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Trifluoroacetylation of amines with trifluoroacetic acid in the presence of trichloroacetonitrile and triphenylphosphine

Joong-Gon Kim [a], Doo Ok Jang [b,*]

[a] Biotechnology Division, Hanwha Chemical R & D Center, Daejeon 305-345, Republic of Korea
[b] Department of Chemistry, Yonsei University, Wonju 220-710, Republic of Korea

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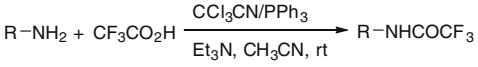
ABSTRACT

We developed a mild and convenient trifluoroacetylation process for amines using a combination of trichloroacetonitrile and triphenylphosphine. The reaction that we designed is applicable to the trifluoroacetylation of a wide variety of amines, including amines with stereogenic centers, which underwent trifluoroacetylation without racemization.

Trifluoroacetylation is important for the protection of a wide variety of amines and amino acids,[1] and is also a valuable technique for the activation of functional groups.[2] Due to its broad applications, various reagents for the trifluoroacetylation of amines have been developed, including *S*-ethyl trifluorothioacetate,[3] trifluoroacetly triflate,[4] *N*-(trifluoroacetoxy) succinimide,[5] *N*-(trifluoroacetyl) succinimide,[6] *N*-(trifluoroacetyl) imidazole,[7] *N*-(trifluoroacetyl) benzotriazole,[8] and 2-[(trifluoroacetyl)oxy]pyridine.[9] However, these agents have drawbacks including instability, sensitivity to moisture, toxicity, prolonged reaction times, and formation of undesirable byproducts that induce side reactions.

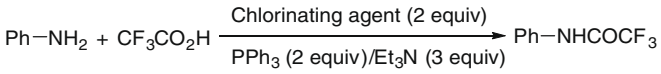
The use of trifluoroacetic acid, trifluoroacetic acid chloride, or trifluoroacetic anhydride for the trifluoroacetylation of amines may seem straightforward. However, trifluoroacetic acid chloride (bp: −27 °C)[10] and trifluoroacetic anhydride (bp: 40 °C)[11] have very low boiling points, which limit their applications in large-scale processes. The trifluoroacetylation of amines with trifluoroacetic acid has been previously reported, but these procedures required microwave assistance,[12] high reaction temperatures,[13] or the addition of condensation agents.[14]

We have developed novel procedures for the preparation of amides and esters by forming acid chlorides in situ with PPh_3 and CCl_3CN.[15,16] In this Letter, we report the trifluoroacetylation of a wide variety of amines with in situ-generated trifluoroacetyl



Scheme 1.

Table 1
Trifluoroacetylation of aniline under various reaction conditions



Entry	Chlorinating agent	Solvent	Time (h)	Yield (%)
1[a]	CCl_3CN	CH_3CN	2	41
2	CCl_3CN	CH_3CN	1	95
3[b]	CCl_3CN	CH_3CN	1	93
4[c]	CCl_3CN	CH_3CN	1	43
5	CCl_3CN	CH_2Cl_2	1	94
6	CCl_3CN	$(CH_2Cl)_2$	1	94
7	CCl_3CN	Toluene	1	93
8	CCl_3CN	EtOAc	1	85
9	CCl_3CN	THF	1	89
10	CCl_3CN	DMF	1	91
11	CCl_3CN	Ether	1	80
12	CCl_4	CH_3CN	10	Trace
13	CCl_3COCCl_3	CH_3CN	5	32
14	CCl_3CO_2Et	CH_3CN	5	17
15	CCl_3CONH_2	CH_3CN	5	10

[a] 1 equiv of CCl_3CN and 1 equiv of PPh_3 were used.
[b] At 0 °C.
[c] 1 equiv of Et_3N was used.

* Corresponding author.
E-mail address: dojang@yonsei.ac.kr (D.O. Jang).

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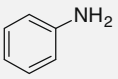
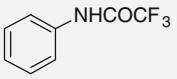
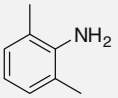
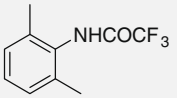
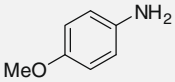
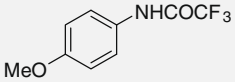
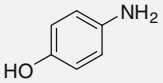
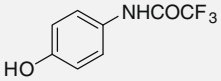
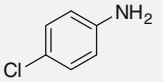
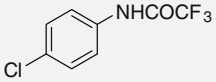
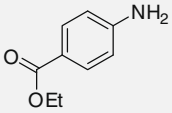
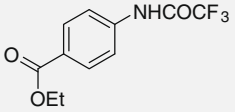
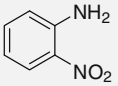
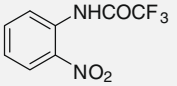
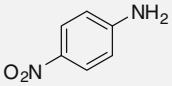
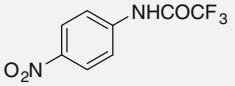
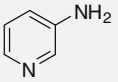
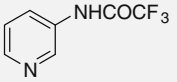
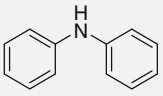
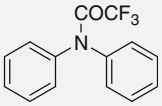
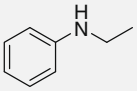
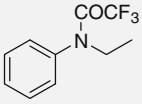
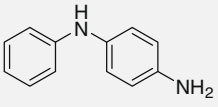
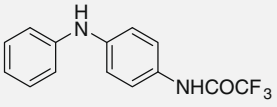
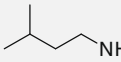
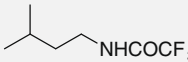
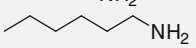
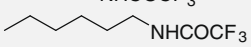
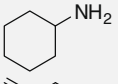
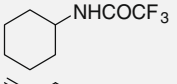
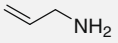
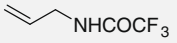
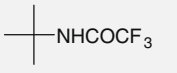
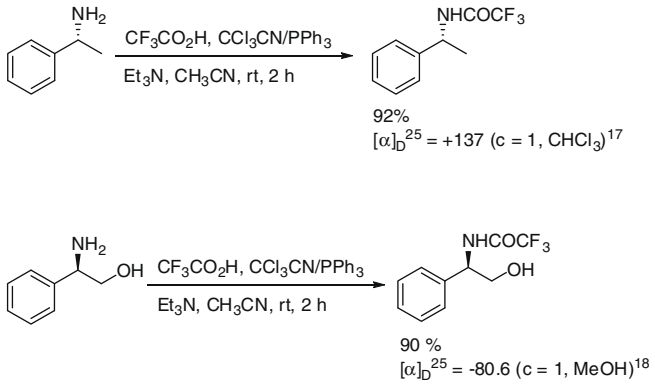
chloride form trifluoroacetic acid using a combination of PPh_3 and CCl_3CN under mild reaction conditions (Scheme 1). Initially, aniline was treated with 1 equiv of CCl_3CN and 1 equiv of PPh_3 in the presence of Et_3N at room temperature, resulting in a low (41%) yield of phenyltrifluoroacetamide (Table 1, entry 1). However, when the reaction was performed with 2 equiv of CCl_3CN and 2 equiv of PPh_3, the amide yield increased dramatically (entry 2). The reaction also proceeded smoothly at 0 °C (entry 3). To attain satisfactory yields of the amide, 3 equiv of Et_3N was required (entry 4). Common organic solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, THF, DMF, and EtOAc could be employed in this process (entries 5–10). Using ether as a solvent resulted in somewhat lower yield (entry 11). The use of other chlorinating reagents including CCl_3COCCl_3, CCl_3CO_2Et, and CCl_3CONH_2 was not as effective as the use of CCl_3CN (entries 12–15).

On the basis of these preliminary results, various amines were subjected to these novel reaction conditions to investigate the scopes and limitations of the reactions produced by our procedure.

Table 2
Trifluoroacetylation of amines

Entry	Amine	Product	Time (h)	Yield (%)
1			1	95
2			1.5	91
3			1	95
4			2	88
5			1	91
6			4	86
7			5	80
8			5	83
9			3	78
10			3	86
11			2	83
12			1	93
13			1	91
14			1	90
15			1	92
16			1	87
17			3	84



Scheme 2.

The results of these experiments are presented in Table 2. The reaction showed generality across a wide range of amines, including amines with low nucleophilicity. Compared to anilines with electron-withdrawing groups, anilines with electron-releasing groups were processed more efficiently under these conditions, affording higher yields of the corresponding products (entries 1–9). Trifluoroacetylation with anilines with very low nucleophilicity such as nitro anilines and *N*-phenyl aniline proceeded smoothly, resulting in high product yields (entries 7 and 10). Secondary amines were also shown to be good substrates for the reaction (entries 10 and 11). In a substrate with both primary amino and secondary amino groups, only the primary amino group was trifluoroacetylated (entry 12). Trifluoroacetylation with aliphatic amines resulted in high product yields (entries 13–16). Even very sterically hindered tertiary amines underwent trifluoroacetylation under these conditions (entry 17).

We applied our new method to the trifluoroacetylation of amines with stereogenic centers (Scheme 2). When (*R*)-1-phenylethanamine was subjected to our reaction conditions, the corresponding amides were obtained at a 92% yield.[17] In the case of (*R*)-2-amino-2-phenylethanol, which has both amino and hydroxyl groups, only the amino group was trifluoroacetylated selectively, demonstrating the good chemoselectivity of our novel reaction.[18] We did not detect any signs of racemization of the stereogenic centers through the analysis of reaction mixtures by HPLC using a chiral stationary phase.[19]

In conclusion, we have developed a mild and selective method for the trifluoroacetylation of a wide variety of amines. The present method has a number of advantages including low cost and availability of the reagents, easy handling and stability of the reagents, and ease of operation and workup. This novel trifluoroacetylation process has the potential to be applied widely for the protection and activation of amines in organic synthesis.

Typical procedure for trifluoroacetylation of amines: To a solution of triphenylphosphine (525 mg, 2 mmol), amine (1 mmol), and triethylamine (420 μL, 3 mmol) in CH_3CN (2 mL) under argon were added trifluoroacetic acid (77 μL, 1 mmol) and trichloroacetonitrile (200 μL, 2 mmol). The mixture was stirred at room temperature for several hours. After evaporation of the solvents, the residue was purified with column chromatography on silica gel to give a pure product.

Acknowledgment

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17. The enantiomer (Aldrich catalogue # 399779) has $[\alpha]_D^{20} = -135$ (*c* 1 in $CHCl_3$).
18. Mp 128 °C (lit.[8] 128–130 °C),^{1}H NMR (300 MHz, DMSO-d_6) δ 4.19 (m, 2H), 5.41 (m, 1H), 5.55 (s, 1H), 7.77 (m, 5H), 10.26 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.1, 63.5, 115.8, 126.7, 127.3, 127.9, 138.9, 156.2.
19. Chiral HPLC analysis for (*R*)-2,2,2-trifluoro-*N*-(2-hydroxy-1-phenylethyl)acetamide: Diacel Chiralcel OC; *n*-hexane/IPA (70/30 v/v); flow rate = 1.0 mL/min; UV (λ = 254 nm); retention time for *R* form = 15.2 min; retention time for *S* form = 23.5 min.