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α-Pentafluoroethylated amines: a new synthetic approach

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Pentafluoroethyllithium generated from pentafluoroethane and *n*-butyl lithium added to selected imines, which were activated using BF_3 etherate, furnished α-pentafluoroethylated amines and, unexpectedly, depending on the stoichiometry of the reactants, bis(pentafluoroethyl)fluoro-*N*-(isopropyl)diisopropyliminium borate, whose molecular structure was confirmed by X-ray diffraction.

Fluorine affects the properties of organic compounds when employed as a substituent.[1] Therefore, fluorinated compounds play an important role in medicinal chemistry.[2] Fluorinated amines represent versatile components in quite a few biologically active systems.[3] Trifluoroethylamines are used as amide isosteres in inhibitors of cathepsine K.[4] Fluorinated pyrrolidine and azetidine amides are effective dipeptidyl peptidase IV inhibitors.[5] 1,1-*gem*-Dialkylperfluoroalkylamines, *e.g.* $R^FMe_2CNH_2$ [$R^F = CF_3$ (80%), C_2F_5 (67%)], were synthesised in good yield reacting the respective amide $R^FC(O)NH_2$ with MeLi followed by treatment with hydrogen chloride.[6] The carboxyl group of amino acids was converted to a CF_3 group in the presence of HF, so $CF_3Me_2CNH_2$ could be obtained in 35% yield.[7] (*S*)- or (*R*)-$CF_3(Ph)RCNH_2$ ($R = Pr^i$, Me) were synthesised when reacting chiral 1,3-oxazolidines [synthesised from 2,2,2-trifluoroacetophenone and (*R*)-phenylglycinol] with RLi and subsequent hydrogenolysis or oxidative cleavage.[8] In a boron trifluoride assisted reaction, perfluoroalkyl iodides (C_2F_5I) and MeLi–LiBr react with Ph(H)C=NEt to afford the respective perfluoroalkylamine in good yield.[9] Interestingly, unstable *n*-$C_6F_{13}Li$ was reported to be possibly transferred from the thermally more stable carrier $(C_6F_{13})_2I^-$ being formed in the presence of $C_6F_{13}I$ at –78 °C with $t_{1/2} = 15$ min. The C_2F_5I/MeLi–LiBr system was also used for the nucleophilic addition of the pentafluoroethyl group to aldehydes, ketones and esters with $t_{1/2} = 8$ h.[10] Substitution of fluorine in BF_3 etherate was not observed. On the other hand, the adducts of imines and $B(C_6F_5)_3$ were described in the context of Lewis acid mediated addition of nucleophiles to imines.[11]

Using a new methodology to generate pentafluoroethyllithium (PFELi)[†,12] from easily available, cheap and environmentally friendly pentafluoroethane and Bu^nLi, we performed the reaction with selected imines $R^1R^2C=NPr^i$ **1a**–**c**, which were activated by BF_3 etherate. Amines **2a**–**c**[‡] were obtained in good yields as colourless liquids (Scheme 1).

In the reaction of **1c**, an unexpected by-product was observed, which can be synthesised selectively by changing stoichiometry and reaction conditions. If imine **1c** is added to one equivalent of BF_3 etherate and an excess of PFELi, iminoborate **3** can be

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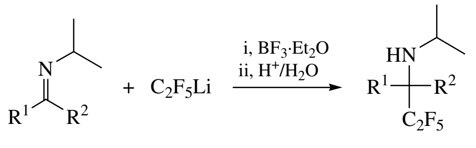
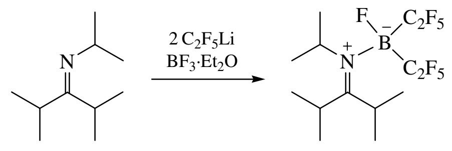
[†] A significant decomposition of PFELi begins at –50 °C. Even at –30 °C there are still signals of PFELi to be observed.[12]



1a–c **2a–c**

a $R^1 = R^2 = Ph$
b $R^1 = Ph$, $R^2 = Me$
c $R^1 = R^2 = Pr^i$

Scheme 1



1c **3**

Scheme 2

isolated in good yield[§] as a white solid stable against moisture and even hydrochloric acid (Scheme 2).

Remarkably, **3** is the only boron species formed, regardless of the stoichiometry. There was no C_2F_5 addition observed reacting **3** with PFELi. The borate salt K[$(C_2F_5)_2BF_2$] was recently reported applying C_2F_5I and MeLi.[13] The molecular structure of **3**[¶] (Figure 1) exhibits a tetrahedral geometry at B(1) with an N(1)–B(1) bond of 162.2 pm found in similar adducts[11,14] and a remarkably short B(1)–F(11) bond of 133.9 pm, possibly one of the shortest measured so far reflecting the push-pull topology of fluorine as a π-donor and the two electronegative pentafluoroethyl groups. In the case of Cs[$B(CF_3)_2F_2$], the B–F bond of 139.1 pm was observed.[15]

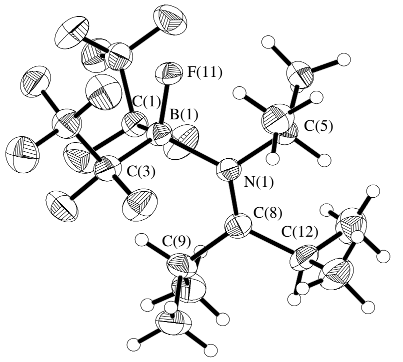


Figure 1 Molecular structure of **3**. Thermal elipsoids with a probability of 40%. Selected bond lengths (pm) and angles (°): C(8)–N(1) 129.5, C(8)–C(9) 151.6, C(8)–C(12) 152.6, N(1)–C(5) 151.5, N(1)–B(1) 162.2, F(11)–B(1) 133.9; C(5)–N(1)-C(8) 119.4, C(5)–N(1)–B(1) 115.7, C(8)–N(1)–B(1) 124.9, F(11)–B(1)–C(1) 106.0, F(11)–B(1)–C(3) 105.6, F(11)–B(1)–N(1) 108.0, C(5)–N(1)–C(8)–C(9) 176.1.

In conclusion, we proposed a methodology for synthesising pentafluoroethylated amines. A new borane-imine adduct was obtained.

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[‡] NMR spectra were recorded on a Bruker DPX 200 spectrometer, ^{1}H at 200.13 MHz, ^{13}C{^{1}H} at 50.32 MHz and ^{19}F at 188.31 MHz. Mass spectrometric data were obtained from a Finnigan MAT CH 7A instrument at 70 eV. The X-ray structure analysis of **3** was carried out on a Siemens P4 diffractometer.

General procedure. BF_3 etherate (2.84 g, 20 mmol) was added at –78 °C to a mixture of imines **1a–c** (20 mmol in 30 ml of diethyl ether) and PFELi (30 mmol in 30 ml of diethyl ether) pregenerated according to ref. 10; the reaction mixture was warmed to ambient temperature for 2 h. Then, the mixture was hydrolysed using 50 ml of 5% hydrochloric acid and extracted three times with 20 ml of diethyl ether. The combined ethereal solutions were dried with $MgSO_4$. After filtration, all volatiles were removed at 15 Torr, and the remaining liquid/solid was distilled or recrystallised. Elemental analyses for compounds **2a–c** were in good agreement with the calculated data.

*1,1-Diphenyl-2,2,3,3,3-pentafluoro-*N*-(isopropyl)propylamine* **2a**: bp 64–66 °C (0.01 Torr), yield 74% (NMR), 4.48 g, 65% (isolated). ^{1}H NMR ($CDCl_3$) δ: 1.09 (d, 6H, CH*Me*$_2$, $^3J_{HH}$ 6.84 Hz), 3.32 (sept., 1H, C*H*Me$_2$, $^3J_{HH}$ 6.84 Hz), 4.24 (s, 1H, NH), 7.58–7.31 (m, 10H, Ph). ^{19}F NMR ($CDCl_3$) δ: –77.4 (s, 3F, CF_3), –112.0 (s, 2F, CF_2). MS (EI, 70 eV, 200 °C) *m/z* (%): 342 (3) M^+, 327 (9) $[M - Me]^+$, 299 (54) $[M - Pr^i]^+$, 265 (24) $[M - Ph]^+$, 223 (100) $[M - C_2F_5]^+$, 180 (43) $[M - C_2F_5 - Pr^i]^+$, 77 (62) $[Ph]^+$, 44 (43) $[Pr^i]^+$ and other fragments.

*1-Methyl-2,2,3,3,3-pentafluoro-1-phenyl-*N*-(isopropyl)propylamine* **2b**: bp 96 °C (25 Torr), yield 81% (NMR), 4.44 g, 79% (isolated). ^{1}H NMR ($CDCl_3$) δ: 1.07 (d, 6H, CH*Me*$_2$, $^3J_{HH}$ 6.21 Hz), 1.82 (s, 3H, Me), 2.79 (sept., 1H, C*H*Me$_2$, $^3J_{HH}$ 6.21 Hz), 3.78 (s, 1H, NH), 7.56–7.31 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$) δ: –78.2 (s, 3F, CF_3), –121.9 (AB system, 2F, CF_2, $\Delta\nu$ = 1.46 Hz, J_{AB} 275.0 Hz). MS (EI, 70 eV, 200 °C) *m/z* (%): 281 (1) M^+, 266 (11) $[M - Me]^+$, 223 (42) $[M - Me - Pr^i]^+$, 204 (4) $[M - Ph]^+$, 162 (100) $[M - C_2F_5]^+$, 120 (82) $[M - C_2F_5 - Pr^i]^+$, 105 (94) $[M - C_2F_5 - Pr^i - Me]^+$, 77 (81) $[Ph]^+$, 44 (85) $[Pr^i]^+$ and other fragments.

*1,1-Diisopropyl-2,2,3,3,3-pentafluoro-*N*-(isopropyl)propylamine* **2c**: bp 91–93 °C, yield 73% (NMR), 3.34 g, 61% (isolated). ^{1}H NMR ($CDCl_3$) δ: 3.52 (sept., 1H, NC*H*Me$_2$, $^3J_{HH}$ 6.4 Hz), 3.02 (s, 1H, NH), 1.44 (sept., 2H, C*H*Me$_2$, $^3J_{HH}$ 5.8 Hz), 1.10 (2d overlap, 18H, CH*Me*$_2$, $^3J_{HH}$ 6.8 Hz). ^{19}F NMR ($CDCl_3$) δ: –79.4 (s, 3F, CF_3), 113.6 (s, 2F, CF_2). MS (EI, 70 eV, 200 °C) *m/z* (%): 274 (2) M^+, 259 (15) $[M - Me]^+$, 216 (33) $[M - Me - Pr^i]^+$, 155 (100) $[M - C_2F_5]^+$, 112 (91) $[M - C_2F_5 - Pr^i]^+$, 44 (89) $[Pr^i]^+$ and other fragments.

[§] *Bis(pentafluoroethyl)fluoro-*N*-(isopropyl)diisopropyliminium borate* **3**. BF_3 etherate (2.84 g, 20 mmol) was added to 80 mmol of PFELi in 150 ml of diethyl ether at –78 °C followed by adding compound **1c** (3.10 g, 20 mmol). The mixture was stirred for 1 h at –78 °C, warmed up to ambient temperature and all volatiles were removed *in vacuo*. The crude product was crystallised from toluene and recrystallised from methylene chloride to yield **3** as a white crystalline solid, mp 137 °C, yield 74% (NMR), 5.41 g, 61% (isolated). ^{1}H NMR ([$^2H_8$]THF) δ: 1.21 (d, 6H, *E*-CH*Me*$_2$, $^3J_{HH}$ 6.35 Hz), 1.40 (d, 6H, *Z*-CH*Me*$_2$, $^3J_{HH}$ 7.33 Hz), 1.47 (d, 3H, CH*Me*$_2$, $^3J_{HH}$ 6.85 Hz), 1.52 (d, 3H, CH*Me*$_2$, $^3J_{HH}$ 6.85 Hz), 3.09 (sept., 1H, *E*-C*H*Me$_2$, $^3J_{HH}$ 6.35 Hz), 3.30 (sept., 1H, *Z*-C*H*Me$_2$, $^3J_{HH}$ 7.33 Hz), 4.53 (sept., 1H, NC*H*Me$_2$, $^3J_{HH}$ 6.85 Hz). ^{19}F NMR ([$^2H_8$]THF) δ: –84.1 (s, 6F, CF_3), –125.8 (AB system, 4F, CF_2, $\Delta\nu$ = 1.74 Hz, J_{AB} 327.3 Hz), –189.5 (m, 1F, F). ^{13}C NMR ([$^2H_8$]THF) δ: 203.5 (s, C=N), 124.9 (m, CF_3), 119.1 (m, CF_2), 58.8 (s, CHN), 38.9 (t, *Z*-CH, *J* 7.06 Hz), 31.9 (s, *E*-CH), 21.2 (s, *Me*CHN), 21.0 (s, *Me*CHN), 19.8 (s, *Z*-Me), 19.3 (s, *E*-Me), 19.2 (s, *E*-Me). MS (CI, negative, NH, 200 °C) *m/z* (%): 423 (100) M^-, 380 (73) $[M - Pr^i - H]^-$, 361 (6) $[M - Pr^i - F - H]^-$ and other fragments. MS: (CI, positive, NH_3, 200 °C) *m/z* (%): 441 (100) $[M + NH_4]^+$, 399 (14) $[M - Pr^i + NH_4]^+$, 156 (22) $[M - BF(C_2F_5)_2 + H]^+$ and other fragments.

[¶] *Crystallographic data for* **3**: at 173 K, the crystals are monoclinic, space group C_2/c, a = 2771.6(6), b = 817.5(2), c = 1665.2(3) pm, β = 99.93(3)°, V = 3716.5(14) Å^3, Z = 8, d_{calc} = 1.512 g cm^{-3}, λ(MoKα) = 0.71073 Å, F(000) = 1728. Intensities of 25216 reflections were measured (2.48 ≤ θ ≤ 26.01°), 3546 (R_{int} = 0.0677) were used for further refinement. The absorption correction was carried out by DIFABS. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2. The positions of hydrogen atoms were calculated from the geometrical point of view. The final refinement converged to wR_2 = 0.1606 [R_1 = 0.0627, $I > 2\sigma(I)$]. The R-values for all data were found to be R_1 = 0.0809, wR_2 = 0.1658. All calculations were performed using the SHELX-97 programm package.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 600078. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2006.

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