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A one-pot procedure for trifluoroacetylation of arylamines using trifluoroacetic acid as a trifluoroacetylating reagent

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ABSTRACT

A convenient procedure for the preparation of aryl trifluoroacetamides from aryl amines is described that employs 2–4 M equiv of trifluoroacetic acid in refluxing xylene as a trifluoroacetylating agent. Addition of an amount of pyridine that is equimolar to the amount of trifluoroacetic acid present in the reaction mixture facilitates the trifluoroacetylation of rather basic arylamines.

N-Trifluoroacetylation has become a common and useful procedure for the protection of a wide variety of amines.[1] Ease of removal is one important factor that has contributed to the many applications of the *N*-trifluoroacetyl protecting group in organic chemistry. Because of this widespread use, several reagents and methods for the trifluoroacetylation of amines have been developed. Reagents for trifluoroacetamidation that have been reported include, for example, trifluoroacetic anhydride,[1] *S*-ethyl trifluorothioacetate,[2] *N*-(trifluoroacetyl)imidazole,[3] 2-[(trifluoroacetyl)oxy]pyridine,[4] trifluoroacetyl triflate,[5] *N*-(trifluoroacetoxy)succinimide,[6] (trifluoroacetyl)benzotriazole,[7] and *N*-(trifluoroacetyl)succinimide.[8] Most of these reagents, however, have drawbacks and limitations due to either formation of undesirable by-products and/or handling issues on a plant scale. A convenient method has been developed for the selective 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate, but the reaction times are prolonged and the presence of 4-dimethylaminopyridine is essential.[9] Recently, a direct microwave-promoted trifluoroacetylation of anilines with trifluoroacetic acid (TFA) was reported.[10] The reaction was carried out without solvent and was simple and clean. However, further experiments might be necessary for the large scale production. Very recently, trifluoroacetylation of arylamines using trifluoroacetic acid (TFA) and poly-phosphoric acid trimethylsilylester as the condensation agent was reported.[11]

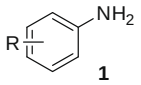
For several reasons, it is evident that the use of TFA alone would be both economically and environmentally advantageous. However, we found only one published report of this process. This described the trifluoroacetylation of anilines using TFA alone in dry ether at 0 °C for 1 h.[12]

However, following this experimental procedure, we could not obtain the trifluoroacetylated product (Table 1, entry 5).

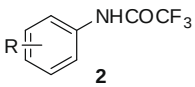
Herein, we report a new, convenient, and environmentally friendly trifluoroacetylation method using TFA as the trifuoroacetylating reagent.

Initially, we examined the trifluoroacetylation of aniline (**1a**) with TFA in various solvents, and the results are presented in Table 1.

The use of excess TFA provided the TFA salt of aniline and a trace amount of the desired product (Table 1, entry 3). When the amount of TFA was reduced, the yield was dramatically increased (Table 1, entry 1).

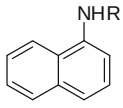


1

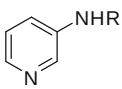


2

a: R=H
b: R=2-Me
c: R=4-Me
d: R=2,6-diMe
e: R=2-OMe
f: R=3-OMe
g: R=4-OMe
h: R=4-OEt
i: R=4-OH
j: R=2-Cl
k: R=4-Cl
l: R=2,4,6-triCl
m: R=4-COOEt
n: R=2-NO_2
o: R=3-NO_2
p: R=4-NO_2



3: R=H **4**: R=$COCF_3$



5: R=H **6**: R=$COCF_3$

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Table 1
Trifluoroacetylation of aniline in various solvents

Entry	Aniline (mmol)	TFA (mmol)	Solvent (mL)	Reaction time (h)	Reaction temp (°C)	Product yield (%)
1	3.0	6.0	Xylene (5)	3.5	150	94
2	3.0	6.0	Toluene (5)	3.5	130	44
3	2.2	—	TFA (5)	1.5	100	—
4	1.1	3.0	THF (5)	2.0	80	13
5	1.0	1.0	Et_2O (3)	2.0	0	—

On the basis of these preliminary results, the application of this procedure to various amines was investigated. The results are presented in Table 2.

Normally, it is assumed that electron-releasing groups in aniline facilitate trifluoroacetylation and electron-withdrawing groups do not. In this case, it is worth noting that the presence of electron-withdrawing groups such as nitro, ester, and chloro groups in anilines facilitates the trifluoroacetylation, whereas the electron-releasing group has less effect and can even retard trifluoroacetylation. However, use of pyridinium trifluoroacetate instead of TFA improved the yields substantially in these cases (Table 2, entries 6–11).

At high temperature (150 °C), the reaction between TFA and an amine has two routes, one is to form a salt by nucleophilic attack of the amine on the hydrogen and the other is to form an amide by the nucleophilic attack of the amine on the carbonyl carbon. The presence of a free amine and TFA in the reaction mixture is required for trifluoroacetamide formation. In excess TFA solution, the concentration of free amine is reduced because of formation of the TFA salt and this results in less efficient amide formation.

A proposed mechanism is illustrated in Scheme 1.

In the case of weak bases such as aniline, in particular anilines which have an electron-withdrawing substituent, the concentration of free aniline remains significant and trifluoroacetylation can proceed with ease.

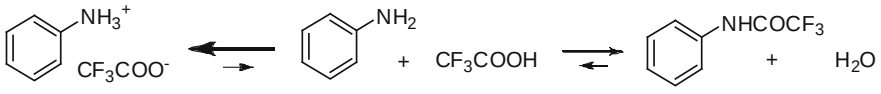
On the other hand, in the case of anilines which have an electron-releasing substituent such as a methoxy or a hydroxyl group, the equilibrium favors salt formation and unreacted TFA salt remains in the reaction mixture. However, addition of an equimolar amount of pyridine to TFA is effective in the trifluoroacetylation of rather strongly basic anilines which have pK_a values similar to those of pyridine (Table 2, entries 6–11). The exact role of pyridine is not clear. However, it is assumed that the population of free amines in the reaction mixture increases by the addition of pyridine. Addition of stronger base such as triethylamine is not effective probably because the TFA salt of triethylamine does not liberate free TFA during the reaction. In this case, **2a** was obtained in 5% yield and **1a** was recovered in 92% yield (Table 2, entry 2). Aliphatic amines which are more basic than anilines form the tight TFA salts with TFA and yields of trifluoroacetylation are low even with addition of pyridine.

In conclusion, we have developed an economic and environmentally friendly procedure for trifluoroacetylation of anilines using trifluoroacetic acid as the acetylating reagent. Low cost and availability of the reagent, and the ease of operation and workup make this method a useful addition to the available methodologies.

Table 2
Trifluoroacetylation of aromatic amines in refluxing xylene[13]

Entry	Starting compd.	Method[a]	Reaction time (h)	Product	Yield (%)	Melting point (°C)	
						Found	Lit.
1	**1a**	A	5.5	**2a**	94 (92)[b]	90.5–91	89–90[14]
2	**1a**	A	6.5	**2a**	5[c]	—	—
3	**1b**	A	7.0	**2b**	86	79–79.5	78–79[14]
4	**1c**	A	5.5	**2c**	85	113–113.5	111[14]
5	**1d**	B	5.5	**2d**	65	94.5–95	89–90[14]
6	**1e**	B	5.0	**2e**	72 (95)[b]	50.5–51	47–48[10]
7	**1f**	A	5.5	**2f**	76 (94)[b]	75.5–76	75[14]
8	**1g**	B	6.5	**2g**	78 (98)[b]	117–117.5	113–115[15]
9	**1g**	B	1.5	**2g**	53 (88)[b]	—	—
10	**1h**	A	2.0	**2h**	68 (98)[b]	144.5–145	141–143[15]
11	**1i**	B	6.5	**2i**	62 (95)[b]	172–173	167–169[14]
12	**1j**	B	3.5	**2j**	89	41.5–42	40–41[10]
13	**1k**	A	3.0	**2k**	92	128–128.5	123–124[16]
14	**1l**	A	5.5	**2l**	20	103–103.5	—[17]
15	**1m**	A	2.5	**2m**	88	129.5–130	—[17]
16	**1n**	B	6.5	**2n**	50	89.5–90	90.4[18]
17	**1o**	A	2.0	**2o**	94	92–92.5	94.2[18]
18	**1p**	B	5.5	**2p**	89	151.5–152	151–152[15]
19	**3**	B	5.0	**4**	73	105.5–106	102–103[14]
20	**5**	A	3.0	**6**	78	130–130.5	127–128[14]

[a] A: TFA (2 equiv) was used. B: TFA (4 equiv) was used.
[b] Figures in parentheses indicate the yields using pyridinium trifluoroacetate instead of TFA.
[c] Triethylaminium trifluoroacetate was used instead of TFA.



Scheme 1.

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13. *Typical procedure for one-pot procedure for trifluoroacetylation of arylamines*: (1) A mixture of aniline (**1a**) (279 mg, 3 mmol), TFA (684 mg, 6 mmol), and xylene (5 mL) was refluxed (bath temp. 150 °C) for 5.5 h. After the reaction, the solvent was evaporated in vacuo. The residue was chromatographed on a column of silica gel with AcOEt/*n*-hexane (1:4) to afford 2,2,2-trifluoro-*N*-phenylacetamide (**2a**) (534 mg, 94%). (2) To pyridinium trifluoroacetate (386 mg, 2 mmol) in xylene (3 mL) was added 4-aminophenol (**1i**) (109 mg, 1 mmol), and the reaction mixture was refluxed for 6.5 h. After the reaction, 10% $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with AcOEt (20 mL × 2). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel with AcOEt/*n*-hexane (1:1) to afford 2,2,2-trifluoro-*N*-(4-hydroxyphenyl)acetamide (**2i**) (195 mg, 95%). (3) Large scale preparation of **2k**: to a solution of 4-chloroaniline (**1k**) (50 g, 0.392 mol) in xylene (580 mL) was added trifluoroacetic acid (58 mL, 0.784 mol) at 0 °C. The mixture was refluxed (bath temp. 150 °C) for 3.0 h. After the reaction, the solvent was evaporated in vacuo. Five percentage HCl (150 mL) was added to the residue and the aqueous layer was extracted with AcOEt (250 mL × 2). The organic layer was washed with brine (200 mL × 2), dried over Na_2SO_4, and concentrated. The crude product was recrystallized from AcOEt-*n*-hexane to afford 2,2,2-trifluoro-*N*-(4-chlorophenyl)acetamide (**2k**) (74 g, 84%); mp 123–124 °C (lit. 123–124 °C[16]).
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17. 2,2,2-Trifluoro-*N*-(2,4,6-trichlorophenyl)acetamide (**2l**): colorless crystal: mp 103–103.5 °C (AcOEt/*n*-hexane); IR (KBr) 3320, 3150, 1770 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.45 (2 H, s), 7.67 (1 H, br s); EI-MS *m/z*; 293, 291 (M^+), 258, 256 (100%), 196, 194, 169, 167. Anal. Calcd for $C_8H_3Cl_3F_3NO$: C; 32.85, H; 1.03, N; 4.79. Found: C; 33.13, H; 1.13, N; 4.91.Ethyl 4-(2,2,2-trifluoroacetylamino)benzoate (**2m**): colorless needle: mp 129.5–130 °C (AcOEt/*n*-hexane); IR (KBr) 3350, 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.40 (3 H, t, *J* = 7.09 Hz), 4.38 (2 H, q, *J* = 7.09 Hz), 7.68 (2 H, d, *J* = 8.57 Hz), 8.09 (2 H, d, *J* = 8.74 Hz)) 8.17 (1 H, br s); EI-MS *m/z*; 261 (M^+), 233, 216 (100%). Anal. Calcd for $C_{11}H_{10}F_3NO_3$: C; 50.58, H; 3.86, N; 5.36. Found: C; 50.73, H; 3.90, N; 5.33.
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