

Difluorination ability of F-TEDA-BF₄ in the transannular cyclization of bicyclo[3.3.1]nonane dienes in monoglyme

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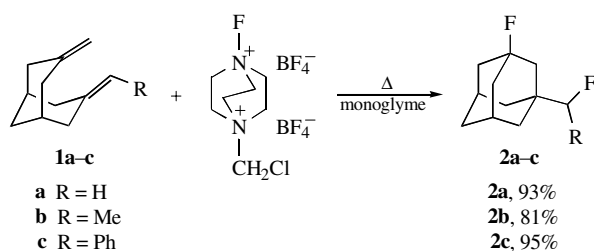
The interaction of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄) with 3,7-bismethylenebicyclo[3.3.1]nonane and its derivatives in monoglyme results in the transannular cyclization of the dienes to form 1-fluoro-3-fluoroalkyladamantanes.

Electrophilic N-F reagents are widely used in the selective fluorination of organic, in particular, unsaturated, substrates.¹ The reactions are usually conducted in nucleophilic or dissociating solvents because in aprotic media with low polarity and small nucleophilicity (CHCl₃, CH₂Cl₂, Freon-113, THF *etc.*) they give a complex mixture of products.²

The side formation of difluorides was observed in the reactions of F-TEDA-BF₄ with unsaturated substrates.^{3,4} For example, 1,2-difluorosaccharides were reported to form as by-products, in addition to monofluorinated carbohydrates, in the fluorination of glycals with F-TEDA-BF₄ in nitromethane in the presence of alcohols.³ Side difluorination occurred in the transannular cyclization of 3,7-bismethylenebicyclo[3.3.1]nonane with F-TEDA-BF₄ in protic solvents, where 1-fluoro-3-fluoromethyladamantane was detected as an impurity among the major products, 1-RO-3-fluoromethyladamantanes (R = H, Alk or Ac).⁴

Here, we report the unusual and intriguing finding: under certain conditions, F-TEDA-BF₄ can act as an effective difluorinating agent in the transannular cyclization of 3,7-bismethylenebicyclo[3.3.1]nonane and its derivatives with a methyl or phenyl substituent at one of the exocyclic methylene groups.

The starting substrates (3,7-bismethylenebicyclo[3.3.1]nonane **1a**, 3-ethylidene-7-methylenebicyclo[3.3.1]nonane **1b** and 3-benzylidene-7-methylenebicyclo[3.3.1]nonane **1c**) were prepared by the published procedures.^{4,5} When the reaction was carried out in monoglyme, difluoro-substituted adamantanes **2a–c** were obtained in high yields.[†]

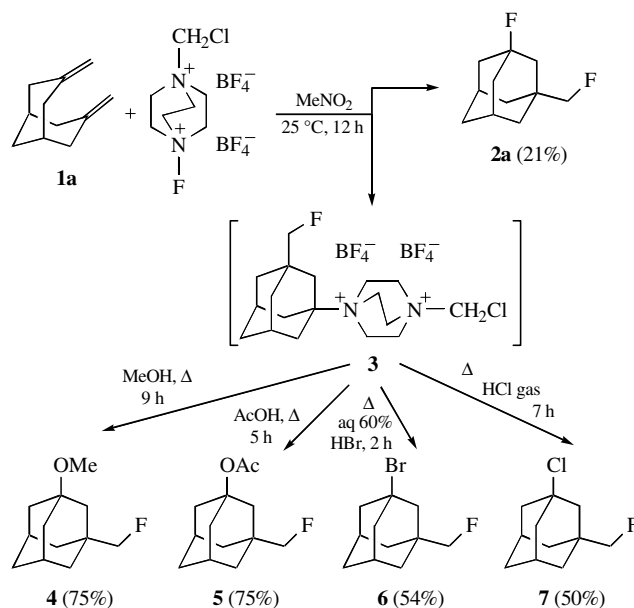


Scheme 1

It was of interest to elucidate whether monoglyme is a specific solvent promoting the difluorination. For this purpose, we conducted the reaction of **1a** with F-TEDA-BF₄ in a series of aprotic polar solvents. In low-polarity solvents such as CH₂Cl₂, C₂H₄Cl₂ and THF, no cyclization was observed even at the stirring the reactants for many days. In polar nitromethane, the reaction occurred; however, the yield of difluoride **2a** was very low. The major product in this solvent was tentatively identified as 1-fluoromethyladamantane with a TEDA-BF₄ residue attached to the bridge-head atom 3-C (Scheme 2, compound **3**).

The formation of similar products was observed in the reactions of glycals with F-TEDA-BF₄.³ We failed to isolate this adduct from the reaction mixture, but its formation was proved by the following transformations caused by ionogenic agents. Upon heating the reaction mixture under reflux for several hours in the presence of methanol, acetic acid, aqueous hydrobromic acid or hydrogen chloride, the TEDA-BF₄ residue in compound **3** was replaced by the external nucleophile with the formation of fluoromethyladamantanes **4–7**.[‡]

Thus, monoglyme is responsible for the high yield of difluorides **2a–c** in the transannular cyclization of dienes **1a–c** with F-TEDA-BF₄. The reaction mechanism can be conceived as follows: at the first step, the 'electrophilic' fluorine in the F-N group of F-TEDA-BF₄ adds to a double bond of the diene to give, after the transannular cyclization, a stable adamantyl cation,⁶ which recombines with a fluoride anion making part of BF₄[–]. The promoting role of monoglyme evidently consists in binding



Scheme 2

[‡] The reaction of **1a** (0.1 g, 0.67 mmol) with F-TEDA-BF₄ (0.263 g, 0.74 mmol) in anhydrous nitromethane (10 ml) was conducted at room temperature for 12 h, until **1a** was completely consumed (TLC test). The yield of **2a** under these conditions was about 21% (GLC). After the addition of 2 ml of absolute methanol to the reaction mixture and heating at reflux for 9 h, 1-fluoromethyl-3-methoxyadamantane **4** was formed in 75% yield (GLC), whereas the yield of difluoride **2a** remained as before. In a similar way, by heating the reaction mixture with 2 ml of acetic acid for 5 h, 1-acetoxy-3-fluoromethyladamantane **5** was obtained in 75% yield (GLC). The ¹H, ¹³C and ¹⁹F NMR spectra of products **4** and **5** are in agreement with published data.⁴ Refluxing the reaction mixture with 3 ml of aqueous 60% HBr for 2 h afforded 1-bromo-3-fluoromethyladamantane **6** in 54% isolated yield. By passing an HCl gas through the reaction mixture over 7 h at 80 °C, 1-chloro-3-fluoromethyladamantane **7** was obtained in 50% isolated yield.

[†] In a typical procedure, 1.2 mmol of appropriate diene **1** and 1.32 mmol of F-TEDA-BF₄ in 10 ml of monoglyme were heated at reflux with stirring for 45–120 h. The reaction mixture was dissolved in 40 ml of water and extracted with CH₂Cl₂ [(4–5)×15 ml]. The combined extracts were washed with water (2×10 ml), dried (Na₂SO₄) and concentrated by evaporation. The products were purified by column chromatography on silica gel (eluent: hexane–diethyl ether, 25:1). Their yields, as determined by GLC, are indicated in Scheme 1.

the liberated BF_3 into a firm etherate complex, which assists in releasing the F^- ion. This also facilitates the interaction of the fluoride anion at the step determining the reaction products and ensures thereby the high selectivity of the difluorination reaction.

All of the new compounds were identified by elemental analysis, NMR spectroscopy and mass spectrometry.[§]

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[§] The ^1H , ^{13}C and ^{19}F NMR spectra were recorded on a Varian VXR-300 instrument at 300, 75.4 and 282.2 MHz, respectively, in CDCl_3 with TMS or CCl_3F as internal standards.

2a: colourless oil. ^1H NMR, δ : 1.40–2.00 (m, 12H, Ad), 2.34 (m, 2H, Ad), 4.05 (d, 2H, CH_2F , J 47.6 Hz). ^{13}C NMR, δ : 30.92 (d, C-5, C-7, J 9.0 Hz), 35.38 (s, C-6), 36.91 (d, C-4, C-10, J 4.5 Hz), 39.12 (dd, C-3, J_1 18.3 Hz, J_2 9.5 Hz), 42.31 (d, C-8, C-9, J 17.2 Hz), 43.42 (dd, C-2, J_1 17.6 Hz, J_2 4.1 Hz), 91.21 (d, CH_2F , J 172.9 Hz), 92.41 (d, C-1, J 185.9 Hz). ^{19}F NMR, δ : –133.41 (s, CF), –230.77 (t, CH_2F , J 47.6 Hz). MS, m/z : 186 (M^+ , 10%), 153 (100%), 133 (7%) (cf. ref. 4).

2b: colourless oil. ^1H NMR, δ : 1.24 (dd, 3H, Me, J_1 24.9 Hz, J_2 6.3 Hz), 1.35–1.95 (m, 12H, Ad), 2.33 (m, 2H, Ad), 4.24 (dq, 1H, CHF, J_1 47.1 Hz, J_2 6.3 Hz). ^{13}C NMR, δ : 14.9 (d, Me, J 24.2 Hz), 31.3 (d, C-5, C-7, J 9.0 Hz), 35.8 (s, C-6), 36.4 (d, C-4, C-10, J 4.5 Hz), 41.9 (dd, C-3, J_1 19.6 Hz, J_2 9.8 Hz), 42.71 (d, C-8, C-9, J 17.3 Hz), 42.9 (dd, C-2, J_1 18.8 Hz, J_2 4.5 Hz), 93.38 (d, C-1, J 183.1 Hz), 96.55 (d, CHF, J 171.1 Hz). ^{19}F NMR, δ : –132.66 (s, CF), –185.87 (dq, CHF, J_1 45.0 Hz, J_2 24.0 Hz). MS, m/z : 200 (M^+ , 11%), 153 (100%), 133 (%) (cf. ref. 7).

2c: white crystals, mp 53–54.5 °C. ^1H NMR, δ : 1.55–1.99 (m, 12H, Ad), 2.30 (m, 2H, Ad), 5.03 (d, 1H, CHF, J 45.3 Hz), 7.19–7.25 (m, 2H, Ph), 7.30–7.40 (m, 3H, Ph). ^{13}C NMR, δ : 30.66 (d, C-5, C-7, J 9.8 Hz), 35.08 (s, C-6), 36.0–36.22 (m, C-4, C-10), 42.05 (dd, C-3, J_1 22.5 Hz, J_2 9.2 Hz), 42.05 (d, C-8, C-9, J 17.0 Hz), 42.45 (dd, C-2, J_1 19.2 Hz, J_2 4.2 Hz), 92.79 (d, C-1, J 183.7 Hz), 100.12 (d, CHF, J 176.8 Hz), 126.86 (d, Ph, J 7.7 Hz), 127.67 (s, Ph), 128.09 (s, Ph), 136.23 (d, Ph, J 21.4 Hz). ^{19}F NMR, δ : –133.62 (s, CF), –190.69 (d, CHF, J 44.9 Hz). MS, m/z : 262 (M^+ , 52%), 242 (6%), 153 (100%), 133 (11%). Found (%): C, 78.00; H, 7.81. Calc. for $\text{C}_{17}\text{H}_{20}\text{F}_2$ (%): C, 77.83; H, 7.68.

6: white crystals, mp 48.5–49.5 °C. ^1H NMR, δ : 1.45–1.84 (m, 6H, Ad), 2.15–2.4 (m, 8H, Ad), 3.99 (d, 2H, CH_2F , J 47.9 Hz). ^{13}C NMR, δ : 31.67 (s, C-5, C-7), 34.86 (s, C-6), 36.26 (d, C-4, C-10, J 4.2 Hz), 39.16 (d, C-3, J 18.8 Hz), 48.48 (s, C-8, C-9), 49.59 (d, C-2, J 4.2 Hz), 64.45 (s, C-1), 91.03 (d, CH_2F , J 172.7 Hz). ^{19}F NMR, δ : –231.51 (t, CH_2F , J 48.0 Hz). MS, m/z : 227 (12%), 167 (100%). Found (%): C, 53.30; H, 6.40; Br, 32.01. Calc. for $\text{C}_{11}\text{H}_{16}\text{BrF}$ (%): C, 53.46; H, 6.53; Br, 32.34.

7: colourless oil. ^1H NMR, δ : 1.45–1.75 (m, 6H, Ad), 1.96 (s, 2H, Ad), 2.10 (m, 4H, Ad), 2.25 (m, 2H, Ad), 4.01 (d, 2H, CH_2F , J 47.7 Hz). ^{13}C NMR, δ : 30.94 (s, C-5, C-7), 34.92 (s, C-6), 36.36 (d, C-4, C-10, J 5.6 Hz), 38.55 (d, C-3, J 17.7 Hz), 46.99 (s, C-8, C-9), 48.17 (d, C-2, J 4.0 Hz), 67.60 (s, C-1), 91.15 (d, CH_2F , J 172.4 Hz). ^{19}F NMR, δ : –231.00 (t, CH_2F , J 48.0 Hz). MS, m/z : 202 (M^+ , 4%), 169 (39%), 167 (100%), 133 (16%). Found (%): C, 65.00; H, 7.70; Cl, 17.51. Calc. for $\text{C}_{11}\text{H}_{16}\text{ClF}$ (%): C, 65.18; H, 7.96; Cl, 17.49.

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