A Convenient, One-Pot Procedure for the Preparation of Acyl and Sulfonyl Fluorides Using Cl_3CCN, Ph_3P, and TBAF(*t*-BuOH)$_4$

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Abstract: Various carboxylic acids were converted into acyl fluorides in excellent yields by treatment with trichloroacetonitrile, triphenylphosphine, and TBAF(*t*-BuOH)$_4$ at room temperature. The reaction was applicable to the preparation of acid-sensitive amino acid fluorides without deprotection or rearrangement.

Key words: carboxylic acid, acyl fluoride, sulfonyl fluoride, amino acid fluoride, trichloroacetonitrile

Acyl fluorides have been used as valuable synthetic intermediates for pharmaceuticals and other organic products.[1] For instance, benzoyl fluoride has been used in the syntheses of antibiotics,[2] antitumor agents,[3] and enzyme inhibitors.[4] Acyl fluorides have also been widely employed for peptide bond formation since they are stable to moisture and are easy to handle.[5] Several approaches for preparing acyl fluorides are available in the literature; these can be classified by the use of either carboxylic acid or acyl chloride as the starting material. Acyl fluorides have been prepared by treatment of carboxylic acids with fluorinating agents such as sulfur tetrafluoride,[6] selenium tetrafluoride,[7] cyanuric fluoride,[8] (diethylamino)sulfur trifluoride,[9] tetramethylfluoroformamidinium hexafluorophosphate,[10] hydrogen fluoride–pyridine/1,3-dicyclohexylcarbodiimide,[11] or aminodifluorosulfinium tetrafluoroborate salts.[12] Acyl fluorides have also been prepared from acyl chlorides by halogen exchange reactions with a fluoride source such as potassium fluoride,[13] potassium hydrogen difluoride,[14] hydrogen fluoride,[15] zinc fluoride,[16] or bromine trifluoride.[17] However, these methods have some drawbacks to practical use because they employ highly toxic, gaseous, thermally unstable, expensive, corrosive and/or highly moisture-sensitive reagents. Some of these methods require low temperature, long reaction times, hazardous solvents, and afford mixtures of products. Therefore, it would be highly desirable to have an efficient and practical method for the synthesis of acyl fluorides.

Reactions that are available for the preparation of acyl fluorides that use metal fluorides as the fluoride source typically require high temperatures and long reaction times and generate mixtures of products because of the low solubility of metal fluorides in organic medium and their hygroscopic nature. Recently, Kim et al. reported the use of tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride [TBAF(*t*-BuOH)$_4$] as a fluoride source, which has low hygroscopicity for easy handling and has good solubility in organic solvents.[18] Herein, we report an efficient and practical procedure for the synthesis of acyl fluorides from carboxylic acids with trichloroacetonitrile, triphenylphosphine, and TBAF(*t*-BuOH)$_4$.

We postulated that carboxylic acid chlorides, prepared in situ from carboxylic acids with a combination of trichloroacetonitrile and triphenylphosphine, might be transformed into the corresponding acyl fluorides by treatment with a fluoride source.[19] We chose benzoic acid as a model compound to establish optimal reaction conditions. When benzoic acid was treated with Cl_3CCN (1 equiv), Ph_3P (1 equiv), and then TBAF(*t*-BuOH)$_4$ (2 equiv) in acetonitrile at room temperature for two hours, the desired benzoyl fluoride was obtained in 42% yield along with unreacted benzoic acid (Table 1, entry 1). However, when the amounts of Cl_3CCN and Ph_3P were increased, benzoic acid was completely converted into benzoyl fluoride within one hour in 91% yield (entry 2). The reaction proceeded efficiently even at 0 °C (entry 3). Further increases in the amounts of Ph_3P, CCl_3CN and TBAF(*t*-BuOH)$_4$ did not affect the yield of benzoyl fluoride (entries 4 and 5), while a decrease in the amount of TBAF(*t*-BuOH)$_4$ significantly decreased the yield of benzoyl fluoride (entry 6). Various organic solvents were screened to find suitable solvents for the reaction (entries 7–11), and acetonitrile and *N*,*N*-dimethylformamide (DMF) were found to give the best results. Other fluoride sources, such as TBAF, CsF, and KF, were also examined for the reaction. With TBAF, the reaction afforded a moderate yield of benzoyl fluoride (entry 12); however, the reaction did not take place with CsF or KF even in the presence of 18-crown-6 for prolonged reaction times (entries 13–15). This may be attributable to the low solubility of these metal fluorides. The efficiency of various chlorinating reagents was investigated, and CCl_3CN was found to be the reagent of choice (entries 16–19).

To investigate the scope and limitations of the reaction, a wide range of aryl and alkyl carboxylic acids were subjected to the reaction conditions. The results are summarized in Table 2. Aryl carboxylic acids with either electron-donating or electron-withdrawing groups were

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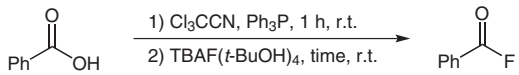
Table 1 Fluorination of Benzoic Acid under Various Reaction Conditions



Entry	Ph_3P (equiv)	Halogenating agent (equiv)	Fluorinating agent (equiv)	Solvent	Time (h)	Yield (%)[a]
1	1	CCl_3CN (1)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	2	42
2	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	1	91
3[b]	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	1	89
4	2.5	CCl_3CN (2.5)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	1	88
5	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (3)	MeCN	2	91
6	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (1)	MeCN	2	65
7	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	$(ClCH_2)_2$	12	0
8	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	toluene	12	0
9	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	Et_2O	12	0
10	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	THF	12	12
11	2	CCl_3CN (2)	TBAF(*t*-BuOH)$_4$ (2)	DMF	1	89
12	2	CCl_3CN (2)	TBAF (2)	MeCN	3	68
13	2	CCl_3CN (2)	CsF (2)	MeCN	12	29
14	2	CCl_3CN (2)	KF (2)	MeCN	24	0
15	2	CCl_3CN (2)	KF (2)/18-crown-6 (0.1)	MeCN	24	5
16	2	CCl_4 (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	10	0
17	2	$Cl_3CCOCCl_3$ (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	10	29
18	2	Cl_3CCO_2Et (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	10	16
19	2	Cl_3CCONH_2 (2)	TBAF(*t*-BuOH)$_4$ (2)	MeCN	10	38

[a] The yield was measured by GC.
[b] The reaction was carried out at 0 °C.

Table 2 Synthesis of Acyl Fluorides from Carboxylic Acids[a,b]

Entry	Acid	Time (h)	Yield (%)	Ref.
1	*p*-methoxybenzoic	1	89	11
2	*p*-bromobenzoic	1	90	13f
3	*p*-nitrobenzoic	0.5	95	11
4	phenylacetic	1	85	13f
5	cyclohexanecarboxylic	1	83	11
6	propionic	1	79	13f
7	octanoic	1	81	17
8	*trans*-cinnamic	1	78	11
9	2,2-diphenylacetic	2	77	11
10	trimethylacetic	2	80	13d
11	5-methoxy-5-oxopentanoic	2	80	17

[a] See the typical experimental procedure for reaction conditions.[20]
[b] Spectroscopic data of the products were consistent with literature values.

Table 3 Synthesis of Sulfonyl Fluorides from Sulfonic Acids

Entry	Acid	Time (h)	Yield (%)	Ref.
1	methanesulfonic	1	87	21
2	benzenesulfonic	1	93	21
3	4-methylbenzenesulfonic	1	94	21
4	4-bromobenzenesulfonic	2	91	21
5	5-(dimethylamino)naphthalene-1-sulfonic	2	89	21

readily converted into the corresponding acyl fluorides in high yields (entries 1–3). Compared to aryl carboxylic acids, alkyl carboxylic acids afforded somewhat lower yields of acyl fluorides (entries 4–7). *trans*-Cinnamic acid was transformed into the corresponding acyl fluoride with the carbon–carbon double bond intact (entry 8). Sterically hindered substrates and dicarboxylic acids such as trimethylacetic acid and 5-methoxy-5-oxopentanoic acid required longer reaction times (entries 9–11). This method of transforming carboxylic acids into the corresponding

Table 4 Synthesis of Amino Acid Fluorides

Entry	Amino acid	Yield (%)[a]	$[\alpha]_D^{22}$	Lit. $[\alpha]_D$
1	*N*-Fmoc-L-Gly-OH	88	–	–
2	*N*-Fmoc-L-Ala-OH	83	+ 3.8 (c 1, EtOAc)	+ 3.6 (c 0.5, EtOAc)[5b]
3	*N*-Fmoc-L-Val-OH	75	+11.0 (c 1, CH_2Cl_2)	+10.7 (c 1, CH_2Cl_2)[5b]
4	*N*-Fmoc-L-Ile-OH	80	+15.9 (c 1, EtOAc)	+15.0 (c 0.5, EtOAc)[5b]
5	*N*-Fmoc-L-Met-OH	76	–13.3 (c 1, EtOAc)	–12.9 (c 0.55, EtOAc)[5b]
6	*N*-Fmoc-L-Asp(*t*-BuO)OH	73	+ 4.1 (c 1, EtOAc)	+ 4.0 (c 0.5, EtOAc)[5b]
7	*N*-*t*-Boc-L-Ala-OH	78	–17.1 (c 1, EtOAc)	–17.2 (c 1, EtOAc)[5c]
8	*N*-*t*-Boc-L-Leu-OH	81	–17.7 (c 1, EtOAc)	–17.4 (c 1, EtOAc)[5c]
9	*N*-*t*-Boc-L-Met-OH	71	–23.3 (c 1, EtOAc)	–23.5 (c 1, EtOAc)[5c]
10	*N*-*t*-Boc-L-Asp(OBn)-OH	87	–13.9 (c 1, EtOAc)	–13.2 (c 1, EtOAc)[5c]
11	*N*-Cbz-L-Ala-OH	81	– 8.0 (c 1, EtOAc)	– 7.8 (c 1, EtOAc)[5c]
12	*N*-Cbz-L-Phe-OH	79	–36.9 (c 1, EtOAc)	–36.4 (c 1, EtOAc)[5c]

[a] Isolated yield after silica gel column chromatography.

acyl fluorides was found to be very mild, efficient, and general. The reaction was also applicable to the synthesis of sulfonyl fluorides from sulfonic acids (Table 3).

Next, we applied our method to the synthesis of amino acid fluorides, which are frequently used in peptide synthesis (Table 4). Treatment of Fmoc, Boc, and Cbz protected amino acids with Cl_3CCN, Ph_3P, and TBAF(*t*-BuOH)$_4$ in acetonitrile for two hours gave the corresponding amino acid fluorides in 71–88% yields without any indication of deprotection or rearrangement.

In summary, we have developed a mild and convenient synthesis of acyl fluorides from carboxylic acids with Cl_3CCN, Ph_3P, and TBAF(*t*-BuOH)$_4$.[21] The process is general for the preparation of acyl fluorides and sulfonyl fluorides from a variety of carboxylic acids and sulfonic acids. The reaction is applicable to the preparation of acid-sensitive amino acid fluorides without deprotection or rearrangement.

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(20) Typical experimental procedure: To a mixture of benzoic acid (1.22 g, 10 mmol) and Ph_3P (5.26 g, 20 mmol) in MeCN (25 mL) under argon, was added Cl_3CCN (2 mL, 20 mmol) dropwise at r.t. The reaction mixture was stirred at r.t. for 1 h. TBAF(t-BuOH)$_4$ (11.2 g, 20 mmol) was added to the above solution, and stirring was continued for 1 h at r.t. After concentration of the reaction mixture by using a rotary evaporator, the residue was purified by distillation under reduced pressure to give benzoyl fluoride (1.12 g, 91%; bp 88–90 °C/100 mmHg (Lit.[13c] 84–86 °C/98 mmHg).
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