Electrolytic Partial Fluorination of Organic Compounds. 22.[1] Highly Regioselective Anodic Monofluorination of Oxindole and 3-Oxo-1,2,3,4-tetrahydroisoquinoline Derivatives: Effects of Supporting Fluoride Salts and Anode Materials

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Highly regioselective monofluorination of 1-aryl-3-(phenylthio)oxindoles and 2-substituted-3-oxo-4-(phenylthio)-1,2,3,4-tetrahydroisoquinolines can be successfully carried out in the presence of $Me_4NF{\cdot}4HF$ or $Et_4NF{\cdot}3HF$ as a supporting electrolyte to provide the corresponding 3-fluorinated oxindole and 4-fluorinated isoquinoline derivatives in good yields. Carbon anodes as well as a platinum anode were found to be effective for the fluorination when $Me_4NF{\cdot}4HF$ was used as the supporting electrolyte.

Introduction

Fluoroorganic compounds have rather unique chemical, physical, and biological properties. For instance, many important biological activities have been found in a number of fluorinated heterocyclic compounds.[2−5] The synthesis of ring-fluorinated heterocyclic systems has been rather limited although a number of new methods for the preparation of fluoroorganics have been developed to date. Direct fluorination is the most simple way to prepare fluorinated heterocyclic compounds. However, direct fluorination is not always straightforward because conventional methods require hazardous, poisonous, or costly fluorinating reagents.[2,5] On the other hand, electrochemical partial fluorination seems to be promising for the synthesis of fluorinated heterocyclic compounds because this method does not require any hazardous reagents.[6,7] However, few examples of anodic fluorination of heterocycles have been reported to date,[8] and the yields were unsatisfactory in all cases.

Recently, electrochemical fluorination of sulfides has been proven to be an elegant and efficient way for the preparation of α-monofluorinated sulfides as reported by Laurent *et al.*[9] and our group[10] independently. In a preceding papers, we have reported a successful application of this electrochemical monofluorination to various aliphatic nitrogen- and/or sulfur-containing heterocycles[11] together with heterocyclic sulfides.[12] Among the anodically fluorinated heterocycles, monofluorinated 3-thiolanone derivatives showed marked biological activity such as PLA_2 inhibition.[13] On the other hand, oxindole and 3-oxo-1,2,3,4-tetrahydroisoquinoline are commonly used as starting materials and intermediates for many pharmaceutical products. These facts prompted us to attempt anodic monofluorination of oxindoles and 3-oxo-1,2,3,4-tetrahydroisoquinolines having a phenylthio group α to the carbonyl group. Furthermore, the effects of supporting fluoride salts and anode materials on the anodic fluorination were also investigated in this work.

Results and Discussion

Preparation of Oxindole and 3-Oxo-1,2,3,4-tetrahydroisoquinoline Derivatives. The starting oxindole and 3-oxo-1,2,3,4-tetrahydroisoquinoline derivatives bearing a phenylthio group at the position α to the carbonyl group were synthesized as shown in Scheme 1 in a manner similar to the procedure for the preparation of the corresponding heterocycles having a methylthio group.[14]

Oxidation Potentials of Oxindole and Isoquinoline Derivatives. The oxidation potentials of oxindole and isoquinoline derivatives were measured by means of cyclic voltammetry using a divided cell with platinum electrodes in 0.1 M $Bu_4N{\cdot}BF_4$/anhydrous acetonitrile. All the compounds chosen in the present study showed irreversible oxidation waves. The peak potentials for the first stage of oxidation are summarized in Table 1.

In comparing compound **1a** with **1b**, we found that substitution at the benzene rings with two electron-

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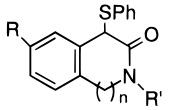
Table 1. Oxidation Potentials (Peak Potentials, E_p^{ox}) of Oxindole and Tetrahydroisoquinoline Derivatives[a]



1

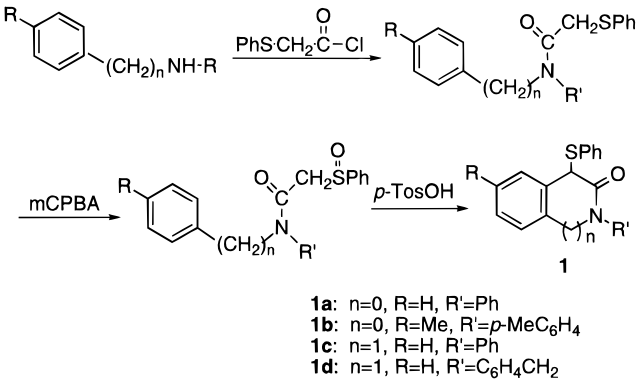
substrate				E_p^{ox}
no.	*n*	R	R′	(V vs SSCE)
1a	0	H	Ph	1.75
1b	0	CH_3	$CH_3C_6H_4$	1.55
1c	1	H	Ph	1.75
1d	1	H	$C_6H_5CH_2$	1.62

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

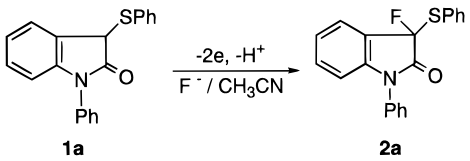
Table 2. Effect of Supporting Electrolyte on Anodic Monofluorination of 1-Phenyl-3-(phenylthio)oxindole (1a)

run	supporting electrolyte	charge passed (F/mol)	yield (%)
1	$Et_3N{\cdot}2HF$	6	3
2	$Et_3N{\cdot}3HF$	6	30
3	$Et_4NF{\cdot}2HF$	4	41
4	$Et_4NF{\cdot}3HF$	3.7	58
5	$Me_4NF{\cdot}4HF$	3.5	64

Scheme 1



Scheme 2



1a **2a**

donating methyl groups affected the oxidation potentials significantly, causing the oxidation peak to shift to less positive potentials. Interestingly, isoquinoline **1c** showed the same oxidation potential as oxindole **1a**, although their ring systems are different.

Anodic Fluorination of Oxindole and 3-Oxo-1,2,3,4-tetrahydroisoquinoline Derivatives. Anodic fluorination was carried out mainly at platinum electrodes in anhydrous acetonitrile with an undivided cell at constant current. Various fluoride salts were used as both the supporting electrolyte and the fluorine source. We determined the optimal experimental conditions by examining the details of electrolysis of 1-phenyl-3-(phenylthio)oxindole (**1a**) as a model compound. The results of anodic fluorination of **1a** are summarized in Table 2 and Scheme 2.

As shown in Table 2, anodic fluorination of 1-phenyl-3-(phenylthio)oxindole (**1a**) proceeded smoothly to give the corresponding 3-fluorinated product **2a** regardless of the supporting electrolytes except for $Et_3N{\cdot}2HF$. Among

Table 3. Effect of Electrode Materials on Anodic Monofluorination of Oxindole 1a[a]

	yield (%)	
anode	$Et_4NF{\cdot}3HF$	$Me_4NF{\cdot}4HF$
Pt	58	64
C-plate	28[b]	60
C-sheet	36[b]	59
C-felt	21[b]	42
Ebonex	24[b]	2

[a] Solvent: CH_3CN. Cathode: Pt. Current density: 4 mA/cm^2. Charge passed: 4 F/mol. [b] Starting material **1a** was recovered.

the fluorides, $Me_4NF{\cdot}4HF$[15] gave the best result and $Et_4NF{\cdot}3HF$ was also effective. Although $Et_3N{\cdot}3HF$ has been shown to be the most effective for anodic fluorination of organic sulfur compounds, owing to its strong nucleophilicity,[7] this fluoride salt gave a much lower yield compared with $Et_4NF{\cdot}3HF$ and $Me_4NF{\cdot}4HF$. Since the oxidation potential of $Et_3N{\cdot}3HF$ is lower than those of $Et_4NF{\cdot}3HF$ and $Me_4NF{\cdot}4HF$, $Et_3N{\cdot}3HF$ seems to be easily oxidized during the anodic fluorination of **1a**. In fact, a large excess amount of electricity was required until the starting **1a** was completely consumed when $Et_3N{\cdot}3HF$ was used. This probably caused a decrease of the yield of the fluorinated product **2a**. When the content (*n*) of HF in $R_4NF{\cdot}nHF$ (R = Me, Et) increased, the oxidation potential of the fluoride salts became more positive. Therefore, it is reasonable that a higher yield of **2a** is obtained with an increase of the HF content (*n*). Thus, $Et_4NF{\cdot}3HF$ or $Me_4NF{\cdot}4HF$ were found to be suitable for the fluorination of such an oxindole derivative.

Next, the effect of anodic materials on the anodic fluorination was investigated. Anodic fluorination of **1a** as a model compound was carried out at various anode materials as shown in Table 3. The starting **1a** was completely consumed when 4 F/mol of electricity was passed at a platinum anode in $Et_4NF{\cdot}3HF$ and $Me_4NF{\cdot}4HF$. Therefore, to compare the electrolytic results, the electrolysis was stopped when 4 F/mol was passed. The results are summarized in Table 3.

Anodic fluorination proceeded regardless of anodic materials expect for one: An Ebonex anode was not effective in $Me_4NF{\cdot}4HF$/MeCN, whereas in $Et_3NF{\cdot}3HF$/MeCN this anode provided the fluorinated product **2a** in a reasonable yield. Thus, the Ebonex anode was not so effective for anodic fluorination although this anodic material is known to be stable in a strongly acidic electrolytic solution. A platinum anode was the most suitable for the fluorination regardless of supporting electrolytes. When $Me_4NF{\cdot}4HF$ was used, carbon plate and sheet anodes as well as a platinum anode were effective for this fluorination. Since the former anodes are much cheaper than the latter one, this finding is quite important from a practical aspect.

Then, this anodic fluorination was extended to the other oxindole derivative **1b**, which has methyl groups on the benzene rings. Even in this case, a fluorine atom was introduced into the 3-position exclusively. Although benzylic anodic nucleophilic substitutions are well-known to take place easily, no benzylic fluorination was observed in the case of **1b**.

Next, we successfully extended this fluorination to 3-oxo-1,2,3,4-tetrahydroisoquinoline derivatives **1c,d** as

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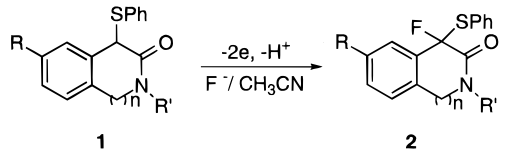
Table 4. Anodic Monofluorination of Oxindole and 3-Oxo-1,2,3,4-tetrahydroisoquinoline Derivatives

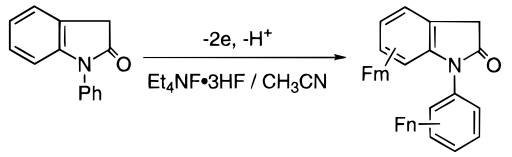
run	substrate no.	*n*	R	R′	supporting electrolyte	charge passed (F/mol)	yield (%)
1	**1a**	0	H	Ph	$Me_4NF{\cdot}4HF$	3.5	64
2	**1b**	0	CH_3	*p*-$CH_3C_6H_4$	$Me_4NF{\cdot}4HF$	3	50
3	**1c**	1	H	Ph	$Et_4NF{\cdot}3HF$	2.6	71
4	**1d**	1	H	$C_6H_5CH_2$	$Et_4NF{\cdot}3HF$	2	70

Scheme 3



1 2

Scheme 4



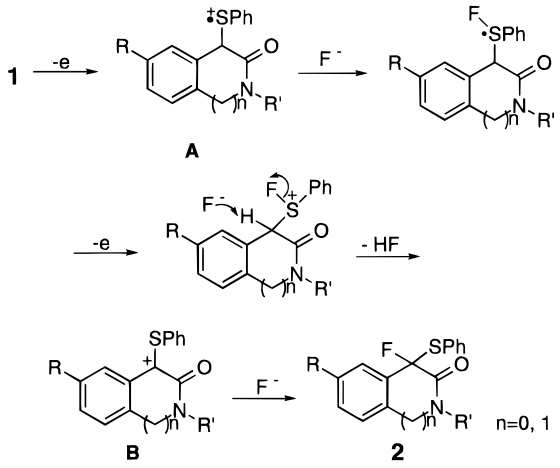
3 4

shown in Table 4. In these cases, even $Et_4NF{\cdot}3HF$ provided the corresponding desired fluorinated products **2c,d** in good yields and with rather good current efficiencies. Although **1d** has three kinds of benzylic carbons, the fluorination took place at the 4-position exclusively.[16] Therefore, it is noted that this anodic fluorination is highly regioselective.

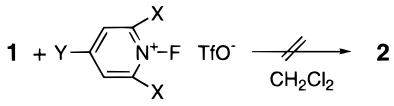
An ECEC mechanism is widely accepted for electrochemical nucleophilic substitution reactions. To clarify the fluorination mechanism in this case, we studied the influence of the phenylthio group on the fluorination reaction. In contrast to the case of **1**, the corresponding oxindole and 3-oxo-1,2,3,4-tetrahydroisoquinoline derivatives devoid of a phenylthio group did not undergo selective anodic fluorination, and complicated products arising from fluorination of the benzene rings were formed as shown in Scheme 4.[17] This clearly suggests that the phenylthio group plays an important role during anodic fluorination.

We have already proposed a Pummerer-type mechanism *via* a fluorosulfonium ion for the anodic fluorination of sulfides.[18] Therefore, the high regioselectivity of this anodic fluorination can be explained as follows. Since the phenylthio group is the most easily oxidized, anodic oxidation takes place at the sulfur atom selectively to generate the radical cation intermediate **A** as shown in Scheme 5. Elimination of the α-proton should be facilitated by the adjacent electron-withdrawing carbonyl group to form the cationic intermediate **B**, which provides the fluorinated product **2** predominantly.

Scheme 5



Scheme 6



(X=Y=H; X=Me,Y=Me; X=Cl, Y=H)

It is well-known that methods for the introduction of fluorine into organosulfur compounds require expensive and dangerous reagents such as xenon difluoride[19] or DAST.[20] In recent years, *N*-fluoropyridinium triflates and tetrafluoroborates have been developed as effective fluorinating reagents with variable fluorinating power.[21] However, fluorination of compound **1** as model compounds with various types of *N*-fluoropyridinium triflates resulted in no formation of desired products as shown in Scheme 6. In the case of *N*-fluoro-2,4,6-trimethylpyridinium and *N*-fluoropyridinium triflates, the starting **1** was almost completely recovered, whereas decomposition of **1** took place in the reaction with *N*-fluoro-2,6-dichloropyridium triflate. Therefore, this electrochemical fluorination is much superior to conventional chemical methods.

In summary, this work reveals that *N*-aryloxindole and 3-oxo-1,2,3,4-tetrahydroisoquinoline derivatives bearing a phenylthio group can be electrochemically fluorinated efficiently in good yields and with high regioselectivity. Thus, we have demonstrated that the electrochemical method is highly promising for direct fluorination of such biologically interesting heterocycles.

Experimental Section

Caution: $Me_4NF{\cdot}4HF$ is toxic and if in contact with skin causes serious burns. $Et_4NF{\cdot}3HF$, $Et_3N{\cdot}3HF$, and $Et_3N{\cdot}2HF$ are much less aggressive. However, proper safety precautions should be taken at all times. It is therefore recommended that hands be protected with rubber gloves. These fluoride salts were obtained from Morita Chemical Industries Co. Ltd. (Japan).

^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded at 270, 254, and 68 MHz, respectively, with $CDCl_3$ as a solvent. The chemical shifts for ^1H and ^{19}F NMR are given in δ (ppm)

(16) The regioselectivity for the fluorination of **1c,d** was determined using ^{19}F NMR, ^{13}CNMR, and DEPT (distortionless enhancement by polarization transfer). In DEPT, primary and tertiary carbon atoms appear with positive phase, while a secondary carbon atom appears in negative phase. Accordingly, by comparing the DEPT spectra of the starting materials with those of their products, we easily determined which carbon was substituted by a fluorine atom.

(17) In the case of anodic fluorination of isoquinolines in $Et_4NF{\cdot}4HF$/MeCN, polyfluorination took place at the benzene ring predominantly but the heterocyclic moiety was not fluorinated at all. Kato, K.; Momota, K. The 18th Symposium on Electroorganic Chemistry, Nagoya, Japan, 1995; Abstract 101.

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downfield from internal Me_4Si and perfluorobenzene, respectively. High-resolution mass spectra were obtained with a JEOL JMS-700 mass spectrometer. Cyclic voltammetry was performed with a Hokutodenko potentiostat/galvanostat HA 6-151, and preparative electrolysis experiments were carried out with a Metronix Corp. Tokyo constant-current power supply.

Preparation of Starting Materials. Oxindole and 3-oxo-1,2,3,4-tetrahydroisoquinoline derivatives **1a**−**d** were prepared in a manner similar to the reported method.[14] Typical synthetic procedure: N-Acylation of *N*-phenylaniline with α-(phenylthio)acetyl chloride[22] followed by oxidation of the resulting *N*-phenyl-α-(phenylthio)acetanilide with 3-chloroben-zoperoxic acid gave *N*-phenyl-α-(phenylsulfinyl)acetanilide in 48% yield. Treatment of the sulfoxide thus formed with 2 equiv of *p*-toluenesulfonic acid in boiling carbon tetrachloride provided 1-phenyl-3-(phenylthio)oxindole (**1a**) in 61% yield. **1a**: ^{1}H NMR δ 4.68 (s, 1H), 6.52−7.54 (m, 14H). Anal. Calcd for $C_{20}H_{15}NSO$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.57; H, 4.75; N, 4.34.

1-(*p*-Tolyl)-3-(phenylthio)-5-methyloxindole (1b): ^{1}H NMR δ 2.39 (s, 3H), 4.65 (s, 1H), 6.40−7.38 (m, 12H); MS *m/z* 345 (M^+), 236 ($M^+ - SPh$). Anal. Calcd for $C_{22}H_{19}NSO$: C, 76.49; H, 5.54; N, 4.05. Found: C, 76.18; H, 5.61; N, 4.03. HRMS: *m/z* calcd for $C_{22}H_{19}NSO$, 345.1221; found, 345.1214.

2-Phenyl-3-oxo-4-(phenylthio)-1,2,3,4-tetrahydroisoquinoline (1c): ^{1}H NMR δ 4.63 (s, 1H), 4.60 (d, 1H, J = 16.1 Hz), 4.90 (d, 1H, J = 16.1 Hz), 6.48−7.48 (m, 14H); MS (FAB) *m/z* 332 ($M + H^+$), 222 ($M^+ - SPh$). Anal. Calcd for $C_{21}H_{17}NSO$: C, 76.10; H, 5.17; N, 4.23. Found: C, 76.65; H, 5.17; N, 4.09. HRMS (FAB): *m/z* ($M + H^+$) calcd for $C_{21}H_{17}NSO$, 332.1109; found, 332.1116.

2-Benzyl-3-oxo-4-(phenylthio)-1,2,3,4-tetrahydroisoquinoline (1d): ^{1}H NMR δ 3.98 (s, 1H), 4.62 (d, 1H, J = 14.5 Hz), 4.71 (d, 1H, J = 14.8 Hz), 4.87 (s, 1H), 6.87−7.36 (m, 14H); MS *m/z* 345 (M^+), 236 ($M^+ - SPh$). Anal. Calcd for $C_{22}H_{19}NSO$: C, 75.68; H, 5.54; N, 4.05. Found: C, 76.24; H, 5.44; N, 3.92: HRMS *m/z* calcd for $C_{22}H_{19}NSO$, 345.1187; found, 345.1187.

Anodic Fluorination of Oxindole and 3-Oxo-1,2,3,4-tetrahydroisoquinoline Derivatives. A typical procedure for the anodic fluorination of oxindoles **1** is as follows. Anodic oxidation of **1a** (1 mmol) was carried out with platinum-plate electrodes (2 × 2 cm^2) in 0.25 M $Me_4NF{\cdot}4HF$[15] (10 equiv of F^- to **1a**)/MeCN (10 mL) in an undivided cell under a nitrogen atmosphere at room temperature. Constant current (4 mA/cm^2) was passed until the starting material **1a** was consumed (checked by TLC). After the electrolysis, the electrolyte was neutralized with 10% aqueous ammonia solution and the resulting aqueous solution was extracted with ether repeatedly. After the combined extracts were dried over anhydrous $MgSO_4$, 1-phenyl-3-(phenylthio)-3-fluorooxindole (**2a**) was isolated by silica gel chromatography (hexane:AcOEt = 5:1).

1-Phenyl-3-(phenylthio)-3-fluorooxindole (2a): ^{1}H NMR δ 6.80−7.65 (m, 14H); ^{19}F NMR δ −62.1 (s); MS (CI) *m/z* 336 ($M + H^+$), 316 ($M^+ - F$), 226 ($M^+ - SPh$). Anal. Calcd for $C_{20}H_{14}FNOS$: C, 71.62; H, 4.21; N, 4.18. Found: C, 71.71; H, 4.21; N, 3.97.

1-(*p*-Tolyl)-3-fluoro-3-(phenylthio)-5-methyloxindole (2b): ^{1}H NMR δ 2.25 (s, 3H), 2.40 (s, 3H), 6.60−7.65 (m, 12H); ^{19}F NMR δ −62.0 (s); MS *m/z* 363 (M^+), 344 ($M^+ - F$), 254 ($M^+ - SPh$). HRMS: *m/z* calcd for $C_{22}H_{18}FNOS$, 363.1093; found, 363.1069.

2-Phenyl-3-oxo-4-fluoro-4-(phenylthio)-1,2,3,4-tetrahydroisoquinoline (2c): ^{1}H NMR δ 4.78 (d, 1H, J = 16.4 Hz), 4.98 (d, 1H, J = 16.4 Hz), 6.66−7.62 (m, 14H); ^{19}F NMR δ −62.9 (s); MS *m/z* 349 (M^+), 330 ($M^+ - F$), 240 ($M^+ - SPh$). Anal. Calcd for $C_{21}H_{16}FNOS$: C, 72.18; H, 4.62; N, 4.01. Found: C, 72.21; H, 4.45; N, 4.02. HRMS: *m/z* calcd for $C_{21}H_{16}FNOS$, 349.0937; found, 349.0924.

2-Benzyl-3-oxo-4-(phenylthio)-4-fluoro-1,2,3,4-tetrahydroisoquinoline (2d): ^{1}H NMR δ 4.20 (d, 1H), 4.58 (d, 1H), 4.70 (d, 1H), 4.82 (d, 1H), 6.94−7.40 (m, 14H); ^{19}F NMR δ −60.8 (s); MS (CI) *m/z* 364 ($M + H^+$), 344 ($M^+ - F$), 254 ($M^+ - SPh$). Anal. Calcd for $C_{22}H_{18}FNOS$: C, 72.70; H, 4.99; N, 3.85. Found: C, 73.42; H, 5.15; N, 3.85. HRMS: *m/z* calcd for $C_{22}H_{18}FNOS$, 363.1093; found, 363.1091.

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