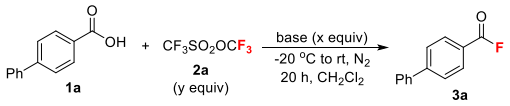
Trifluoromethyl trifluoromethanesulfonate ($CF_3SO_2OCF_3$) has been confirmed as a versatile reagent in the trifluoromethoxylation and trifluoromethanesulfonylation reactions, despite that it has a boiling point of 21 °C.[7-9] The nucleophilic trifluoromethoxy anion, derived from the breakage of the S-OCF_3 bond of $CF_3SO_2OCF_3$ by diverse fluorides, represents the most prevalent trifluoromethoxylation reagent, which reacted with organic halides, metal complexes, *α*-diazo compounds, and alkenes under transition-metal-catalyzed or -free conditions to form a variety of useful trifluoromethoxylated compounds.[8] Moreover, $CF_3SO_2OCF_3$ can be employed as a promising click ligation for primary and secondary amines in the preparation of urea derivatives, heterocycles, and carbamoyl fluorides under additive-free conditions.[10] In addition to these achievements, application of $CF_3SO_2OCF_3$ in other reactions has rarely been explored. It was known that $CF_3SO_2OCF_3$ is a low-cost, modest, bench-stable, air- and moisture-insensitive reagent, and resistant to hydrolysis even in an aqueous NaOH solution at a low temperature.[7] It can also be readily synthesized from CF_3SO_3H and P_2O_5 in a large scale (**Scheme 2**). The $^-OCF_3$ anion originated *in situ* from $CF_3SO_2OCF_3$ is thermally unstable and quickly decomposes to form fluorophosgene and fluoride ion at room temperature. In this regard, $CF_3SO_2OCF_3$ can be considered as a convenient and efficient reservoir of $O{=}CF_2$ and ^-F anions.[10] Furthermore, fluorophosgene and anhydrous fluorine anions have been evidenced to be important condensation and nucleophilic fluorination reagents, respectively.[11] We envisioned that decomposition of $CF_3SO_2OCF_3$ by an appropriate initiator would result in a viable fluorination reagent for organic synthetic chemistry. In this article, the reaction of carboxylic acids with

$CF_3SO_2OCF_3$ in the presence of a tertiary amine was explored, which provided exclusively acyl fluorides as the products via deoxyfluorination.



Scheme 2. A facile synthesis of $CF_3SO_2OCF_3$ from CF_3SO_3H.

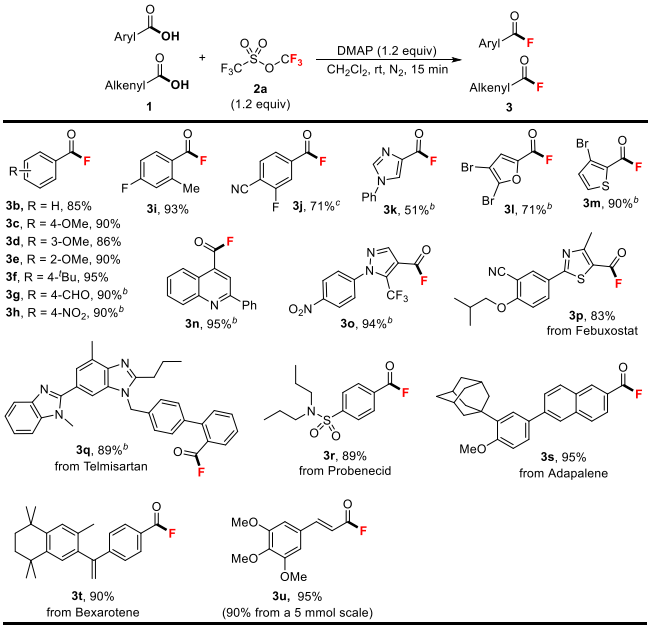
Table 1. Deoxyfluorination of **1a** with $CF_3SO_2OCF_3$ under different reaction conditions.



Entry[a]	Base (x equiv)	**2a** (y equiv)	Yield (**3a**, %)
1	NEt_3 (1.0)	2.0	86
2	DABCO (1.0)	2.0	89
3	DBU (1.0)	2.0	83
4	pyridine (1.0)	2.0	91
5	2,4,6-collidine (1.0)	2.0	81
6	2,6-bis(*tert*-butyl)pyridine (1.0)	2.0	79
7	1-methylimidazole (1.0)	2.0	84
8	DMAP (1.0)	2.0	94
9	CsF (1.0)	2.0	87
10	NaOH (1.0)	2.0	0
11	none	2.0	0
12	DMAP (0.5)	2.0	78
13	DMAP (1.5)	1.5	98
14	DMAP (1.2)	1.2	94, 95[b]
15	DMAP (1.0)	1.0	80
16[b],[c]	DMAP (1.2)	1.2	97 (92)
17[b],[c],[d]	DMAP (1.2)	1.2	94
18[b],[c],[e]	DMAP (1.2)	1.2	91

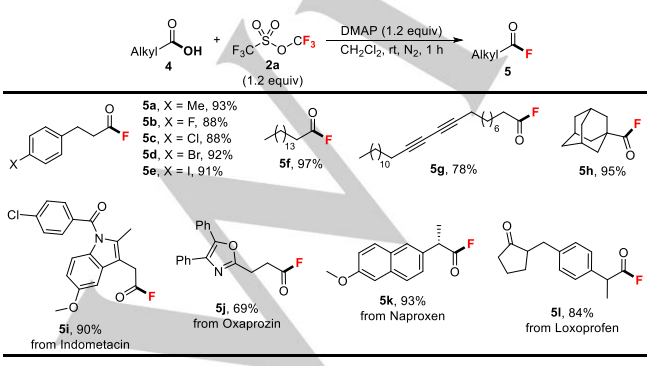
[a] Reaction conditions: **1a** (0.2 mmol), base (0.2, 0.1, 0.24 or 0.3 mmol), **2a** (0.4, 0.3, 0.24 or 0.2 mmol), CH_2Cl_2 (2 mL), -20 °C to rt, N_2, 20 h. Yields were determined by HPLC using **3a** as an external standard (t_R = 9.457 min, λ_{max} = 260 nm, water/methanol (v/v) = 20 : 80). Isolated yield was depicted in the parentheses. [b] The reaction was run at room temperature. [c] The reaction was run for 15 min. [d] $TsOCF_3$ (**2b**) was used instead of **2a**. [e] $PhCOOCF_3$ (**2c**) was used instead of **2a**.

The investigation started by using 4-phenylbenzic acid (**1a**) as a model substrate to optimize the reaction conditions. It was found that reaction of **1a** and **2a** (2 equiv) with triethylamine (1 equiv) in DCM at -20 °C to room temperature under a N_2 atmosphere for 20 h afforded [1,1'-biphenyl]-4-carbonyl fluoride (**3a**) in 86% yield (**Table 1**, entry 1). A series of organic and inorganic bases were evaluated in this deoxyfluorination. 1,4-Diazabicyclo[2.2.2]octane (DABCO), diazabicycloundecene (DBU), pyridine, 2,4,6-collidine, 2,6-bis(*tert*-butyl)pyridine, 1-methylimidazole, and 4-dimethylaminopyridine (DMAP) proved to be comparably effective for the reaction, giving **3a** in 79-94% yields (**Table 1**, entries 2-8). CsF was also a suitable initiator for the deoxyfluorination, furnishing **3a** in 87% yield (**Table 1**, entry 9). Nevertheless, reaction of **1a** and **2a** with NaOH or without bases provided no desired product (**Table 1**, entries 10-11), suggesting that use of an appropriate base was very essential for the transformation. Moreover, the equivalent of bases had an influence on the reaction. When **1a** reacted with **2a** (2 equiv) and DMAP (0.5 equiv) under the same conditions, **3a** was formed in 78% yield (**Table 1**, entry 12). Further decreasing the amount of DMAP from 0.5 equiv to 0.2 equiv led to only 28% of **3a** (Table S2). Varying the molar ratios of **1a**/**2a**/DMAP from 1:2:1 to 1:1.5.1:5, 1:1.2:1.2 and 1:1:1 provided **3a** in 98%, 94% and 80% yield, respectively (**Table 1**, entries 13-15). If **1a** was mixed with **2a** (1.2 equiv) and DMAP (1.2 equiv) at room temperature for 20 h, **3a** was obtained in 95% yield (**Table 1**, entry 14), indicating that lower reaction temperature was not necessary for the deoxyfluorination. In addition, the reaction time could be significantly shortened (Table S3). Reaction of **1a** with **2a** (1.2 equiv) and DMAP (1.2 equiv) at room temperature for 15 min supplied **3a** in 97% yield (92% isolated yield) (**Table 1**, entry 16). If **2a** was replaced by $TsOCF_3$ (**2b**) or $PhCOOCF_3$ (**2c**) in the same reaction, **3a** was formed in 94% or 91% yield, suggesting that **2b-c** were also efficient fluorination reagents for the conversion (**Table 1**, entries 17-18, and Table S5).[12] Further studies showed that Et_2O, toluene, hexane, 1,4-dioxane, THF, DME, diglyme, CH_3CN, DCE, and ethyl acetate were reliable solvents for the reaction of **1a**, **2a** and DMAP, which gave similar yields of **3a** to that obtained in CH_2Cl_2 (Table S4). The use of hydrophobic solvents was beneficial for the purification of the product by simply washing the reaction mixture with aqueous HCl solution and water, which readily removed the byproduct and afforded the pure acyl fluoride without using column chromatography. Additionally, the present deoxyfluorination is not sensitive to moisture as a mixture of **1a**, **2a** and DMAP reacted in air at room temperature for 1 h to give **3a** in 87% yield (Table S3).



Scheme 3. Deoxyfluorination of aromatic carboxylic acids (**1**) with $CF_3SO_2OCF_3$ (**2a**) in the presence of DMAP. [a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), DMAP (0.24 mmol), r.t., N_2, 15 min. Isolated yields. [b] 1 h. [c] 8 h.

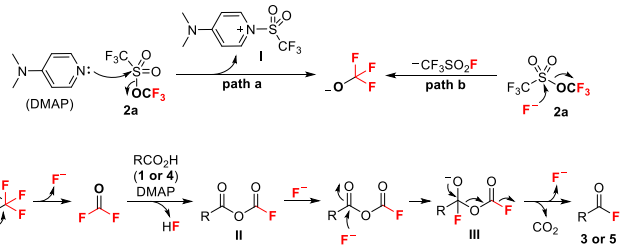
Taking an assembly of **1**, **2a** (1.2 equiv), DMAP (1.2 equiv), DCM, room temperature, N_2, and 15 min as one of the optimal reaction conditions, the substrate scope of the reaction was examined (**Scheme 3**). To our delight, a wide range of aromatic carboxylic acids ($ArCO_2H$) were efficiently converted under the standard conditions to form the corresponding ArCOF products in good yields. Benzoic acids (**1b-j**) bearing either electron-donating (e.g., OMe, *t*-Bu, Me) or electron-withdrawing functionalities (e.g., CHO, NO_2, F, CN) on the aryl rings provided the desired products (**3b-j**) in 71-95% yields. The strong electron-withdrawing groups like CHO, CN, and NO_2 slowed down the transformation, which needed longer reaction times for complete conversion of the starting acids. 4-Methoxybenzoic acid (**1c**), 3-methoxybenzoic acid (**1d**), and 2-methoxybenzoic acid (**1e**) reacted with **2a** under the standard conditions to afford 90% of **3c**, 86% of **3d**, and 90% of **3e**, respectively, implying that the position of the substituent on the aryl groups had few effects on the reaction. The deoxyfluorination was also amenable to heteroaromatic systems. Reactions of 1-phenyl-1*H*-imidazole-4-carboxylic acid (**1k**), 4,5-dibromofuran-2-carboxylic acid (**1l**), 3-bromothiophene-2-carboxylic acid (**1m**), 2-phenylquinoline-4-carboxylic acid (**1n**), and 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (**1o**) with **2a** (1.2 equiv)/DMAP (1.2 equiv) at room temperature for 1 h supplied **3k-o** in 51-95% yields. Similarly, treatment of Febuxosta (**1p**, an agent to treat gout), Telmisartan (**1q,** an antihypertensive drug), Probenecid (**1r**, a uricosuric and renal tubular blocking agent), Adapalene (**1s**, an antiacne drug), and Bexarotene (**1t,** an anticancer drug) with **2a** and DMAP furnished **3p-t** in 83-95% yields. The results demonstrated that heterocycles, sulfamide, and carbon-carbon double bond were well tolerated in this transformation and that the reaction was applicable to the late-stage functionalization of complex molecules and drug agents. Additionally, deoxyfluorination of (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid (**1u**) by **2a** and DMAP under the standard reaction conditions produced **3u** in 95% yield, indicating that alkenyl carboxylic acid was the suitable substrate in the conversion. The good functional group tolerance and the easily scale-up synthesis of **3u** (as an example) showcased the great synthetic potentials of this deoxyfluorination method.



Scheme 4. Deoxyfluorination of aliphatic carboxylic acids (**4**) with $CF_3SO_2OCF_3$ (**2a**) in the presence of DMAP. [a] Reaction conditions: **4** (0.2 mmol), **2a** (0.24 mmol), DMAP (0.24 mmol), r.t., N_2, 1 h. Isolated yields.

Furthermore, deoxyfluorination of alkyl carboxylic acids with **2a** initiated by DMAP could yield the respective acyl fluorides (**Scheme 4**). Reactions of 3-arylpropanoic acids (**4a-e**), palmitic acid (**4f**), pentacosa-10,12-diynoic acid (**4g**) and (3r,5r,7r)-adamantane-1-carboxylic acid (**4h**) with **2a** (1.2 equiv)/DMAP (1.2 equiv) at room temperature for 1 h constructed **5a-h** in up to 97% yield. The drug molecules like Indometacin (**4i**), Oxaprozin (**4j**), Naproxen (**4k**) and Loxoprofen (**4l**) were easily transformed under the same conditions to provide the acyl fluoride derivatives (**5i-l**) in 69-93% yields. These observations confirmed that the primary, secondary and tertiary carboxylic acids were all suitable substrates in the reaction and that the functional groups such as carbon-carbon triple bond, amide, and oxazole were very compatible in this deoxyfluorination, which hinted at good practicability of the approach.[13]

Since $CF_3SO_2OCF_3$ always decomposes via the S-OCF_3 bond cleavage rather than the O-CF_3 bond breakage in the presence of nucleophiles,[7e,8] a plausible reaction mechanism is suggested (**Scheme 5**) according to the above results. First, fragmentation of trifluoromethyl trifluoromethanesulfonate (**2a**) by DMAP through nucleophilic attack at the sulfur center *in situ* generates a $^-OCF_3$ anion (**path a**). The $^-OCF_3$ anion rapidly degrades to difluorophosgene (COF_2) and fluoride ion via α-F elimination. Then, carboxylic acid (RCO_2H, **1** or **4**) reacts with COF_2 in the presence of DMAP to yield an acyl carbonofluoridic anhydride (**II**). The intermediate (**II**) undergoes an attack at the carbonyl site of RCO group by fluorine anion to form an unstable species (**III**). Finally, disassociation of **III** provides the desired product (RCOF, **3** or **5**) and releases the gaseous carbon dioxide and the useful fluoride ions. The fluorides derived from degradation of $^-OCF_3$, condensation of COF_2 with RCO_2H, and disassociation of intermediate **III** are also the possible initiators for the decomposition of $CF_3SO_2OCF_3$ (**2a**), which produces the $^-OCF_3$ anion again (path **b**) and sustains the subsequent fluorination of carboxylic acid. DMAP might play an essential role in both initiation of $CF_3SO_2OCF_3$ and activation of COF_2 during the fluorination as the reactions of **1a** and **2a** with catalytic amounts of DMAP gave dramatically decreased yields of **3a** (Table S2).



Scheme 5. A plausible reaction mechanism for the deoxyfluorination of carboxylic acids with $CF_3SO_2OCF_3$ (**2a**)

In summary, we have accomplished a convenient and efficient deoxyfluorination of carboxylic acids with trifluoromethyl trifluoromethanesulfonate and DMAP under mild conditions. The reaction provides a powerful tool for the preparation of acyl fluorides, which are very useful building blocks in organic synthesis. Advantages of the method include simplicity, speediness, high efficiency, ease of handling, transition-metal-free conditions, good functional group tolerance, a wide range of

substrates, excellent yields, with no use of air- and moisture-sensitive reagents, and effortless purification of the products because of the formation of easily removable byproducts. More importantly, $CF_3SO_2OCF_3$ (**2a**) and its analogues (e.g. $TsOCF_3$ (**2b**) and $PhCOOCF_3$ (**2c**)) have been verified as safe precursors or replacements for difluorophosgene and anhydrous fluoride and as promising deoxyfluorination reagents for carboxylic acids, only when appropriate initiators were employed. This reaction represents the first example of using $CF_3SO_2OCF_3$ as a viable fluorination reagent. Application of $CF_3SO_2OCF_3$ and its analogues in other fluorination reactions is currently underway in our laboratory.

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Keywords: acyl fluorides • carboxylic acids • trifluoromethyl trifluoromethanesulfonate • deoxyfluorination

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[13] Unfortunately, the reactions of ((benzyloxy)carbonyl)phenylalanine and (*tert*-butoxycarbonyl)alanine (as examples of amino acids) with $TfOCF_3$ (**2a**) and DMAP under the standard conditions gave complicated mixtures, from which we couldn't isolate the corresponding pure acyl fluorides.

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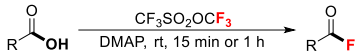

(R = aryl, alkenyl, alkyl)

33 examples
up to 97% yield

- convenience, speediness
- high efficiency, easy handling
- transition-metal-free conditions
- no harsh reagents
- good functional group tolerance
- a wide range of substrates
- excellent yields of products
- effortless removal of byproducts
- the first use of $CF_3SO_2OCF_3$ as a fluorination reagent

Amine-triggered deoxyfluorination of carboxylic acids with $CF_3SO_2OCF_3$ is described. The reaction proceeds rapidly at room temperature under metal-free conditions to form various acyl fluorides in up to 97% yield. This protocol represents the first utilization of trifluoromethyl trifluoromethanesulfonate as a convenient and efficient fluorination reagent.