Direct Fluorination of Adamantanes with IF_5

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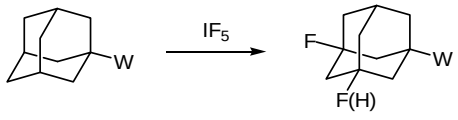
Abstract: Direct fluorination of adamantanes was achieved by IF_5 and one or two fluorine atoms were introduced on tert-carbons of the adamantanes selectively.

Key words: adamantane, direct fluorination, regioselectivity, hypervalent iodine, iodine pentafluoride

Adamantane ($C_{10}H_{16}$) is a simple tricyclic cage compound consisting of only two kinds of carbons: four *tert*-carbons and six *sec*-carbons. Adamantane derivatives such as aminoadamantanes are known to have interesting biological properties,[1] and 1-aminoadamantane (amantadine) and 3,5-dimethyl-1-aminoadamantane (memantine) are used as medicines for treating influenza, Parkinson's disease, and Alzheimer's disease. As the introduction of fluorine atoms into bioactive compounds can enhance or modify their activities,[2] preparation of fluorine derivatives has attracted the attention of organic and medicinal chemists.[3] Fluorination of adamantanes has been carried out through the deoxyfluorination of adamantanols,[4] halogen exchange reaction from other haloadamantanes,[5] or direct fluorination of the adamantane itself.[6] Among them, the direct fluorination method is preferable for synthesis of the fluoroadamantanes because its starting materials are easily available. However, for the direct fluorination of the adamantanes, strong oxidizing reagents, such as F_2, are required, which are generally hazardous and require special skill to use. Moreover, their high reactivity causes a low selectivity of the reaction, which makes it difficult to introduce fluorine atoms only at the desired positions by the direct method.[6a,d,e,g,h] Therefore, a new selective method for the direct fluorination of the adamantanes has been desired.

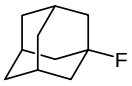
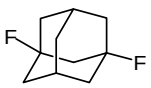
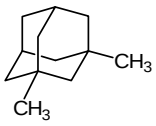
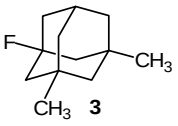
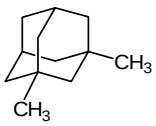
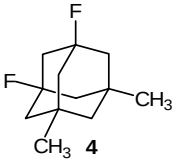
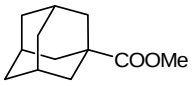
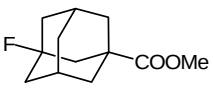
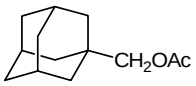
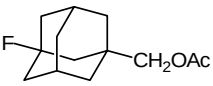
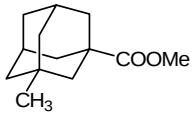
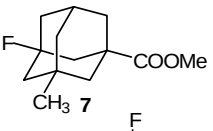
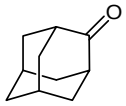
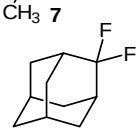


Equation 1

Recently we found that IF_5 is an effective reagent to introduce fluorine atoms into organosulfur compounds.[7] During the course of the study, we found that one or two fluorine atoms can be selectively introduced to adamantanes by IF_5 (Equation 1).

When adamantane was allowed to react with excess IF_5 at room temperature, fluorination took place at *tert*-carbon selectively to give a mixture of 1-fluoroadamantane **1** and 1,3-difluoroadamantane **2**. Selective preparation of **1** was achieved by carrying out the reaction at 0 °C using 0.8 equiv of IF_5, and **1** was obtained in 90% yield.[8] On the contrary, **2** was selectively formed by carrying out the reaction at 75 °C using 3 equiv of IF_5. Under the conditions, neither trifluorination of adamantane nor fluorination at *sec*-carbon occurred, and **2** was obtained in 75% yield. Similarly,

Table 1 Fluorination of Adamantanes with IF_5[a]

Substrate	Conditions	Product	Yield (%)[b]
	0 °C 12h[c]	 **1**	90
	75 °C 12h[d]	 **2**	75
	10 °C 12h[c]	 **3**	85
	80 °C 12h[d]	 **4**	86
	40 °C 12h	 **5**	90
	40 °C 12h	 **6**	90
	40 °C 12h	 **7**	87
	95 °C 12h[e]	 **8**	70

[a]Unless otherwise stated, the reaction was carried out in CH_2Cl_2 using 3 equiv of IF_5. [b] Isolated yield based on substrate. [C] The reaction was carried out in CH_2Cl_2 using 0.8 equiv of IF_5. [d] 1,2-Dichloroethane was used as solvent. [e]Heptane was used as solvent

from 1,3-dimethyladamantane, 1-fluoro-3,5-dimethyladamantane **3** or 1,3-difluoro-5,7-dimethyladamanatane **4** was selectively obtained by carrying out the reaction at 10 °C or 80 °C, respectively. On the other hand, from methyl adamantan-1-carboxylate or 1-acetoxymethyladamatane, only monofluorinated product was obtained selectively even at high temperature.[9] The reaction must proceed through a carbocation intermediate generated by oxidation with IF_5. It was reported that oxidation potential of methyl adamantan-1-carboxylate and 1-acetoxymethyladamatane is comparable to that of 1-fluoroadamantane, and higher than that of adamantane itself.[10] Therefore, introduction of a fluorine atom to them raises their oxidative potentials, and makes it difficult to introduce another fluorine atom to them. Under the conditions, the products were obtained in good yield without influence on the ester group. When 2-adamantanone was used for the reaction, carbonyl group was converted to *gem*-difluoride without fluorination on *tert*-carbon and 2,2-difluoroadamantane **8** was obtained in 70% yield (Table 1).

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz), ^{19}F NMR (376 MHz), and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. IF_5 in a stainless-steel cylinder was supplied by Asahi Glass Co., Ltd. From the cylinder, IF_5 was transferred through a Teflon™ tube into a Teflon™ FEP bottle under an N_2 atmosphere. From the bottle to the reaction vessel made of Teflon ™ FEP, IF_5 was transferred quickly in open air. IF_5 decomposes in air emitting HF fume, and, therefore, it should be carefully handled in a bench hood with rubber-gloved hands.

1-Fluoroadamantane (1); Typical Procedure

Adamantane (136 mg, 1 mmol), CH_2Cl_2 (2 mL), and IF_5 (178 mg, 0.8 mmol) were introduced into the reaction vessel made of Teflon ™ FEP with a tight screw cap at 0 °C and the mixture was stirred at 0 °C for 12h. The mixture was poured into aq $NaHCO_3$ and extracted with ether (10 mL × 3). The combined organic layer was washed with aq $Na_2S_2O_3$ and dried over $MgSO_4$. The purification by column chromatography (silica gel/ hexane:ether = 10:1) gave **1** (139 mg) in 90% yield; white solid; mp 200–204 °C (sealed tube) (lit.[5a] 210–212 °C).

IR (KBr) 2910, 2855, 1353, 1071 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (brs, 3H), 1.90–1.88 (m, 6H), 1.66–1.56 (m, 6H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –129.02 to –129.07 (m, 1F) {lit.[4e] –128.95 to –129.01 (m)}.

^{13}C NMR (100MHz, $CDCl_3$) δ 92.5 (d, $^1J_{C\text{-}F}$ = 182.6 Hz), 42.7 (d, $^2J_{C\text{-}F}$ = 17.3 Hz, 3C), 35.8 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, 3C), 31.5 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, 3C).

HRMS (EI) calcd for $C_{10}H_{15}F$ 154.1158, found 154.1159.

1,3-Difluoroadamantane (2)

Adamantane (136 mg, 1 mmol), 1,2-dichloroethane (2 mL), and IF_5 (666 mg, 3 mmol) were introduced into the reaction vessel made of Teflon ™ FEP with a tight screw cap and the mixture was stirred at 75 °C for 12h. The mixture was poured into aq $NaHCO_3$ and extracted with ether (10 mL × 3). The combined organic layer was washed with aq $Na_2S_2O_3$ and dried over $MgSO_4$. The purification by column chromatography (silica gel/ hexane:ether = 10:1) gave **2** (129 mg) in 75% yield; white solid; mp 189–190 °C (sealed tube).

IR (KBr) 2947, 1352, 992 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (brs, 2H), 2.09 (t, J = 5.5 Hz, 2H), 1.84 (brs, 8H), 1.50 (brs, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –134.51 (s, 2F) {lit.[6d] –137 (brs)}.

^{13}C NMR (100MHz, $CDCl_3$) δ 93.3 (dd, $^1J_{C\text{-}F}$ = 187.9, $^3J_{C\text{-}F}$ = 13.4 Hz, 2C), 48.0 (t, $^2J_{C\text{-}F}$ = 18.9 Hz), 41.4–41.0 (m, 4C), 34.2 (t, $^4J_{C\text{-}F}$ = 2.1 Hz, 2C), 31.3 (t, $^3J_{C\text{-}F}$ = 10.3 Hz).

HRMS (EI) calcd for $C_{10}H_{14}F_2$ 172.1064, found 172.1066.

1-Fluoro-3,5-dimethyladamantane (3)

IR (neat) 2968, 1456, 1331, 1009, 912, 732cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (brs, 1H), 1.74 (brs, 2H), 1.59-1.50 (m, 4H), 1.35-1.26 (m, 4H), 1.49 (brs, 2H), 0.90 (s, 6H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –134.25 (s, 1F) {lit.[5b] –134.2 (s)}.

^{13}C NMR (100MHz, $CDCl_3$) δ 93.9 (d, $^{1}J_{C\text{-}F}$ = 183.2 Hz), 50.3 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz), 48.6 (d, $^{2}J_{C\text{-}F}$ = 16.8 Hz, 2C), 42.3 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, 2C), 41.2 (d, $^{2}J_{C\text{-}F}$ = 17.3 Hz), 34.8 (d, $^{4}J_{C\text{-}F}$ = 9.6 Hz, 2C), 31.5 (d, $^{3}J_{C\text{-}F}$ = 12.0 Hz), 29.6 (d, $^{4}J_{C\text{-}F}$ = 1.4 Hz, 2C).

1,3-Difluoro-5,7-dimethyladamanatane (**4**)

IR (neat) 2957, 1458, 1332, 1026, 987 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (t, *J* = 5.1 Hz, 2H), 1.60-1.50 (m, 8H), 1.21 (brs, 2H), 1.01 (s, 6H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –139.33 (s, 2F); ^{13}C NMR (100MHz, $CDCl_3$) δ 93.8 (dd, $^{1}J_{C\text{-}F}$ = 187.6, $^{3}J_{C\text{-}F}$ = 14.1 Hz, 2C), 49.0 (t, $^{4}J_{C\text{-}F}$ = 1.9 Hz), 47.6-47.3 (m, 4C), 46.6 (t, $^{2}J_{C\text{-}F}$ = 19.2 Hz), 35.3 (t, $^{3}J_{C\text{-}F}$ = 10.4 Hz, 2C), 28.6 (t, $^{4}J_{C\text{-}F}$ = 1.6 Hz, 2C).

HRMS (EI) calcd for $C_{12}H_{18}F_2$ 200.1377, found 200.1372.

Methyl 3-fluoroadamantane-1-carboxylate (**5**)

IR (neat) 2918, 2864, 1731, 1254, 1230 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.34 (brs, 2H), 2.03 (d, *J* = 5.7 Hz, 2H), 1.88–1.77 (m, 8H), 1.61–1.58 (m, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –132.97 (s, 1F).

^{13}C NMR (100MHz, $CDCl_3$) δ 176.2 (d, $^{4}J_{C\text{-}F}$ = 2.3 Hz), 92.1 (d, $^{1}J_{C\text{-}F}$ = 183.8 Hz), 51.8, 44.8 (d, $^{3}J_{C\text{-}F}$ = 10.2 Hz), 43.6 (d, $^{2}J_{C\text{-}F}$ = 19.8 Hz), 41.8 (d, $^{2}J_{C\text{-}F}$ = 17.7 Hz, 2C), 37.5 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, 2C), 34.7 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 30.8 (d, $^{3}J_{C\text{-}F}$ = 10.0 Hz, 2C).

HRMS (EI) calcd for $C_{12}H_{17}FO_2$ 212.1213, found 212.1199.

1-(Acetoxymethyl)-3-fluoroadamantane (**6**)

IR (neat) 2916, 1743, 1245, 1038 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 2H), 2.32 (brs, 2H), 2.07 (s, 3H), 1.86 (brs, 4H), 1.70 (d, *J* = 5.8 Hz, 2H), 1.59–1.56 (m, 2H), 1.47 (brs, 4H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –132.64 (s, 1F).

^{13}C NMR (100MHz, $CDCl_3$) δ 171.1, 92.6 (d, $^{1}J_{C\text{-}F}$ = 183.8 Hz), 72.4 (d, $^{4}J_{C\text{-}F}$ = 1.4 Hz), 44.2 (d, $^{2}J_{C\text{-}F}$ = 18.4 Hz), 42.1 (d, $^{2}J_{C\text{-}F}$ = 17.4 Hz, 2C), 37.9 (d, $^{3}J_{C\text{-}F}$ = 10.1 Hz), 37.8 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz, 2C), 35.2 (d, $^{4}J_{C\text{-}F}$ = 2.1 Hz), 30.8 (d, $^{3}J_{C\text{-}F}$ = 10.1 Hz, 2C), 20.8.

HRMS (EI) calcd for $C_{13}H_{19}FO_2$ 226.1369, found 226.1361.

Methyl 3-fluoro-5-methyladamantane-1-carboxylate (**7**)

IR (neat) 2949, 1734, 1260, 1228, 1009 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.38-2.35 (m, 1H), 1.96 (brs, 2H), 1.81-1.79 (m, 2H), 1.72 (brs, 2H), 1.61 (d, *J* = 5.7 Hz, 2H), 1.56 (brs, 2H), 1.38 (brs, 2H), 0.95 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –135.38 (s, 1F).

^{13}C NMR (100MHz, $CDCl_3$) δ 176.2 (d, $^{5}J_{C\text{-}F}$ = 2.4 Hz), 92.9 (d, $^{1}J_{C\text{-}F}$ = 184.4 Hz), 51.9, 48.5 (d, $^{2}J_{C\text{-}F}$ = 16.8 Hz), 45.2 (d, $^{3}J_{C\text{-}F}$ = 10.5 Hz), 44.5 (d, $^{4}J_{C\text{-}F}$ = 1.9 Hz), 43.0 (d, $^{2}J_{C\text{-}F}$ = 20.1 Hz), 41.9 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 41.0 (d, $^{3}J_{C\text{-}F}$ = 17.5 Hz), 36.9 (d, $^{2}J_{C\text{-}F}$ = 1.9 Hz), 34.4 (d, $^{2}J_{C\text{-}F}$ = 10.1 Hz), 30.9 (d, $^{2}J_{C\text{-}F}$ = 10.1 Hz), 29.5 (d, $^{2}J_{C\text{-}F}$ = 1.2 Hz).

HRMS (EI) calcd for $C_{13}H_{19}FO_2$ 226.1369, found 226.1366

2,2-Difluoroadaimantane (**8**)

white solid; mp 104-105 °C (lit.[11] 106 °C).

IR (KBr) 2918, 1638, 1121, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (brs, 2H), 1.97-1.72 (m, 12H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –100.30 (s, 2F) {lit.[12] –100.23 (s)}.

^{13}C NMR (100MHz, $CDCl_3$) δ 125.5 (t, $^1J_{C\text{-}F}$ = 246.8 Hz), 36.6 (t, $^4J_{C\text{-}F}$ = 1.4Hz, 2C), 35.9 (t, $^2J_{C\text{-}F}$ = 21.0 Hz, 2C), 34.0 ($^3J_{C\text{-}F}$ = 4.1 Hz, 4C), 26.4 ($^5J_{C\text{-}F}$ = 0.9 Hz).

Acknowledgment

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(8) More than one fluorine atom of IF_5 is used and one equiv of IF_5 is not necessary for the fluorination.[7a]
(9) Even at 75 °C, difluorinated product of methyl adamantan-1-carboxylate or 1-acetoxymethyladamatane was not obtained.
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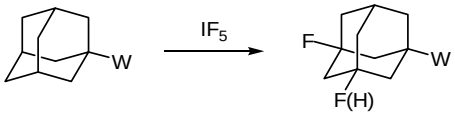
Direct Fluorination of Adamantanes with IF_5



W = H, Me, COOMe, CH_2OAc