Novel conversion of perfluoro(2,6-dimethyl-1-azacyclohexene) to 3,3,4,4,5-pentafluoro-2,6-diphenyl-2,6-bis(trifluoromethyl)-1-azabicyclo[3.1.0]hexane

R. Eric Banks,* Mohamed K. Besheesh, Nicholas J. Lawrence,* Robin G. Pritchard and David J. Tovell

Chemistry Department, UMIST, PO Box 88, Manchester, UK M60 1QD. E-mail: n.lawrence@umist.ac.uk

Received (in Liverpool, UK) 2nd October 1998, Accepted 17th November 1998

Unexpectedly, treatment of perfluoro(2,6-dimethyl-1-azacyclohexene) with 2 equiv. of PhLi in cyclohexane–Et_2O at −50 to 40 °C gives a good yield (72%) of (±)-3,3,4,4,5-pentafluoro-2,6-diphenyl-2,6-bis(trifluoromethyl)-1-azabicyclo-[3.1.0]hexane 1; the nitranion implicated in this novel conversion can be trapped with sulfuric acid, giving 2,2,4,4,5,5-hexafluoro-2(e),6(e)-diphenyl-2(a),6(a)-bis(trifluoromethyl)piperidine 5.

1-Azabicyclo[3.1.0]hexanes are not new: synthesis of the parent compound was reported in the mid-1960s,[1,2] and synthetic studies on its derivatives[3] gained impetus in the late 1980s owing to the isolation of the azinomycin antitumour antibiotics[4] which possess this ring system. Surprisingly, however, no fluorinated derivatives appear to have been described heretofore.

The polyfluorinated species **1** disclosed here was obtained serendipitously during research into the electronic and steric influences of α-substituents on the effectiveness and modes of action of 3,3,4,4,5,5-hexafluoro-*N*-fluoropiperidines, *e.g.* **3**, as selective electrophilic fluorinating agents, the ultimate objective being to develop chiral analogues of perfluoro-*N*-fluoropiperidine, the prototypical 'F^+' delivery agent of the N–F class.[5] The synthesis strategy being used centres on nucleophilic attack on perfluoro-(2,6-dimethyl-1-azacyclohexene) **2**.[6] This worked well (Scheme 1) when MeLi was used as the nucleophilic reagent: acidic work-up of the reaction mixture gave the expected N–H compound **4**† in 63% yield, and this was converted smoothly to 3,3,4,4,5,5-hexafluoro-2(a),6(a)-dimethyl-2(e),6(e)-bis(trifluoromethyl)-*N*-fluoropiperidine **3** (82% yield) on treatment with F_2 in cold $CFCl_3$ containing anhydrous KF. The stereochemistry of this new N–F compound was established beyond doubt by X-ray analysis,[7] hence the geometry of its N–H precursor **4** follows.

By contrast, similar treatment of the perfluoro imine **2** with PhLi [in c-C_6H_{12}–Et_2O (7:3) at −25 °C] gave a complex product from which, after careful addition of aqueous H_2SO_4 at −50 °C followed by flash chromatography, were isolated samples of (±)-3,3,4,4,5-pentafluoro-2,6-diphenyl-2,6-bis(trifluoromethyl)-1-azabicyclo[3.1.0]hexane **1** and 3,3,4,4,5,5-hexafluoro-2(e),6(e)-diphenyl-2(a),6(a)-bis(trifluoromethyl)-piperidine **5** in 4 and 28% yield, respectively. The structures of these products were established unambiguously by X-ray analysis (Fig. 1).‡ The *cis* disposition of the CF_3 substituents in each compound, coupled with the subsequent discovery that the yield of the azabicycloheptane **1** can be increased to 72% simply by not quenching the presumptive nitranion **6** formed from **2** and PhLi, but gradually raising the temperature of the reaction mixture to about 40 °C, prompts us to favour the reaction mechanism shown in Scheme 2. The ease of ring contraction presumably stems from the considerable relief of 1,3-diaxial $CF_3\cdots CF_3$ repulsions in the monocyclic moiety, the distance between the carbon centres of the trifluoromethyl substituents in the azabicyclohexane **1** being 33% greater than in the piperidine **5**; this belief is supported by our failure to convert the lithium salt of the diequatorial $(CF_3)_2$ analogue **4** of **5** to an

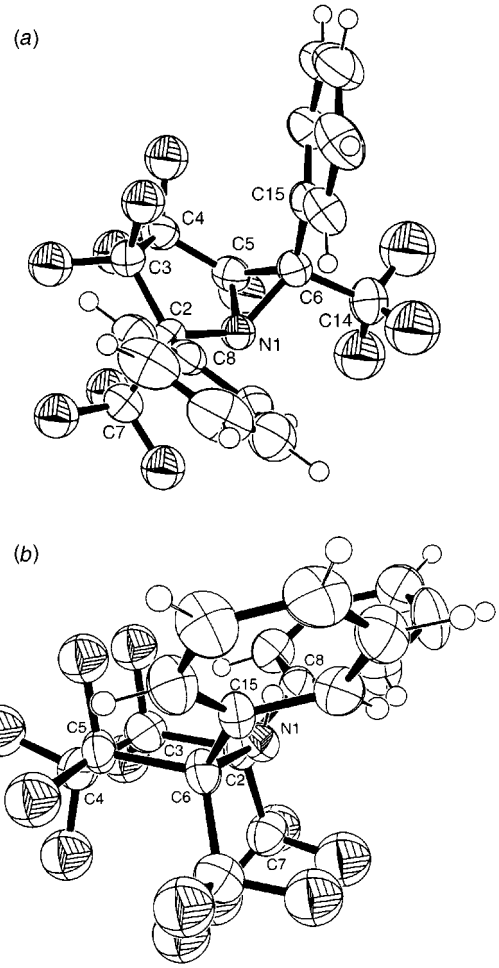
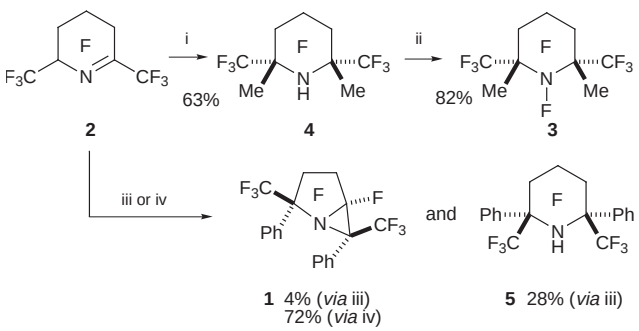
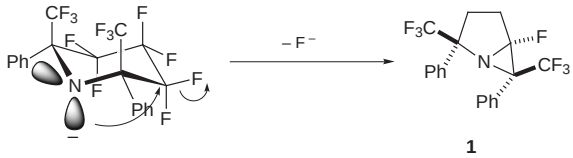


Fig. 1 ORTEP diagrams of (*a*) azabicycloheptane **1** and (*b*) piperidine **5** with 50% thermal ellipsoids.



Scheme 1 *Reagents and conditions*: i, MeLi (2 equiv.), Et_2O, −78 °C, then aq. H_2SO_4; ii, F_2–N_2 (*ca.* 1:9 v/v), KF, $CFCl_3$, −30 °C; iii, PhLi (2 equiv.), c-C_6H_{12}–Et_2O (7:3), −25 °C, then aq. H_2SO_4, − 50 °C; iv, PhLi (2 equiv.), c-C_6H_{12}–Et_2O (7:3), −25 °C, then 40 °C.



1

Scheme 2

azabicyclo[3.1.0]hexane in boiling Et_2O. Interestingly, the conversion **5**→**1** finds something of a parallel in the preparation of (5*S*)-1-azabicyclo[3.1.0]heptane in abysmal yield *via* basification of the sulfuric acid ester derived from 3-hydroxypiperidine.[2]

Notes and references

† All new compounds (**1**, **3**–**5**) possessed consistent NMR parameters (^{1}H, ^{13}C, and ^{19}F); good elemental analyses (C, H, F, and N) were obtained for **1**, **3** and **5** except that the F value for **1** was low.

‡ *Crystal data* for **1**: $C_{19}H_{10}F_{11}N$, M = 461.28, monoclinic, a = 10.217(2), b = 8.6426(10), c = 21.054(3) Å, β = 101.22(2)°, U = 1823.5(5) Å^3, T = 293(2) K, space group $P2_1/c$ (no. 14), monochromated Mo-Kα radiation, λ = 0.71069 Å, Z = 4, D_c = 1.680 Mg m^{-3}, F(000) = 920, colourless plates, dimensions 0.40 × 0.35 × 0.25 mm, μ(Mo-Kα) = 0.178 mm^{-1}, Rigagku AFC6S diffractometer, ω–2θ scan, 4 < 2θ < 50°, 3378 reflections measured, 3197 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares (SHELX 97). All non-hydrogen atoms were refined anisotropically; hydrogens were constrained to chemically reasonable positions. The final cycle of least-squares refinement (for 320 parameters) converged with $wR2$ = 0.1057 (for all data) and $R1$ = 0.0389 (for 1926 reflections [I > 2σ(I)]). Selected bond distances: C(7)–(14), 4.76(1); C(5)–N, 1.436; C(6)–N, 1.499; C(5)–(6), 1.485 Å. Selected bond angles: C(5)–N–(6), 60.75; C(5)–C(6)–N, 57.51; C(6)–(5)–N, 61.74°.

For **5**: $C_{19}H_{11}F_{12}N$, M = 481.29, orthorhombic, a = 27.339(2), b = 8.3850(10), c = 15.593(2) Å, U = 3574.5(7) Å^3, T = 203(2) K, space group *Pbcn* (No. 60), monochromated Mo-Kα radiation, λ = 0.71069 Å, Z = 8, D_c = 1.789 Mg m^{-3}, F(000) = 1920, colourless needles, dimensions 0.40 × 0.25 × 0.15 mm, μ(Mo-Kα) = 0.193 mm^{-1}, Nonius Mach3 diffractometer, ω–2θ scan, 4 < 2θ < 50°, 3129 reflections measured, 3129 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares (SHELX 97). All non-hydrogen atoms were refined anisotropically; hydrogens were constrained to chemically reasonable positions. The final cycle of least-squares refinement (for 333 parameters) converged with $wR2$ = 0.0808 (for all data) and $R1$ = 0.0355 (for 2295 reflections [I > 2σ(I)]). Selected bond distances: C(2)–N, 1.464(3); C(2)–C(3), 1.549(3); C(2)–C(7), 1.554(3); C(2)–C(8), 1.540(3); C(3)–C(4), 1.531(3); C(4)–C(5), 1.533(3); C(4)–F, 1.339(3); C(5)–C(6), 1.547(3); C(6)–N, 1.460(3); C(6)–C(14), 1.551(3); C(6)–C(15), 1.554(3); C(7)–F, 1.321(3); C(8)=C(9), 1.387(3); C(14)–F, 1.322(3) Å. Selected bond angles: C(2)–N–C(6), 128.05(18); N–C(2)–C(8), 106.77(17); N–C(2)–C(7), 112.03(17); N–C(2)–C(3), 109.38(17); C(4)–C(3)–C(2), 116.25(18); C(5)–C(4)–C(3), 112.99(18); C(4)–C(5)–C(6), 115.88 (18); N–C(6)–C(5), 109.67(17)°. CCDC 182/1092. This data is available as two .cif files from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/47

1 A. L. Logothetis, *J. Am. Chem. Soc*., 1965, **87**, 749.
2 P. G. Gassman and A. Fentiman, *J. Org. Chem*., 1967, **32**, 2388.
3 For example, see D. St. C. Black and J. E. Doyle, *Aust. J. Chem*., 1978, **31**, 2247; E. Breuer and S. Zbaida, *J. Org. Chem*., 1977, **42**, 1904; J. Mulzer, R. Becker and E. Brunner, *J. Am. Chem. Soc*., 1989, **111**, 7500; E. J. Moran, J. E. Tellew, Z. Zhao and R. W. Armstrong, *J. Org. Chem*., 1993, **58**, 7848.
4 S. Ishizaki, M. Ohtsuka, K. Irinoda, K. Kukita, K. Nagaoka and T. Nakashima, *J. Antibiot*., 1987, **40**, 60.
5 R. E. Banks and G.E. Williamson, *Chem. Ind* (*London*), 1964, 1864; R. E. Banks, V. Murtagh and E. Tsiliopoulos, *J. Fluorine Chem*., 1991, **52**, 389; R. E. Banks and V. Murtagh, *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, New York, 1995, **6**, 3942.
6 R. E. Banks, M. G. Barlow and M. Nickkho-Amiry, *J. Fluorine Chem*., 1979, **14**, 383.
7 D. J. Tovell, Ph.D. Thesis, UMIST, 1997; R. E. Banks, M. K. Besheesh, N. J. Lawrence, R. G. Pritchard and D. J. Tovell, publication in preparation.

Communication 8/07673A