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Improved Syntheses of Fluorinated Tertiary Butylamines

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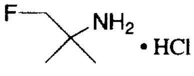
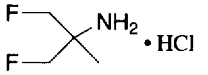
Abstract: Two new and efficient methods using cyclic sulfamidate and nitrone chemistry were developed for the synthesis of the sterically congested 1,1-dimethyl-2-fluoroethylamine (**1**), 2-fluoro-1-(fluoromethyl)-1-methylethylamine (**2**) and 2-fluoro-1,1-bis-(fluoromethyl)-ethylamine (**3**). © 1999 Elsevier Science Ltd. All rights reserved.

Recently, medicinal chemistry efforts in our group required several low molecular weight fluorinated amines (**1** - **3**). While there are several literature procedures for the synthesis of these fluorinated *t*-butylamines,[1-5] we found them problematic when carried out on small scale. Bayer researchers[1-4] reported the preparation of **1** - **3** in a 4-step procedure beginning from the corresponding mono-, di- or trichloropivaloyl chloride. This method requires the distillation of labile fluorinated pivaloyl fluorides and isocyanates. Remuzon and coworkers[5] modified the Bayer procedure to obtain **2** and **3** in a single pot process, eliminating the need for the isolation of intermediates. According to Remuzon's procedures, the di- and trifluoro-*tert*-butylamines were obtained in good purity but in low yield (35% and 25%, respectively) while the monofluoro analog **1** was prepared using a modified Ritter reaction (23% yield). However, despite repeated attempts on our part to prepare **1** - **3** by these procedures on a 5 - 10 g scale, we were unable to generate the desired fluoro amines with appropriate purity and yield. As a result of this, we developed two new complementary methods for the efficient syntheses of these three fluorinated *tert*-butyl amines.[6]



1



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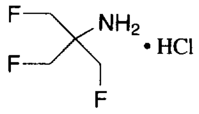

3

Two successful approaches towards monofluoro amine **1** are illustrated in Schemes 1 and 2. The first procedure starts with commercially available 2-amino-2-methyl-1-propanol (**4**) and involves a nucleophilic ring opening of cyclic sulfamidate **7** to introduce the fluorine moiety.[7] The second approach to **1** begins with commercially available monofluoroacetone (**9**) and utilizes nitrone[8] chemistry to produce the requisite amine. These protocols were subsequently adapted to the preparation of the corresponding di- and trifluoro-*tert*-butyl amines **2** and **3**.

As shown in Scheme 1,[9] reductive alkylation of 2-amino-2-methyl-1-propanol (**4**) yields benzyl amine **5**. Cyclization of **5** to sulfamidite **6** was carried out using thionyl chloride in CH_2Cl_2 at -20 °C followed by oxidation with periodate catalyzed by ruthenium afforded sulfamidate **7**. The fluoride was then introduced *via* treatment of **7** with tetrabutylammonium fluoride followed by hydrolysis with 20% H_2SO_4.[10] Finally, catalytic

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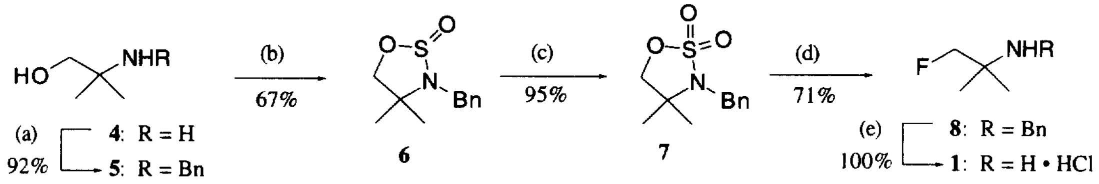
hydrogenolysis of benzylamine **8** under acidic conditions furnished the monofluoro-*t*-butylamine **1** as an easily isolated hydrochloride salt in 42% overall yield from **4** (yields not optimized) with no detectable by-products.

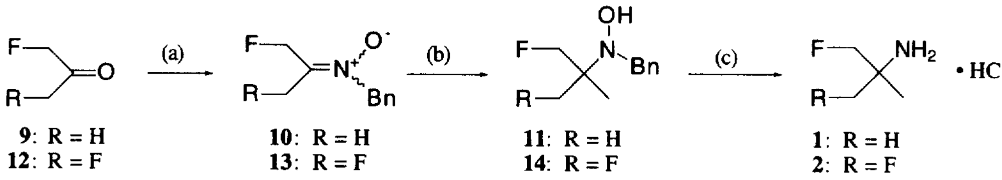
Scheme 1



Reagents and conditions: (a) i. PhCHO, cat. TsOH, benzene, reflux, 5 h; ii. $NaBH_3CN$, CH_3OH; (b) $SOCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -20 °C, 1 h; (c) $NaIO_4$, $RuCl_3 \cdot xH_2O$, CH_3CN, H_2O, rt, 5 h; (d) i. $Bu_4N^+F^-$, THF, rt, 3 h; ii. 20% H_2SO_4, ether, rt, 20 h; iii. aq. $NaHCO_3$; (e) H_2, 50 psi, Pd/C (10%), CH_3OH, conc. HCl, rt, 20 h.

As illustrated in Scheme 2, monofluoro-*tert*-butylamine **1**[11] could also be prepared in three steps from fluoroacetone (**9**). Condensation of **9** with N-benzylhydroxylamine was carried out in benzene at room temperature to give the moisture sensitive N-benzyl nitrone **10** which, upon reaction with methylmagnesium bromide, furnished the N-protected hydroxylamine **11** in 84% yield after chromatographic purification. Hydrogenation of **11** again afforded the desired amine **1** as the hydrochloride salt in quantitative yield. Using a similar protocol for the preparation of **1**, difluoro-*tert*-butylamine **2** could be prepared in 82% overall yield[12] from 1,3-difluoroacetone **12**.[13]

Scheme 2

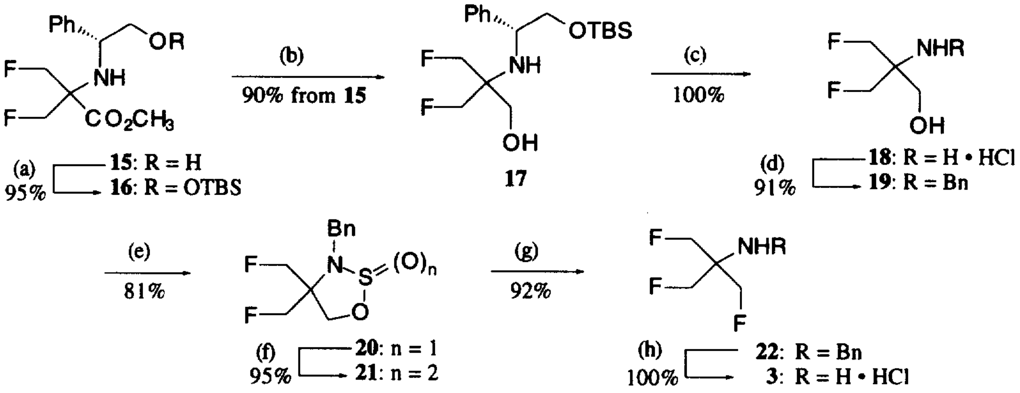


Reagents and conditions: (a) BnNHOH, anhydrous $MgSO_4$, benzene, rt, 1 h; (b) CH_3MgBr, ether, -40 °C, 1 h; (c) H_2, 40 psi, Pd/C (10%), CH_3OH, conc. HCl, 50 °C, 20 h.

The sulfamidate chemistry was also utilized to introduce the fluoro moiety in a synthesis of the trifluorinated-*tert*-butylamine **3** (Scheme 3).[14] Synthesis of **3** began with ester **15** which was prepared in 3 steps from **12** (60%) by a known literature method.[15] The hydroxyl group of **15** was protected as the TBS ether (**16**) and then reduced with LAH (-40 °C) to afford alcohol **17** in 90% yield along with a small amount of unreduced aldehyde. The key intermediate amino-alcohol **18**, obtained from **17** by catalytic hydrogenolysis with Pd/C,[16] was then converted into trifluoro-*t*-butylamine **3** in 55% overall yield according to the same methodology used for first preparation of **1** in Scheme 1.

In summary, we have developed efficient strategies to access a series of fluorinated *tert*-butylamines from readily available starting materials. These scaleable routes are reproducible and generate the desired compounds in high purity as stable hydrochloride salts. The chemistry disclosed herein is also amenable to the introduction of other functionality into these hindered amines.

Scheme 3



Reagents and conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, rt, 18 h; (b) $LiAlH_4$, ether, -40 °C; (c) H_2, 50 psi, Pd/C (10%), CH_3OH, conc. HCl, rt, 18 h; (d) i. PhCHO, cat. TsOH; benzene, reflux, 3 h; ii. $NaBH_3CN$, THF; (e) $SOCl_2$, i-Pr_2NEt, CH_2Cl_2, -20 °C, 1 h; (f) $NaIO_4$, $RuCl_3 \bullet xH_2O$, CH_3CN, H_2O, 0 °C, 1 h; (g) i. $Bu_4N^+F^-$, THF, rt, 5 h; ii. 20% H_2SO_4, ether, rt, 18 h; iii. aq. $NaHCO_3$; (h) H_2, 50 psi, Pd/C (10%), CH_3OH, conc. HCl, rt, 20 h.

Acknowledgment

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References and Notes

1. Baasner, B.; Hagemann, H.; Schwamborn, M. *U.S. Patent* 5,019,654, **1991**.
2. Böhm, S.; Marhold, A.; Bielefeldt, D. *U. S. Patent* 5,276,218, **1994**.
3. Schwamborn, M.; Hagemann, H.; Heywang, G.; Behrenz,W. *U.S. Patent* 4,609,648, **1986**.
4. Hagemann, H.; Klauke, E.; Kysela, E. *U.S. Patent* 4,549,994, **1985**.
5. Remuzon, P.; Bouzard, D.; Cesare, P. D.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Ledoussal, B.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1991**, *34*, 29-37.
6. NMR spectra (^1H at 500 MHz, ^{19}F at 470 MHz and ^{13}C at 125 MHz) were recorded on a Varian Unity Inova using $CDCl_3$ as solvent, unless otherwise noted. Electrospray ionization LC/MS or electron impact GC/MS was used to verify monoisotopic molecular weights. All spectra were consistent with the assigned structures.
7. For a review of cyclic sulfate chemistry, see Lohray, B. B. *Synthesis* **1992**, 1035-1052.
8. Nitrones readily undergo addition of organometallic reagents and other nucleophiles. See Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464-3474 and 3475-3483 and references cited therein.
9. **2-Fluoro-1,1-dimethylethylamine (1)**. (a) A solution of **4** (10 g, 112 mmol) and benzaldehyde (12.5 g, 118 mmol) in benzene (300 mL) containing TsOH (3 mg) was heated at reflux with azeotropic removal of water for 5 h. The mixture was concentrated and the crude imine was used in the subsequent reaction without any purification. The imine in CH_3OH (200 mL) at 0°C was treated with $NaBH_3CN$ (8.4 g, 134 mmol) over 5 min. After 30 min., the reaction mixture was concentrated and the residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (1/10/90 $NH_4OH/CH_3OH/CH_2Cl_2$) to give **5** (16.5 g, 92%): ^1H NMR δ 7.35 (m, 5H), 3.7 (s, 2H), 3.38 (s, 2H), 1.18 (s, 6H). (b) To a solution of **5** (8 g, 49.7 mmol) and *i*-Pr_2NEt (25.7 g, 199 mmol) in CH_2Cl_2 (100 mL) at -20 °C was added dropwise thionyl chloride (6.5 g, 54.6 mmol) in CH_2Cl_2 (10 mL). After 1 h at -20 °C, the reaction mixture was concentrated and the residue was purified by silica gel chromatography (15% ethyl acetate in hexane) to give sulfamidite **6** (7.5 g, 67%): ^1H NMR δ 7.35 (m, 5H), 4.63 (m, 1H), 4.30-4.15 (m, 3H), 1.47(s, 3H), 1.23 (s, 3H). (c) To a

solution of **6** (6.0 g, 26.6 mmol) in acetonitrile (30 mL) and water (30 mL) at 0 °C was added ruthenium (III) chloride hydrate (6 mg) followed by sodium periodate (8.53 g, 40 mmol). After 5 h, the mixture was extracted with ether. The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to give sulfamidate **7** (6.1 g, 95%) as a white solid; ^{1}H NMR δ 7.35 (m, 5H), 4.27 (br s, 4H), 1.3 (s, 6H). (d) To a solution of **7** (4.5 g, 21 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (42 mL, 42 mmol, 1.0 M in THF). After 3 h at room temperature, the reaction mixture was concentrated and the residue was treated with ether (60 mL) and 20% H_2SO_4 (20 mL). After 20 h, the mixture was neutralized with $NaHCO_3$ (s) and extracted with ether. The ether extracts were dried (Na_2SO_4) and concentrated and the residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to give benzylamine **8** (2.7 g, 71%) as a colorless oil; ^{1}H NMR δ 7.32 (m, 5H), 4.3 (d, $^2J_{HF}$ = 47 Hz, 2H), 3.76 (s, 2H), 1.20 (s, 6H). (e) A mixture of **8** (2.2 g, 12.15 mmol), 10% Pd/C (100 mg) and conc. HCl (2 ml) in CH_3OH (50 ml) was shaken under H_2 (50 psi) for 20 h. The mixture was filtered through Celite and concentrated in vacuo to afford **1** as its hydrochloride salt (1.56 g, 100%); mp 245 °C (lit.[1] mp 248 °C): ^{1}H NMR (CD_3OD) δ 4.42 (d, $^2J_{HF}$ = 47.1 Hz, 2H), 1.37 (d, $^4J_{HF}$ = 1.9 Hz, 6H); ^{13}C NMR (CD_3OD) δ 87.4 (d, $^1J_{CF}$ = 174.4 Hz), 54.2, 20.8; ^{19}F NMR (CD_3OD) δ -122.1 (t, $^2J_{HF}$ = 47.0 Hz); [m/z: 91.5 $(M+H)^+$].

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11. **2-Fluoro-1,1-dimethylethylamine** (**1**). (a) To a solution of fluoroacetone **9** (2.82 g, 37 mmol) and N-benzylhydroxylamine (3.8 g, 30.9 mmol) in benzene (50 mL) was added anhydrous $MgSO_4$ (1.5 g). After 2 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give pure nitrone **10** (5.52 g); ^{1}H NMR δ 7.38 (m, 5H), 5.33 (d, $^2J_{HF}$ = 48 Hz, CH_2F, major isomer), 5.1 (d, $^2J_{HF}$ = 48 Hz, CH_2F, minor isomer), 5.18 (s, CH_2, minor isomer), 5.06 (s, CH_2, major isomer), 2. 22 (s, CH_3, minor isomer), 2.18 (s, CH_3, major isomer). This material was converted to **11** without any purification due to its moisture sensitivity. (b) To a solution of **10** in ether (50 mL) at -40 °C was added methylmagnesium bromide (35 mmol, 11.5 mL, 3.0 M in ether). After 1 h at -40 °C, the reaction was quenched with aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (8% ethyl acetate in hexane) to give benzylhydroxylamine **11** (5.10 g, 84% from **7**) as a white solid; ^{1}H NMR δ 7.34 (m, 5H), 4.43 (d, $^2J_{HF}$ = 48 Hz), 3.9 (s, CH_2, 2H), 2.06 (br s, 1H), 1.25 (s, 6H). (c) The hydrochloride salt of **1** was prepared in quantitative yield from **11** according to the procedure described in 9e. However, more consistent results were obtained at 50 °C.

12. **2-Fluoro-1-(fluoromethyl)-1-methyl-ethylamine** (**2**). As described above, **2** was prepared from **12**. (a) **13**: ^{1}H NMR δ 7.40 (m, 5H), 5.37 (d, $^2J_{HF}$ = 47 Hz, CH_2F), 5.25 (d, $^2J_{HF}$= 47 Hz, CH_2F), 5.21 (s, CH_2). (b) **14** (82% from **10**): ^{1}H NMR δ 7.28 (m, 5H), 4.58 (d, $^2J_{HF}$ = 47 Hz, 4H), 3.98 (s, 2H), 1.28 (s, 3H). (c) **2** (hydrochloride salt), 100%; mp 215 °C (lit.[1] mp 214 °C): ^{1}H NMR (CD_3OD) δ 4.68 (12 lines, $^2J_{HH}$ =10.4 Hz, $^2J_{HF}$ = 46.7 Hz, $^4J_{HF}$ = 2.5 Hz, 4H), 1.37 (t, $^4J_{HF}$ = 1.9 Hz, 3H); ^{13}C NMR (CD_3OD) δ 84.52 (d, $^1J_{CF}$ = 174.0 Hz), 57.67, 16.28; ^{19}F NMR (CD_3OD) δ -128.1 (t, $^2J_{HF}$ = 46.7 Hz); [m/z: 109.6 $(M+H)^+$].

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14. **2-Fluoro-1,1-bis-(fluoromethyl)-ethylamine** (**3**). (a) To a stirred solution of alcohol **15** (25 g, 91.57 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added sequentially imidazole (12.5 g, 183 mmol) and TBDMSCl (17.9 g, 117 mmol) in portions. The solution was warmed to rt and aged for 18 h, then aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford **16** (33.7g, 95%); ^{1}H NMR δ 7.32 (m, 5H), 4.8-4.3 (m, 4H, CH_2F), 3.92 (m, 1H), 3.58 (m, 1H), 3.44 (m, 1H), 3.41 (s, 3H), 2.67 (br s,1H), 0.9 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); [m/z: 388.1 (M+1)]. (b) To a stirred solution of ester **16** (22 g, 56.76 mmol) in ether (500 mL) at -78 °C was added $LiAlH_4$ (3.23 g, 85.14 mmol) in portions while maintaining the temperature below -40 °C. After being stirred at -40 °C for 1 h, the reaction was quenched with CH_3OH (5 mL) and 2N NaOH solution (5 mL). After filtration and evaporation, the residue was purified by silica gel chromatography (25% ethyl acetate in hexane) to provide the alcohol **17** as a white solid (18.35 g, 90%); ^{1}H NMR δ 7.32 (m, 5H), 4.51-4.23 (m, 4H), 4.05 (m, 1H, NH), 3.61 (m, 2H), 3.41 (m, 2H), 2.62 (m, 1H), 2.25 (m, 1H), 0.95 (s, 9H), 0.09 (two s, 6H); [m/z: 360.1 $(M+H)^+$]. This was converted to **3** as described in Scheme 1. (c) **18**: ^{1}H NMR (CD_3OD) δ 4.68 (12 line pattern, $^2J_{HH}$ = 10.3 Hz, $^2J_{HF}$ = 46.7 Hz, $^4J_{HF}$ = 10.3 Hz, 4H), 3.74 (t, $^4J_{HF}$ = 1.6 Hz). **19**: ^{1}H NMR δ 7.36 (m, 4H), 7.30 (m, 1H), 4.56 (16 line pattern, $^2J_{HF}$ = 47.3 Hz, $^2J_{HH}$ = 9.4 Hz, $^4J_{HF}$ = 1.7 Hz, 4H), 3.86 (s, 2H), 3.64 (t, $^4J_{HF}$ = 1.6 Hz, 2H). (e) **20**: ^{1}H NMR δ 7.40 (m, 5H), 4.84-4.30 (m, 8H); [m/z: 261.8 $(M+H)^+$]. (f) **21**: ^{1}H NMR δ 7.38 (m, 5H), 4.52-4.35 (m, 8H); [m/z: 277.1 $(M+H)^+$]. (g) **22**: ^{1}H NMR δ 7.35 (m, 5H), 4.56 (d, $^2J_{HF}$ = 46 Hz, 6H), 3.94 (s, 2H); [m/z: 218.8 $(M+H)^+$]. (h) **3** (hydrochloride salt): mp 221 °C (lit.[1] mp 220 °C): ^{1}H NMR (CD_3OD) δ 4.76 (dt, $^2J_{HF}$ = 45.9 Hz, $^4J_{HF}$ = 1.7 Hz, 6H); ^{13}C NMR (CD_3OD) δ 79.79 (d, $^1J_{CF}$ = 173.6 Hz), 58.92 (q, $^2J_{CF}$ = 17.1 Hz); ^{19}F NMR (CD_3OD) δ -133.1 (t, $^2J_{HF}$ = 46.0 Hz); [m/z: 127.6 $(M+H)^+$].

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16. Due to competitive removal of the TBS during the subsequent fluoride displacement reaction and the resulting production of side products, better results are obtained if the hydroxy phenethyl group is replaced with a simple benzyl protecting group.