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A new, convenient and selective 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate

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Abstract

A new, convenient, and selective 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate is described. Anilines, containing other functional groups, e.g. alcohols, phenols, hindered secondary amines, and secondary anilines, are also selectively trifluoroacetylated in high yields under these newly developed conditions.

Trifluoroacetylation is an important transformation for the protection of several functional groups, e.g. alcohols, phenols, amines, and anilines.[1] In one of our projects we needed to selectively trifluoroacetylate an aniline. There are a number of reagents and methods reported[2–9] for the trifluoroacetylation of anilines and other functional groups, with trifluoroacetic anhydride[10] being the most popular reagent of choice. Most of these reagents, however, have drawbacks and limitations due to either undesired by-products and handling issues on a plant scale, or they are not readily available and have to be synthesized. Additionally, selective trifluoroacetylation of anilines in the presence of other functional groups with these reagents, including commercially readily available trifluoroacetic anhydride, has not been reported. Because it is important in organic synthesis to distinguish between various functional groups in a polyfunctional molecule to avoid a cumbersome and time-consuming protection and deprotection sequence, we became interested in studying the selective trifluoroacetylation of anilines with ethyl trifluoroacetate.[11] Ethyl trifluoroacetate is a commercially available reagent, which is also easy to handle on a large scale. Herein, we report a new, convenient, and selective 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate (Scheme 1).

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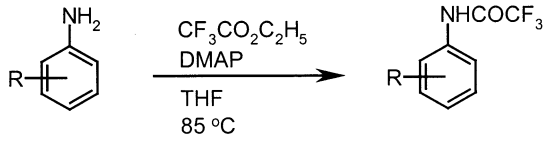
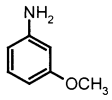
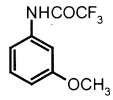
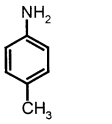
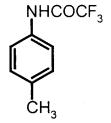
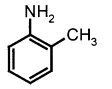
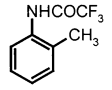
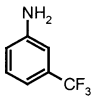
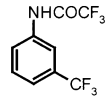
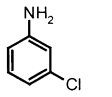
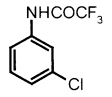
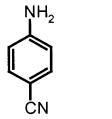
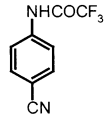
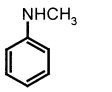
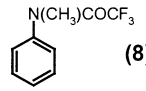


Scheme 1.

Trifluoroacetylation of aniline itself was first chosen as the representative example to develop appropriate conditions. Treatment of a solution of aniline (10 mmol) in THF (7.0 mL) with ethyl trifluoroacetate (1.13 equiv.) at 85°C for 24 h gave only 5% of *N*-phenyltrifluoroacetamide (**1**). Use of catalytic amounts of pyridine (0.1 equiv.) and triethylamine (0.1 equiv.) under these conditions led to only a slight increase in the yield of **1** to 10 and 26%, respectively. An increase in the amount of ETFA to 2.0 equiv. also led to a slight increase in the yield of **1** to 10%. However, use of 0.1 equiv. of 4-dimethylaminopyridine (DMAP)[12,13] yielded **1** in 79% yield. An increase in the amount of ETFA to 2.0 equiv. in the presence of 0.1 equiv. of DMAP further increased the yield of **1** to 85%. Such a 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate is not known to the best of our knowledge. To test the general synthetic utility[14] of these newly developed conditions (Scheme 1) we studied the trifluoroacetylation of several anilines. The results are listed in Table 1. All the anilines gave excellent yields of the corresponding *N*-aryltrifluoroacetamides (**2**–**7**). *ortho*-Toluidine yielded only 30% of **4** (entry 4, Table 1) under these conditions, perhaps due to steric hindrance. An increase in the amount of ETFA led to an increase in the yield of **4** to 49% (entry 5). However, an increase in the amount of DMAP to 1.0 equiv. led to a substantial increase in the yield of **4** to 93% (entry 6). Use of 1.0 equiv. of DMAP also led to a satisfactory trifluoroacetylation of 4-cyanoaniline, an aniline containing a strong electron-withdrawing group, affording **7** in 79% yield (entry 9). No trifluoroacetylation was observed with *N*-methylaniline even with 1.0 equiv. of DMAP and 2.0 equiv. of ETFA (entry 10).

Selective trifluoroacetylation of anilines in the presence of other functional groups, e.g. alcohols, phenols, secondary amines, and secondary anilines, will be of great importance. We next demonstrated the synthetic utility of our newly developed conditions in selective trifluoroacetylation of various anilines containing these functional groups. The results are summarized in Table 2. Results in entries 1–5 clearly demonstrated that anilines containing an alcohol or phenol functionality were selectively trifluoroacetylated in high yields. Towards studying the selective trifluoroacetylation of anilines in the presence of hindered secondary amines, first an equimolar mixture of aniline and *N*-benzylisopropylamine was treated with ETFA in THF in the presence of DMAP at 85°C. Only aniline underwent trifluoroacetylation to afford **1**. No trifluoroacetylation of *N*-benzylisopropylamine was observed. These results suggested that anilines could be selectively trifluoroacetylated in the presence of hindered secondary amines. This supposition was confirmed by trifluoroacetylation of anilines reported in entries 6 and 7 (Table 2), containing a hindered secondary amine functionality. These results clearly demonstrated that anilines are selectively trifluoroacetylated in excellent yields in the presence of hindered secondary amines under our new conditions. This method, however, is not suitable for selective trifluoroacetylation of anilines in the presence of unhindered secondary amines as treatment of an equimolar mixture of aniline and *N*-benzylmethylamine led to trifluoroacetylation of *N*-benzylmethylamine.

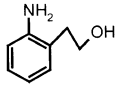
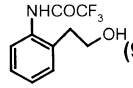
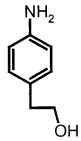
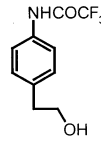
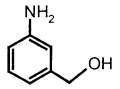
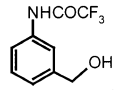
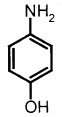
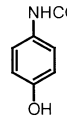
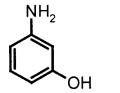
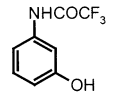
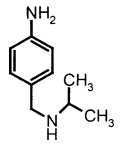
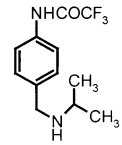
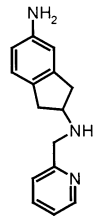
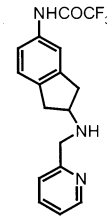
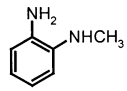
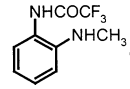
Table 1
Trifluoroacetylation of anilines with ETFA in the presence of DMAP

Entry	Substrate	ETFA (mol. eq.)	DMAP (mol. eq.)	Time (h)	Product	Isolated Yield (%)
1		1.135	0.1	24	 (2)	75
2		2.52	0.1	22		91
3		1.135	0.1	20	 (3)	78
4		1.135	0.1	24	 (4)	30
5		2.52	0.1	72		49
6		2.0	1.0	22		98
7		2.0	0.1	48	 (5)	93
8		2.0	0.1	22	 (6)	90
9		2.27	1.0	24	 (7)	79
10		2.0	1.0	24	 (8)	0

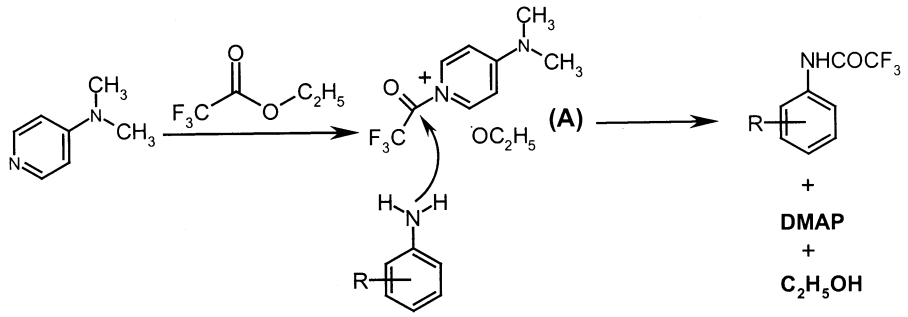
Selective trifluoroacetylation of primary anilines in the presence of secondary anilines was studied next. Trifluoroacetylation of an equimolar mixture of aniline and *N*-methylaniline was carried out in the presence of 1.0 equiv. of DMAP and 2.0 equiv. of ETFA in THF at 85°C. Only aniline underwent trifluoroacetylation to afford **1**. These results suggested that primary anilines could be selectively trifluoroacetylated in the presence of secondary anilines. To this end, trifluoroacetylation of *N*-methyl-1,2-phenylenediamine, a molecule containing both primary and secondary aniline, was studied. Only primary aniline group underwent trifluoroacetylation affording **16** in excellent yield (entry 8, Table 2). These results confirmed that primary anilines are selectively trifluoroacetylated in the presence of secondary anilines under our new conditions. Selective protection of primary amines in the presence of secondary amines is known in the literature.[15–17]

A plausible mechanism for the DMAP-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate is depicted in Scheme 2. The *N*-acylpyridinium salt (**A**)[18,19] undergoes a nucleophilic attack with aniline to afford a tetrahedral intermediate, which liberates *N*-arytrifluoroacetamide product, ethanol by-product and DMAP.

Table 2
Selective trifluoroacetylation of anilines with ETFA in the presence of DMAP

Entry	Substrate	ETFA (mol. eq.)	DMAP (mol. eq.)	Time (h)	Product	Isolated Yield (%)
1		1.135	0.1	6	 **(9)**	82
2		1.135	0.1	24	 **(10)**	96
3		1.135	0.1	24	 **(11)**	82
4		1.135	0.1	19	 **(12)**	87
5		1.135	0.1	23	 **(13)**	83
6		1.135	0.1	24	 **(14)**	90
7		1.135	0.25	24	 **(15)**	91
8		2.0	0.1	23	 **(16)**	90

In summary, a new, convenient, and selective 4-dimethylaminopyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate is described. Anilines, containing other functional groups, e.g. alcohols, phenols, hindered secondary amines, and secondary anilines, are also selectively trifluoroacetylated in high yields under these newly developed conditions.



Scheme 2.

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14. **General Procedure**: A round-bottomed flask, equipped with a magnetic stirrer bar and a reflux condenser, was charged with an appropriate aniline (10.0 mmol), THF (7.0 mL), ethyl trifluoroacetate (11.35 mmol or specified amount in Tables 1 and 2), and 4-dimethylaminopyridine (1.0 mmol or specified amount in Tables 1 and 2). The flask was immersed in an 85–90°C oil bath and the mixture was refluxed for 24 h (or specified time in Tables 1 and 2). The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with 2N HCl and water sequentially (the organic layer was washed with water only for entries 6–8 in Table 2). The organic layer was dried over anhydrous sodium sulfate and concentrated. The product was purified either by recrystallization from ethyl acetate and hexane mixture or by a flash chromatography on silica gel. All the compounds gave satisfactory spectroscopic data. **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 1H), 2.89 (t, 2H, J=5.2 Hz), 4.02 (t, 2H, J=5.2 Hz), 7.2 (m, 2H), 7.31 (m, 1H), 7.86 (d, 1H, J=7.9 Hz), 10.31 (bs, 1H). **11**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.16 (d, 1H, J=7.53 Hz), 7.35 (dd, 1H, J=7.53 and 8.28 Hz), 7.53 (d, 1H, J=8.28 Hz), 7.67 (s, 1H), 11.23 (bs, 1H). **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 6H, J=6.4 Hz), 2.77 (m, 1H), 3.7 (s, 2H), 7.26 (d, 2H, J=8.46 Hz), 7.42 (d, 2H, J=8.46 Hz). **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (bs, 1H), 2.66 (m, 2H), 3.02 (m, 2H), 3.57 (m, 1H), 3.85 (s, 2H), 7.02–7.16 (m, 3H), 7.23 (d, 1H, J=7.9 Hz), 7.32 (s, 1H), 7.56 (m, 1H), 8.45 (d, 1H, J=4.71 Hz), 9.12 (bs, 1H). **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, 3H, J=4.9 Hz), 7.36–7.43 (m, 3H), 7.86 (m, 1H).
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