Selective transannular cyclization of 3,7-bismethylenebicyclo[3.3.1]nonane with F-TEDA-BF_4 in protic solvents

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The reaction of 3,7-bismethylenebicyclo[3.3.1]nonane with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) F-TEDA-BF_4 in protic solvents ROH affords 1-RO-3-fluoromethyladamantanes (R = H, Alk, Ac).

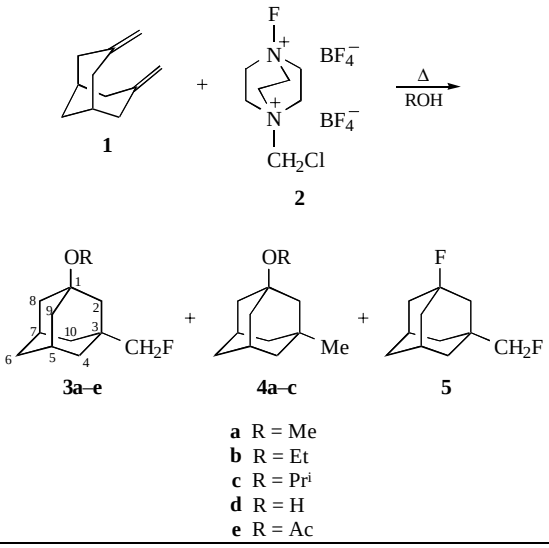
Under the action of electrophilic agents (iodine,[1] bromine,[2,3] acids[4]), dienes of the bicyclononane series undergo transannular cyclization to adamantane derivatives, among which were found compounds with antiviral and other kinds of physiological activity.[5,6] Fluorine substituents are known to modify the biological properties of organic compounds.[7] Therefore, the development of selective synthesis methods for fluorinated adamantanes is of practical importance.[8,9]

There is no data on transannular cyclization of bicyclo[3.3.1]-nonane dienes by traditional electrophilic fluorinating agents such as F_2, XeF_2, CF_3OF and RCO_2F. In recent years, mild electrophilic agents with N–F bonds are increasingly applied to the selective fluorination of organic compounds.[10] Here we report the reaction of 3,7-bismethylenebicyclo[3.3.1]nonane **1** with a suitable commercial agent, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4).[11]

Compound **1** was prepared by the published procedure.[12] Its interaction with F-TEDA-BF_4 **2** in protic solvents,† as established, leads to transannular cyclization into fluorinated adamantanes.‡

The fluorinated adamantanes are formed in high yield (Table 1) when the reaction is conducted in protic solvents (water, acetic acid, alcohols).

In methanol, ethanol and propan-2-ol, in addition to the transannular fluorocyclization leading, respectively, to form 3-fluoromethyl-1-methoxyadamantane **3a**, 1-ethoxy-3-fluoromethyladamantane **3b** and 3-fluoromethyl-1-isopropoxyadamantane **3c**, respectively, cyclization with the addition of an alcohol molecule to the adamantane structure also proceeds to give fluorine-free products **4a–c**. When the reaction is carried out in propan-2-ol, 1-fluoro-3-fluoromethyladamantane **5** is formed in 12.1% yield. The contribution of the protic cyclization decreases with increasing basicity of the alcohol solvents in the order MeOH < < EtOH < Pr^{i}OH. The protic cyclization is



1 **2** **3a–e** **4a–c** **5**

a R = Me
b R = Et
c R = Pr^i
d R = H
e R = Ac

† In a typical procedure, 2 mmol of diene **1** and 2 mmol of F-TEDA-BF_4 were dissolved in 20 ml of a solvent and heated at reflux for 9 to 45 h. The reaction mixture was washed with water and extracted with 30 ml of dichloromethane. The extract was washed with 10% aq. $NaHCO_3$ and water, dried with Na_2SO_4 and evaporated. The products were separated by column chromatography on silica gel. Their purity and yields were determined by GLC.

Table 1 Product yields in the reaction of diene **1** with F-TEDA-BF_4 in different media.

Solvent	Reaction time/h	Yield (%)[a]		
		3	**4**	**5**
MeOH	10	**3a**, 47.6	**4a**, 52.4	Traces
MeOH[b]	9	**3a**, 93.0	—	—
EtOH	12	**3b**, 47.4	**4b**, 41.5	Traces
EtOH[b]	9	**3b**, 65.6	**4b**, 30.3	3.2
Pr^{i}OH	16	**3c**, 75.6	**4c**, 12.0	12.1
Dioxane–H_2O (12.5:1)	24	**3d**, 83.0[c]	—	—
AcOH–CH_2Cl_2 (1:2.5)[b]	45	**3e**, 72.8	—	16.4

[a]As determined by GLC. [b]With 5% AcONa. [c]Isolated.

‡ The new compounds were identified by elemental analysis, IR, NMR and mass spectra. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ with TMS or CCl_3F as an internal standard on a Varian VXR-300 instrument at 299.5, 75 and 292 MHz, respectively. The IR spectra were measured on a Specord IR-75 spectrophotometer in CH_2Cl_2.

3a: colourless oil. ^{1}H NMR, δ: 1.40–2.35 (m, 14H, Ad), 3.30 (s, 3H, MeO), 4.15 (d, 2H, CH_2F, J 47.9 Hz). ^{19}F NMR, δ: –230.21 (t, CH_2F, J 47.7 Hz). MS, m/z: 198 $[M]^+$.

3b: colourless oil. ^{1}H NMR, δ: 1.17 (t, 3H, Me, J 6.9 Hz), 1.3–2.4 (m, 14H, Ad), 3.48 (q, 2H, CH_2O, J 6.9 Hz), 4.00 (d, 2H, CH_2F, J 47.1 Hz). ^{19}F NMR, δ: –230.9 (t, CH_2F, J 47.1 Hz). MS, m/z: 213 $[M + 1]^+$.

3c: colourless oil. ^{1}H NMR, δ: 1.11 (d, 6H, 2Me, J 6.3 Hz), 1.43–2.3 (m, 14H, Ad), 3.43 (spt, 1H, CHO, J 6.3 Hz), 4.00 (d, 2H, CH_2F, J 47.6 Hz). ^{19}F NMR, δ: –230.9 (t, CH_2F, J 47.0 Hz).

3d: white crystals, mp 123–125.5 °C. ^{1}H NMR, δ: 1.39–2.25 (m, 15H, Ad, OH), 4.02 (d, 2H, CH_2F, J 47.6 Hz). ^{13}C NMR, δ: 30.34 (C-5, C-7), 35.62 (C-6), 37.12 (d, C-4, C-10, J 4 Hz), 38.13 (d, C-3, J 18.1 Hz), 44.9 (C-8, C-9), 46.02 (d, C-2, J 4.2 Hz), 68.67 (C-1), 91.83 (d, CH_2F, J 172.5 Hz). ^{19}F NMR, δ: –230.91 (t, CH_2F, J 47.7 Hz). IR (ν/cm^{-1}): 3580, 3510–3200 (ν_{OH}). MS, m/z: 185 $[M + 1]^+$. Found (%): C, 71.50; H, 9.15. Calc. for $C_{11}H_{17}FO$ (%): C, 71.64; H, 9.30.

3e: colourless oil. ^{1}H NMR, δ: 1.33–2.05 (m, 12H, Ad), 2.07 (s, 3H, Ac), 2.27 (br. s, 2H, Ad), 4.02 (d, 2H, CH_2F, J 47.9 Hz). ^{13}C NMR, δ: 22.55 (Me), 30.38 (C-5, C-7), 35.86 (C-6), 37.29 (d, C-4, C-10, J 3.3 Hz), 38.09 (d, C-3, J 17.1 Hz), 40.94 (C-8, C-9), 42.08 (d, C-2, J 3.8 Hz), 77.20 (C-1), 91.22 (d, CH_2F, J 174.3 Hz), 169.49 (C=O). ^{19}F NMR, δ: –231.01 (t, CH_2F, J 48.0 Hz). IR (ν/cm^{-1}): 1700 ($\nu_{C=O}$). MS, m/z: 226 $[M]^+$. Found (%): C, 69.20; H, 8.21. Calc. for $C_{13}H_{19}FO_2$ (%): C, 69.00; H, 8.40.

4a: colourless oil. ^{1}H NMR, δ: 0.86 (s, 3H, CMe), 1.30–2.22 (m, 14H, Ad), 3.23 (s, 3H, OMe). MS, m/z: 180 $[M]^+$.

4b: colourless oil. ^{1}H NMR, δ: 0.85 (s, 3H, CMe), 1.15 (t, 3H, CH_2*Me*, J 6.9 Hz), 1.30–2.22 (m, 14H, Ad), 3.47 (q, 2H, OCH_2, J 6.9 Hz).

4c: colourless oil. ^{1}H NMR, δ: 0.85 (s, 3H, CMe), 1.10 [d, 6H, CH*Me*$_2$, J 6 Hz], 1.2–2.2 (m, 14H, Ad), 3.93 [spt, 1H, C*H*Me$_2$, J 6 Hz].

5: colourless oil. ^{1}H NMR, δ: 1.40–1.65 (m, 6H, Ad), 1.71 (d, 2H, Ad, J 5.4 Hz), 1.75–2.40 (m, 6H, 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 (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 $[M]^+$.

inhibited in the presence of sodium acetate (Table 1). In the AcOH–CH_2Cl_2–AcONa system, the major product is 1-acetoxy-3-fluoromethyladamantane **3e**, and difluoride **5** is formed as a by-product.

The reaction of **1** with F-TEDA-BF_4 in aqueous dioxane affords 3-fluoromethyl-1-hydroxyadamantane **3d**, in a 83% yield.

The transannular cyclization of **1** is highly selective and proceeds, probably, *via* an adamantyl carbocation intermediate. The high stability of the intermediate, which is close to that of the *tert*-butyl cation,[13] facilitates its recombination with an external nucleophile and is responsible for the high selectivity of transannular cyclization.

The detailed mechanism of transannular cyclization reactions between dienes of the bicyclo[3.3.1]nonane series and electrophilic N–F agents will be published elsewhere.

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