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Electrochemical synthesis of methyl-3,5,7-trifluoroadamantane-1-carboxylate under recycling use of ionic liquid media

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ABSTRACT

Methyl-3,5,7-trifluoroadamantane-1-carboxylate, a key intermediate for the synthesis of 1-amino-3,5,7-trifluoroadamantane (trifluoroamantadine), was synthesized by the electrochemical fluorination of methyl adamantane-1-caroxylate in pyridine–5HF under constant current conditions. After the reaction, the product was extracted from pyridine–5HF by hexane–CH_2Cl_2, and recovered pyridine–5HF was used repeatedly.

1. Introduction

Adamantane is a simple cage compound consisting of four *tert*-carbons and six *sec*-carbons. Bioactive derivatives of adamantane are known, and namely, 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) are used medicinally [1]. The 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. Previously, a Pfizer group reported the synthesis of 1-amino-3,5,7-trifluoroadamantane, (trifluoroamantadine) from methyl 3-hydroxyadamantane-1-carboxylate [2]. However, their process involved multi step operations and the overall yield was poor. Therefore, a more effective method is desired. Recently, we reported that methyl-3,5,7-trifluoroadamantane-1-carboxylate **2**, a precursor for 1-amino-3,5,7-trifluoroadamantane, can be synthesized directly from methyl adamantane-1-carboxylate **1** in high yield by using the electrochemical fluorination method [3]. However, in this method, the fluorination reaction was performed under high and constant potential conditions, and an expensive amine–HF complex was used as a solvent, as well as a fluorine source and a supporting electrode. For the bulk and economical synthesis of **2**, the fluorination reaction under constant current conditions is preferred and recycling of the solvent is required. Therefore, the electrochemical synthesis of **2** under constant current conditions and the recycling use of the amine–HF complex were examined.

2. Results and discussion

Initially, the electrochemical fluorination of **1** was performed using an undivided cell in Et_3N–5HF and pyridine–5HF, which are typical amine–HF complexes, under constant current conditions (19 mA/cm^2) until 11 F/mol of electricity had passed [4]. The desired product **2** was obtained in pyridine–5HF as well as in Et_3N–5HF in reasonable yield with a minor amount of methyl-3,5-difluoroadamantane-1-carboxylate **3** as shown in Table 1.

Amine–HF complexes are known to have an ionic-liquid character, and the products in them can be extracted by an appropriate organic solvent without aqueous work-up and neutralization [6]. Therefore, the extraction of **2** from the amine–HF complexes using diethyl ether, CH_2Cl_2, diethyl ether–hexane (1:1), and CH_2Cl_2–hexane (1:1) was examined. Et_3N–5HF was well or partially miscible with all solvents and solvent systems used, and an adequate solvent for the extraction could not be found [7]. On the other hand, pyridine–5HF was also miscible with diethyl ether, CH_2Cl_2, and diethyl ether–hexane, but was immiscible with CH_2Cl_2–hexane. Therefore, the application of pyridine–5HF to the reaction media and the use of CH_2Cl_2–hexane as the extraction solvent were found to be suitable for the present purpose, i.e., recycling use of the reaction media.

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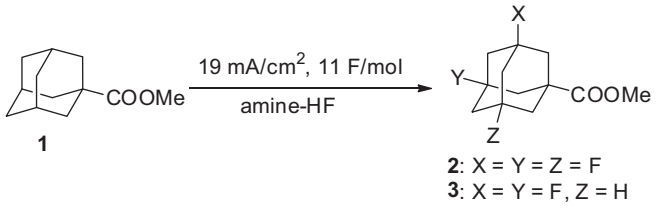
Table 1
Electrochemical fluorination of adamantane-1-carboxylate **1** under constant current conditions in amine–HF complexes.



Entry	Solvent	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	Et_3N–5HF	74	6
2	Pyridine–5HF	70	24

[a] ^{19}FNMR yield based on **1**.

The optimal conditions for the synthesis of **2** by the electrochemical fluorination of **1** in pyridine–5HF under constant current conditions were then examined. The reaction was performed using 2 mmol of **1** in 20 mL of pyridine–5HF at room temperature. When the current density was changed from 19 to 30 mA/cm^2 under constant electricity (11 F/mol) (entries 1–3 in Table 2), **2** was obtained in the highest yield at a current density of 25 mA/cm^2 (entry 3). Finally, the best result was obtained when the reaction was carried out at a current density of 25 mA/cm^2 and 18 F/mol of electricity had passed. Under these conditions, **2** was formed in 87% yield and **3** was not formed (entry 5).

After the reaction, **2** was extracted with CH_2Cl_2/hexane (1:1) and the separated solvent was analyzed by GC. The extraction was repeated until no product was found in the extracted solvent. Recovered pyridine–5HF was washed twice with hexane to remove trace amounts of CH_2Cl_2 [8]. This recovered pyridine–5HF was used repeatedly, and until the third run, **2** was formed in higher than 80% as shown Table 3. However, from the fourth run, the yield decreased to less than 80%. After the fifth run, HF concentration in the complex was measured by titration and was found to have decreased from 83 mol% (pyridine–5HF) to 80 mol% (pyridine–3.9HF). This decrease in HF concentration was due to the consumption of HF in the complex for fluorination. Prior to the sixth run, 4.5 mL of the complex with high HF concentration (pyridine–9HF) was added to compensate for the consumed HF. This operation increased the yield of **2** to higher than 80% in the sixth and seventh runs.

3. Conclusion

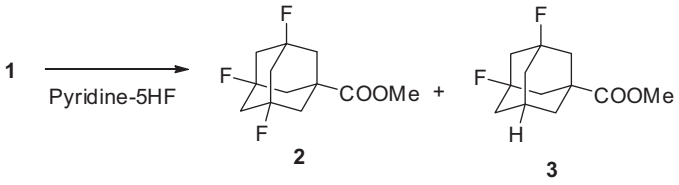
The electrochemical fluorination reaction of methyl adamantane-1-carboxylate **1** was performed in pyridine–5HF under constant current conditions, and methyl-3,5,7-trifluoroadamantane-1-carboxylate **2** was obtained in good yield. The product **2** was extracted by CH_2Cl_2–hexane from pyridine–5HF without aqueous work-up, and recovered pyridine–5HF was used repeatedly. During the repeated use of pyridine–5HF, HF concentration in the complex and the yield of **2** decreased. This decrease in HF concentration was compensated for by supplying HF, and the yield of **2** increased. Consequently, only HF and electricity were consumed for the preparation of **2** and the present process can be used for the bulk and economical synthesis of **2**.

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. Et_3N–5HF, pyridine–5HF, and pyridine–9HF were prepared according to the literature [9]. Et_4NF–4HF was donated from Morita Chemical Industries Co., LTD. They should be handled in bench hood with rubber gloves using Teflon wears.

Table 2
Electrochemical fluorination of **1** in pyridine–5HF under various conditions.



Entry	Current density (mA/cm^2)	Electricity (F/mol)	Yield of **2** (%)[a]
1	19	11	70(24)
2	25	11	82(14)
3	30	11	79(16)
4	25	14	79(8)
5	25	18	87(0)

[a] ^{19}FNMR yield based on **1**. In parentheses, yield of **3**.

Table 3
Repeated use of pyridine–5HF in the electrochemical fluorination of **1**.

	1	2	3	4	5	6[b]	7
Yield of **2** (%)[a]	85	84	85	78	76	84	81

[a] ^{19}FNMR yield based on **1**.
[b] Pyridine–9HF was added.

4.2. Electrochemical fluorination of methyl adamantane-1-carboxylate in pyridine–5HF and the recovery of pyridine–5HF

To an undivided cell made of TeflonPFA™ with two smooth Pt sheets (20 mm × 20 mm) for the anode and cathode, methyl adamantan-1-carboxylate (388 mg, 2 mmol) and pyridine–5HF (20 mL) were introduced. The electrolysis was carried out at room temperature under constant current (25 mA/cm^2) until 18 F/mol of electricity had passed. The content of the cell was poured into a mixture of hexane (10 mL) and CH_2Cl_2 (10 mL). The separated pyridine–5HF layer was extracted with the hexane–CH_2Cl_2 mixture again. The extraction operation was repeated ten times, and a combined organic layer was washed with saturated aqueous $CuSO_4$ and $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the yield of the product **2** was determined by ^{19}F NMR using fluorobenzene as an internal standard. Pure product was isolated by column chromatography (silica gel/hexane–ether). The recovered pyridine–5HF was washed with hexane (30 mL) twice to remove CH_2Cl_2 and reused. After the fifth run, 4.5 mL of pyridine–9HF was added to recover the concentration of HF in pyridine.

4.2.1. Methyl 3,5,7-trifluoroadamantane-1-carboxylate (2)

Purification by column chromatography (silica gel/hexane–CH_2Cl_2): 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 (100 MHz, $CDCl_3$) δ 173.4 (q, $^4J_{C-F}$ = 3.4 Hz), 91.7 (dt, $^1J_{C-F}$ = 191.2, $^3J_{C-F}$ = 15.3 Hz, 3C), 52.6, 46.6–46.0 (m, 3C), 43.2 (q, $^3J_{C-F}$ = 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.

4.2.2. Methyl-3,5-difluoroadamantane-1-carboxylate (3)

Purification by column chromatography (silica gel/hexane–CH_2Cl_2): mp 56–58 °C (sealed tube); IR (KBr) 2955, 1733, 1259, 1224, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.53 (brs, 1H), 2.11 (t, J = 5.3 Hz, 2H), 2.00 (brs, 4H), 1.84 (brs, 4H), 1.72 (brs, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −137.68 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (t, $^4J_{C-F}$ = 2.8 Hz), 92.8 (dd, $^1J_{C-F}$ = 189.2, $^3J_{C-F}$ = 13.9 Hz, 2C), 52.2, 47.4 (t, $^2J_{C-F}$ = 19.2 Hz), 45.6 (t, $^3J_{C-F}$ = 10.8 Hz), 42.8 (t, $^3J_{C-F}$ = 5.7 Hz), 42.6 (t, $^3J_{C-F}$ = 5.9 Hz), 40.4 (t, $^3J_{C-F}$ = 5.6 Hz), 40.3 (t, $^3J_{C-F}$ = 11.0 Hz), 36.4 (t, $^4J_{C-F}$ = 1.9 Hz), 30.5 (t, $^3J_{C-F}$ = 10.8 Hz); HRMS (EI) calcd for $C_{12}H_{16}O_2F_2$ 230.1118, found 230.1101.

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