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Short communication

Electrolytic partial fluorination of organic compounds Part 26.¹ Anodic monofluorination of ethyl isonicotinate

Akinori Konno², Moriyasu Shimojo, Toshio Fuchigami *

Department of Electronic Chemistry, Tokyo Institute of Technology, 4259 Nagatsuta, Yokohama 226, Japan

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Abstract

Anodic fluorinations of ethyl isonicotinate (1) and related compounds have been attempted. Desired fluorinated product, 2-fluoroisonicotinate (2) was obtained in reasonable yield by direct anodic monofluorination of ethyl isonicotinate 1. The yield of 2 and the conversion of the electrochemical reaction could be improved by applying relatively lower anodic potential and by increasing the concentration of supporting electrolyte $Et_3N \cdot 3HF$. © 1998 Elsevier Science S.A.

Keywords: Anodic monofluorination; Ethyl isonicotinate; Electrochemistry

1. Introduction

A number of partially fluorinated compounds especially heterocyclic compounds have been reported to show unique biological activities [2–5]. Therefore, efficient methods for the partial fluorination of heterocyclic compounds are becoming important [6]. However, the selective fluorination of heterocyclic compounds is not always straightforward because conventional direct fluorination usually requires hazardous, poisonous, or costly fluorinating reagents [7]. From this viewpoint, electrochemical partial fluorination is a promising method since it can be performed under safe conditions using fluoride anion as a fluorine source and a supporting electrolyte. We have demonstrated that anodic partial fluorination of sulfides is an excellent method in order to introduce a fluorine atom into the α -carbon to the sulfur atom selectively [8–13]. However, very few examples of anodic partial fluorination of heterocyclic compounds have been reported to date and the yields and/or selectivities are generally quite low [14–18]. For example, the anodic fluorination of pyrazole derivative occurred non-regioselectively to afford the mixture of fluorinated products (Scheme 1) [14]. Ballinger and Teare [15] reported that the anodic fluorination of pyridine afforded 2-fluoropyridine in 22% yield, but detailed method of isolation and characterization of the fluorinated product were not described. Furthermore, in the anodic fluorination



of quinoline, isoquinoline and 1,10-phenanthroline, fluorination took place at the benzene ring exclusively and the pyridine moiety was not fluorinated at all [17,19]. Therefore, selective anodic fluorination of nitrogen-containing heteroaromatics is quite difficult. With this in mind, anodic fluorinations of ethyl isonicotinate (1) and related compounds have been attempted. This paper presents the first example of electrochemical direct fluorination of ethyl isonicotinate 1. The effect of electrochemical reaction conditions on the efficiency of fluorination and characterization of the fluorinated product are described.

2. Results and discussion

2.1. Current-potential curve

The current-potential curves of electrolyte were recorded in the absence and presence of 1 in acetonitrile containing 0.37 M of $Et_3N \cdot 3HF$ (Fig. 1). It is clear that the oxidation of 1 and electrolyte occurred competitively. It is also noted that the oxidation potential of the electrolyte shifted anodi-

^{*} Corresponding author.

¹ For Part 25, see Ref. [1].

² Present address: Faculty of Engineering, Shizuoka University.

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Fig. 1. Current-potential curves of electrolytic solution in the presence (\bigcirc) and the absence (\triangle) of ethyl isonicotinate. (\bigcirc) : Ethyl isonicotinate (5 mmol) in 0.37 M Et₃N · 3HF/CH₃CN solution (50 ml), (\triangle) : 0.37 M Et₃N · 3HF/CH₃CN solution (50 ml),

cally by ca. 0.5 V, in the presence of 1. This is not so common in the anodic oxidation of organic compounds. Although the reason for this anodic shift is not clear, the formation of low conductive thin film from 1 on the surface of anode is suggested.

2.2. Anodic fluorination of nitrogen-containing heteroaromatic compounds

The anodic fluorination of several nitrogen-containing heteroaromatic compounds was carried out using undivided cell at a constant potential in acetonitrile containing $Et_3N \cdot 3HF$ as a supporting electrolyte and a fluorine source (the same conditions of anodic monofluorination of sulfides [11–13]). The results are summarized in Table 1. Anodic monofluorination of 1, methyl nicotinate (3), isonicotinonitrile (4) and 4-benzoylpyridine (5) proceeded to provide the fluorinated products even in low yields (runs 1–4). The fluorination position of these products except for 2 could not be established because of extremely low yields. The low yields and current efficiencies could be attributed to relatively high oxidation potentials of substrates bearing an electron-withdrawing group at the aromatic ring. On the other hand, anodic fluorination of 2,6-dimethoxypyridine (6) bearing electron-

Table 1 Anodic fluorination of heteroaromatic compounds ^a

donating groups could be oxidized at lower anodic potential (1.9 V vs. SSCE), but resulted in decomposition of the starting material (run 5). Anodic fluorination of pyrazine and pyrazole did not afford fluorinated products and black polymer deposited on the anode during the electrolysis in both cases. From these results, it is concluded that an electronwithdrawing group at aromatic ring was responsible for proceeding with direct anodic fluorination of aromatic nitrogen heterocycles.



2.3. Anodic fluorination of ethyl isonicotinate

Anodic fluorination of 1 was further investigated under a variety of electrochemical reaction conditions, since appreciable amount of monofluorinated product was obtained by anodic fluorination of 1. As shown in Table 2, the yields and current efficiencies were varied depending on the electrochemical conditions. When lower anodic potential (3.1-3.2)V vs. SSCE) than run 1 (3.3 V vs. SSCE) was applied for the anodic fluorination of 1 and the electrolysis was stopped with low conversion of 1 (4.0 F/mol of charge passed), the yield based on consumed 1 of monofluorinated product 2 was improved more than twice (run 2). However, continuing electrolysis did not increase the yield of 2 and led to the decomposition of 1 and 2. On the other hand, increasing the concentration of supporting electrolyte Et₃N · 3HF, the isolated yield of 2 increased even at higher conversion of 1 (run 3 and 4). Using a graphite as an anode instead of a platinum, anodic fluorination of 1 did not proceed at all (run 5). Changing an electrolytic solvent from acetonitrile to THF, which

Run	Substrate	Anodic potential (V vs. SSCE)	Charge passed (F/mol)	Product yield ^b (%)	Recovery (%)	
1	1	3.3	6.0	(2) 12	14	
2	3	3.3	5.0	Complex mixture ^c	18	
3	4	3.3–3.4	7.0	Complex mixture ^d	19	
4	5	3.2	7.0	Complex mixture °	0	
5	6	1.9	4.0	Decomposition	0	

^a Substrate: 0.1 M, electrolyte (0.37 M Et₃N · 3HF/MeCN): 50 ml, Pt anode and cathode (4×3 cm²), undivided cell.

^b Isolated yield.

^c Monofluorinated product was detected by mass $[m/e = 155 \text{ (M}^+), 124 \text{ (M}^+-\text{OMe})]$ and ¹⁹F NMR $[\delta = +14.8 \text{ (s)}]$ spectroscopy.

^d Monofluorinated product was detected by mass spectroscopy $[m/e = 122 (M^+), 103 (M^+-F), 96 (M^+-CN)]$.

^c Mono- and difluorinated products were detected by mass spectroscopy $[m/e=219 (M^+) \text{ and } m/e=201 (M^+), \text{ respectively}].$

 Table 2

 Anodic fluorination of ethyl isonicotinate (1)^a



Run	Solvent	$Et_3N \cdot 3HF$ (M)	Electrodes anode–cathode $(4 \times 3 \text{ cm}^2)$	Anodic potential (V vs. SSCE)	Charge passed (F/mol)	Conversion (%)	Yield ^h (%)
1	MeCN	0.37	Pt-Pt	3.3	6.0	86	14 (12)
2	MeCN	0.37	Pt-Pt	3.1 ~ 3.2	4.0	58	31 (18)
3	MeCN	0.72	Pt-Pt	3.2	7.0	76	30 (23)
4	MeCN	1.9	Pt-Pt	3.2	6.0	85	27 (23)
5	MeCN	0.37	Graphite-Pt	2.4 ~ 3.3	4.5	100	0(0)
6	THF	0.37	PtPt	4.0	5.6	20	0(0)

^a Substrate 1: 0.1 M, electrolyte: 50 ml, undivided cell.

^b Based on consumed 1. Figures in parenthesis show isolated yields.

was reported to improve the yield of anodic monofluorination of methyl phenyl sulfide [20], resulted in prevailing oxidation of THF over substrate 1 and any fluorinated products were not obtained at all (run 6). We have recently observed that novel molten salt $Et_4NF \cdot 4HF$ was an efficient supporting electrolyte especially for the anodic fluorination of the compounds having high oxidation potentials [21]. However, using $Et_4NF \cdot 4HF$ as a supporting electrolyte instead of $Et_3N \cdot 3HF$, 1 was not oxidized at all even at a higher anodic potential because 1 was protonated by $Et_4NF \cdot 4HF$ due to stronger acidity of $Et_4NF \cdot 4HF$ than that of $Et_3N \cdot 3HF$.

In conclusion, ethyl 2-fluoroisonicotinate 2 was obtained in reasonable yield by direct anodic monofluorination of ethyl isonicotinate 1. The yield of fluorinated product and the conversion of the electrochemical reaction could be improved by applying relatively lower anodic potential and by increasing the concentration of supporting electrolyte Et₃N · 3HF.

3. Experimental

3.1. Apparatus

¹H NMR and ¹⁹F NMR spectra were recorded at 60 MHz on Varian EM 360 NMR and Hitachi R-1200F NMR spectrometers, respectively. The chemical shifts for ¹H and ¹⁹F NMR are given in δ ppm downfield from internal Me₄Si and from external CF₃COOH, respectively. IR spectra were obtained with a Hitachi 295 infrared spectrometer. Mass spectra were obtained with a JEOL JMS-D100 GC-mass spectrometer. Preparative electrolysis experiment was carried out using a Hokutodenko HA-501 Potentiostat/Galvanostat equipped with a Hokutodenko HF-201 digital coulometer.

3.2. Anodic fluorination of heteroaromatic compounds

A typical electrolysis was performed potentiostatically in an undivided cell using a platinum anode and cathode (4×3) cm²) in 0.37 M Et₃N·3HF/MeCN (50 ml) containing 5 mmol of substrate. The electrolysis was performed at room temperature. After the starting material was almost consumed (monitoring by silica gel TLC and/or mass spectrometry), 50 ml of CH₂Cl₂ was added to the electrolysis solution which was then neutralized by bubbling ammonia gas. After removal of precipitated salt by filtration, resulting filtrate was concentrated by evaporation. The product was then isolated by column chromatography on silica gel (hexane/ethyl acetate = 1:1).

Ethyl 2-fluoroisonicotinate (**2**): ¹H NMR δ: 1.42 (t, 3H, J=7.1 Hz, CH₃); 4.44 (q, 2H, J=7.1 Hz, CH₂); 7.50 (m, 1H, aromatic H); 7.73–7.76 (m, 1H, aromatic H); 8.36–8.38 (m, 1H, aromatic H) ppm. ¹⁹F NMR δ: +10.8 (s) ppm. IR (cm⁻¹): 3000; 1745 (C=O); 1610; 1575; 1480; 1405; 1370; 1300; 1250; 1210; 1095; 1015; 935; 760. MS m/z: 169 (M⁺); 141; 124. Calc. for C₈H₈FNO₂: m/z 169.0538. Found: m/z 169.0528.

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