Selective introduction of fluorine atoms to the *tert*-carbons of functionalized adamantanes by BrF_3

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Abstract

The direct fluorination reaction of the functionalized adamantanes was achieved by using BrF_3. In the reaction with methyl adamantane-1-caroxylate **1** and dimethyl adamantane-1,3-dicarboxylate **3**, three and two fluorine atoms, respectively, were introduced selectively to their *tert*-carbons. On the other hand, in the reactions with 1-acetoxymethyladamantane **5**, and 2-adamantanone **9**, not only the expected fluorination of their *tert*-carbons, but also unexpected reactions such as fluorination of carbonyl functionality occurred.

1. Introduction

Adamantane is a simple cage compound consisting of four *tert*-carbons and six *sec*-carbon atoms. Bioactive derivatives of adamantane are known, and 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) have medicinal uses [1]. Introduction of fluorine atoms in bioactive compounds can enhance their activities and reduce undesirable side-effects. Therefore, the synthesis of

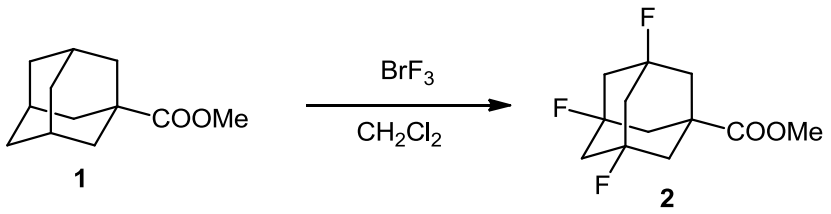
fluorinated adamantane derivatives has received significant attention [2]. Recently, we reported the direct fluorination of adamantanes by an electrochemical method [3]. One to three fluorine atoms can be introduced selectively on the *tert*-carbons of the adamantanes by controlling the conditions, and functional groups such as ester or cyano groups could survive under the conditions. However, a drawback is that special equipment is required for the electrochemical reaction. Therefore, we also studied the fluorination of adamantanes by non-electrochemical methods, and succeeded in the fluorination of adamantanes with IF_5, without the special equipment needed for electrolysis [4]. However, owing to the inherent reactivity of IF_5, only one or two fluorine atoms could be introduced. Moreover, when electron-withdrawing groups were attached on the substrate, fewer (or no) fluorine atoms could be introduced. For example, 1-cyanoadamantane and dimethyl adamantane-1,3-dicarboxylate were inert to IF_5, and only one fluorine atom could be introduced to methyl adamantane-1-carboxylate. For the introduction of more fluorine atoms to adamantane derivatives with low reactivity, a more reactive fluorination reagent than IF_5 is required [5]. Herein, we report the direct fluorination of adamantanes using BrF_3 [6], which is more reactive than IF_5 [8].

2. Results and discussion

Initially, the reaction of methyl adamantane-1-carboxylate **1** with BrF_3 was performed. The reaction proceeded even at -78 °C, and three fluorine atoms were introduced to its *tert*-carbons (Entry 1 in Table 1). The best result was obtained by performing the reaction using 4 eq of BrF_3 at 0 °C for 3 h, and methyl 3,5,7-trifluoroadamantane-1-carboxylate **2** was obtained in 88% yield (Entry 3). These results demonstrated the higher reactivity of BrF_3 compared to IF_5 in the direct fluorination reaction of the adamantanes.

Table 1

Reaction of methyl adamantane-1-carboxylate **1** with BrF_3

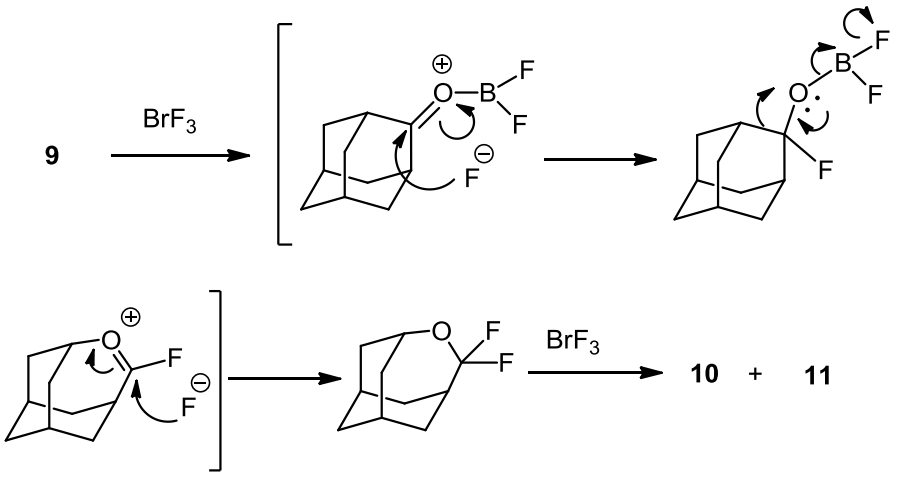


Entry	BrF_3 / **1**	Temperature (0 °C)	React time (h)	Yield of **2** (%)[a]
1	6	-78	1	72
2	4	0	2	(88)
3	4	0	3	88 (95)

[a] Isolation yield based on **1**, in parentheses, ^{19}FNMR yield.

Next, we applied BrF_3 to the fluorination of dimethyl adamanatane-1,3-dicarboxylate **3**, which was inert to IF_5, and obtained dimethyl 5,7-difluoroadamantane-1,3-dicarboxylate **4** in 86 % yield (Entry 2 in Table 2). Unexpected reactions also occurred during the fluorination reaction using BrF_3. When 1-acetoxymethyladamantane **5** was reacted with BrF_3 at -78 °C for 0.5 h, two fluorine atoms were selectively introduced and 1-acetoxymethyl-3,5-difluoroadamantane **6** was obtained in 94 % yield (Entry 3). On the other hand, when the reaction was carried out at 0 °C for 6 h, three fluorine atoms were introduced and 1-acetoxymethyl-3,5,7-trifluoroadamantane **7** was obtained in 62 % yield (Entry 4). However, unexpectedly, 1-((1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane **8** was also formed in 14 % yield. Under these conditions, the fluorination of the carbonyl group also occurred [9]. In the reaction with 2-adamantanone **9**, a mixture of

tetrafluorinated compounds **10** and **11** was obtained (Entry 5). Rearrangement of the carbonyl group occurred in addition to the fluorination of the carbonyl group and *tert*-carbons [11] (**Scheme 1**).

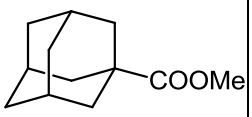
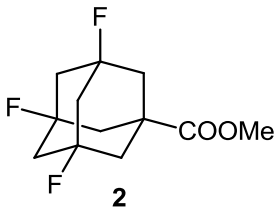
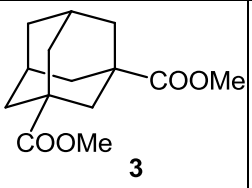
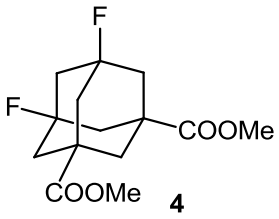
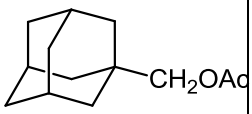
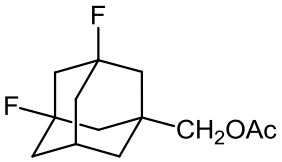
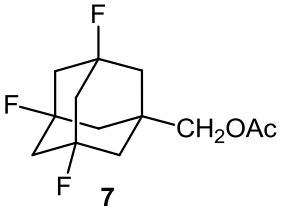
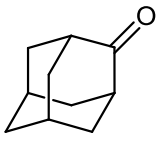
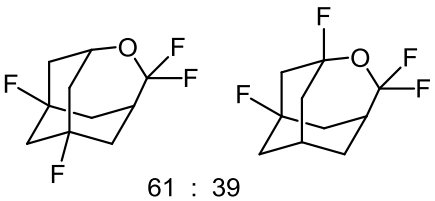


Scheme 1. Plausible mechanism for the formation of **10** and **11**

These unexpected reactions were due to the high reactivity of BrF_3, and were not observed in the case of IF_5.

Table 2

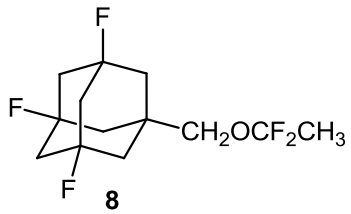
Reaction of functionalized adamantanes with BrF_3[a]

Entry	Adamantane	Conditions	Product	Yield (%)[b]
1	 **1**	0 °C, 2 h	 **2**	88
2	 **3**	0 °C, 6 h	 **4**	86
3	 **5**	-78 °C, 0.5 h	 **6**	94
4	**5**	0 °C, 6 h	 **7**	62[c]
5	 **9**	0 °C, 6 h	 61 : 39 **10** **11**	67

[a]If otherwise not mentioned, the reaction was carried out in CH_2Cl_2 using 4 eq of BrF_3.

[b]Isolated yield based on **1** used. In parentheses, ^{19}F NMR yield.

[c]1-((1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane **8** was also formed in 14% yield.



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3. Conclusion

Various functionalized adamantanes were reacted with BrF_3, and two to three fluorine atoms were introduced selectively on their *tert*-carbons. Even when less reactive substrates such as methyl adamantane-1-carboxylate **1** or dimethyl adamantane-1,3-dicarboxylate **3**, were used, multiple fluorine atoms were introduced to their *tert*-carbons. On the other hand, in the reaction of 1-acetoxymethyladamantane **5** and 2-adamantanone **9**, unexpected reactions occurred, such as the fluorination of carbonyl group, and rearrangement.

4. Experimental

4.1. General

The melting points were measured with a Yanagimoto micro melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. BrF_3 in a cylinder was purchased from Galaxy Chemicals, LLC and used without purification. BrF_3 was transferred from cylinder to a

Teflon™ bottle through a Teflon™ tube using nitrogen pressure, and a small quantity of BrF_3 in a small Teflon bottle was kept in a freezer [12]. It decomposes in air by humidity emitting HF fume and was handled in a bench hood with rubber-gloved hands under atmosphere of nitrogen. It is highly reactive and a special care is required for its use. BrF_3 is stable in glasswear but the reaction was carried out in a centrifuge tube of Teflon™ FEP with a tight screw cap because generation of HF occurs during the reaction.

4.2. Fluorination of adamantane derivatives by BrF_3.

Methyl 3,5,7-trifluoroadamantane-1-carboxylate (2): To a CH_2Cl_2 solution (1.5 mL) of BrF_3 (378 mg, 2.76 mmol) in a Teflon™ FEP reactor, methyl adamantane-1-carboxylate (134mg, 0.69 mmol) in CH_2Cl_2 (0.8 mL) was added at -78 °C through a Teflon™ cannula and the mixture was stirred at 0 °C for 2h. Then the mixture was cooled to -78 °C again, and 2mL of Me_3SiCl was added slowly to decompose the excess of BrF_3. The mixture was brought up to room temperature and neutralized with aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (20 mL X 3) and the combined organic phase was washed with aq $Na_2S_2O_3$ and dried over $MgSO_4$. After concentration under reduced pressure, **2** was isolated by column chromatography (silica gel, hexane-ether) in 88 % yield. mp 109–112 °C (sealed tube) (lit.[2] 108.5-110 °C); IR (KBr) 2958, 1737, 1339, 1259, 1226, 964 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 2.16–1.99 (m, 12H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –144.00 (s, 3F); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.4 (q, $^4J_{C\text{-}F}$ = 3.4 Hz), 91.7 (dt, $^1J_{C\text{-}F}$ = 191.2, $^3J_{C\text{-}F}$ = 15.3 Hz, 3C), 52.6, 46.6-46.0 (m, 3C), 43.2 (q, $^3J_{C\text{-}F}$ = 11.8 Hz), 42.1–41.7 (m, 3C); HRMS (EI) calcd for $C_{12}H_{15}O_2F_3$ 248.1024, found 248.1013.

Dimethyl 5,7-difluoroadamantane-1,3-dicarboxylate (4): mp 87–89 °C (sealed tube);

IR (KBr) 2960, 1738, 1435, 1275 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 6H), 2.12 (t, *J* = 5.3 Hz, 2H), 2.05–1.97 (m, 8H), 1.93 (brs, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –140.21 (s, 2F); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.9 (t, $^{4}J_{C-F}$ = 2.6 Hz, 2C), 92.4 (dd, $^{1}J_{C-F}$ = 189.1, $^{3}J_{C-F}$ = 14.3 Hz, 2C), 52.4 (2C), 46.7 (t, $^{2}J_{C-F}$ = 19.3 Hz), 45.0 (t, $^{3}J_{C-F}$ = 11.0 Hz, 2C), 42.2 (t, $^{3}J_{C-F}$ = 6.0 Hz, 2C), 42.0 (t, $^{3}J_{C-F}$ = 5.9 Hz, 2C), 38.3 (t, $^{4}J_{C-F}$ = 2.0 Hz*)*; HRMS (EI) calcd for $C_{14}H_{18}O_4F_2$, 288.1173, found 288.1183.

1-(Acetoxymethyl)-3,5-difluoroadamantane (**6**)**:** IR (neat) 2949, 1741, 1243 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 2H), 2.49 (brs, 1H), 2.10 (brs, 2H), 2.08 (s, 3H), 1.83–1.65 (m, 8H), 1.43(brs, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –137.54 (s, 2F); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.9, 93.0 (dd, $^{1}J_{C-F}$ = 188.1, $^{3}J_{C-F}$ = 13.6 Hz, 2C), 71.1 (t, $^{4}J_{C-F}$ = 1.9 Hz), 47.5 (t, $^{2}J_{C-F}$ = 19.0 Hz), 43.3 (t, $^{4}J_{C-F}$ = 5.5 Hz), 43.1 (t, $^{4}J_{C-F}$ = 5.6 Hz), 40.8 (t, $^{4}J_{C-F}$ = 5.4 Hz), 40.6 (t, $^{4}J_{C-F}$ = 5.4 Hz), 39.2 (t, $^{3}J_{C-F}$ = 10.3 Hz), 36.6 (t, $^{4}J_{C-F}$ = 2.1 Hz), 30.4 (t, $^{3}J_{C-F}$ = 10.6 Hz), 20.7; HRMS (EI) calcd for $C_{13}H_{18}O_2F_2$ 244.1275, found 244.1285.

1-(Acetoxymethyl)-3,5,7-trifluoroadamantane (**7**)**:** mp 58–63 °C (sealed tube); IR (KBr) 2947, 1749, 1336, 1237, 1217, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 2H), 2.16–2.08 (m, 6H), 2.10 (s, 3H), 1.69 (brs, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –144.07 (s, 3F); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.7, 92.0 (dt, $^{1}J_{C-F}$ = 190.5, $^{3}J_{C-F}$ = 15.0 Hz, 3C), 70.2 (q, $^{4}J_{C-F}$ = 2.1 Hz), 46.7–46.2 (m, 3C), 42.4–42.1 (m, 3C), 37.0 (q, $^{3}J_{C-F}$ = 11.4 Hz), 20.7; HRMS (EI) calcd for $C_{13}H_{17}O_2F_3$ 262.1181, found 262.1167.

1-((1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane (8): IR (neat) 2964, 1336, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 2H), 2.15-2.04 (m, 6H), 1.75 (t, *J* = 13.3 Hz, 3H), 1.69 (brs, 6H) ; ^{19}F NMR (376 MHz, $CDCl_3$) δ –69.92 (q, *J* = 13.3 Hz, 2F), –144.07 (s, 3F); ^{13}C NMR (100MHz, $CDCl_3$) δ 124.8 (t, $^{1}J_{C-F}$ = 260.6 Hz), 92.1 (dt,

$^{1}J_{C\text{-}F}$ = 191.6, $^{3}J_{C\text{-}F}$ = 3.2 Hz, 3C), 69.2-69.0 (m), 47.0 -46.2 (m, 3C), 42.5-42.2 (m, 3C), 37.1 (t, $^{4}J_{C\text{-}F}$ = 11.5 Hz), 22.5 (t, $^{2}J_{C\text{-}F}$ = 32.6 Hz) ; HRMS (EI) calcd for $C_{13}H_{17}F_5O$ 284.11996, found 284.11940.

1,5,5,8-Tetrafluoro-4-oxatricyclo[4.3.1.13,8]undecane (10): mp 102-104 °C, IR (KBr) 2965, 1389, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 2.79 (brs, 1H), 2.31–2.25 (m, 4H), 2.18–2.04 (m, 2H), 2.03–2.00 (m, 2H), 1.91 (brs, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.71 (s, 2F) –135.66 (s, 2F); ^{13}C NMR (100MHz, $CDCl_3$) δ 128.2 (t, $^{1}J_{C\text{-}F}$ = 248.2 Hz), 93.0 (dd, $^{1}J_{C\text{-}F}$ = 185.9 Hz, $^{3}J_{C\text{-}F}$ = 13.2 Hz, 2C), 71.6–71.2 (m), 47.1 (t, $^{3}J_{C\text{-}F}$ = 18.8 Hz), 41.2-40.8 (m, 2C), 36.4-35.5 (m, 2C), 34.5-34.2 (m); HRMS (EI) calcd for $C_{10}H_{12}F_4O$ 224.08243, found 224.08195.

1,3,5,5-Tetrafluoro-4-oxatricyclo[4.3.1.13,8]undecane (11): mp 85-87 °C, IR (KBr) 2961, 1371, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (brs, 1H), 2.59-2.50 (m, 2H), 2.37–2.21 (m, 3H), 2.10–2.02 (m, 2H), 1.96–1.89 (m, 3H), 1.72–1.68 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.87 (d, J = 166.3 Hz, 1F), –63.34 (d, J = 166.3 Hz, 1F), –95.10 (d, J = 9.0 Hz, 1F), –135.99 (s, 1F); ^{13}C NMR (100MHz, $CDCl_3$) δ 124.4 (dt, $^{3}J_{C\text{-}F}$ = 11.5 Hz, $^{1}J_{C\text{-}F}$ = 254.2 Hz), 114.3 (dt, $^{1}J_{C\text{-}F}$ = 217.0 Hz, $^{3}J_{C\text{-}F}$ = 15.3 Hz), 90.2 (dd, $^{1}J_{C\text{-}F}$ = 184.1 Hz, $^{3}J_{C\text{-}F}$ = 14.3 Hz), 46.6 (dt, $^{4}J_{C\text{-}F}$ = 2.9 Hz, $^{3}J_{C\text{-}F}$ = 23.8 Hz), 40.6–40.1 (m, 2C), 39.8 (dt, $^{3}J_{C\text{-}F}$ = 12.2 Hz, $^{2}J_{C\text{-}F}$ = 30.5 Hz), 35.3–35.0 (m), 28.8 (dd, $^{3}J_{C\text{-}F}$ = 12.4 Hz, $^{3}J_{C\text{-}F}$ = 10.5 Hz), 28.2 (brd, $^{4}J_{C\text{-}F}$ = 6.9 Hz); HRMS (EI) calcd for $C_{10}H_{12}F_4O$ 224.08243, found 224.08157.

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