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, 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, preparation of fluorine derivatives has attracted the attention of organic and medicinal chemists. Fluorination of adamantanes has been carried out through the deoxyfluorination of adamantanol, halogen exchange reaction from other haloadamantanes, or direct fluorination of the adamantane itself. 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.

Recently we found that IF$_5$ is an effective reagent to introduce fluorine atoms into organosulfur compounds. 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. 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,
from 1,3-dimethyladamantane, 1-fluoro-3,5-dimethyladamantane 3 or 1,3-difluoro-5,7-dimethyladamantan 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-acetoxymethyladamantane, only mono-fluorinated product was obtained selectively even at high temperature.\(^9\) The reaction must proceed through a carboxylation intermediate generated by oxidation with IF\(_5\). It was reported that oxidation potential of methyl adamantan-1-carboxylate and 1-acetoxymethyladamantane is comparable to that of 1-fluoroadamantane, and higher than that of adamantane itself.\(^9\) 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, \(\delta\), 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\(\textsuperscript{FEP}\) bottle under an N\(_2\) atmosphere. From the bottle to the reaction vessel made of Teflon\(\textsuperscript{FEP}\), 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\(_2\)Cl\(_2\) (2 mL), and IF\(_5\) (178 mg, 0.8 mmol) were introduced into the reaction vessel made of Teflon\(\textsuperscript{FEP}\) with a tight screw cap and the mixture was stirred at 0 °C for 12h. The mixture was poured into aq NaHCO\(_3\) and extracted with ether (10 mL \(\times\) 3). The combined organic layer was washed with aq Na\(_2\)S\(_2\)O\(_3\) 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) \((\text{lit}^{5a} 210–212 \text{ °C})\).

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

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.23 (brs, 3H), 1.90–1.88 (m, 6H), 1.66–1.56 (m, 6H).

\(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –129.02 to –129.07 (m, 1F) \({\text{lit.}^{6e} –128.95 \text{ to } –129.01 \text{ (m)}}\).  

\(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 156.1 (d, \(^1\)J\(_{C,F}\) = 182.6 Hz), 13.7 (d, \(^2\)J\(_{C,F}\) = 17.3 Hz, 3C), 37.8 (d, \(^4\)J\(_{C,F}\) = 2.7 Hz, 3C), 31.5 (d, \(^3\)J\(_{C,F}\) = 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\(\textsuperscript{FEP}\) 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 \(\times\) 3). The combined organic layer was washed with aq Na\(_2\)S\(_2\)O\(_3\) 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\(_3\)) \(\delta\) 2.44 (brs, 2H), 2.09 (t, \(J = 5.5 \text{ Hz}, 2\)H), 1.84 (brs, 8H), 1.50 (brs, 2H).

\(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –134.51 (s, 2F) \({\text{lit.} 6d –137 \text{ (brs)}}\).  

\(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 93.3 (dd, \(^1\)J\(_{C,F}\) = 187.9, 3\)J\(_{C,F}\) = 13.4 Hz, 2C), 48.0 (t, \(^2\)J\(_{C,F}\) = 18.9 Hz), 41.4–41.0 (m, 4C), 34.2 (t, \(^4\)J\(_{C,F}\) = 2.1 Hz, 2C), 31.3 (t, \(^3\)J\(_{C,F}\) = 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\(^{-1}\).
1H NMR (400 MHz, CDCl3) 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).

19F NMR (376 MHz, CDCl3) δ −134.25 (s, 1F) {lit.5b – 134.2 (s)}.

13C NMR (100MHz, CDCl3) δ 93.9 (d, $J_{CF} = 183.2$ Hz), 50.3 (d, $J_{CF} = 1.9$ Hz), 48.6 (d, $J_{CF} = 16.8$ Hz, 2C), 42.3 (d, $J_{CF} = 1.9$ Hz, 2C), 41.2 (d, $J_{CF} = 17.3$ Hz), 34.8 (d, $J_{CF} = 12.0$ Hz), 29.6 (d, $J_{CF} = 1.4$ Hz, 2C).

1,3-Difluoro-5,7-dimethyladamantane (4)

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

1H NMR (400 MHz, CDCl3) δ 1.99 (t, $J = 5.1$ Hz, 2H), 1.60–1.50 (m, 8H), 1.21 (brs, 2H), 1.01 (s, 6H).

19F NMR (376 MHz, CDCl3) δ −139.33 (s, 2F); 13C NMR (100MHz, CDCl3) δ 93.8 (dd, $J_{CF} = 187.6, 3J_{CF} = 14.1$ Hz, 2C), 49.0 (t, $J_{CF} = 1.9$ Hz), 47.6–47.3 (m, 4C), 46.6 (t, $J_{CF} = 19.2$ Hz), 35.3 (t, $J_{CF} = 10.4$ Hz, 2C), 28.6 (t, $J_{CF} = 1.6$ Hz, 2C).

HRMS (EI) calcd for C12H18F2 200.1377, found 200.1372.

Methyl 3-fluoroadamantane-1-carboxylate (5)

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

1H NMR (400 MHz, CDCl3) δ 3.68 (s, 3H), 2.34-2.35 (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).

19F NMR (376 MHz, CDCl3) δ −135.38 (s, 1F).

13C NMR (100MHz, CDCl3) δ 176.2 (d, $J_{CF} = 2.4$ Hz), 92.9 (d, $J_{CF} = 184.4$ Hz), 51.9, 48.5 (d, $J_{CF} = 16.8$ Hz), 45.2 (d, $J_{CF} = 10.5$ Hz), 44.5 (d, $J_{CF} = 1.9$ Hz), 43.0 (d, $J_{CF} = 20.1$ Hz), 41.5 (d, $J_{CF} = 2.2$ Hz), 41.0 (d, $J_{CF} = 17.5$ Hz), 36.9 (d, $J_{CF} = 1.9$ Hz), 34.4 (d, $J_{CF} = 10.1$ Hz), 30.9 (d, $J_{CF} = 10.1$ Hz), 29.5 (d, $J_{CF} = 1.2$ Hz).

HRMS (EI) calcd for C13H19FO2 226.1369, found 226.1366.

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

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

1H NMR (400 MHz, CDCl3) 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).

19F NMR (376 MHz, CDCl3) δ −132.64 (s, 1F).

13C NMR (100MHz, CDCl3) δ 171.1, 92.6 (d, $J_{CF} = 183.8$ Hz), 72.4 (d, $J_{CF} = 1.4$ Hz), 44.2 (d, $J_{CF} = 18.4$ Hz), 42.1 (d, $J_{CF} = 17.4$ Hz, 2C), 37.9 (d, $J_{CF} = 10.1$ Hz), 37.8 (d, $J_{CF} = 1.9$ Hz, 2C), 35.2 (d, $J_{CF} = 2.1$ Hz), 30.8 (d, $J_{CF} = 10.1$ Hz, 2C), 20.8.

HRMS (EI) calcd for C13H19FO2 226.1369, found 226.1361.

2,2-Difluoroadamantane (8)

white solid; mp 104-105 °C {lit.11 106 °C}.

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

1H NMR (400 MHz, CDCl3) δ 2.17 (brs, 2H), 1.97-1.72 (m, 12H).

HRMS (EI) calcd for C13H19FO2 226.1366, found 226.1366.

1-(Acetoxymethyl)-3-fluoroadamantane (6)
\[^{13}\text{C}\text{ NMR (100MHz, CDCl}_3\text{)}\ \delta\ 125.5\ (t, \ {^1J_{CF} = 246.8}\text{ Hz}),\ 36.6\ (t, \ {^4J_{CF} = 1.4}\text{Hz, 2C}),\ 35.9\ (t, \ {^2J_{CF} = 21.0}\text{ Hz},\ 2C),\ 34.0\ (t, \ {^3J_{CF} = 4.1}\text{Hz, 4C},\ 26.4\ (t, \ {^5J_{CF} = 0.9}\text{Hz}).\]

**Acknowledgment**

We are grateful to Asahi Glass Co., Ltd. for their gift of IF\(_5\).

**References**


Direct Fluorination of Adamantanes with IF$_5$

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\begin{align*}
\text{W} & \quad \xrightarrow{\text{IF}_5} \quad \text{F(H)} \\
\text{W} &= \text{H, Me, COOMe, CH$_2$OAc}
\end{align*}
\]