Difluorination ability of F-TEDA-BF$_4$ 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-BF$_4$) with 3,7-bis-methylenebicyclo[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 (CHCl$_3$, CH$_2$Cl$_2$, 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-BF$_4$ 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-BF$_4$ 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-BF$_4$ 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-BF$_4$ 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.[†]
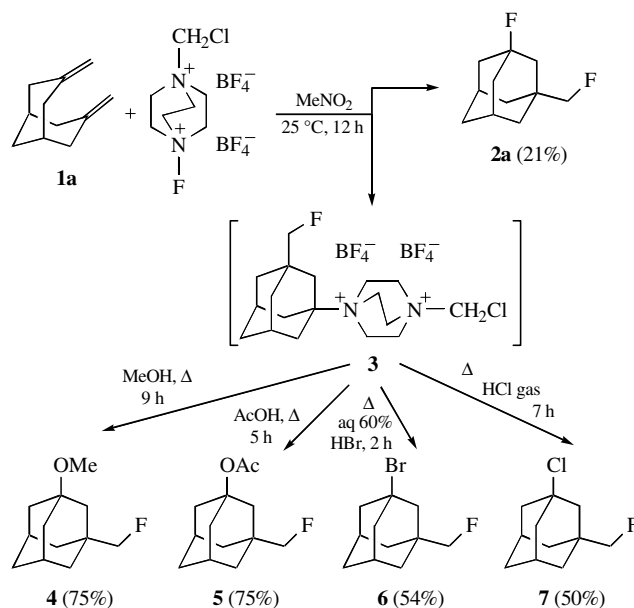

Scheme 1

1a–c

a R = H
b R = Me
c R = Ph

2a, 93%
2b, 81%
2c, 95%
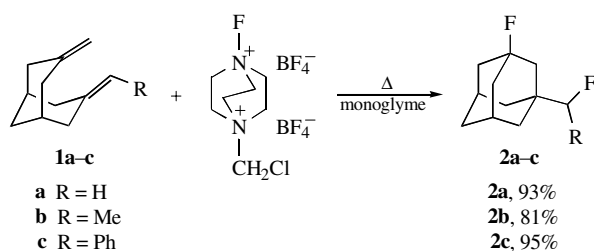
It was of interest to elucidate whether monoglyme is a specific solvent promoting the difluorination. For this purpose, we conducted the reaction of **1a** with F-TEDA-BF$_4$ in a series of aprotic polar solvents. In low-polarity solvents such as CH$_2$Cl$_2$, C$_2$H$_4$Cl$_2$ and THF, no cyclization 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-BF$_4$ 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-BF$_4$.[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-BF$_4$ 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-BF$_4$. The reaction mechanism can be conceived as follows: at the first step, the 'electrophilic' fluorine in the F–N group of F-TEDA-BF$_4$ 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 BF$_4^-$. The promoting role of monoglyme evidently consists in binding

Scheme 2

2a (21%)

4 (75%)
5 (75%)
6 (54%)
7 (50%)

[†] In a typical procedure, 1.2 mmol of appropriate diene **1** and 1.32 mmol of F-TEDA-BF$_4$ 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 CH$_2$Cl$_2$ [(4–5)×15 ml]. The combined extracts were washed with water (2×10 ml), dried (Na$_2$SO$_4$) 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 reaction of **1a** (0.1 g, 0.67 mmol) with F-TEDA-BF$_4$ (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% (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 ^{1}H, ^{13}C and ^{19}F 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 ºC, 1-chloro-3-fluoromethyladamantane **7** was obtained in 50% isolated yield.

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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