Facile new method for synthezising *N*-polyfluoroalkylated heterocycles – molecular structure of *N*-(bromodifluoromethyl)-4-dimethylaminopyridinium bromide

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Carbon–bromine bond cleavage is observed when 4-dimethylaminopyridine is treated with CF_2Br_2 and $BrCF_2CF_2Br$ to yield *N*-(bromodifluoromethyl) and *N*-(2-bromo-1,1,2,2-tetrafluoromethyl)pyridinium bromides, 1-Br and 2-Br, which are reductively debrominated using Bu_3SnH and fluorinated by anhydrous $Me_4N^+F^-$; the molecular structure of 1-Br is determined by single crystal X-ray crystallography to reveal a partial quinoidal character in the pyridine system and a hypervalent $Br^- \cdots BrCF_2$ pairing.

The introduction of polyfluoroalkyl groups into organic molecules is of considerable importance in medicine and agrochemistry.[1] To the best of our knowledge neither the polyfluoroalkylation of nitrogen-containing heterocycles nor a successful displacement of bromine in CF_2Br_2 using a nitrogen nucleophile has been reported.[2,3,4] The reaction of 4-(dimethylamino)pyridine (DMAP) towards fluorinated organyls has not been studied to a great extent, only hexafluorobenzene and 1,2-dichloro-tetrafluorcyclobutene fluorine and chlorine have been substituted to form hexakis- or bispyridinium salts.[5,6] Here we report some preliminary results on a new versatile synthesis of the first *N*-polyfluoroalkylated *N*-heterocycle starting from dibromodifluoromethane, 1,2-dibromotetrafluoromethane and DMAP.

In polar solvents, like DMF and acetonitrile the reaction (Scheme 1) was completed within 1 h after adding small amounts of activated zinc or copper forming the colourless pyridinium bromides, **1**-Br and **2**-Br.†‡ When *p*-dinitrobenzene was added to the $BrCF_2CF_2Br$/DMAP mixture no product was observed. This was probably due to a single-electron transfer (SET) process initiating an $S_{RN}1$ sequence,[7] whereas in the case of CF_2Br_2/DMAP no influence due to a possible difluorocarbene-mediated ionic chain mechanism was observed.[8] No reaction was observed in diethylether, THF or diglyme.

Using tributylstannane,[9] compounds **1**-Br and **2**-Br were hydrogenated to give the colourless *N*-difluoromethylated and *N*-(1,1,2,2-tetrafluoro)ethylated pyridinium salts,§ **3**-Br and **4**-Br respectively (Scheme 1). The $BrCF_2$ group was successfully fluorinated with anhydrous tetramethylammonium fluoride[10] to furnish *N*-trifluoromethyl-4-dimethylamino-pyridium bromide which was converted to the respective tetrafluoroborate **5**-BF_4.¶

The single crystal X-ray structure determination of **1**-Br (Fig. 1)‖ showed an almost planar six-membered ring with an 8.9° deviation of the exocyclic C(1)–N(1) bond. An angle of 10.6° was observed between the planes through C(3)–C(4)–C(5) and N(2)–C(7)–C(8). There was a substantial degree of quinoidal character[5,6] in the pyridinium systems, since the bond length C(2)–C(3) and C(5)–C(6) was significantly shorter (134 pm) than the C(3)–C(4) or C(4)–C(5) distance (143 pm). The bond length C(4)–N(2) (134 pm) was between a carbon–nitrogen single and double bond (147 and 127 pm respectively),[6] indicating significant conjugation. There was not much evidence for an sp^3 lone pair neither at N(1) (sum of the angles 359.2°) nor at N(2) (sum of the angles 358.9°).

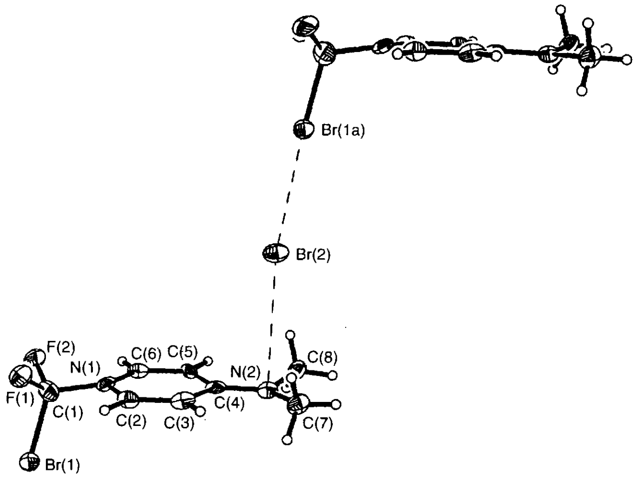
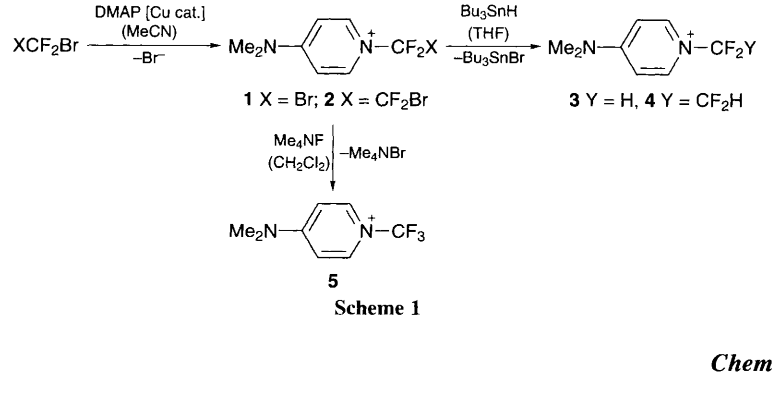


Fig. 1 Crystal structure of **1** with thermal ellipsoids. Selected bond distances (pm) and angles (°): C(1)–Br(1) 191.5(7), C(1)–F(1) 135.6(8), C(1)–N(1) 145.4(9), C(2)–N(1) 137.0(8), C(2)–C(3) 134.3(10), C(3)–C(4) 143.5(9), C(4)–N(2) 133.7(8), C(7)–N(2) 145.9(7); Br(1)–C(1)–F(1) 110.0(4), F(1)–C(1)–F(2) 107.3(5), Br(1)–C(1)–N(1) 112.3(4), C(2)–N(1)–C(6) 119.7, C(2)–C(3)–C(4) 121.5(6), C(3)–C(4)–C(5) 116.3(5), C(7)–N(2)–C(8) 117.2(5).



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Scheme 1

Surprisingly the Br$^-$(2)···Br(1a)CF$_2$ distance was 315.7 pm, much less than the sum of the Van der Waals radii (370 pm) accounting for a hypervalent ion-pairing,[11] whereas the distance Br$^-$(2)···N(2)Me$_2$ was 361.2 pm. The Br(1)–C bond in **1**-Br seems to be uneffected by the close distance of the Br$^-$ anion since similar values were found in CF$_2$BrC(O)NH$_2$ and BrCF$_2$CF$_2$Br, 190(2) and 192.0 pm respectively.[12,13]

Footnotes

† All reactions were performed under nitrogen in carefully dried solvents. All new compounds gave satisfactory elemental analyses. Mass spectra were recorded under DCI-positive conditions (reactand gas NH$_3$), NMR spectra at 80.13 (^{1}H, TMS) and 75.39 MHz (^{19}F, CClF$_3$).

‡ *Synthesis* of **1**-Br and **2**-Br: To a solution of DMAP (10 mmol) in MeCN (10 ml) and Cu powder (5 μm), CF$_2$Br$_2$ (3.14 g, 15 mmol) or C$_2$F$_4$Br$_2$ (3.90 g, 15 mmol) were added. After 1 h at ambient temperature the solid formed was filtered, washed with diethylether (2 × 10 ml) and recrystallized from MeCN. Yields: **1**-Br 2.50 g (75%) (mp 233 °C), **2**-Br 3.00 g (80%) (mp 261 °C). *Selected data* for **1**: ^{1}H NMR δ_H 3.2 (CH$_3$, 6 H), 6.34, 7.78 (AB system, CH, 4 H, J_{AB} 7.7 Hz); ^{19}F NMR δ_F −36.8. IR ν/cm^{-1} (KBr): 3450, 3035 and 1649. MS (%): 253 (^{81}Br, M$^+$, 20), 239 (^{81}Br, M$^+$ CH$_2$, 50), 123 (C$_7$H$_{11}$N$_2$$^+$, 100). For **2**: ^{19}F NMR δ_F −68.6 (CF$_2$Br), −98.7 (CF$_2$, $^3J_{FF}$ 4.2 Hz). MS (%): 303 (^{81}Br, M$^+$, 30), 123 (C$_7$H$_{11}$N$_2$$^+$, 100).

§ *Synthesis* of **3**-Br and **4**-Br: To a solution of **1**-Br (1.60 g, 5 mmol) or **2**-Br (1.90 g, 5 mmol) in THF (10 ml), BuSnH (1.70 g, 6 mmol) was added and the solution stirred for 2 h at 50 °C. The solution was then filtrated and the remaining solid washed with diethylether (2 × 10 ml) and recrystallized from MeCN. Yields: **3**-Br 1.12 g (95%) (mp 140 °C); **4**-Br 1.32 g (88%) (mp 171 °C). *Selected data* for **3**: ^{1}H NMR δ_H 8.4 (CF$_2$H, $^2J_{FH}$ 59.3 Hz); ^{19}F NMR δ_F −98.1. MS (%): 173 (M$^+$, 60), 123 (C$_7$H$_{11}$N$_2$$^+$, 100). For **4**: ^{1}H NMR δ 7.2 (CF$_2$H, $^2J_{FH}$ 52.4, $^3J_{FH}$ 3.1 Hz); ^{19}F NMR δ_F −101.8 (CF$_2$, $^3J_{FF}$ 6.3 Hz), −137.2 (CF$_2$H). MS (%): 223 (M$^+$, 100).

¶ *Synthesis* of **5**-BF$_4$: To a solution of **1**-Br (3.32 g, 10 mmol) in CH$_2$Cl$_2$ (15 ml), Me$_4$N$^+$F$^-$ (2.00 g, 21.4 mmol) was added and stirred for 12 h at ambient temperature. The solvent was pumped off and the residue dissolved in MeOH (10 ml) and NH$_4$BF$_4$ (20 mmol) added. After filtration the solvent was removed and the solid recrystallized from THF–Et$_2$O (1 : 1). Yield **5**-BF$_4$ 1.12 g (40%) (mp 210 °C). *Selected data* for **5**: ^{19}F NMR δ_F −61.0. MS (%): 191 (M$^+$, 100).

|| *Crystal data* for **1**-Br: C$_8$H$_{10}$Br$_2$F$_2$N$_2$, M = 332.0 orthorhombic, space group $P2_12_12_1$, a = 575.2(2), b = 1097.3(2), c = 1752.7(2) pm, V = 1106.3(3) Å^3, Z = 4, D_c = 1.993 g cm^{-3}, λ(Mo-Kα) = 0.71073 Å, Siemens R3 m/v diffractometer 2θ-scan type, 5.0° ≤ 2θ ≤ 55.0°, 173 K; 10357 reflection collected, 2560 independent reflection (R_{int} = 1.86%), observed reflections 1875 [$F > 4.0\sigma(F)$]; full-matrix least-squares refinement [Siemens SHELXTL PLUS (VMS)], direct methods, hydrogen atoms were treated as riding models wR = 3.27% (observed data). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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