Selective Anodic Fluorination of Flavones[1]

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Received 28 April 1998

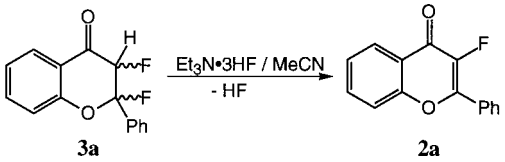
Abstract: Anodic fluorination of flavone and 6-chloroflavone was carried out using Et_3N•3HF and Et_4NF•4HF as supporting electrolytes. The former supporting electrolyte provided 3-monofluorinated flavones **2** preferentially while the latter one gave 2,3-difluorinated flavones **3** predominantly. It was also found that the yields of **2** increased significantly at a higher temperature as 30°C. Furthermore, it was confirmed that **2** was formed by dehydrofluorination of **3** with free Et_3N in Et_3N•3HF.

Although many methods of preparation of fluoroorganics have been developed to date, the construction of ring-fluorinated heterocyclic systems has been less explored. Recently, selective electrochemical fluorination has been shown to be a highly efficient new tool to synthesize various fluoroorganic compounds. The reaction can be carried out under mild conditions using a relatively simple equipment to avoid hazardous or toxic reagents which are necessary in chemical fluorination.[2] However, only limited successful examples of anodic fluorination of heterocycles have been reported to date, and in all the cases, low yields and poor selectivities appear to be the major problems in electrochemical synthesis.[3]

From these viewpoints, we have developed highly selective anodic fluorination of various kinds of heterocyclic compounds.[1,4] On the other hand, flavone and its derivatives are commonly used as precursors for many pharmaceutical products such as anticancer.[5] It is also well recognized that incorporation of fluorine atoms into the organic molecules used for medicines can profoundly influence their biological properties.[6]

With these facts in mind, anodic fluorination of biologically interesting flavone **1a** and its chloro derivative **1b** was attempted by using a conventional supporting electrolyte, Et_3N•3HF and a recently developed supporting electrolyte, Et_4NF•4HF.[7] So far, a few limited examples of anodic fluorination of oxygen-containing heterocycles have been reported but their yields were low except for α-phenylthiolactones.[8] Anodic fluorination of **1** was carried out with platinum electrodes in anhydrous acetonitrile containing Et_3N•3HF or Et_4NF•4HF using a divided cell with an anion exchange membrane at ambient temperature except for two cases (see Table 1).[9]

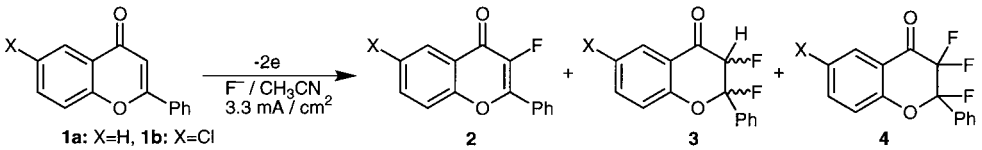
As shown in Table 1, a conventional supporting electrolyte, Et_3N•3HF provided monofluorinated product **2** preferentially.[10] In this case, difluorinated product **3** was not formed. At a higher temperature such as 30°C, the yield of **2** increased significantly. Such a temperature effect has never been reported on the anodic partial fluorination so far. However, the reason is not clear at present. In sharp contrast, a different type of supporting electrolyte, Et_4NF•4HF[7] gave mainly difluorinated product **3** as a stereoisomeric mixture and only a small amount of **2** was formed. Since Et_3N•3HF contains a appreciable amount of free Et_3N,[11] **2** seems to be formed by dehydrofluorination of **3** with free Et_3N during the electrolysis. In fact, **3** was treated with Et_3N•3HF / MeCN to provide **2** in reasonable yield as 63%(Scheme 1).



Scheme 1

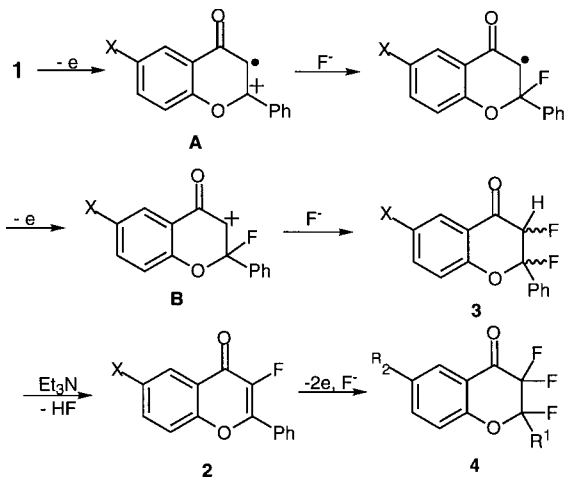
From these results, the reaction mechanism can be shown in Scheme 2. Since the double bond of the enol ether moiety is most easily oxidized, anodic oxidation takes place selectively at the olefin to generate the radical cation intermediate **A** as shown in Scheme 2. Then, this radical cation reacts with a fluoride ion followed by further oxidation to form cationic intermediate **B**, which provides the difluorinated product **3**. As explained above (Scheme 1), **2** should be formed from **3**. Since **2a** is more easily oxidized by 0.08 V than the starting flavone **1a**, **4** seems to be formed by further oxidation of **2**.

Table 1. Anodic Partial Fluorination of Flavone and 6-Chloroflavone



Flavones	Supporting Electrolyte	Charge Passed (F / mol)	Yield (%) 2	3(*cis-/trans*)	4	Total Yield (%)
1a	Et_3N•3HF	3.5	43	0	6	49
1a	Et_3N•3HF	3.5[a]	58	0	19	77
1a	Et_4NF•4HF	3.5	7	68(2/1)	9	84
1b	Et_3N•3HF	4.8	41	0	9	50
1b	Et_3N•3HF	4.8[a]	62	0	24	86
1b	Et_4NF•4HF	4.8	2	44(2/1)	9	55

a) Electrolysis was carried out at 30°C



Scheme 2

Thus, we have shown efficient and selective anodic fluorination of biologically interesting oxygen-containing heterocycles, flavones. Furthermore, we have demonstrated for the first time fluorinated product selectivity greatly depending on the kind of supporting fluoride salts. These findings seem to be of importance for developing selective anodic fluorination of organic molecules.

Acknowledgment. We thank Morida Chemical Industrials Co. Ltd. for a generous gift of $Et_4NF•4HF$.

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(9) A typical procedure for the anodic fluorination of flavone **1a** is as follows. Anodic oxidation of **1a** (1 mmol) was carried out with platinum plate electrodes (3x2 cm^2) in 0.2 M $Et_4NF•4HF$ or 0.33 M $Et_3N•3HF$ (20 equiv. of F^- to **1a**)/MeCN (20 mL) using a divided cell with an anion exchange membrane (IE-DF34-5 TOSOH) under a nitrogen atmosphere at room temperature. Constant current (3.3 mA/cm^2) was passed. After the electrolysis, the electrolyte was neutralized with saturated $NaHCO_3$ solution and the resulting aqueous solution was extracted with ether repeatedly. After the combined extracts were dried over anhydrous $MgSO_4$, *trans*-2,3-fluoroflavone **3a** and 2,3,3-trifluoroflavone **4a** were isolated by silica gel chromatography (hexane:$CHCl_3$=5:1). Or, crude products were treated with $Et_3N•3HF$ / MeCN (stirring at room temperature for 3 h). After evaporation, the pure monofluorinated flavone **2a** was obtained by recrystallization from methanol. In the case of 6-chloroflavone (**1b**), in order to dissolve the starting materials completely in the electrolytic solution, a small amount of CH_2Cl_2 was added.

(10) **3-Fluoroflavone (2a)**: ^1H NMR δ 7.42~8.30 (m, 9H); ^{19}F NMR δ -84.26 (s). MS (EI) m/z: 240 (M^+), 212 (M^+-CO). Anal. Calcd for $C_{15}H_9FO_2$: C, 75.00; H, 3.78; F, 7.91. Found: C, 74.86; H, 3.89; F, 7.92. ***trans*-2,3-Difluoroflavone (3a)**: ^1H NMR δ 7.19~8.05 (m, 9H), 4.80 (d, 46.85 Hz); ^{19}F NMR δ -114.92 (dd, 46.89Hz, 20.23 Hz), -39.85 (d, 20.22 Hz). MS (EI) m/z: 260 (M^+), 240 (M^+-HF), 212 (M^+-HF-CO), 183 (M^+-Ph). HRMS m/z calcd for $C_{15}H_{10}F_2O_2$, 260.0649, found 260.0645. ***cis*-2,3-Difluoroflavone (3a):** ^{19}F NMR δ -135.93 (dd, 45.96 Hz, 15.63 Hz), -52.09 (dd, 28.50 Hz, 15.63 Hz). **2,3,3-Trifluoroflavone (4a)**: ^1H NMR δ 7.20~8.06 (m, 9H); ^{19}F NMR δ -60.88 (dd, 285.87 Hz, 11.49 Hz), -48.59 (t, 11.49 Hz), -36.78 (dd, 285.87 Hz, 11.03 Hz). MS (EI) m/z: 278 (M^+), 259 (M^+-F), 231 (M^+-F-CO). HRMS m/z calcd. for $C_9H_5FO_2$, 278.0555, found 278.0553. **3-Fluoro-6-chloroflavone (2b)**: ^1H NMR δ 7.52~8.27 (m, 8H); ^{19}F NMR δ -83.81 (s). MS (EI) m/z: 274 (M^+), 246 (M^+-CO), 207 (M^+-CO-CF). HRMS m/z calcd for $C_{15}H_8ClFO_2$ 274.0197, found 274.0211. **2,3-Difluoro-6-chloroflavone (3b)**: MS (EI) (*cis*, *trans* isomeric mixture) m/z: 294 (M^+), 274 (M^+-HF), 246 (M^+-HF-CO), 217 (M^+-Ph). HRMS m/z calcd for $C_{15}H_9ClF_2O_2$ 294.0259, found 294.0253. *trans form:* ^{19}F NMR δ -115.01 (dd, 46.89 Hz, 20.22 Hz), -40.12 (d, 20.22 Hz). *cis form:* ^{19}F NMR δ -135.90 (dd, 45.90 Hz, 15.63 Hz), -52.09 (dd, 28.24 Hz, 15.63 Hz). **2,3,3-Trifluoro-6-chloroflavone (4b)**: ^{19}F NMR δ -61.18 (dd, 285.87 Hz, 11.48 Hz), -48.69 (t, 11.48), -36.81 (dd, 285.87 Hz, 11.04 Hz). MS (EI) m/z: 312 (M^+), 274 (M^+-2F), 265 (M^+-F-CO). HRMS m/z calcd. for $C_{15}H_8ClF_3O_2$ 312.0165, found 312.0146.

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