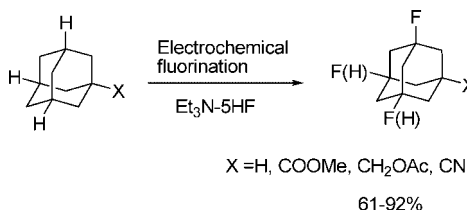# Selective Fluorination of Adamantanes by an Electrochemical Method

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Received March 9, 2008

X =H, COOMe, CH₂OAc, CN

61-92%

Selective fluorination of adamantanes was achieved by the electrochemical fluorination method, using Et_3N-5HF as electrolyte and a fluorine source. Mono-, di-, tri-, and tetrafluoroadamantanes were selectively prepared from adamantanes by controlling the oxidation potential, and the fluorine atoms were introduced selectively at the tertiary carbons. Adamantanes that have functional groups such as ester, cyano, and acetoxymethyl were also fluorinated selectively.

Introduction

Adamantane ($C_{10}H_{16}$) is a simple tricyclic cage compound consisting of only two kinds of carbons: four tertiary carbons and six secondary 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 the 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 generally 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, the fluorinated analogues of the aminoadamantane were synthesized via the deoxyfluorination reaction from the corresponding hydroxy compounds,[3b,c] which is a more reliable and safer way than the direct method, although it requires a multistep process. Recently, an electrochemical fluorination reaction with Et_3N-5HF as a fluorine source and an electrolyte has been developed as a useful method for the partial fluorination of organic compounds.[7] There are three advantages of using the electrochemical fluorination method with Et_3N-5HF. (1) The oxidation potential can be controlled precisely by using

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TABLE 1. Electrochemical Fluorination of Adamantane[a]

entry	applied potential (V vs Ag/Ag$^+$)	electricity (F/mol)	temp (°C)	solvent (Et$_3$N−5HF:CH$_2$Cl$_2$)	yield of products (%)[b]			
					2	3	4	5
1[c]	2.30	2.2	35	2:1	74	(2)		
2	2.30	2.5	35	2:1	67	15		
3	2.50	4.4	35	1:1	(2)	79	(1)	
4[d]	2.70	11.0	35	5:1		(6)	49	(2)
5[e]	2.70	14.0	45	1:0		(6)	61	
6[f]	3.00	60.0	35	1:0				41

[a] If otherwise not mentioned, the reaction was carried out with 1 mmol of substrate in 12 mL of solvent. [b] Isolated yield based on substrate used. In parentheses, GC yield. [c] 4% of **1** remained. [d] Chlorinated product was also formed (5%). [e] The reaction was carried out with a solution of 0.5 mmol of **1** in 12 mL of Et$_3$N−5HF. [f] **4** was used as the starting material.

electrochemistry, and only the desired reaction occurs selectively. (2) Et$_3$N−5HF is less acidic than HF, and many organic compounds are soluble in it. Therefore, the method can be used for the fluorination of various organic compounds. (3) Et$_3$N−5HF is stable under oxidation conditions up to ~2.8 V and the method can be used for the fluorination of substrates that are difficult to oxidize.[7d] Therefore, we used the electrochemical fluorination with Et$_3$N−5HF for the direct fluorination of various adamantanes.

Results and Discussion

Oxidation Potential of Adamantane. The oxidation potentials of the adamantane (**1**) and 1-fluoroadamantane (**2**) were reported to be 2.35 and 2.50 V, respectively, vs Ag/Ag$^+$ in CH$_3$CN,[8] and the oxidation occurs selectively at the tertiary carbons. When the oxidation potential of the adamantane (**1**) was measured by cyclic voltammetry with a Pt wire electrode in Et$_3$N−5HF, three peaks appeared at 2.30, 2.50, and 2.70 V vs Ag/Ag$^+$ as shown in Figure 1. Two of them correspond to the reported potential values of **1** and **2**, and therefore, mono- and difluorination of **1** must occur at 2.30 and 2.50 V in Et$_3$N−5HF, respectively. Trifluorination of **1** can be expected to occur at 2.70 V from the observed oxidation potential value. On the other hand, a distinct peak corresponding to the tetrafluorination of **1** did not appear in the cyclic voltammetry, which indicates that a higher potential than 2.80 V will be required for the tetrafluorination.

Anodic Fluorination of the Adamantane. As **1** is only slightly soluble in neat Et$_3$N−5HF at room temperature, the fluorination reaction of **1** was carried out in a 2:1 mixture of
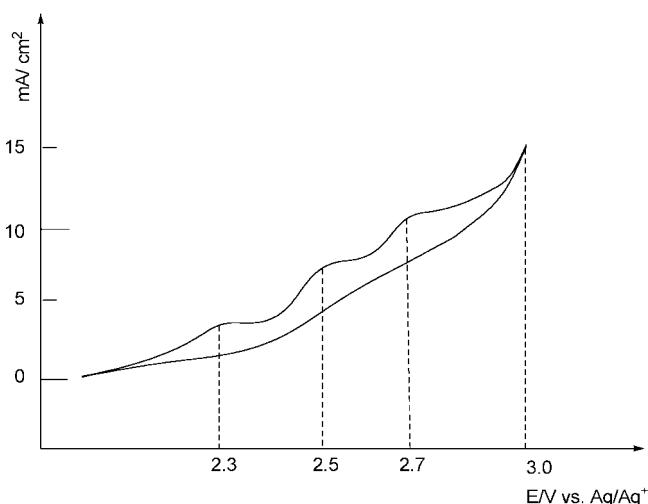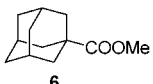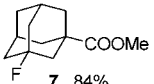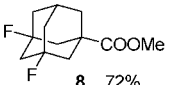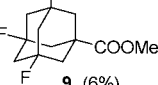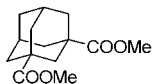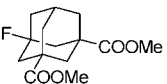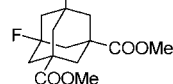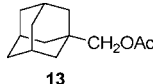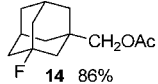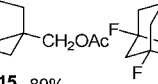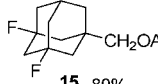

FIGURE 1. Cyclic voltammograms for the oxidation of adamantane (0.04 M) in Et$_3$N−5HF: working, 1 mm × 10 mm Pt, counter, 20 mm × 20 mm Pt; scan rate 50 mv/s.

Et$_3$N−5HF and CH$_2$Cl$_2$ (0.08 M) at 35 °C. When the electrolysis of **1** was carried out at 2.30 V until 2.2 F/mol of electricity had passed, monofluorination occurred selectively at the tertiary carbon to form 1-fluoroadamantane (**2**) in 74% yield with 2% of 1,3-difluoroadamantane (**3**) (entry 1 in Table 1). Under these conditions, 4% of **1** remained unchanged. However, when the electrolysis was continued until the complete consumption of **1** (2.5 F/mol), the yield of **2** decreased to 67%, and the yield of **3** increased to 15% (entry 2). Difluorinated product **3** could be prepared selectively by carrying out the electrolysis at 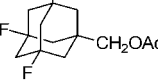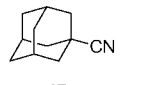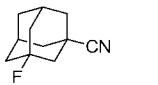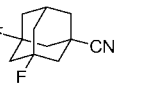2.50 V until 4.4 F/mol of electricity had passed. Under these conditions, **3** could be obtained in 79% yield with 2% of **2**, which is separable from **3** by silica gel column chromatography. When the electrolysis of **1** was carried out at 2.70 V to obtain 1,3,5-trifluoroadamantane (**4**), a large excess of electricity was required to complete the reaction (11.0 F/mol), and **4** was obtained in a moderate yield (entry 4). At this potential, a chlorinated byproduct was formed by the chloride ion generated from CH$_2$Cl$_2$. Therefore, in the preparation of **4**, CH$_2$Cl$_2$ could not be used as the cosolvent, and the reaction was carried out in neat Et$_3$N−5HF. To dissolve **1** in neat Et$_3$N−5HF, the reaction was carried out at a higher temperature (45 °C) in a lower concentration (0.04 M). Under these conditions, the yield of **4** increased to 61%, although a large excess of electricity was still required (14.0 F/mol) (entry 5). Under the same

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TABLE 2. Electrochemical Fluorination of Functionalized Adamantanes[a]

Entry	Substrate	Applied potential (V vs. Ag/Ag+)	Electricity (F/mol)	Yield of products[b]
1	6	2.45	2.8	7 84%
2	6	2.60	6.6	8 72% 9 (6%)
3	6	2.90	10.3	9 92%
4	10	2.53	3.1	11 76% 12 (5%)
5	10	2.80	6.4	12 86%
6	13	2.45	2.6	14 86%
7	13	2.70	5.2	14 6% 15 80% 16 (5%)
8	17	2.70	3.6	18 80% 19 (7%)

[a] The reaction was carried out with 1 mmol of substrate in 12 mL of $Et_3N–5HF$ at room temperature. [b] Isolated yield based on substrate used. In parenthese, GC yield.

conditions, the oxidation of $Et_3N–5HF$ also occurred competitively, causing the low current efficiency of the reaction. The preparation of 1,3,5,7-tetrafluoroadamantane (**5**) is more difficult because the reaction must be carried out at a higher potential. When the electrolysis of **1** was carried out at 3.0 V, the reaction mixture turned dark brown, and **5** was obtained only in low yield with the formation of insoluble solid materials. Therefore, we adopted trifluoroadamantane **4** as the starting material for **5**, which is more soluble than **1** in neat $Et_3N–5HF$. Then, the reaction could be carried out at a lower temperature (35 °C). Under these conditions, **5** could be obtained in 41% yield, although a large excess of electricity was required (60 F/mol) (entry 6).

Fluorination of Functionalized Adamantanes. The electrochemical fluorination of functionalized adamantanes, methyl adamantane-1-carboxylate (**6**), dimethyl adamantane-1,3-dicarboxylate (**10**), 1-(acetoxymethyl)adamantane (**13**), and adamantane-1-carbonitrile (**17**), was attempted. They are more soluble in $Et_3N–5HF$ than **1**, and the reactions could be carried out in neat $Et_3N–5HF$ at room temperature. Methyl adamantane-1-carboxylate **6** exhibited three anodic peaks at 2.45, 2.60, and 2.90 V vs Ag/Ag+ in its cyclic voltammogram.[9] When the electrolysis of **6** was carried out at 2.45 V until 2.8 F/mol of

electricity had passed, the monofluorination of **6** occurred selectively to produce methyl 3-fluoroadamantane-1-carboxylate (**7**) in 84% yield (entry 1 in Table 2). A difluorinated product, methyl 3,5-difluoroadamantan-1-carboxylate (**8**), was obtained in 72% yield with 6% of a trifluorinated product (**9**) by carrying out the electrolysis at 2.60 V (6.6 F/mol of electricity) (entry 2). For the selective preparation of the trifluorinated product **9**, although the reaction was carried out at a high oxidation potential (2.90 V), **9** could be selectively obtained in 92% yield (entry 3). The trifluorinated product **9** was prepared previously from methyl 3-hydroxyadamantane-1-carboxylate in nine steps in low overall yield and used for the synthesis of 3,5,7-trifluoro-1-aminoadamantane (trifluoroamantadine) as a key intermediate.[3b] In our method, **9** can be directly prepared from **6** in high yield. Similarly, from dimethyl adamantane-1,3-dicarboxylate **10**, a monofluorinated product (**11**) and a difluorinated product (**12**) were obtained selectively in 76% and 86% yield, respectively, by carrying out the reaction at 2.53 and 2.80 V (entries 4 and 5). The monofluorination of 1-(acetoxymethyl)-adamantane **13** occurred at 2.45 V to produce 1-(acetoxymethyl)-3-fluoroadamantane (**14**) in 86% yield (entry 6). The difluorination of **13** occurred at 2.70 V, and a difluorinated product (**15**) was obtained in 80% yield with 6% of **14** and 5% of a trifluorinated product (**16**) (entry 7). The fluorination of

(9) Koch, V. R.; Miller, L. L. *J. Am. Chem. Soc.* **1973**, *95*, 8631.

adamantane-1-carbonitrile **17** was carried out at 2.70 V to produce a monofluorinated product (**18**) in 80% yield with 7% of a difluorinated product (**19**) (entry 8). Thus, the electrochemical fluorination of the adamantanes possessing the functional groups such as ester, cyano, and acetoxymethyl groups proceeded selectively without influencing the functional groups. On the other hand, the fluorination of the heteroatom-substituted adamantanes, such as 1-adamantanol, 1-aminoadamantane, 1-(acetoxyamino)adamantane, and 1-bromoadamantane, was unsuccessful, and the carbon–heteroatom bond was cleaved to produce the 1-fluoroadamantane **2** instead of the expected functionalized fluoroadamantanes.[9]

Summary

We succeeded in the selective fluorination of adamantanes by use of the electrochemical fluorination method with Et$_3$N–5HF as an electrolyte and a fluorine source. The selective introduction of 1–3 fluorine atoms into the adamantanes was achieved by carrying out the reaction under the control of the oxidation potential, and the fluorine atoms were introduced selectively into the tertiary carbons of adamantanes. Functional groups, such as ester, cyano, and acetoxy, can tolerate the reaction conditions, and 1–3 fluorine atoms could be selectively introduced into the functionalized adamantanes.

Experimental Section

Preparation of 1-Fluoroadamantane (2). Adamantane (136 mg, 1 mmol) was dissolved in a mixture of Et$_3$N–5HF (8 mL) and CH$_2$Cl$_2$ (4 mL) and introduced into an undivided cell made of Teflon PFA (20 mL). The electrolysis was carried out at 35 °C with use of two smooth Pt sheets (20 mm × 20 mm) for the anode and cathode at 2.30 V (vs Ag/Ag$^+$)[7d] until 2.2 F/mol of electricity had passed. Then, the reaction mixture was poured into water and extracted with CH$_2$Cl$_2$ three times. The combined organic layers were washed with aq NaHCO$_3$ and dried over MgSO$_4$. GC analysis showed the adamantane **1**, 1-fluoroadamantane (**2**), and 1,3-difluoroadamantane (**3**) were present in a ratio of 5:92.5:2.5 in the reaction mixture.[10] Purification by column chromatography (silica gel/hexane–ether) gave **2** (114 mg, 0.74 mmol) in 74% yield: mp 200–204 °C (sealed tube) (lit.[5a] mp 210–212 °C); IR (KBr) 2910, 2855, 1353, 1071 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.23 (br s, 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 (100 MHz, CDCl$_3$) δ 92.5 (d, $^1J_{C-F}$ = 182.6 Hz), 42.7 (d, $^2J_{C-F}$ = 17.3 Hz, 3C), 35.8 (d, $^4J_{C-F}$ = 2.7 Hz, 3C), 31.5 (d, $^3J_{C-F}$ = 9.3 Hz, 3C); HRMS (EI) calcd for C$_{10}$H$_{15}$F 154.1158, found 154.1159.

Preparation of Methyl 3-Fluoroadamantane-1-carboxylate (7). The reaction was carried out as in the case of **4** except that the electrolysis was carried out with **6** (194 mg, 1 mmol) at room temperature in Et$_3$N–5HF (12 mL) at 2.45 V (vs Ag/Ag$^+$)[7d] until 2.8 F/mol of electricity had passed. Methyl 3-fluoroadamantane-1-carboxylate (**7**) was obtained in 84% yield (purification by column chromatography; silica gel/hexane–CH$_2$Cl$_2$): IR (neat) 2918, 2864, 1731, 1254, 1230 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.68 (s, 3H), 2.34 (br s, 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 (100 MHz, CDCl$_3$) δ 176.2 (d, $^4J_{C-F}$ = 2.3 Hz), 92.1 (d, $^1J_{C-F}$ = 183.8 Hz), 51.8, 44.8 (d, $^3J_{C-F}$ = 10.2 Hz), 43.6 (d, $^2J_{C-F}$ = 19.8 Hz), 41.8 (d, $^2J_{C-F}$ = 17.7 Hz, 2C), 37.5 (d, $^4J_{C-F}$ = 1.9 Hz, 2C), 34.7 (d, $^4J_{C-F}$ = 2.2 Hz), 30.8 (d, $^3J_{C-F}$ = 10.0 Hz, 2C); HRMS (EI) calcd for C$_{12}$H$_{17}$O$_2$F 212.1213, found 212.1199.

Supporting Information Available: General methods and procedures for the preparation of fluoroadamantanes; ^{1}H and ^{13}C NMR spectra of all fluoroadamantane products. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) A capillary column (25 m × 0.20 mm) of 100% polydimethylsiloxane was used.