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Electrochemical partial fluorination of phenylacetic acids esters and 1-tetralone

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Abstract

Anodic oxidation of some benzyl derivatives (phenylacetic acids esters) **1**, and 1-tetralone **4**, using ammonium fluorides or ammonium tetrafluoroborate as fluorine sources and supporting electrolytes and CH_2Cl_2 as solvent, allowed the introduction of a fluorine atom in the α position of an electron withdrawing group via carbocation (**C**), (EC_BEC_N mechanism).

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1. Introduction

The selective fluorination of organic molecules has attracted much interest because a number of partially fluorinated organic molecules are reported to show special chemical and physical properties and, in some cases, biological activities [1–5].

Electrochemical partial fluorination (ECF) has become a more attractive method by using as a fluorine source, HF combined with an organic base [6].

The electrochemical partial fluorination of organic compounds using $Et_3N\cdot nHF$ ($n = 2$–3) as a fluorine source and supporting electrolyte has been developed in the last few years [7]. Recently, a new electrolyte, $Et_3N\cdot 5HF$, has been found to be electrochemically highly stable and an excellent agent for the electrochemical fluorination of aldehydes and ketones to produce the corresponding acylfluorides and alkylfluorides in good yields [8].

The mono- and difluorination of benzylic groups was reported by Laurent et al. [9], using CH_3CN as a solvent and $Et_3N\cdot 3HF$ as fluorine source. This anodic fluorination allowed the introduction of a fluorine atom in the α position of an electron withdrawing group; by raising the potential of working electrodes after the monofluorination step, *gem*-difluorides can be directly prepared.

Continuing our efforts on the regioselective anodic fluorination of organic compounds, we report in this paper the anodic fluorination of benzyl derivatives **1** and 1-tetralone **4**, using $Et_3N\cdot nHF$ ($n = 3$–5), $Et_4N\cdot BF_4$ and $Et_4NF\cdot nHF$ ($n = 1$–3) as fluorine sources. The influence of the nature of fluorine sources and of the electrolytic temperature on anodic oxidation of benzyl derivatives was studied.

2. Results and discussion

The anodic fluorinations of phenylacetic acids esters **1** were investigated toward various fluorine agents and supporting electrolytes in CH_2Cl_2 as electrolytic solvent (Scheme 1) and the results are summarized in Table 1. It was found that the anodic fluorination of **1** proceeds highly regioselectively and the fluorine atom was exclusively introduced at the α position to the ester group, giving the α-monofluorinated esters **2**. (Compounds **2b**, and **2c**, were previously obtained by Laurent et al. [9], using CH_3CN as electrolytic solvent.)

A subsequent oxidation of fluorinated derivative **2b**, using $Et_4NF\cdot 2HF$ as fluorine source and CH_2Cl_2 as solvent, yields *geminal* difluoro compound **3** (obtained also by Laurent et al. [9], in other anodic fluorination conditions), as shown in Scheme 2.

Monofluorination of ester **1a** in the presence of $Et_3N\cdot 5HF$ as fluorine source and supporting electrolyte gave the corresponding α-monofluorinated ester **2a** in a low yield (17%),

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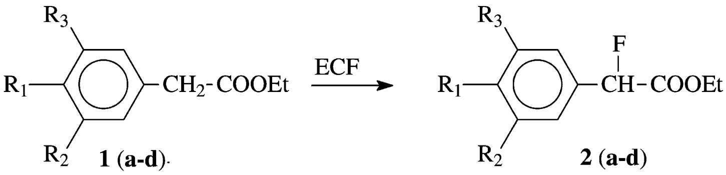
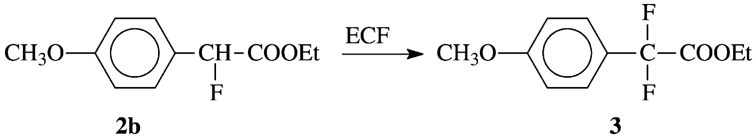


a: $R_1 = R_2 = R_3 = H$; **b**: $R_1 = OCH_3$; $R_2 = R_3 = H$; **c**: $R_1 = R_2 = OCH_3$; $R_3 = H$;

d: $R_1 = R_2 = R_3 = OCH_3$

Scheme 1.



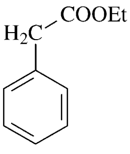
Scheme 2.

(Table 1, entry 1). Next, we investigated the anodic fluorination of the benzylic derivative **1b**, which contains a *para*-methoxy group in the aromatic ring, toward various fluorine sources (Table 1, entries 2–8). The anodic fluorination of ester **1b** had been previously attempted in $Et_4N{\cdot}BF_4/CH_2Cl_2$ but no fluorine derivative was found and the substrate was recovered (Table 1, entry 2). We re-examined the fluorination of **1b** in various fluorine sources and the desired α-monofluorinated esters **2b** were obtained (Table 1, entries 3–12).

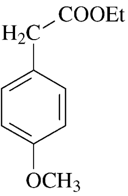
The influence of the nature of the fluorine sources on the anodic fluorination of benzyl derivatives **1b** at 0 °C was studied (Table 1, entries 3–8). It was found that, $Et_4NF{\cdot}1HF$, $Et_4NF{\cdot}2HF$ and $Et_3N{\cdot}3HF$ are good fluorine sources and

Table 1

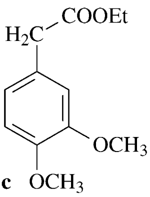
Anodic fluorination of phenylacetic acids esters **1** and ethyl fluoro-[4-methoxyphenyl]acetic acid ester **2b**



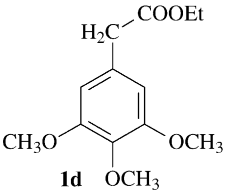
1a



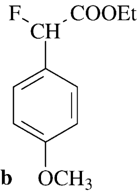
1b



1c



1d

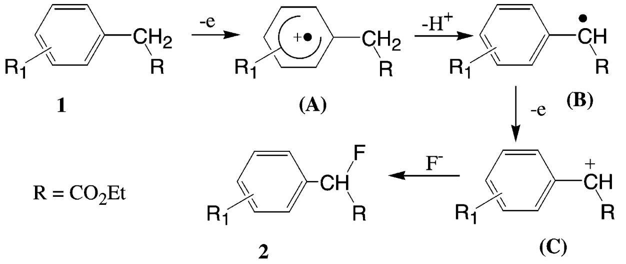


2b

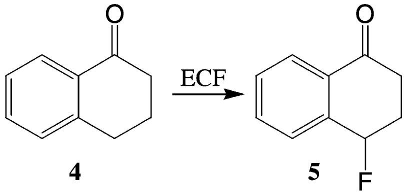
Entry	Compound	Electrolyte	Potential V vs. Ag/Ag$^+$	Charge passed (F mol^{-1})	Temperature (°C)	Time (h)	Product yield[a] (%) **2** and **3**
1	**1a**	$Et_3N{\cdot}5HF$	2.10	3.0	−46	4.5	17
2	**1b**	$Et_4N{\cdot}BF_4$	1.90	1.4	RT	6	0[c]
3	**1b**	$Et_4NF{\cdot}HF$	1.45	3.6	0	4	54
4	**1b**	$Et_4NF{\cdot}2HF$	1.40	4.6	0	6	60
5	**1b**	$Et_4NF{\cdot}3HF$	1.40	2.6	0	4	34
6	**1b**	$Et_3N{\cdot}3HF$	1.45	2.6	0	3	61
7	**1b**	$Et_3N{\cdot}4HF$	1.30	2.6	0	4.5	8
8	**1b**	$Et_3N{\cdot}5HF$	1.40	2.6	0	3	Traces[b]
9	**1b**	$Et_4NF{\cdot}2HF$	1.45	3.6	−46	6	50
10	**1b**	$Et_4NF{\cdot}2HF$	1.45	2.6	−15	3	50
11	**1b**	$Et_4NF{\cdot}2HF$	1.35	5.3	−15	8	44
12	**1b**	$Et_4NF{\cdot}2HF$	1.35	3.7	RT	4	57
13	**1c**	$Et_4NF{\cdot}2HF$	1.00	2.6	0	3	63
14	**1c**	$Et_4NF{\cdot}2HF$	1.10	3.0	RT	3.5	62
15	**1d**	$Et_4NF{\cdot}2HF$	1.10	4.0	0	6.5	50
16	**2b**	$Et_4NF{\cdot}2HF$	1.65	4.0	0	6	46

[a] Isolated yield.

[b] The substrate was recovered.



Scheme 3.



Scheme 4.

support electrolytes for these reactions that produce the corresponding α-monofluorinated esters **2b** in good yields (Table 1, entries 3, 4 and 6). Using $Et_3N·4HF$ and $Et_3N·5HF$ gave low yields and the substrate was recovered (Table 1, entries 7 and 8).

The study of the influence of electrolytic temperature on the anodic fluorination of benzylic derivatives **1b** in the presence of $Et_4NF·2HF$ as fluorine source and supporting electrolyte (Table 1, entries 9–12) shows that similar results were obtained at different temperatures. Good yields were obtained when the substrates in anodic fluorination contained two or three methoxy groups in aromatic ring (Table 1, entries 13–15).

A subsequent anodic fluorination of monofluoro-ester **2b** yielded *geminal* difluoro compound **3**, in the presence of $Et_4NF·2HF$ as fluorine source and CH_2Cl_2 as electrolytic solvent in 46% yield (Table 1, entry 16).

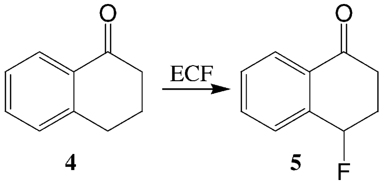
An EC_BEC_N (electrochemical–chemical–electrochemical–chemical) mechanism is widely accepted for that type of electrochemical partial fluorination reactions [9,10], and most likely the reactions in our study follow the same pathway (Scheme 3).

The one-electron oxidation of the substrate **1** gave the radical cation species (**A**), which was deprotonated by a fluoride ion to afford the benzylic radical (**B**). The subsequent oxidation of (**B**) yielded the carbocation (**C**). Finally, α-monofluorinated ester **2** was formed by the attack of the fluoride ion toward (**C**).

Next, we turned our attention to the anodic fluorination of 1-tetralone (Scheme 4) in CH_2Cl_2 as solvent. Using $Et_3N·5HF$ as fluorine source, and 0 °C as electrolytic temperature, no fluorination occurred when the charge passed was $2.1\ F\ mol^{-1}$. Increasing the amount of electricity to $3.7\ F\ mol^{-1}$, fluorination took place at the benzylic position and monofluoro derivative **5** was obtained with 28% isolated yield (Table 2, entry 2). A better yield was obtained when the electrolyte temperature was −46 °C (Table 2, entry 3). The anodic fluorination of 1-tetralone in the presence of $Et_4NF·2HF$ as supporting electrolyte and fluorinating agent, in CH_2Cl_2 as electrolytic solvent, gave monofluoro product **5** with 65% yield when charge passed was $5.2\ F\ mol^{-1}$ (Table 2, entry 6); the yield decreases to 18% when only $2.6\ F\ mol^{-1}$ were used (Table 2, entry 5).

In summary, we have reported a selective electrochemical fluorination of benzyl derivatives **1** and 1-tetralone **4**, using different fluoride supporting electrolytes such as $Et_3N·nHF$ ($n = 3–5$) and $Et_4NF·2HF$ in CH_2Cl_2, which allowed the introduction of a fluorine atom in benzyl position. The highest yields were obtained when $Et_4NF·2HF$ and $Et_3N·3HF$ were used as fluorine sources in the ECF of benzyl derivatives **1** and when $Et_4NF·2HF$ and $Et_3N·5HF$ were used in ECF of 1-tetralone **4**.

Table 2
Anodic fluorination of 1-tetralone



Entry	Substrate	Electrolyte	Anodic potential V vs. Ag/Ag^+	Charge passed ($F\ mol^{-1}$)	Temperature (°C)	Product yield[a] (%) **5**
1	**4**	$Et_3N·5HF$	2.0	2.1	0	–
2	**4**	$Et_3N·5HF$	2.0	3.7	0	28
3	**4**	$Et_3N·5HF$	2.0	3.8	−46	56
4	**4**	$Et_3N·4HF$	2.1	3.7	−46	35
5	**4**	$Et_4NF·2HF$	2.1	2.6	−15	18
6	**4**	$Et_4NF·2HF$	2.1	5.2	−15	65

[a] Isolated yield.

3. Experimental

3.1. General

Caution: $Et_3N{\cdot}n$HF and $Et_4NF{\cdot}2HF$ are toxic; if they come in contact with skin, they cause a serious burn. Therefore, it is recommended that rubber gloves be used.

Typical anodic difluorination conditions were as follows. Anodic oxidations of **1** (1 mmol) and **4** (1 mmol), were carried out with an undivided cell with a platinum anode and cathode (2 cm × 2 cm) in 15 ml fluorine source or in 8 ml fluorine source and 8 ml CH_2Cl_2. Anodic potentials were determined by cyclic voltammertry. The reference electrode was $Ag/AgNO_3$ (0.01 M) in MeCN containing $Et_4N{\cdot}BF_4$ (0.1 M).

Since positive oxidative potentials were involved, careful handling of the solvent supporting electrolyte system was needed, moisture avoided, to ensure polymerization-free electrolysis. IR spectra were obtained on a FT/IR-410 Jasco spectometer. ^{1}H and ^{19}F NMR spectra were recorded, in $CDCl_3$ as a solvent, on a JEOL Datum (400 MHz) spectrometer.

The chemical shifts for ^{1}H NMR are reported in δ ppm downfield from internal TMS, and those for ^{19}F NMR are given in δ ppm downfield from internal C_6F_6, $\delta(CFCl_3)$ of the C_6F_6 reference being -162.2 ppm.

All reactions with air-sensitive compounds were carried out under a dinitrogen atmosphere. Column chromatography was conducted with silica gel. GC Analyses were performed using a Hitachi G-5000 instrument (flame ionization detector, FID) with a 30 m column Neutra Bond.

3.2. Materials

The electrolytes, $Et_3N{\cdot}n$HF and $Et_4NF{\cdot}n$HF, and $Et_4NF{\cdot}BF_4$, were kind gifts of Morita Chemical Industries Co. Ltd. (Japan) and were used without purification.

3.3. Separation and analysis of products

The electrolytic mixture was diluted with water and extracted with three portions of CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After the removal of $MgSO_4$ by filtration, the products were isolated by column chromatography on silica gel and identified by ^{1}H and ^{19}F NMR spectra, IR-spectra, MS-spectra and HMRS.

Ethyl fluoro-phenylacetate (**2a**) was purified by flash chromatography on silica gel, eluting with 10:1 mixture of hexane and ethyl acetate to give a colorless oil.

^{1}H NMR: 1.29 (t, $J = 7.3$ Hz, 3H); 4.25 (q, $J = 7.3$ Hz, 2H); 5.76 (d, $J = 48.2$ Hz, 1H); 7.10–7.48 (m, 5H); ^{19}F NMR: -18.50 (d, $J = 48.2$ Hz, 1F); IR (neat, cm^{-1}) 1760 ($\nu_{C=O}$); MS (*m/z*): 182 ($M^+ + H^+$). HRMS. Calcd. for $C_{10}H_{11}FO_2$ (*m/e*): 182.0743; Found: 182.0739.

Ethyl fluoro-[4-methoxyphenyl]acetate (**2b**) was purified by flash chromatography on silica gel, eluting with 7:1 mixture of hexane and ethyl acetate to give a colorless oil.

^{1}H NMR: 1.26 (t, $J = 7.3$ Hz, 3H); 3.88 (s, 3H); 4.25 (q, $J = 7.3$ Hz, 2H); 5.73 (d, $J = 48.2$ Hz, 1H); 6.92 and 7.38 (2d, AB, $J = 8.5$ Hz, 4H); ^{19}F NMR: -12.88 (d, $J = 48.2$ Hz, 1F); IR (neat, cm^{-1}) 1760 ($\nu_{C=O}$); MS (*m/z*): 212 ($M^+ + H^+$). HRMS. Calcd. for $C_{11}H_{13}FO_3$ (*m/e*): 212.0849; Found: 212.0832.

Ethyl fluoro-[3,4-dimethoxyphenyl]acetate (**2c**) was purified by flash chromatography on silica gel, eluting with 10:3 mixture of hexane and ethyl acetate to give a colorless oil.

^{1}H NMR: 1.29 (t, $J = 7.3$ Hz, 3H); 3.89 (s, 6H); 4.26 (q, $J = 7.3$ Hz, 2H); 5.70 (d, $J = 48.8$ Hz, 1H); 6.88 (d, $J = 8.0$ Hz, 2H); 6.98 (m, 1H); ^{19}F NMR: -13.54 (d, $J = 48.8$ Hz, 1F); IR (neat, cm^{-1}) 1757 ($\nu_{C=O}$); MS (*m/z*): 242 ($M^+ + H^+$). HRMS. Calcd. for $C_{12}H_{15}FO_4$ (*m/e*): 242.0954; Found: 242.0953.

Ethyl fluoro-[3,4,5-trimethoxyphenyl]acetate (**2d**) was purified by flash chromatography on silica gel, eluting with 2:1 mixture of hexane and diethyl ether to give a colorless oil.

^{1}H NMR: 1.29 (t, $J = 7.1$ Hz, 3H); 3.85–3.95 (m, 9H); 4.29 (q, $J = 7.1$ Hz, 2H); 5.70 (d, $J = 47.8$ Hz, 1H); 6.68 (s, 2H); ^{19}F NMR: -16.23 (d, $J = 47.8$ Hz, 1F); IR (neat, cm^{-1}) 1758 ($\nu_{C=O}$); MS (*m/z*): 272 ($M^+ + H^+$). HRMS. Calcd. for $C_{13}H_{17}FO_5$ (*m/e*): 272.1060; Found: 272.1043.

Ethyl difluoro-[4-methoxyphenyl]acetate (**3**) was purified by flash chromatography on silica gel, eluting with 7:1 mixture of hexane and ethyl acetate to give a colorless oil.

^{1}H NMR: 1.32 (t, $J = 8$ Hz, 3H); 3.83 (s, 3H); 4.29 (q, $J = 8$ Hz); 6.94 (d, $J = 8.5$ Hz, 2H); 7.53 (d, $J = 8.5$ Hz, 2H); ^{19}F NMR: 59.17 (s, 2F); IR (neat, cm^{-1}): 1764 ($\nu_{C=O}$); MS (*m/z*): 230 ($M^+ + H^+$). HRMS. Calcd. for $C_{10}H_9FO$ (*m/e*): 230.0754; Found: 230.0748.

4-Fluoro-1-tetralone (**5**) was purified by flash chromatography on silica gel, eluting with 2:1 mixture of hexane and diethyl ether to give a colorless oil.

^{1}H NMR: 2.50 (m, 2H); 2.61 (m, 1H); 2.95 (m, 1H); 5.75 (dt, $J = 49.7$ Hz, $J = 5.4$ Hz, 1H); 7.50–8.08 (m, 4H); ^{19}F NMR: -8.8 (m, 1F); IR (neat, cm^{-1}) 1692 ($\nu_{C=O}$); MS (*m/z*): 164 ($M^+ + H^+$). HRMS. Calcd. for $C_{10}H_9FO$ (*m/e*): 164.0637; Found: 164.0654.

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