Direct Fluorination of Adamantanes with IF$_5$

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Received: The date will be inserted once the manuscript is accepted.

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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, 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 adamantanols, 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. Therefore, a new selective method for the direct fluorination of the adamantanes has been desired.

\[ W = H, \text{Me, COOMe, CH}_2\text{OAc} \]

Equation 1

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-dimethyladamantane 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. The reaction must proceed through a carbocation intermediate generated by oxidation with IF₅. 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. Therefore, introduction of a fluorine atom to them raises their oxidative potentials, and makes it difficult to introduce another fluorine atom to them. 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 ¹H NMR (400 MHz), ¹⁹F NMR (376 MHz), and ¹³C NMR (100 MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (¹H, ¹³C) and CFCl₃ (¹⁹F), respectively. IF₅ in a stainless-steel cylinder was supplied by Asahi Glass Co., Ltd. From the cylinder, IF₅ was transferred through a Teflon™ tube into a Teflon™ FEP bottle under an N₂ atmosphere. From the bottle to the reaction vessel made of Teflon™ FEP, IF₅ was transferred quickly in open air. IF₅ 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), CH₂Cl₂ (2 mL), and IF₅ (178 mg, 0.8 mmol) were introduced into the reaction vessel made of Teflon™ FEP with a tight screw cap and the mixture was stirred at 0 °C for 12h. The mixture was poured into aq NaHCO₃ and extracted with ether (10 mL × 3). The combined organic layer was washed with aq Na₂S₂O₃ and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃) δ 2.23 (brs, 3H), 1.90–1.88 (m, 6H), 1.66–1.56 (m, 6H).

¹⁹F NMR (376 MHz, CDCl₃) δ –129.02 to –129.07 (m, 1F) {lit. 4e –128.95 to –129.01 (m)}.

¹³C NMR (100MHz, CDCl₃) δ 92.5 (d, ¹JC-F = 182.6 Hz), 42.7 (d, ²JC-F = 17.3 Hz, 3C), 35.8 (d, ⁴JC-F = 2.7 Hz, 3C), 31.5 (d, ³JC-F = 9.3 Hz, 3C).

HRMS (EI) calcd for C₁₀H₁₅F 154.1158, found 154.1159.

1,3-Difluoroadamantane (2)

Adamantane (136 mg, 1 mmol), 1,2-dichloroethane (2 mL), and IF₅ (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 NaHCO₃ and extracted with ether (10 mL × 3). The combined organic layer was washed with aq Na₂S₂O₃ and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃) δ 2.44 (brs, 2H), 2.09 (t, J = 5.5 Hz, 2H), 1.84 (brs, 8H), 1.50 (brs, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ –134.51 (s, 2F) {lit. 6d –137 (brs)}.

¹³C NMR (100MHz, CDCl₃) δ 93.3 (dd, ¹JC-F = 187.9, ³JC-F = 13.4 Hz, 2C), 48.0 (t, ²JC-F = 18.9 Hz), 41.4–41.0 (m, 4C), 34.2 (t, ⁴JC-F = 2.1 Hz, 2C), 31.3 (t, ³JC-F = 10.3 Hz).

HRMS (EI) calcd for C₁₀H₁₄F₂ 172.1064, found 172.1066.

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

IR (neat) 2968, 1456, 1331, 1009, 912, 732 cm⁻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) {lit5b – 134.2 (s)}.

13C NMR (100MHz, CDCl3) δ 93.9 (d, 1JC,F = 183.2 Hz), 50.3 (d, 4JC,F = 1.9 Hz), 48.6 (d, 2JC,F = 16.8 Hz, 2C), 42.3 (d, 4JC,F = 1.9 Hz, 2C), 41.2 (d, 2JC,F = 17.3 Hz), 34.8 (d, 4JC,F = 9.6 Hz, 2C), 31.5 (d, 1JC,F = 12.0 Hz), 29.6 (d, 4JC,F = 1.4 Hz, 2C).

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

IR (neat) 2957, 1458, 1332, 1026, 987 cm⁻¹.

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

IR (neat) 2949, 1734, 1260, 1228, 1009 cm⁻¹.

IR (neat) 2918, 1731, 1254, 1230 cm⁻¹.

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

IR (neat) 2918, 2864, 1731, 1254, 1230 cm⁻¹.

IR (neat) 2918, 1731, 1254, 1230 cm⁻¹.

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

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).

1H NMR (400 MHz, CDCl3) δ 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).

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

IR (KBr) 2918, 1638, 1121, 1030 cm⁻¹.

HRMS (EI) calced for C13H19FO2 226.1366, found 226.1366

2,2-Difluoroadamantane (8)

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

IR (KBr) 2918, 1638, 1121, 1030 cm⁻¹.

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

**Methyl 3-fluoroadamantane-1-carboxylate (7)**

IR (neat) 2949, 1734, 1260, 1228, 1009 cm⁻¹.

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

HRMS (EI) calced for C13H19FO2 226.1377, found 226.1372.
$^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 125.5 (t, $^1 J_{C-F} = 246.8$ Hz), 36.6 (t, $^4 J_{C-F} = 1.4$Hz, 2C), 35.9 (t, $^2 J_{C-F} = 21.0$ Hz, 2C), 34.0 ($^3 J_{C-F} = 4.1$ Hz, 4C), 26.4 ($^5 J_{C-F} = 0.9$ Hz).

Acknowledgment
We are grateful to Asahi Glass Co., Ltd. for their gift of IF$_5$.

References
(8) More than one fluorine atom of IF$_5$ is used and one equiv of IF$_5$ is not necessary for the fluorination.
(9) Even at 75 °C, difluorinated product of methyl adamantane-1-carboxylate or 1-acetoxymethyladamantane was not obtained.
Direct Fluorination of Adamantanes with IF₅

W = H, Me, COOMe, CH₂OAc