Electrolytic Partial Fluorination of Organic Compounds. 32.[1] Regioselective Anodic Mono- and Difluorination of Flavones

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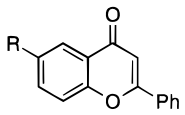
Introduction

Recently, selective electrochemical fluorination has been shown to be a highly efficient new tool for synthesizing various fluoroorganic compounds. The reaction can be carried out under mild conditions using relatively simple equipment and also avoids hazardous or toxic reagents which are necessary in chemical fluorination.[2,3] However, only limited examples of selective anodic fluorination of heterocycles have been reported to date, and in all cases, low yields and poor selectivities appeare to be the major problems in electrochemical synthesis.[4] Therefore, highly selective anodic fluorination of various nitrogen- and/or sulfur-containing heterocyclic compounds has been developed in our group.[3,5] However, only a few examples of anodic fluorination of oxygen-containing heterocycles have been reported so far. Although α-phenylthiolactones[6] and 1,3-oxathiolanones[7] were efficiently fluorinated, aromatic oxygen-containing heterocyclic compounds such as benzofuran and furan did not give any isolable fluorinated products due to their instability.[4b] On the other hand, flavone and its derivatives are commonly used as precursors for many pharmaceutical products such as anticancer pharmaceuticals.[8] It is also well recognized that incorporation of fluorine atoms into the organic molecules used for medicines can significantly alter their biological function.[9]

With these facts in mind, anodic fluorination of biologically interesting flavones **1** was attempted by using a conventional $Et_3N{\cdot}3HF$ supporting electrolyte and a recently developed $Et_4NF{\cdot}4HF$ supporting electrolyte.[10]

Table 1. Oxidation Potentials (Peak Potentials, E_p^{ox}) of Flavone and Its Derivatives[a]



1

substrate no.	R	E_p^{ox} (V vs SSCE)
1a	H	2.50
1b	CH_3	2.36
1c	Cl	2.52

[a] In 0.1 M $Bu_4N{\cdot}BF_4/CH_3CN$. Sweep rate: 100 mV/s.

Table 2. Effect of Supporting Electrolyte on Anodic Partial Fluorination of Flavone 1a[a]

run	supporting electrolyte	yield (%) **2a**	**3a** (cis/trans)	**4a**
1	$Et_3N{\cdot}3HF$	43	0	6
2	$Et_3N{\cdot}5HF$	9	28 (3/1)	4
3	$Et_4NF{\cdot}3HF$	3	54 (2/1)	6
4	$Et_4NF{\cdot}4HF$	7	68 (2/1)	9

[a] Constant current (3.3 mA/cm^2) electrolysis was carried out at room temperature, and 3.5 F/mol of electricity was passed.

Results and Discussion

Oxidation Potential of Flavone and Its Derivatives. The oxidation potentials of **1a**−**1c** were determined using a platinum electrode in 0.1 M $Bu_4N{\cdot}BF_4$/MeCN and a SSCE (sodium saturated calomel electrode) reference electrode by cyclic volammetry. All the compounds chosen in the present study showed irreversible oxidation peaks. The first oxidation peak potentials (E_p^{ox}) were observed in the range of 2.36−2.52 V as shown in Table 1. 6-Methylflavone **1b** was oxidized at a less positive potential compared with the other two derivatives, owing to the electron-donating methyl substituent on the benzene ring.

Anodic Fluorination of Flavone and Derivatives. Anodic fluorination was carried out at platinum electrodes in anhydrous acetontrile using a divided cell fitted with an anion exchange membrane. Various fluoride salts were used as both the supporting electrolyte and fluoride ion source. A constant current was applied until the starting material, flavone **1**, was almost consumed. The results of **1a** are summarized in Table 2 and Scheme 1.

As shown in Table 2, the conventional supporting electrolyte, $Et_3N{\cdot}3HF$ provided monofluorinated product **2a** preferentially. In this case, difluorinated product **3a** was not formed. In sharp contrast, the other supporting electrolytes gave mainly difluorinated product **3a** as a stereoisomeric mixture and only a small amount of **2a**

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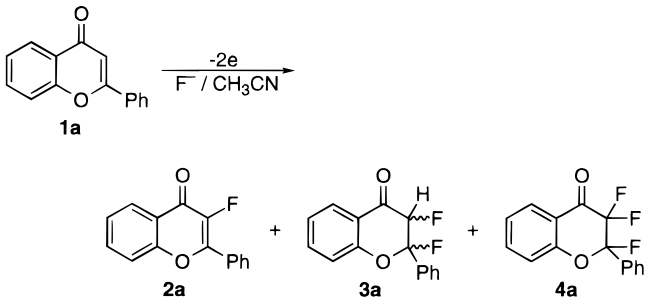
Scheme 1



Scheme 2

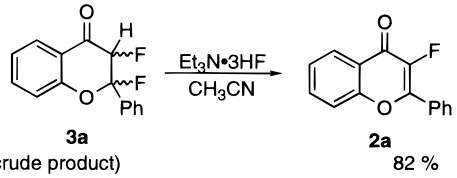


Table 3. Effect of Temperature on Anodic Partial Fluorination of Flavone 1a Using Et_3N·3HF as a Supporting Electrolyte

run	temperature (°C)	yield (%) 2a	4a
1	−10	9	trace
2	0	27	3
3	10	31	4
4	20	43	6
5	30	58	19

[a] 3.5 F/mol of electricity was passed.

was formed. This product distribution dependency on the choice of the supporting fluoride salt has not been previously reported for the case of anodic partial fluorination. Since Et_3N·3HF contains a considerable amount of free Et_3N,[11] **2a** seems to be formed by dehydrofluorination of **3a** with free Et_3N during the electrolysis. In fact, **3a** treated with Et_3N·3HF/MeCN produced **2a** in good yield as high as 82% (Scheme 2).

Next, the effect of temperature on the anodic fluorination was investigated. Anodic fluorination using **1a** as a model compound was carried out using Et_3N·3HF at various temperatures as shown in Table 3. When the temperature increased, the yield of **2a** also significantly increased and a 58% **2a** yield was obtained at 30 °C. On the other hand, the **2a** yield decreased sharply at lower temperatures such as −10 °C. Such temperature effects have also not been previously reported for the case of anodic partical fluorination. Although, the reason is presently not clear, the increased amount of free Et_3N in Et_3N·3HF produced at a higher temperature[12] is expected to facilitate dehydrofluorination of **3a** formed during the electrolysis, resulting in an increase **2a** yield.

Then, this anodic fluorination method was applied to the flavone derivatives **1b** and **1c**, which have a chloro or a methyl group on the benzene ring. Et_3N·3HF and Et_4NF·4HF were used as the supporting electrolyte as shown in Scheme 3. The results are summarized in Tables 4, and 5. Typically, when Et_3N·3HF was used, a

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(12) We found that the amount of free Et_3N in Et_3N·3HF increased with increase of temperature: Furuta, S.; Fuchigami, T. Unpublished results.

Scheme 3

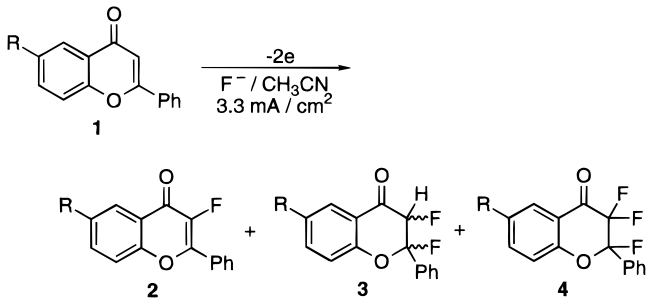


Table 4. Anodic Partial Fluorination of Flavone and Derivatives Using Et_3N·3HF as a Supporting Electrolyte

run	substrate no.	R	temp (°C)	charge passed (F/mol)	yield (%) 2	3	4
1	**1a**	H	rt	3.5	43	0	6
2	**1a**	H	30	3.5	58	0	19
3	**1b**	CH_3	rt	3.0	19	trace	2
4	**1b**	CH_3	30	3.0	20	trace	2
5	**1c**	Cl	rt	4.8	41	0	9
6	**1c**	Cl	30	4.8	62	0	24

Table 5. Anodic Partial Fluorination of Flavone and Derivatives Using Et_4NF·4HF as a Supporting Electrolyte[a]

run	substrate no.	R	charge passed (F/mol)	yield (%) 2	3 (cis/trans)	4
1	**1a**	H	3.5	7	68 (2/1)	9
				63[b]	0	9
2	**1b**	CH_3	3.0	2	29 (3/1)	4
				25[b]	0	4
3	**1c**	Cl	4.8	2	54 (2/1)	9
				40[b]	0	9

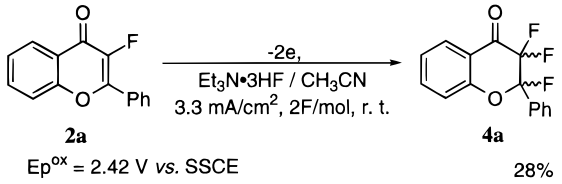
[a] The reactions were carried out at room temperature. [b] The yield of **2** obtained after dehydrofluorination of crude product **3** with Et_3N·3HF/MeCN.

fluorine atom was mainly introduced into the 3-position of **1b** and **1c** as shown in Table 4. When a higher temperature such as 30 °C was used, the **2c** and **4c** yields increased significantly in a manner similar to that of the case of **1a**. However, in contrast to the **1a** and **1c** cases, the fluorination of **1b** became more complicated, and the yield of **2b** did not increase even at a higher temperatures. This can be attributed to the **1b** benzylic protons being easily subject to nucleophilic substitution. In fact, the benzylic fluorination was confirmed by ^{19}F NMR. In sharp contrast, Et_4NF·4HF produced different main products, the corresponding difluorinated products **3**. As already explained, **2a** was found to be derived from **3a**. Therefore, conversion of **3b**,**c** to **2b**,**c** was also similarly attempted. The yields obtained by dehydrofluorination of crude products with Et_3N/CH_3CN are summarized in Table 5.

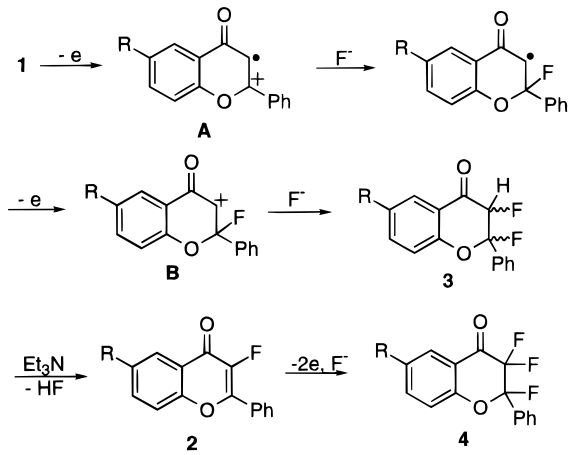
It is notable that trifluorinated product **4** was always produced regardless of which supporting fluoride salt was used. To clarify the trifluoroflavones **4** formation mechanism, anodic oxidation of monofluoroflavone **2a** was used as a model compound under the same electrolytic conditions used for anodic fluorination of **1a**. Only trifluoroflavone **4a** was produced in reasonable yield as shown in Scheme 4, and no difluorinated flavone **3a** was formed at all.

Since **2a** is more easily oxidized at a 0.08 bias voltage than the starting flavone **1a**, **4** seems to have been formed by further oxidation of **2**. Although acetamidation com-

Scheme 4



Scheme 5



monly takes place in chemical[13] and electrochemical[2] fluorination of olefines,[13] it is noted that no product related to acetamidation was detected in the anodic fluorination of **1**.

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 5. Then, this radical cation reacts with a fluoride ion followed by further oxidation to form cationic intermediate **B**,[14] which provides the difluorinated products **3**. It is noted that the *cis*-difluoro isomer of **3** was always formed as a major product in such reactions.[16] This is probably due to the adsorption of the intermediate **B** on the anode. Similar adsorption effects leading to the preferable formation of a *cis*-difluoro isomer have been reported by Laurent et al.[17,18] As already explained (Scheme 1), **2** should be formed from **3** by dehydrofluorination with Et_3N in $Et_3N{\cdot}3HF$.

It is well-known that methods for the introduction of fluorine into organic compounds require expensive and/or hazardous reagents. In recent years, *N*-F type reagents such as *N*-fluoropyidinium salts[19] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA)[20] have been developed and have been shown to be effective fluorinating reagents. Fluorination of compound **1a** as a model compound with various *N*-fluoropyridinium triflates was attempted (Scheme 6), and the results are summarized in Table 6. A less powerful *N*-fluoropyridinium salt did not produce any fluorinated products, and the starting material **1a** was almost all recovered. On the other hand, a more powerful *N*-fluoro(2,6-dichloro)pyridinium salt provided the monofluorinated product **2a** under reflux; however, the yield was very low. Therefore, this electrochemical fluorination is a superior procedure to the conventional chemical fluorination methods.

Scheme 6

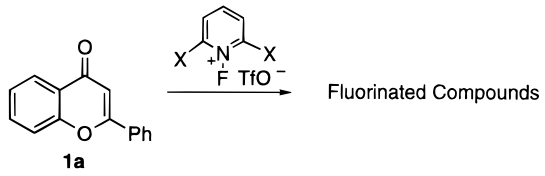


Table 6. Chemical Fluorination of Flavone 1a Using *N*-Fluoropyridinium Salts

run	*N*-fluoro-pyridinium salt (X)	temp	solvent	reaction time (h)	yield (%) 2a	3a	4a
1	Cl	rt	CH_3CN	10	trace	0	0
2	Cl	reflux	CH_3CN	4	17	0	4
3	Cl	reflux	CH_2Cl_2	4	21	0	4
4	H	rt	CH_3CN	10	0	0	0
5	H	reflux	CH_3CN	6	0	0	0

In summary, we have successfully carried out anodic partial fluorination of flavones, and we have also demonstrated for the first time fluorinated product distribution greatly depending on the kind of supporting fluoride salts. These findings are of importance for further development of anodic partical fluorination of organic molecules.

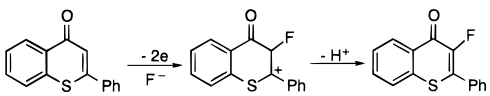
Experimental Section

Caution: $Et_4NF{\cdot}4HF$ and $Et_3N{\cdot}5HF$ were obtained from Morita Chemical Industries Co. Ltd. They are toxic and may cause serious burns if they come in contact with unprotected skin, while $Et_4NF{\cdot}3HF$ and $Et_3N{\cdot}3HF$ are much less aggressive. However, proper safety precautions should be taken at all times.[21] It is therefore recommended to provide hand protection. ^1H NMR and ^{19}F NMR spectra were recorded at 270 and 254 MHz, respectively, using $CDCl_3$ as a solvent. The chemical shifts for ^1H and ^{19}F NMR are given in δ ppm downfield from internal Me_4Si and C_6F_6 [δ ($CFCl_3$) of the C_6F_6 reference is -162.2 ppm], respectively. Fluorinated anion-exchange membrane (IE-DF34-5 TOSOH) is purchased from Tosoh Corporation, Japan.

Anodic Fluorination of Flavone and Its Derivatives. A typical procedure for anodic fluorination of flavone **1a** is as follows. Anodic oxidation of **1a** (1 mmol) was carried out with platinum plate electrodes (3 cm × 2 cm) in 0.2 M $Et_4NF{\cdot}4HF$ or 0.33 M $Et_3N{\cdot}3HF$ (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. A constant current (3.3 mA/cm^2) was passed. After the electrolysis,

(13) Zupan, M.; Skulj, P.; Stavber, S. *Chem. Lett.* **1998,** 641.

(14) Recently, Laurent et al. reported anodic fluorination of 2-phenylthiochromen-4-one in a quite similar manner to that of flavones using $Et_3N{\cdot}3HF$/MeCN to provide 3-mono- and 2,3,3-trifluoroproducts.[15] Since they did not obtain 2,3-difluorinated product (similar to **3**), they propsed that 3-fluoro-2-phenylthiochromen-4-one was directly formed from 3-fluoro cationic intermediate as follows:



(15) Andres, D.; Dietrich, U.; Laurent, E.; Marquet, B. *Tetrahedron* **1997**, *53*, 647.

(16) However, the separation of the trans and cis isomers was unsuccessful in most cases. The cis isomers could not be isolated in all cases due to their instability. The stereochemistry of **3** was determined on the basis of the vicinal fluorine−hydrogen coupling constants of ^{19}F NMR similar to the case of 2-amino-1-fluoro-1-phenylcyclohexane reported by Wade and Guedj: Wade, T. N.; Guedj, R. *Tetrahedron Lett.* **1978**, 3247.

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(21) Peters, D.; Metchen, R. *J. Fluorine Chem.* **1996**, *79*, 161.

the electrolyte was neutralized with a satutated $NaHCO_3$ solution and the resulting aqueous solution was extracted with ether repeatedly. After the combined extracts were dried over anhydrous $MgSO_4$, *trans*-2,3-difluoroflavone **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 tempeture for 3 h). Pure monofluorinated flavone **2a** was obtained by recrystallization from methanol. In the anodic fluorination of 6-chloroflavone (**1c**), to dissolve the starting materials completely in the electrolytic solution, 20 mL of CH_2Cl_2/CH_3CN (1:2) was used as an electrolytic solvent. The results shown in Tables 2−6 are easily reproducible.

3-Fluoroflavone (2a): ^{1}H 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.

2,3-Difluoroflavone (3a). **Trans form:** ^{1}H NMR δ 7.19−8.05 (m, 9H), 4.80 (d, 46.85 Hz, 1H); ^{19}F NMR δ −114.92 (dd, 46.89 Hz, 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 form:** ^{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): ^{1}H 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 $C_{15}H_9F_3O_2$, 278.0555, found 278.0553.

3-Fluoro-6-methylflavone (2b): ^{1}H NMR δ 7.38−8.22 (m, 8H), 2.41 (s, 3H); ^{19}F NMR δ −84.22 (s). MS (EI) *m*/*z*: 254 (M^+), 226 ($M^+ - CO$), 208 ($M^+ - CF - CH_3$), 134 [$M^+ - (PhC{\equiv}CF)$]. HRMS: *m*/*z* calcd for $C_{16}H_{11}FO_2$, 254.0743, found 254.0743.

2,3-Difluoro-6-methylflavone (3b): MS (EI) (cis and trans isomeric mixture) *m*/*z*: 274 (M^+), 254 ($M^+ - HF$), 226 ($M^+ - HF - CO$), 197 ($M^+ - Ph$). HRMS: *m*/*z* calcd for $C_{16}H_{12}F_2O_2$, 274,0805, found 274.0793. **Trans form**: ^{19}F NMR δ −114.85 (dd, 20.22, 46.88 Hz), −40.42 (d, 20.22 Hz). **Cis form:** ^{19}F NMR δ −135.90 (dd, 16.08, 45.96 Hz), −51.59 (dd, 16.08, 28.10).

2,3,3-Trifluoro-6-methylflavone (4b): ^{19}F NMR δ −61.04 (dd, 11.95, 285.87), −48.69 (t, 11.49), −36.76 (dd, 11.03, 285.87). MS (EI) *m*/*z*: 292 (M^+), 254 ($M^+ - 2F$), 226 ($M^+ - 2F - CO$). HRMS: *m*/*z* calcd for $C_{16}H_{11}F_3O_2$, 292.0711, found 292.0699.

3-Fluoro-6-chloroflavone (2c): ^{1}H NMR δ 7.52−8.27 (m, 8H); ^{19}F NMR δ −83.81 (s). MS (EI) *m*/*z*: 276 ($M^+ + 2$), 274 (M^+), 258 ($M^+ - O$), 246 ($M^+ - CO$), 138 ($M^+ - CO - CF - Ph$). HRMS: *m*/*z* calcd for $C_{15}H_8ClFO_2$ 274.0197, found 274.0211.

2,3-Difluoro-6-chloroflavone (3c): MS (EI) (cis and trans isomeric mixture) *m*/*z*: 296 ($M^+ + 2$), 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 (4c): ^{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*: 314 ($M^+ + 2$), 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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