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Electrochemical fluorination of β-dicarbonyl compounds using *p*-iodotoluene difluoride as a mediator

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Abstract

The selective and direct introduction of the fluorine atom into the α-position of β-dicarbonyl compounds was electrochemically achieved using iodotoluene difluoride as the mediator. The resulting α-fluoro-β-dicarbonyl compounds are important building blocks for biologically active compounds. © 1998 Elsevier Science S.A.

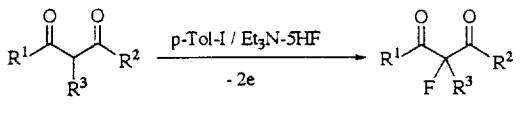
Keywords: *p*-Iodotoluene difluoride; α-Fluoro-β-dicarbonyl compounds; Electrochemical fluorination

1. Introduction

α-Fluoro-β-dicarbonyl compounds (**2**) have been synthesized by treating the parent β-dicarbonyl compounds (**1**) or their enolates with elemental fluorine [1–4] or one of the many electrophilic fluorinating agents such as $FClO_3$ [5,6], XeF_2 [7–9], AcOF [10–12], RfOF [13], and $CsSO_4F$ [14]. However, most of these agents are highly aggressive, unstable and even explosive, and require special equipment and experience for safe handling. Recently, *N*-fluoro-compounds [15–21] have been developed as stable and effective fluorinating reagents of carbonyl compounds, but they need elemental fluorine for their preparation and are expensive. Quite recently, we found that *p*-iodotoluene difluoride (**3**) is also effective for the selective and direct introduction of a fluorine atom into the α-position of β-ketoesters [22]. As **3** can be prepared without using hazardous elemental fluorine [23], this method is attractive for the synthesis of **2** [24]. However, the iodotoluene difluoride method had the disadvantage that a mercury salt was used in the conventional preparation procedure. In order to overcome this difficulty, we applied an electrochemical method for the preparation of **3** and the direct fluorination of β-dicarbonyl compounds **1** using the fluorinating reagent prepared without elemental fluorine or mercury salts.

2. Results and discussion

Fuchigami and Fujita [25] succeeded in the preparation of $ArIF_2$ such as *p*-$NO_2C_6H_4IF_2$ or *p*-$MeOC_6H_4IF_2$ by the anodic oxidation of the corresponding ArI in Et_3N–3HF–MeCN and their application for the fluorination of dithioacetals as an in-cell mediator. However, they failed in the preparation of **3** from iodotoluene under similar conditions. Recently, we found that Et_3N–5HF is superior to Et_3N–3HF as the electrolyte for the electrochemical oxidation of carbonyl compounds [26–29] and we applied Et_3N–5HF for the preparation of **3**. The anodic oxidation of iodotoluene was carried out in Et_3N–5HF using a divided cell made of Teflon PFA, and the formation of **3** was confirmed from the ^1H and ^{19}F NMR spectra of the reaction mixture. While the prepared iodotoluene difluoride **3** could be used for the fluorination of β-ketoesters as the chemically prepared **3**, it was applied for the direct fluorination of β-dicarbonyl compounds **1** as an in-cell mediator without isolation. The electrolysis of a 1:1 mixture of iodotoluene and **1** was carried out in Et_3N–5HF in an undivided cell under constant potential (1.5 V vs. Ag/Ag^+) and the desired α-fluoro-β-dicarbonyl compounds **2** could be obtained in good yield (Eq. (1)).



1 **2** (1)

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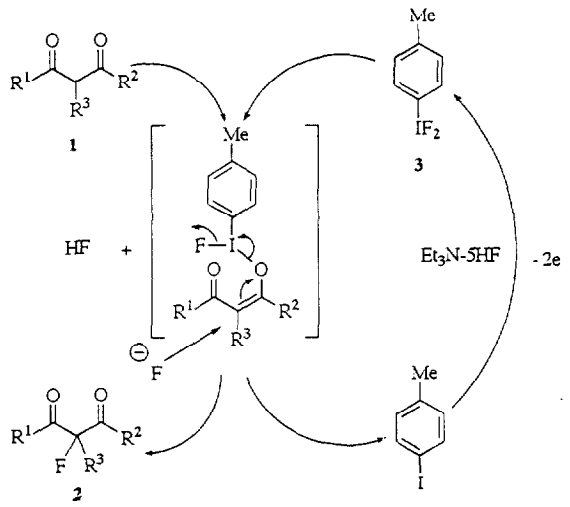
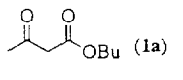
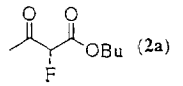
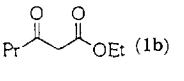
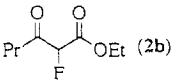
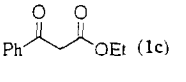
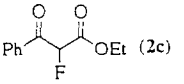
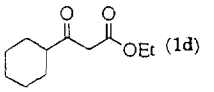
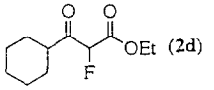
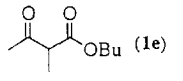
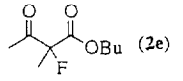
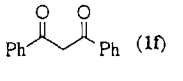
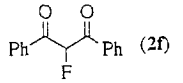
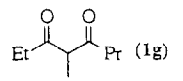
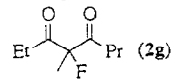
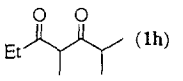
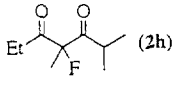


Scheme 1.

As the reaction took place at a relatively low oxidation potential (1.5 V) and iodotoluene is indispensable for the preparation of **2**, iodotoluene difluoride **3**, generated electrochemically from iodotoluene, must be working as an in-cell mediator for the fluorination reaction of **1** as shown in Scheme 1. [2] Under the given reaction conditions, β-ketoesters having no substituent at the α-position provided the monofluorinated products selectively. On the other hand, the fluorination of the unsubstituted β-diketone proceeded less selectively and a small amount of the difluorinated product was also obtained (Table 1). Consequently, we succeeded in the direct fluorination of β-dicarbonyl compounds **1** by **3** prepared without hazardous fluorine gas or mercury salts.

Table 1
Electrochemical fluorination of β-dicarbonyl compounds

1	Products 2	Electricity (F/mol)	Yield/%[b]
 (1a)	 (2a)	10.0	79 (<1)
 (1b)	 (2b)	10.0	72 (<1)
 (1c)	 (2c)	10.0	72 (<1)
 (1d)	 (2d)	10.0	70 (2)
 (1e)	 (2e)	10.0	56
 (1f)	 (2f)	3.0	50 (6)
 (1g)	 (2g)	6.0	67
 (1h)	 (2h)	6.0	60

[a] The reaction was carried out as described in the text.
[b] Isolated yields based on dicarbonyl compounds used. In parentheses, the yields of difluorinated compounds were shown.

3. Experimental details

IR spectra were recorded using a Hitachi 260-30 infrared spectrometer. ^{1}H NMR spectra and ^{19}F NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-A400 II FT NMR and chemical shifts, δ, are referred to TMS (^{1}H) and $CFCl_3$ (^{19}F) respectively. High-resolution mass spectra were taken at the Center for Instrumental Analysis, Hokkaido University.

Cyclic voltammetry was carried out using an undivided cell (30 ml) made of Teflon PFA. The working electrode was a smooth platinum (Pt) wire (1 mmϕ × 10 mm) and the counter electrode was a smooth Pt sheet (20 mm × 20 mm). The reference electrode was Ag/$AgNO_3$ (0.01 M) in MeCN containing Et_4NBF_4 (0.1 M). The potential was scanned with a potential scanner (Nichia ES 512A) connected to a potentio/galvanostat (Nichia NP-100M), and the voltammograms were recorded on an X-Y recorder (Riken Denshi F-35). The electrochemical reactions were carried out in an undivided cell (30 ml) made of Teflon PFA or a divided cell (30 ml × 2) made of Teflon PFA with a Nafion® 117 film using two smooth Pt sheets (20 mm × 20 mm) for the anode and cathode. The quantity of electricity passed was monitored with a coulometer (Nichia N-CR760).

Anhydrous HF was obtained from Hashimoto Chemical in a cylinder. [3]

3.1. Preparation of Et_3N–5HF

Et_3N–5HF was prepared by the addition of freshly distilled Et_3N to 5 equivalent of anhydrous HF in a Teflon PFA bottle under nitrogen at −78°C. After the addition, Et_3N–5HF was brought to room temperature and can be kept in a Teflon bottle with a tight cap at room temperature for a month without change.

3.2. Preparation of α-fluoro-β-ketoesters 2a–2e

Under an inert atmosphere of nitrogen, **1** (2 mmol) and *p*-iodotoluene (0.436 g, 2 mmol) were dissolved in Et_3N–5HF (15 ml) in an undivided cell at 0°C. The electrolysis was carried out at 1.5 V (vs. Ag/Ag^+) until 10 F/mol of electricity had passed and the anode and cathode were exchanged every 2 s to avoid the formation of polymer films on the

[2] When the electrolysis of **1a** was carried out in a divided cell, 0.5 equivalent of *p*-iodotoluene to **1a** was enough to obtain **2a** in 71% yield. In that case, *p*-iodotoluene, regenerated after the fluorination of **1a**, was oxidized to **3** and used for the fluorination of **1a** repeatedly.

[3] As anhydrous HF is highly corrosive, toxic, and has a low boiling point, a special care is required to handle it.

electrode. The reaction mixture was then poured into ice-water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After the removal of $MgSO_4$ by filtration, **2** was isolated by column chromatography (silica gel/CH_2Cl_2).

Butyl 2-fluoro-3-oxobutanoate (**2a**): IR: 1750, 1730 cm^{-1}. ^1H NMR (400 MHz) δ: 0.94 (t, 3H, J=7.3 Hz, CH_3); 1.34–1.46 (m, 2H, CH_2); 1.62–1.72 (m, 2H, CH_2); 2.35 (d, 3H, J=4.1 Hz, CH_3CO); 4.26 (t, 2H, J=6.6 Hz, CH_2O); 5.20 (d, 1H, J=52.5 Hz, CHF) ppm. ^{19}F NMR (376 MHz) δ: −193.56 (d, J=52.5 Hz) ppm. HRMS: Calc. for $C_8H_{13}O_3F$, 176.0849. Found 176.0844.

Ethyl 2-fluoro-3-oxohexanoate (**2b**): IR: 1760, 1730 cm^{-1}. ^1H NMR (400 MHz) δ: 0.94 (t, 3H, J=7.3 Hz, CH_3); 1.33 (t, 3H, J=7.1 Hz, CH_3); 1.59–1.70 (m, 2H, CH_2), 2.60–2.67 (m, 2H, CH_2CO); 4.31 (q, 2H, J=7.1 Hz, CH_2O); 5.20 (d, 1H, J=49.3 Hz, CHF) ppm. ^{19}F NMR (376 MHz) δ: −195.37 (d, J=49.3 Hz) ppm. HRMS: Calc. for $C_8H_{13}O_3F$, 176.0849. Found 176.0834.

Ethyl 2-fluoro-3-phenyl-3-oxopropionate (**2c**): IR: 1750, 1690 cm^{-1}. ^1H NMR (400 MHz) δ: 1.26 (t, 3H, J=7.1 Hz, CH_3); 4.30 (q, 2H, J=7.1 Hz, CH_2O); 5.88 (d, 1H, J=48.8 Hz, CHF); 7.49–8.05 (m, 5H) ppm. ^{19}F NMR (376 MHz) δ: −190.89 (d, J=48.8 Hz) ppm. HRMS: Calc. for $C_{11}H_{11}O_3F$, 210.0692. Found 210.0690.

Ethyl 3-cyclohexyl-2-fluoro-3-oxopropionate (**2d**): IR: 1750, 1720 cm^{-1}. ^1H NMR (400 MHz) δ: 1.16–1.90 (m, 10H, CH_2); 1.32 (t, 3H, J=7.1 Hz, CH_3); 2.84–2.92 (m, 1H, CHCO); 4.31 (q, 2H, J=7.1 Hz, CH_2O); 5.27 (d, 1H, J=49.3 Hz, CHF) ppm. ^{19}F NMR (376 MHz) δ: −196.04 (d, J=49.3 Hz). HRMS: Calc. for $C_{11}H_{17}O_3F$, 216.1162. Found 216.1141.

Butyl 2-fluoro-2-methyl-3-oxobutanoate (**2e**): IR: 1750, 1730 cm^{-1}. ^1H NMR (400 MHz) δ: 0.94 (t, 3H, J=7.6 Hz, CH_3); 1.30–1.43 (m, 2H, CH_2); 1.55–1.75 (m, 2H, CH_2); 1.68 (d, 3H, J=22.2 Hz, CH_3CF); 2.32 (d, 3H, J=4.6 Hz, CH_3CO); 4.21 (t, 2H, J=6.3 Hz, CH_2O) ppm. ^{19}F NMR (376 MHz) δ: −157.47 (q, J=22.5 Hz) ppm. HRMS: Calc. for $C_9H_{15}O_3F$, 190.1006. Found 190.0988.

3.3. Preparation of 2-fluoro-1,3-diphenyl-1,3-propandione (2f)

Under an inert atmosphere of nitrogen, Et_3N–5HF (50 ml) was introduced into a divided cell, and **1f** (0.448 g, 2 mmol) and *p*-iodotoluene (0.436 g, 2 mmol) were dissolved in Et_3N–5HF in an anodic cell at 0°C. The electrolysis was carried out under constant current (20 mA/h) until 3 F/mol of electricity had passed. The reaction mixture was then poured into ice-water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After the removal of $MgSO_4$ by filtration, a mixture of **2f** (50%) and the 2,2-difluoro-1,3-diphenyl-1,3-propandione (6%) was obtained by column chromatography (silica gel/CH_2Cl_2) (the ratio was determined by GPC). IR: 1690, 1670 cm^{-1}. ^1H NMR (400 MHz) δ: 6.52 (d, 1H, J=49.6 Hz, CHF); 7.36–8.13 (m, 10H, arom) ppm. ^{19}F NMR (376 MHz) δ: −187.43 (d, J=49.6 Hz, CFH), −169.29 (s, CF_2). HRMS: Calc. for $C_{15}H_{11}O_2F$, 242.0743. Found 242.0743.

3.4. Preparation of α-fluoro-β-diketones 2g–2h

The operation is the same as in Section 3.2 but the reaction was carried out in a mixture of Et_3N–5HF (14 ml) and EtOH (1 ml), and 6 F/mol of electricity was passed.

4-Fluoro-4-methyl-3,5-octandione (**2g**): IR: 1740, 1720 cm^{-1}. ^1H NMR (400 MHz) δ: 0.91 (t, 3H, J=7.5 Hz, CH_3); 1.07 (t, 3H, J=7.1 Hz, CH_3); 1.56–1.62 (m, 2H, CH_2); 1.61 (d, 3H, J=16.4 Hz, CH_3CF); 2.48–2.78 (m, 4H, CH_2CO) ppm. ^{19}F NMR (376 MHz) δ: −161.40 (q, J=16.4 Hz) ppm. HRMS: Calc. for $C_9H_{15}O_2F$, 174.1057. Found 174.1050.

4-Fluoro-2,4-dimethyl-3,5-heptandione (**2h**): IR: 1740, 1710 cm^{-1}. ^1H NMR (400 MHz) δ: 1.05–1.11 (m, 9H, CH_3); 1.63 (d, 3H, J=22.2 Hz, CH_3CF); 2.51–2.78 (m, 2H, CH_2CO); 3.12–3.19 (m, 1H, CHCO) ppm. ^{19}F NMR (376 MHz) δ: −162.69 (q, J=22.2 Hz) ppm. HRMS: Calc. for $C_9H_{15}O_2F$, 174.1057. Found 174.1041.

Acknowledgements

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