The trifluoromethylation of iminium salts by the addition of trifluoromethyltrimethylsilane

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Eleven trifluoromethylated amines were synthesised in high yield (up to 98%) under metal-free and oxidant-free conditions using iminium salts as starting material and the addition of trifluoromethyltrimethylsilane in dimethylformide containing potassium fluoride.

Keywords: trifluoromethylation, trifluoromethylated amines, iminium salts, cyanation, Ruppert–Prakash reagent, metal-free, oxidant-free

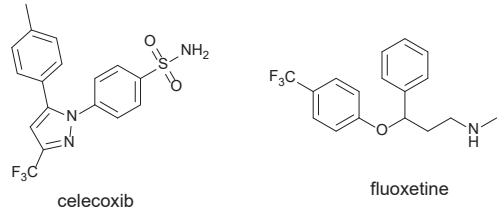
Fluorine-containing compounds play a significant role in modern pharmaceutical and agrochemistry. Approximately 20–25% of all drugs available in the market contains at least one fluorine substituent.[1–3] The unique nature of fluorine imparts many desirable physicochemical properties to therapeutic and diagnostic small molecule drugs that possess an appropriately positioned fluorine substituent. These include enhanced metabolic stability, better binding affinity for target biomolecules, higher lipophilicity, and stronger dipole moments compared to their non-fluorinated analogs.[4–6] Celecoxib and fluoxetine are both examples of top-selling pharmaceuticals containing trifluoromethyl groups (Scheme 1).[7,8] The trifluoromethyl group can have dramatic effects on the bioavailability and efficacy of organic molecules, and therefore, there has been considerable interest in the development of synthetic methodologies for the direct and selective introduction of the trifluoromethyl moiety into industrially important molecules. Recently, amines with a trifluoromethyl substituent at the alpha position have attracted considerable attention as synthetic building blocks for pharmaceutical products and agrochemicals.[9–14]

Preformed iminium salts are of great theoretical and practical interest. Nevertheless, there are only a few examples in the literature concerning the synthesis and applications of these compounds.[15–22] In this paper, we describe an efficient synthesis of trifluoromethylated amines through trifluoromethylation of iminium salts with trimethyl(trifluoromethyl)silane under metal-free and oxidant-free reaction conditions.

Results and discussion

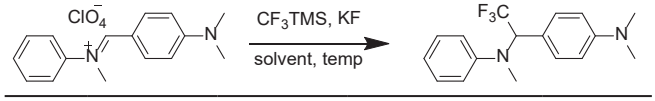
Based on Qing's work on benzoyl peroxide (BPO)-promoted oxidative trifluoromethylation of tertiary amines with the Ruppert–Prakash reagent,[23,24] we examined the synthesis of trifluoromethylated amines by reacting CF_3TMS with iminium salts **1a** in the presence of KF in DCM at 50 °C. The reaction proceeded smoothly giving a novel product **3a** in 37% yield, (Table 1, entry 1) which was unambiguously characterised by HRMS, ^1H NMR, and ^{13}C NMR. In order to improve the yield, various ratios of iminium salts, CF_3TMS and KF were examined. Increasing the amount of CF_3TMS and KF increased the yield of the product (entries 2–4). When the ratio of iminium salts/CF_3TMS/KF was 1:3:3, an excellent yield (92%) of the desired product was obtained (entry 3). Any further increase in the ratio proved to be detrimental to the reaction (entry 4). Screening the solvent for the reaction indicated that MeCN, toluene, THF, and 1,4-dioxane were not suitable because of the poor solubility of **1a** in these solvents (entries 5–8). DMF gave the desired product in moderate yield (entry 9). An excellent yield (96%) was obtained when the reaction was performed at low temperature in DMF (entry 10).

With the optimised reaction conditions in hand (3 equiv. of CF_3TMS, 3 equiv. of KF in DMF under –20 °C), we examined the scope of the reaction with a variety of iminium salts. Representative examples are listed in Table 2. For aromatic iminium salts, the reaction often provided good to excellent yields of the desired products. For aliphatic iminium salts, the corresponding product was also formed in good yield (**3d**). The reaction conditions also tolerated the presence of an alcohol functional group in the starting materials (**3i** and **3j**). Cyclic aromatic iminium salts such as **1e**, **1h**, and **1i** can be smoothly converted into the corresponding trifluoromethylated derivatives in 93%, 95% and 71% isolated yield, respectively. In general, iminium salts bearing electron-rich aryl substituents (4-(*N*,*N*-dimethylamino)phenyl) afforded better yields than



Scheme 1

Table 1 Effect of variation of solvent-, base- and CF_3TMS-loading on the yield of trifluoromethylated amine (**3a**) formed by the trifluoromethylation of iminium salt (**1a**)[a]



Entry	CF_3TMS	KF	Solvent	Yield/%[b]
1	1.0	1.0	DCM	37
2	2.0	2.0	DCM	81
3	3.0	3.0	DCM	92
4	5.0	5.0	DCM	78
5	3.0	3.0	MeCN	39
6	3.0	3.0	Toluene	32
7	3.0	3.0	THF	27
8	3.0	3.0	1,4-Dioxane	29
9	3.0	3.0	DMF	67
10	3.0	3.0	DMF	96[c]

[a]The reaction was carried out with 0.5 mmol of **1a**, 1.5 mmol of CF3TMS, 1.5 mmol of KF, in solvents (0.2 M).
[b]Isolated yield.
[c]The reaction was performed under –20 °C.

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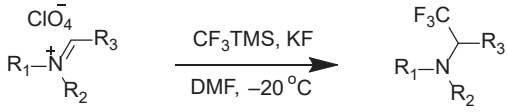
Table 2 Yields of trifluoromethylated amines **3a–k** formed by the trifluoromethylation of iminium salts **1a–k** with CF_3TMS under optimised reaction conditions[a]



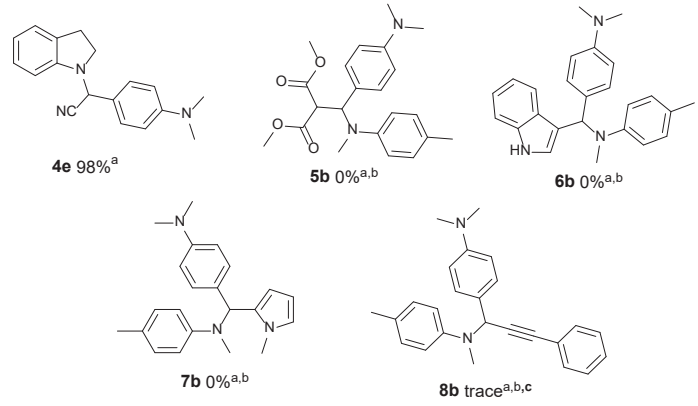
Entry	1	R1	R2	R3	3	Yield/% of 3[b]
1	**1a**	Ph	Me	4-$Me_2NC_6H_4$	**3a**	96
2	**1b**	4-MeC_6H_4	Me	4-$Me_2NC_6H_4$	**3b**	95
3	**1c**	Ph	Et	4-$Me_2NC_6H_4$	**3c**	95
4	**1d**	Bn	Me	4-$Me_2NC_6H_4$	**3d**	83
5	**1e**	Bn	-CH_2-	4-$Me_2NC_6H_4$	**3e**	97
6	**1f**	3-Me C_6H_4	Et	4-$Me_2NC_6H_4$	**3e**	97
7	**1g**	3-Me C_6H_4	Me	4-$Me_2NC_6H_4$	**3g**	97
8	**1h**	Bn	-$(CH_2)_2$-	4-$Me_2NC_6H_4$	**3h**	98
9	**1i**	Bn	-CH_2-	4-HOC_6H_4	**3i**	81
10	**1j**	4-MeC_6H_4	Me	4-HOC_6H_4	**3j**	78
11	**1k**	Ph	Me	furan-2-yl	**3k**	75

[a]The reaction was carried out with 0.5 mmol of 1, 1.5 mmol of CF_3TMS, 1.5 mmol of KF, in DMF (0.2 M) under –20 °C.

[b]Isolated yield after chromatography.

those containing electron-poor substituents (4-hydroxl-phenyl and 2-furanyl). This result was expected since electron-rich aryl substituents would increase the carbonium ion character of the iminium carbon due to the diminished ability of the nitrogen to contribute its lone pair to the C–N bond. Overall, these results demonstrate the versatility of the present methodology.

We also examined the direct functionalisation of iminium salts with other nucleophiles. We were delighted when TMSCN afforded the desired cyanide product **4e** in 98% yields. However, nucleophiles derived from dimethylmalonate, indole, *N*-methylindole, *N*-methylpyrrole, and phenylethynyl groups did not react with iminium salts **1b** to afford the desired products. Moreover, (phenylethynyl) copper also failed to react with iminium salts **1b** to afford the desired product in solvents such as MeCN, MeOH, and DMF at temperatures ranging from –20 °C to 90 °C (Scheme 2).



Scheme 2

Experimental

All reagents including analytical-grade solvents were purchased from Sigma-Aldrich (USA), Aladdin (P.R. China), or Sinopharm Chemical Reagent (P.R. China) and were used without further purification. Melting points are uncorrected. NMR spectra were obtained on a Bruker 300 MHz spectrometer (^{1}H NMR at 300 Hz, ^{13}C NMR at 75 Hz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. Mass spectra (MS) were obtained from Finnigan (USA) MAT-95 Spectrometry Services. The synthesised compounds were obtained as detailed below. Silica gel (200–300 μm) for flash chromatography was purchased from Qingdao Haiyang Chemical (P.R. China).

Synthesis of iminium salts; general procedure

The amine (10 mmol) in ethanol (10 mL) was added to a round-bottom flask and was cooled to 0–5 °C. Whilst stirring, perchloric acid (10 mmol) (aqueous solution, 70% by weight) was added dropwise. Stirring was continued for an additional 20 min at 0–5 °C, and then the pH value was measured and corrected to 4–5 by the dropwise addition of amine. The solvent was evaporated and the residue was dried *in vacuo*. The crude crystalline product was purified by recrystallisation from dichloromethane and isopropyl alcohol.

A mixture of 4 mmol of *N*-alkylanilinium perchlorate and the respective aldehyde (5 mmol) in dry chloroform (10 mL) in the presence of catalytic amounts of DBU and aluminium chloride (or in the presence P_2O_5) was refluxed for 16 h under an argon atmosphere. The solvent was removed under reduced pressure and the residual oil was dissolved in DCM. Dry THF was added to the DCM solution and the crystalline product was precipitated from the solution. The resulting solid was dried under high vacuum to give the corresponding iminium salts **1a**–**1k**.

Synthesis of α*-trifluoromethylated amines* (**3a**–**3k**)*; general procedure*

DMF (2.5 mL) was added to a flask (10 mL) containing an iminium salt (0.5 mmol) and anhydrous potassium fluoride (87 mg, 1.5 mmol). The reaction mixture was cooled to –20 °C. Ruppert's reagent (213 mg, 1.5 mmol) was then slowly added to the reaction mixture which was then stirred at this temperature for 2–10 h and the formation of the product was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the crude product was purified by column chromatography using DCM and hexane to afford corresponding pure products.

N,N-*Dimethyl-4-(2,2,2-trifluoro-1-(methyl(phenyl)amino)ethyl) aniline* (**3a**): Colourless oil; ^{1}H NMR: δ 7.12–7.24 (m, 4H), 6.84 (d, 2H, *J* = 8.1 Hz), 6.77 (t, 1H, *J* = 7.2, 14.4 Hz), 6.60 (d, 2H, *J* = 9.0 Hz), 5.35 (dd, 1H, *J* = 8.4, 17 Hz), 2.89 (s, 3H), 2.64 (s, 3H); ^{13}C NMR: δ 150.22, 131.98, 129.25, 128.95, 128.17, 124.38, 122.62, 119.69, 118.46, 113.98, 112.10, 64.78, 64.39, 64.01, 63.63, 40.30, 33.27; HRMS (ESI) for $C_{17}H_{20}F_3N_2$ $[M + H]^+$ calcd 309.1579; found: 309.1588.

N-*(1-(4-(Dimethylamino)phenyl)-2,2,2-trifluoroethyl)*-N,*4-dimethylaniline* (**3b**): Colourless oil; ^{1}H NMR: δ 7.08 (m, 2H, *J* = 8.4, 9.1 Hz), 6.97 (d, 2H, *J* = 8.4), 6.72 (d, 2H, *J* = 8.4), 6.56 (d, 2H, *J* = 9.0), 5.19 (dd, 1H, *J* = 8.4, 17 Hz), 2.85 (s, 6H), 2.58 (s, 3H), 2.18 (s, 3H); ^{13}C NMR: δ 150.25, 148.29, 132.08, 129.77, 129.01, 128.28, 127.87, 124.49, 120.68, 119.88, 114.42, 112.13, 65.39, 65.01, 64.63, 64.25, 40.30, 33.43, 20.29; HRMS (ESI) for $C_{18}H_{22}F_3N_2$ $[M + H]^+$ calcd 323.1735; found: 323.1745.

4-(1-(Ethyl(phenyl)amino)-2,2,2-trifluoroethyl)-N,N-*dimethyl-aniline* (**3c**): Colourless oil; ^{1}H NMR: δ 7.10–7.20 (m, 4H), 6.83 (d, 2H, *J* = 8.1), 6.72 (t, 1H, *J* = 7.2), 6.56 (d, 2H, *J* = 9.0), 5.25 (dd, 1H, *J* = 8.4, 17 Hz), 3.05 (m, 2H), 2.85 (s, 6H), 0.88 (t, 3H, *J* = 6.9); ^{13}C NMR: δ 150.18, 148.23, 132.07, 129.23, 129.11, 129.09, 128.28, 124.50, 120.47, 118.54, 115.37, 112.10, 40.29, 39.85, 12.71; HRMS (ESI) for $C_{18}H_{22}F_3N_2$ $[M + H]^+$ calcd 323.1735; found: 323.1751.

4-(1-(Benzyl(methyl)amino)-2,2,2-trifluoroethyl)-N,N-*dimethylaniline* (**3d**)**:** Colourless oil; ^{1}H NMR: δ 7.12 (m, 2H), 6.93 (m, 2H), 6.49–6.58 (m, 4H), 4.95 (dd, 1H, *J* = 9.0, 18 Hz), 3.43 (m, 1H), 3.09 (m, 1H), 2.85(m, 8H); ^{13}C NMR: δ 150.62, 150.48, 131.85, 129.85, 129.83, 129.18, 128.06, 127.29, 124.72, 124.28, 120.50, 118.61, 117.90, 112.05, 106.25, 61.96, 61.56, 61.17, 60.77, 48.36, 40.24, 28.28; HRMS (ESI) for $C_{18}H_{22}F_3N_2$ $[M + H]^+$ calcd 323.1735; found: 323.1744.

N,N-*Dimethyl-4-(2,2,2-trifluoro-1-(indolin-1-yl)ethyl)aniline* (**3e**): Colourless oil; ^{1}H NMR: δ 7.15–7.26 (m, 6H), 6.63 (d, 2H, *J* = 8.7), 4.01 (dd, 1H, *J* = 8.8, 17.7 Hz), 3.67 (d, 1H, *J* = 13.8), 3.40 (d, 1H, *J* = 13.5), 2.89 (s, 6H), 2.23 (s, 3H); ^{13}C NMR: δ 150.34, 139.10, 132.25,

130.35, 128.73, 128.47, 128.34, 127.12, 124.69, 120.93, 119.18, 111.91, 67.81, 67.45, 67.09, 66.72, 59.37, 40.32, 38.80, 38.78; HRMS (ESI) for $C_{18}H_{20}F_3N_2$ $[M + H]^+$ calcd 321.1579; found: 321.1594.

N-*(1-(4-(Dimethylamino)phenyl)-2,2,2-trifluoroethyl)*-N-*ethyl-3-methylaniline* (**3f**): Colourless oil; ^{1}H NMR: δ 7.18–7.28 (m, 3H), 6.69–6.80 (m, 5H), 5.41 (dd, 1H, *J* = 8.8, 17.2 Hz), 3.24 (m, 2H), 2.99 (s, 6H), 2.38 (s, 3H), 1.02 (t, *J* = 6.8, 3H); ^{13}C NMR: δ 150.22, 148.37, 138.91, 129.13, 129.11, 129.09, 127.85, 125.01, 120.69, 119.56, 116.28, 112.65, 112.14, 109.98, 65.04, 64.76, 64.47, 64.19, 40.27, 40.26, 39.85, 21.86, 12.79; HRMS (ESI) for $C_{19}H_{24}F_3N_2$ $[M + H]^+$ calcd 337.1892; found: 337.1904.

N-*(1-(4-(Dimethylamino)phenyl)-2,2,2-trifluoroethyl)*-N,*3-dimethylaniline* (**3g**): Colourless oil; ^{1}H NMR: δ 7.04–7.14 (m, 4H), 6.55–6.64 (m, 4H), 5.27 (dd, 1H, *J* = 8.5, 17.0 Hz), 2.85 (s, 6H), 2.60 (s, 3H), 2.24 (s, 3H); ^{13}C NMR: δ 150.37, 150.23, 138.97, 132.00, 129.08, 128.94, 128.21, 124.42, 120.63, 119.89, 119.42, 114.78, 112.14, 111.19, 64.77, 64.39, 64.01, 63.63, 40.29, 33.29, 29.68, 21.86; HRMS (ESI) for $C_{18}H_{22}F_3N_2$ $[M + H]^+$ calcd 323.1735; found: 323.1750.

*4-(1-(3,4-Dihydroquinolin-1(2*H*)-yl)-2,2,2-trifluoroethyl)*-N,N-*dimethylaniline* (**3h**): Colourless oil; ^{1}H NMR: δ 7.13 (m, 2H), 7.0 (m, 1H), 6.85 (m, 1H), 6.76 (m, 1H), 6.56 (m, 3H), 5.39 (dd, 1H, *J* = 8.6, 17.2 Hz), 2.90–3.12 (m, 2H), 2.85 (s, 6H), 2.50–2.72 (m, 2H), 1.55 (m, 1H), 1.75 (m, 1H); ^{13}C NMR: δ 150.23, 145.22, 132.07, 129.75, 129.22, 129.20, 128.27, 127.15, 124.47, 123.42, 119.87, 117.19, 112.11, 111.61, 62.57, 62.18, 61.80, 61.41, 44.10, 40.29, 29.70, 28.26, 21.74; HRMS (ESI) for $C_{19}H_{22}F_3N_2$ $[M + H]^+$ calcd 335.1735; found: 335.1745.

4-(2,2,2-Trifluoro-1-(indolin-1-yl)ethyl)phenol (**3i**): Colourless oil; ^{1}H NMR: δ 7.17 (d, 2H, *J* = 7.5 Hz), 7.0 (m, 2H), 6.71 (d, 2H, *J* = 8.7), 6.58 (m, 1H), 6.49 (d, 1H, *J* = 7.8), 5.00 (dd, 1H, *J* = 8.7, 17.5 Hz), 3.45 (m, 1H), 3.08 (m, 1H), 2.83 (m, 2H); ^{13}C NMR: δ 156.00, 150.32, 131.57, 130.33, 130.31, 129.12, 127.79, 127.33, 124.82, 124.02, 123.65, 120.25, 118.16, 115.58, 106.23, 61.74, 61.34, 60.95, 60.55, 48.32, 29.69, 28.27; HRMS (ESI) for $C_{16}H_{15}F_3NO$ $[M + H]^+$ calcd 294.1106; found: 294.1117.

4-(2,2,2-Trifluoro-1-(methyl(p-tolyl)amino)ethyl)phenol (**3j**): Colourless oil; ^{1}H NMR: δ 7.34 (s, 1H), 7.01 (d, 2H, *J* = 8.4 Hz), 6.77 (d, 2H, *J* = 8.4 Hz), 6.31–6.39 (m, 2H), 5.27 (dd, 1H, *J* = 7.7, 15.5 Hz), 2.70 (s, 3H), 2.21 (s, 3H); ^{13}C NMR: δ 147.77, 146.41, 143.00, 130.72, 129.79, 128.81, 126.94, 123.16, 119.42, 115.05, 110.27, 110.19, 110.17, 61.57, 61.16, 60.75, 60.34, 33.65, 33.63, 20.31; HRMS (ESI) for $C_{16}H_{17}F_3NO$ $[M + H]^+$ calcd 296.1262; found: 296.1271.

N-*Methyl*-N-*(2,2,2-trifluoro-1-(furan-2-yl)ethyl)aniline* (**3k**): Colourless oil; ^{1}H NMR: δ 7.29 (d, 1H, *J* = 1.2 Hz), 7.12 (m, 2H), 6.77 (d, 2H, *J* = 8.4 Hz), 6.72 (m, 3H), 6.3 (m, 2H), 5.3 (dd, 1H, *J* = 7.7, 15.3 Hz), 2.68 (s, 3H); ^{13}C NMR: δ 149.78, 146.29, 143.08, 129.29, 126.89, 119.34, 114.60, 61.01, 60.59, 60.18, 59.79, 33.44, 29.69; HRMS (ESI) for $C_{13}H_{13}F_3NO$ $[M + H]^+$ calcd 256.0949; found: 256.0957.

2-(4-(Dimethylamino)phenyl)-2-(indolin-1-yl)acetonitrile (**4e**): Colourless oil; IR (KBr, ν_{max}/cm^{-1}): 2151 (CN). ^{1}H NMR: δ 7.43 (d, 2H, *J* = 8.4 Hz), 7.15 (m, 2H), 6.84 (m, 2H), 6.75 (m, 2H), 6.75 (m, 2H), 5.69 (s, 1H), 3.25 (m, 2H), 3.01 (m, 8H); ^{13}C NMR: δ 150.84, 149.32, 130.79, 128.43, 127.41, 124.98, 120.24, 119.61, 116.43, 112.29, 108.54, 53.79, 53.69, 50.01, 40.37, 28.07; HRMS (ESI) for $C_{17}H_{19}N_2^+$ $[M – CN]^+$ calcd 251.1543; found: 251.1547.

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