Electrolytic Partial Fluorination of Organic Compounds. 35.[1] Anodic Fluorination of 2-Pyrimidyl, 2-Pyridyl, and 2-Quinazolinonyl Sulfides

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Highly regioselective electrochemical fluorination of 2-pyrimidyl sulfides having an electron-withdrawing group (EWG) at the position α to the sulfur atom was successfully carried out using $Et_4NF{\cdot}nHF$ (n = 3, 4) or $Et_3N{\cdot}3HF$ as a supporting electrolyte and a fluoride ion source in 1,2-dimethoxyethane (DME) in an undivided cell. 2-Methylthiopyrimidine devoid of an EWG was also selectively fluorinated in DME to provide 2-(fluoromethylthio)pyrimidine in a moderate yield as 63%, while corresponding 2-methylthiopyridine was less selectively fluorinated in lower yield along with α,α-difluorinated product. In contrast, the corresponding 2-quinazolinonyl sulfides underwent similarly α-fluorination along with unexpected ipso-fluorination through anodic desulfurization.

Introduction

4(3*H*)-Quinazolinones are well-known as biologically active compounds that exhibit antilipidemic,[3] immunotropic,[4] antitumor,[5] anticonsulvant,[6] antimicrobial,[7] antifungal,[8] and insecticidal activities.[9] They are also useful as antiinflammatory,[10] antiulcer,[11] and antiemetic agents[12] and as potent fibrinogen receptor[13] and potential cholecystokinin antagonists.[14] On the other hand, fluoroorganic compounds have distinct chemical, physical, and biological properties;[15] in particular, they are useful as pharmaceuticals and plant protection agents. Therefore, introduction of fluorine atom(s) into the quinazolinone moiety or its side chain may have profound effects on their biological importance.

As part of our systematic research on anodic fluorination of heterocyclic sulfides,[16] we report herein a comparative study on the anodic behavior of 2-pyrimidyl sulfides **1**, 2-methylthiopyridyl sulfide (**2**), and 2-quinazolinonyl sulfides **3** toward various fluoride salts. In our previous work, we successfully carried out the anodic fluorination of 2-pyridyl sulfides having an electron-withdrawing group (EWG) at the position α to the sulfur atom using acetonitrile as an electrolytic solvent; however, the fluorination of 2-pyridyl sulfides devoid of an EWG did not proceed at all.[17]

In the present work, we examined the anodic fluorination of 2-pyrimidyl sulfides **1** having and devoid of an EWG and 2-methylthiopyridine (**2**) using 1,2-dimethoxyethane (DME) as an electrolytic solvent, and in all cases, the fluorination took place exclusively at the α-position to the sulfur atom. On the other hand, we carried out the anodic fluorination of 2-quinazolinonyl sulfides **3**, and an unprecedented and unexpected anodic ipso-fluorination at the 2-position of the quinazolinone moiety was observed along with the monofluorination at α to the sulfur atom.

Results and Discussion

Oxidation Potentials of Heterocyclic Sulfides 1a−d, 2, and 3a−c. The oxidation peak potentials (E_p^{ox}) of the starting sulfides were measured at a platinum anode in 0.1 M $Bu_4N{\cdot}BF_4/CH_3CN$ by cyclic voltammetry. All sulfides showed irreversible oxidation peaks, and the

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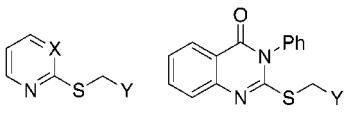
Table 1. Oxidation Potentials of 2-Pyrimidyl, 2-Pyridyl, and 2-Quinazolinonyl Sulfides

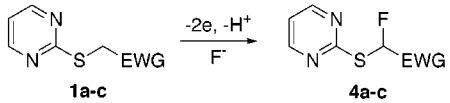


1, 2, 4d, 5 3

sulfide			
no.	X	Y	E_p^{ox}(V vs SSCE)[a]
1a	N	COMe	2.14
1b	N	COOEt	2.23
1c	N	CN	2.45
1d	N	H	2.06
2	CH	H	1.74
4d	N	F	2.35
5	CH	F	1.83
3a		COMe	1.83
3b		COOEt	2.01
3c		H	1.76

[a] In 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Anode: Pt plate. Sweep rate: 100 mV s^{-1}

Scheme 1



1a-c 4a-c

EWG = COMe. COOEt, CN

Table 2. Anodic Fluorination of 2-Pyrimidyl and 2-Pyridyl Sulfides 1 and 2[a]

	sulfide		supporting		charge passed	yield of **4**, **5**[b]
run	no.	EWG	electrolyte	solvent	(F/mol)	(%)
1	**1a**	COMe	$Et_4NF{\cdot}4HF$	DME	8	**4a**, 81 (74)[c]
2	**1a**	COMe	$Et_4NF{\cdot}3HF$	DME	9	**4a**, 65
3	**1a**	COMe	$Et_3N{\cdot}3HF$	DME	8	**4a**, 92 (78)[c]
4	**1a**	COMe	$Et_4NF{\cdot}4HF$	MeCN	8	**4a**, 0
5	**1b**	COOEt	$Et_4NF{\cdot}4HF$	DME	7	**4b**, 98 (78)[c]
6	**1b**	COOEt	$Et_4NF{\cdot}3HF$	DME	7	**4b**, 87
7	**1b**	COOEt	$Et_3NF{\cdot}3HF$	DME	9	**4b**, 84
8	**1c**	CN	$Et_4NF{\cdot}4HF$	DME	12	**4c**, 39 (35)[c]
9	**1c**	CN	$Et_4NF{\cdot}3HF$	DME	12	**4c**, 38
10	**1c**	CN	$Et_3NF{\cdot}3HF$	DME	12	**4c**, 20
11	**1d**	H	$Et_4NF{\cdot}4HF$	DME	10	**4d** 63 (46)[c,d]
12	**1d**	H	$Et_3NF{\cdot}3HF$	DME	10	**4d**, 52[d]
13	**2**	H	$Et_4NF{\cdot}4HF$	DME	10	**5**, 42[e] (22)[c]

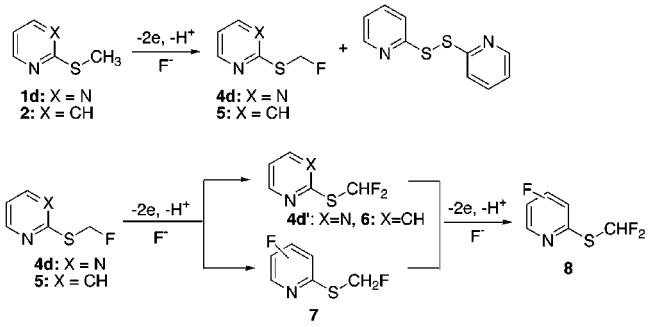
[a] Constant current electrolysis was carried out in an undivided cell. [b] Calculated on the basis of ^{19}F NMR. [c] Isolated yield. [d] Trace amount of 2-(α,α-difluoromethylthio)pyrimidine (**4d'**) was detected. [e] 8% yields of 2-(α,α-difluoromethylthio)pyridine (**6**) and trace amounts of 2-(α-fluoromethylthio)-6-fluoropyridine (**7**) and 2-(α,α-difluoromethylthio)-6-fluoropyridine (**8**) were detected.

values of E_p^{ox} are listed in Table 1. The oxidation potentials of 2-pyrimidyl sulfides **1** were higher than those of their corresponding 2-quinazolinonyl sulfides **3** by 0.2−0.3 V, and the presence of EWG at the position α to the sulfur atom caused the oxidation potential to increase in the following ascending order: H < COMe < COOEt < CN.

Anodic Fluorination of 2-Pyrimidyl and 2-Pyridyl Sulfides 1 and 2. We first investigated the anodic behavior of 2-(acetonylthio)pyrimidine (**1a**) toward various fluorine sources and electrolytic solvents (Scheme 1), and the results are summarized in Table 2.

It was found that the anodic fluorination of **1a** proceeded highly regioselectively and the fluorine atom was exclusively introduced to the α position to the sulfur atom, giving the α-monofluorinated sulfide **4a** in rather high yield, particularly when $Et_3N{\cdot}3HF$ was used as a fluorine source and a supporting electrolyte in DME (run 3). However, acetonitrile was not suitable at all as an electrolytic solvent, and an unidentified solid product was obtained but no desired fluorinated product was formed (run 4). Acetonitrile has been most commonly used as an electrolytic solvent for anodic partial fluorination so far; however, DME was found to be suitable for the fluorination of 2-pyrimidyl sulfide **1a**. Since DME has a much higher donor number (23.9) than acetontrile (14.1), DME seems to solvate the cationic part of the fluoride salt. The resulting naked fluoride anion easily attacks on the anodically generated cationic intermediate of **1a**.[18]

Scheme 2



1d: X = N 4d: X = N
2: X = CH 5: X = CH

4d: X = N 4d': X=N, 6: X=CH
5: X = CH 7 8

In a similar manner, anodic fluorination of the other 2-pyrimidyl sulfides **1b**,**c** was studied, and the regioselective α-monofluorination was also achieved. In contrast to the case of **1a**, **1b** proved to be readily and efficiently fluorinated when $Et_4NF{\cdot}4HF$/DME was used as the electrolytic solution, giving an almost quantitative yield of α-fluorosulfide **4b** (run 5). However, the yield was drastically decreased in the case of **1c** even using the same electrolytic solution, $Et_4NF{\cdot}4HF$/DME (run 8). The extremely high oxidation potential of **1c** compared to **1a**,**b** seems to be mainly attributable to the low yield of the fluorinated product, **4c**.

Furthermore, we carried out the anodic fluorination of 2-methylthiopyrimidine **1d** and 2-methylthiopyridine **2** devoid of EWG in $Et_4NF{\cdot}4HF$/DME and $Et_3N{\bullet}3HF$/DME. It was found that the fluorination of **1d** proceeded exclusively at the methyl group to give the α-monofluorosulfide **4d** in 63% yield with a trace amount of the α,α-difluorinated product **4d′** (Scheme 2).

The anodic fluorination of 2-methylthiopyridine **2** had been previously attempted in $Et_3N{\cdot}3HF/CH_3CN$, but only a trace amount of the desired α-fluorinated product was obtained.[17] We reexamined the fluorination of **2** in $Et_4NF{\cdot}4HF$/DME, and the desired α-monofluorinated product **5** (Scheme 2) was obtained in 42% yield, along with α,α-difluorinated product **6** in 8% yield, a significant amount of bis(2-pyridyl) disulfide, and trace amounts of **7** and **8**, which were the ring-fluorinated products of **5** and **6**, respectively. Their molecular ion peaks, a fragment ion peak due to fluoropyridine (*m*/*e* 97), and their chemical shifts together with coupling of ^{19}F NMR (δ around −44, doublet, J = 9.2 Hz) suggest the formation of the products of which rings (the 6-position) and α-positions are simultaneously fluorinated. The results of the fluorination of **1d** and **2** are summarized in Scheme 2.

The fluorination of **1d** takes place exclusively at the methyl group, since the electron density of the pyrimidine

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Table 3. Anodic Fluorination of 2-Quinazolinonyl Sulfides 3[a]

run	sulfide no.	sulfide EWG	solvent	supporting electrolyte	charge passed (F/mol)	conversion (%)	yield[b] (%) 9	yield[b] (%) 10
1	**3a**	COMe	DME	$Et_4NF{\cdot}4HF$	6	100	**9a**, 30	4
2	**3a**	COMe	DME	$Et_4NF{\cdot}3HF$	8	100	**9a**, 59 (48)	11 (9)
3	**3a**	COMe	DME	$Et_3NF{\cdot}3HF$	8	100	**9a**, 25	8
4	**3a**	COMe	CH_2Cl_2	$Et_4NF{\cdot}3HF$	7	100	**9a**, 3	
5[c]	**3a**	COMe	CH_3CN	$Et_4NF{\cdot}3HF$	8	100		
6	**3a**	COMe	DME	$Et_3N{\cdot}3HF$	10	51	**9a**, 31	6
7	**3b**	COOEt	DME	$Et_4NF{\cdot}3HF$	8.5	40	**9b**, 20 (15)	8 (4)
8	**3b**	COOEt	DME	$Et_4NF{\cdot}3HF$	12	62	**9b**, 11	2
9	**3b**	COOEt	DME	$Et_4NF{\cdot}4HF$	6	70	**9b**, 11	2
10	**3c**	H	DME	$Et_4NF{\cdot}3HF$	8.5	90	**9c**, 6[d]	15 (8)

[a] Constant current electrolysis was carried out in an undivided cell. [b] Calculated on the basis of ^{19}F NMR, and the values in the paranthese show the isolated yields. [c] Using H-type divided cell. [d] **9c**: ^{19}F NMR −114.69 (t, J_{HF} = 50.55 Hz); MS *m/e* 286 (M^+), 267 ($M^+ - F$), 253 ($M^+ - CH_2F$), 221 ($M^+ - SCH_2F$).

ring is much more decreased than **2** by the two nitrogen atoms, and this implies the SOMO of the cation radical of **1d** is mainly localized on the sulfur atom. Moreover, the oxidation potential (E_p^{ox} 2.35 V) of the resulting α-fluorinated product **4d** is much higher than those of **1d** (2.06 V) and **5** (1.83 V); therefore, further oxidation of **4d** does not easily take place, and consequently, the α-monofluorinated product **4d** was selectively obtained.

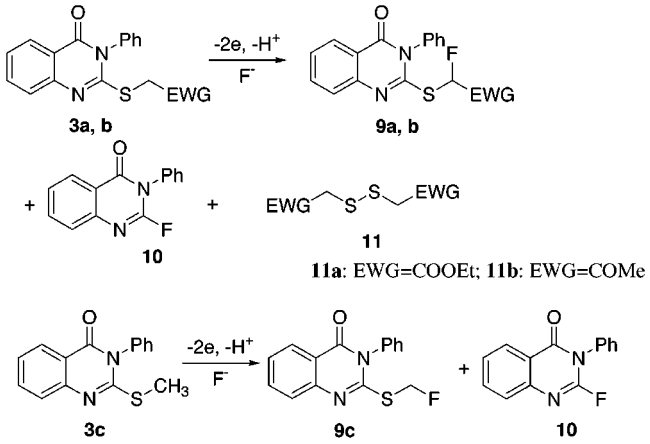
On the contrary, in the case of the fluorination of **2**, the oxidation potential (E_p^{ox} 1.83 V) of the fluorinated product **5** is only 90 mV higher than that of **2**.[19] Therefore, further oxidation takes place to give α,α-difluorinated product **6**. In addition to α-fluorinated products **5** and **6**, the formation of the ring fluorinated products imply the SOMO of the cation radicals of **5** and **6** are less localized on the sulfur atom than **4d** and delocalized to the pyridine moiety to some extent. Thus, some fluoride ions attacked to the ring moieties of the cation radicals of **5** and **6**. As shown above, it is noted that even 2-pyrimidyl and 2-pyridyl sulfides devoid of an EWG underwent anodic α-fluorination by using DME as a solvent.

Anodic Fluorination of 4-Oxo-2-quinazolinonyl Sulfides 3. As a comparative study with the foregoing results, we carried out anodic fluorination of 2-acetonylthio-3-phenyl-4(3*H*)-quinazolinone **3a** as a benzo analogue to the pyrimidine derivatives **1**, using several fluorine sources and electrolytic solvents. The results are listed in Table 3.

Monofluorination took place similarly to give α-monofluoro compound **9a**. DME was a suitable electrolytic solvent, but dichloromethane and acetonitrile were not. Interestingly, anodic ipso substitution of the acetonylthio group of **3a** by a fluoride ion also took place to give 2-fluoro-3-phenyl-4(3*H*)-quinazolinone (**10**) in addition to α-fluorination regardless of the fluorine source (Scheme 3 and Table 3). The structures of the products **9a** and **10** were established from their elemental analyses and spectral data.

These results prompted us to conduct a similar anodic fluorination of 4-oxo-2-quinazolinyl sulfides having an ester group **3b** and lacking an EWG **3c**. Similar results were obtained. As shown in Table 3 (runs 7 and 8), it is clear that passing a larger amount of electricity was not suitable because the yields of the fluorinated products **9b** and **10** decreased sharply; even the starting materials

Scheme 3

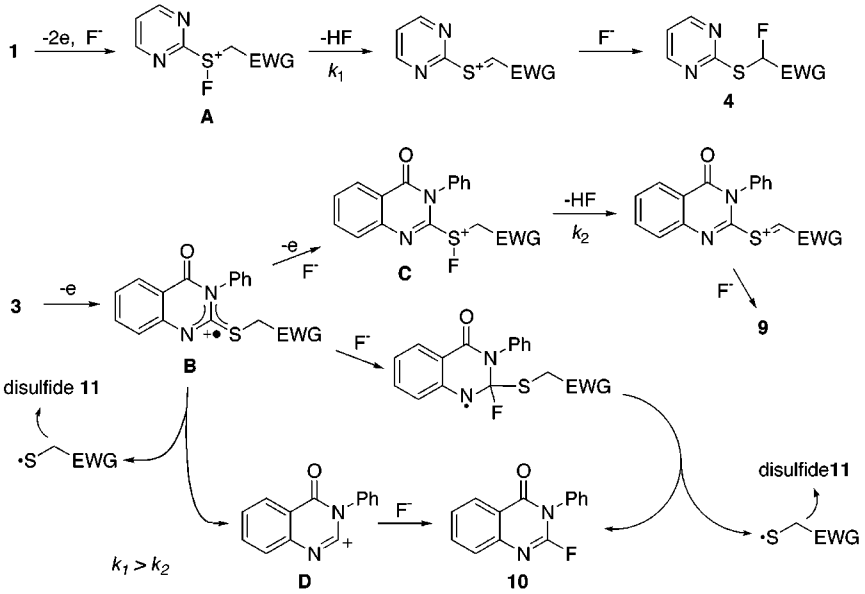


were not completely consumed. This may be due to unstability of **9b** and **10** under electrolytic conditions. It is also noted that the ratio of ipso- to α-fluorination of a sulfide devoid of an EWG **3c** was higher than that of sulfides having an EWG **3a**,**b**. The structure of α-fluorination product **9c** was determined on the basis of ^{19}F NMR and mass spectral data since the yield of **9c** was very low. The overall yields of fluorinated products of 4-oxo-2-quinazolinyl sulfides **3a**−**c** are much less than those of 2-pyrimidyl sulfides **1a**−**d**, although the latter sulfides are more difficult to oxidize than the former ones. Since the oxidation potentials of **1** and **3** reflect the acidity of the protons at α to the sulfur atom, deprotonation of the fluorosulfonium ion intermediate[17,19] **A** generated from **1** seems to be faster compared with **C** from **3** ($k_1 > k_2$) as shown in Scheme 4. This may be one of the reasons for more efficient selective α-fluorination taking place in the case of sulfides **1**. Since disulfides **11** were detected from the electrolytic solutions by mass spectroscopic analysis [**11a** (EWG = CO_2Et), *m/e* 238 (M^+); **11b** (EWG = COMe), *m/e* 178(M^+)], ipso-fluorination may proceed via intermediate **B** or **D** as shown in Scheme 4.

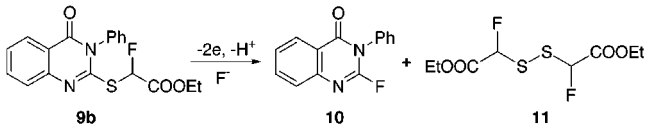
On the other hand, α-monofluorosulfide **9b** was subjected to further anodic fluorination under the same conditions to form the product **10** in 14% yield and bis-[(1-carboethoxy-1-fluoro)methyl] disulfide **11** as shown in Scheme 5. The disulfide **11** was detected by mass spectrometry [*m/e* 274 (M^+)] of the electrolytic solution. Therefore, ipso-fluorination may also proceed via α-fluorinated product **9**. Such ipso-fluorination of anodic partial fluorination has not been reported so far, although

(19) We have already reported that α-monofluorination of sulfides caused 0.33−0.45 V increase of their oxidation potentials: Fuchigami, T.; Shimojo, M.; Konno, A. *J. Org. Chem.* **1995**, *60*, 3459. Fuchigami, T.; Konno, A.; Nakagawa, K.; Shimojo, M. *J. Org. Chem.* **1994**, 59, 5937.

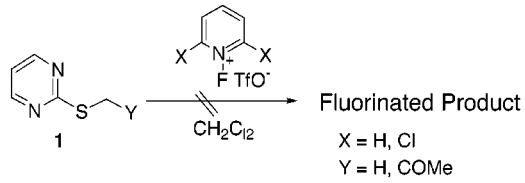
Scheme 4



Scheme 5



Scheme 6



ipso-fluorination is known in the case of anodic perfluorination of substituted benzenes.[20]

It is well-known that methods for introduction of fluorine atom into organic compounds required expensive or hazardous reagents. In recent years, *N*-fluoropyidinium triflates have been developed as effective fluorinating reagents with variable fluorinating power, and they were shown to be effective for α-fluorination of sulfides.[21] However, fluorination of **1a** and **1d** as model compounds with various types of *N*-fluoropyridinium triflates even under reflux resulted in no formation of the desired product as shown in Scheme 6. Therefore, the electrochemical fluorination is a superior procedure to the conventional chemical fluorination methods.

Experimental Section

Caution. $Et_3N{\cdot}3HF$ was purchased from Aldrich, and $Et_4NF{\cdot}nHF$ (n = 3, 4) was obtained from Morita Chemical Industries Co. Ltd. $Et_4NF{\cdot}4HF$[22] is toxic and may cause serious burns if it comes in contract 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.[23] ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded at 270, 254, and 68 MHz, respectively, in $CDCl_3$ as a solvent. The chemical shifts for ^{19}F NMR were given in δ ppm downfield from external CF_3COOH. Cyclic voltammetry was performed at a scan speed of 100 mV s^{-1} in 0.1 M $Bu_4N{\cdot}BF_4/CH_3CN$.

Synthesis of Heterocyclic Sulfides. General Procedure. To a stirred solution of 2-thioxopyridine, 2-thioxopyrimidine, or *N*-phenol-2-thioquinazolin-4-one (20 mmol) in tetrahydrofuran (40 mL), in the presence of K_2CO_3 (3.4 g, 25 mmol), was added α-chloroacetone, ethyl α-chloroacetate, α-chloroacetonitrile, or methy iodide (20 mmol). The reaction mixture was refluxed for 30 min and then left to cool to room temperature. The inorganic salts were filtered off, and the filtrate was evaporated under vacuum. The oily products were purified by evaporation under reduced pressure using bulb-to-bulb distillation, and solid products were recrystallized from ethanol or methanol to give the corresponding sulfides.

1-[(2-Pyrimidyl)thio]-2-propanone (1a): 85% yield; yellow oil; ^1H NMR δ 2.34 (s, 3H), 3.97 (s, 2H), 7.01 (m, 1H), 8.50 (d, 2H, J = 4.62 Hz); MS *m/e* 168 (M^+), 153 ($M^+ - CH_3$), 126 ($M^+ - CH_2{=}C{=}O$), 80 (pyrimidine). Anal. Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 49.99; H, 4.70; N, 17.06.

Ethyl α-[(2-pyrimidyl)thio]acetate (1b):[24] 70% yield; yellow oil; ^1H NMR δ 1.27 (t, 3H, J = 7.25 Hz), 3.95 (s, 2H), 4.22 (q, 2H, J = 7.26 Hz), 7.01 (t, 1H, J = 4.95 Hz), 8.51 (d, 2H, J = 4.95 Hz); MS *m/e* 198 (M^+), 152 (M^+ − EtOH), 125 (M^+ − COOEt), 80 (pyrimidine). Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.57; H, 4.94; N, 14.56.

α-[(2-Pyrimidyl)thio]acetonitrile (1c):[24] 80% yield; mp 103−104 °C (MeOH); ^1H NMR δ 3.94 (s, 2H), 7.11 (t, 1H, J = 4.95 Hz), 8.61 (d, 2H, J = 4.95 Hz); MS *m/e* 151 (M^+), 124 (M^+ − HCN), 80 (pyrimidine). Anal. Calcd for $C_6H_5N_3S$: C, 47.67; H, 3.33; N, 27.79. Found: C, 47.60; H, 3.11; N, 28.04.

1-[(3,4-Dihydro-4-oxo-3-phenyl-2-quinazolinyl)thio]-2-propanone (3a):[25] mp 161−162 °C (EtOH); ^1H NMR δ 2.40 (s, 3H), 3.92 (s, 2H), 7.36 (m, 2H), 7.42 (d, 1H, J = 7.92 Hz), 7.54 (m, 4H),7.72 (dd, 1H, J = 8.58, 8.25 Hz), 8.23 (d, 1H, J = 8.58 Hz); MS *m/e* 310 (M^+), 295 ($M^+ - CH_3$), 268 ($M^+ - CH_2{=}C{=}O$), 221 ($M^+ - SCH_2COCH_3$). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.96; H, 4.46; N, 9.03.

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Ethyl α-[(3,4-dihydro-4-oxo-3-phenyl-2-quinazolinyl)-thio]acetate (3b):[26] mp 117−118 °C (EtOH); ^{1}H NMR δ 1.30 (t, 3H, J = 7.25 Hz), 3.89 (s, 2H), 4.22 (q, 2H, J = 7.25 Hz), 7.39 (m, 3H), 7.55 (m, 4H), 7.71 (ddd, 1H, J = 8.58, 8.25, 1.65 Hz), 8.23 (dd, 1H, J = 8.25, 1.65 Hz); MS *m/e* 340 (M^+), 295 ($M^+ - OEt$), 267 ($M^+ - COOEt$), 253 ($M^+ - CH_2COOEt$), 221 ($M^+ - SCH_2COOEt$). Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.57; H, 4.74; N, 8.23.

Anodic Fluorination of Heterocyclic Sulfides. Typical anodic fluorination was carried out as follows:

Electrolysis was carried out with platinum electrodes (3 × 2 cm^2) in 0.3 M fluoride salt/DME (20 mL) to which heterocyclic sulfide **1**, **2**, or **3** (1 mmol) was added, using an undivided cell or H-type divided cell with an anion-exchange membrane (IE-DF 34-5 TOSOH) under nitrogen atmosphere at room temperature. Constant current electrolysis (5 mA·cm^{-2}) was applied until the starting sulfide was almost consumed (monitored by TLC or GC). After the electrolysis, the resulting electrolytic solution was passed through a short column chromatography on silica gel using ethyl acetate to remove fluoride salts. The eluents were collected and evaporated under reduced pressure, and the residue was further purified by passing through a long column chromatography on silica gel using hexane/ethyl acetate (10:1−3) as an eluent.

1-Fluoro-1-[(2-pyrimidyl)thio]-2-propanone (4a): yellow oil; ^{1}H NMR δ 2.46 (d, 3H, J = 3.30 Hz), 6.85 (d, 1H, J = 50.14 Hz), 7.14 (t, 1H, J = 4.62 Hz), 8.59 (d, 2H, J = 4.62 Hz); ^{19}F NMR δ −89.27 (dq, J = 50.56, 3.68 Hz); ^{13}C NMR (DEPT) δ 26.25 (CH_3), 96.37 (dd, CHF, J = 232, 4.9 Hz), 118.1, 157.25, 157.63 (3 CH), 167.37, 200.24 (2 C); MS *m/e* 186 (M^+), 166 ($M^+ - HF$), 143 ($M^+ - COCH_3$), 124 ($M^+ - CH_3COF$), 80 (pyrimidine). Anal. Calcd for $C_7H_7FN_2OS$: C, 45.15; H, 3.79; N, 15.04. Found: C, 45.27; H, 3.82; N, 15.25.

Ethyl α-fluoro-α-[(2-pyrimidyl)thio]acetate (4b): colorless oil; ^{1}H NMR δ 1.25 (t, 3H, J = 7.26 Hz), 4.26 (q, 2H, J = 7.26 Hz), 7.01 (d, 1H, J = 50.55 Hz), 7.07 (t, 1H, J = 4.95 Hz), 8.52 (d, 2H, J = 4.95 Hz); ^{19}F NMR δ −88.61 (d, J = 50.55 Hz); ^{13}C NMR (DEPT) δ 13.55 (CH_3), 62.34 (CH_2), 90.67 (dd, CHF, J = 229.5, 4.9 Hz), 118.21 (CH), 157.55 (2 CH), 165.51, 166.95 (2 C); MS *m/e* 216 (M^+), 196 ($M^+ - HF$), 171 ($M^+ - OEt$), 143 ($M^+ - COOEt$,), 124 ($M^+ - F - COOEt$), 80 (pyrimidine). Anal. Calcd for $C_8H_9FN_2O_2S$: C, 44.44; H, 4.20; N, 12.96. Found: C, 44.15; H, 4.09; N, 12.62.

α-Fluoro-α-[(2-pyrimidyl)thio]acetonitrile (4c): mp 90−91 °C (hexane/*i*-PrOH); ^{1}H NMR δ 7.21 (t, 1H, J = 4.95 Hz), 7.41 (d, 1H, J = 48.83 Hz), 8.65 (d, 2H, J = 4.62 Hz); ^{19}F NMR δ −84.26 (d, J = 48.71 Hz); MS *m/e* 169 (M^+), 149 ($M^+ - HF$), 142 ($M^+ - HCN$), 111 ($M^+ - CHFCN$), 80 (pyrimidine). Anal. Calcd for $C_6H_4FN_3S$: C, 42.60; H, 2.38; N, 24.84. Found: C, 42.73; H, 2.40; N, 24.74.

2-(Fluoromethylthio)pyrimidine (4d): colorless oil; ^{1}H NMR δ 6.14 (d, 2H, J = 51.14 Hz), 7.08 (t, 1H, J = 4.95 Hz), 8.61 (d, 2H, J = 4.95 Hz); ^{19}F NMR δ -114.26 (t, J = 51.47 Hz); ^{13}C NMR (DEPT) δ 83.36 (dt, CH_2F, J = 216, 7.3 Hz), 117.81, 157.07, 157.68 (3CH), 168.80 (C); MS *m/e* 144 (M^+), 124 ($M^+ - HF$), 111 ($M^+ - CH_2F$), 80 (pyrimidine); HRMS *m/e* calcd for $C_5H_5FN_2S$ 144.0157, found 144.0144. **2-(Difluoromethylthio)pyrimidine (4d′):** ^{19}F NMR δ −22.49 (d, J = 56.1 Hz); MS *m/e* 162 (M^+), 112 ($M^+ - CF_2$), 80 (pyrimidine); HRMS *m/e* calcd for $C_6H_4F_2N_2S$ 162.0063, found 162.0038.

2-(Fluoromethylthio)pyridine (5): ^{1}H NMR δ 6.15 (d, 2H, J = 51.5 Hz), 7.11 (dd, 1H, J = 7.4, 4.8 Hz), 7.28 (d, 1H, J = 8.3 Hz), 8.51 (d, 1H, J = 4.3 Hz); ^{19}F NMR δ -111.00 (t, J = 51.5 Hz); ^{13}C NMR δ 83.40 (d, J = 214.9 Hz), 121.02, 122.84, 149.79, 155.23 (d, J = 3.6 Hz); MS *m/e* 143 (M^+), 123 ($M^+ - HF$), 110 ($M^+ - CH_2F$), 79 (pyridine); HRMS *m/e* calcd for C_6H_6FNS 143.0205, found 143.0206.

2-(Difluoromethylthio)pyridine (6): ^{1}H NMR δ 7.15 (dd, 1H, J = 7.6, 5.0 Hz), 7.35 (d, 1H, J = 8.6 Hz), 7.61 (m, 1H), 7.71 (t, 1H, J = 56.4 Hz), 8.36 (d, 1H, J = 4.6 Hz); ^{19}F NMR δ −19.71 (d, J = 56.1 Hz); MS *m/e* 161 (M^+), 141 ($M^+ - F$), 111 ($M^+ - CF_2$), 79 (pyridine); HRMS *m/e* calcd for $C_6H_5F_2NS$: 161.0111, found 161.0080.

2-(Fluoromethylthio)-6-fluoropyridine (7): ^{19}F NMR δ −112.39 (t, 1F, J = 51.5 Hz), −44.53 (d, 1F, J = 9.2 Hz); MS *m/e* 161 (M^+), 141 ($M^+ - HF$), 97 (fluoropyridine); HRMS *m/e* calcd for $C_6H_5F_2NS$ 161.0111, found 161.0082.

2-(Difluoromethylthio)-6-fluoropyridine (8): ^{19}F NMR δ −42.77 (d, 1F, J = 9.2 Hz) −20.53 (t, 2F, J = 56.1 Hz); MS *m/e* 179 (M^+), 160 ($M^+ - F$), 129 ($M^+ - CHF_2$), 97 (fluoropyridine); HRMS *m/e* calcd for $C_6H_4F_3NS$ 179.0017, found 179.0012.

1-Fluoro-1-[(3,4-dihydro-4-oxo-3-phenyl-2-quinazolinyl)-thio]-2-propanone (9a): mp 63 °C (hexane/*i*-PrOH); ^{1}H NMR δ 2.45 (d, 3H, J = 3.63 Hz), 6.73 (d, 1H, J = 48.83 Hz), 7.35 (m, 2H), 7.45 (dd, 1H, J = 7.92, 7.26 Hz), 7.55 (m, 3H), 7.61 (d, 1H, J = 7.92 Hz), 7.76 (dd, 1H, J = 7.92, 7.26 Hz), 8.24 (d, 1H, J = 7.26 Hz); ^{19}F NMR δ −89.15 (dq, J = 48.72, 3.68 Hz); MS *m/e* 328 (M^+), 286 ($M^+ - CH_2{=}C{=}O$), 253 ($M^+ - CHFCOCH_3$), 221 ($M^+ - SCHFCOCH_3$); HRMS *m/e* calcd for $C_{17}H_{13}FN_2O_2S$ 328.0682, found 328.0675. Anal. Calcd for $C_{17}H_{13}FN_2O_2S$: C, 62.18; H, 3.99; N, 8.53. Found: C, 61.69; H, 3.99; N, 8.35.

Ethyl α-fluoro-α-[(3,4-dihydro-4-oxo-3-phenyl-2-quinazolinyl)thio]acetate (9b): mp 42 °C (hexane); ^{1}H NMR δ 1.18 (t, 3H, J = 7.26 Hz), 4.16 (q, 2H, J = 7.26 Hz) 7.03 (d, 1H, J = 50.49 Hz), 7.24 (m, 2H), 7.33 (dd, 1H, J = 7.56, 7.26 Hz), 7.44 (m, 3H), 7.53 (d, 1H, J = 7.91 Hz), 7.64 (dd, 1H, J = 7.92, 7.26 Hz), 8.12 (d, 1H, J = 7.92 Hz); ^{19}F NMR δ −88.73 (d, J = 49.63 Hz); ^{13}C NMR (DEPT) δ 13.78 (CH_3), 62.66 (CH_2), 90.32 (dd, CHF, J = 233.2, 4.9 Hz), 126.29, 126.56, 127.04, 128.93, 129.06, 129.72, 130.04, 130.26, 134.74 (9 CH), 119.91, 146.79, 151.93, 161.26, 165.12, 165.52 (6 C); MS *m/e* 358 (M^+), 313 ($M^+ - OEt$), 285 ($M^+ - COOEt$), 253 ($M^+ - CHFCOOEt$), 221 ($M^+ - SCHFCOOEt$); HRMS *m/e* calcd for $C_{18}H_{15}FN_2O_3S$ 358.0787, found 358.0783. Anal. Calcd for $C_{18}H_{15}FN_2O_3S$: C, 60.33; H, 4.22; N, 7.82. Found: C, 59.88; H, 4.19; N, 7.74.

3,4-Dihydro-2-fluoro-4-oxo-3-phenylquinazoline (10): mp 164−165 °C (EtOH); ^{1}H NMR δ 7.33 (m, 2H), 7.52 (m, 4H), 7.66 (d, 1H, J = 8.25, 7.26 Hz), 8.29 (d, 1H, J = 7.91 Hz); ^{19}F NMR δ 23.45 (s); MS *m/e* 240 (M^+), 144 ($M^+ - F - Ph$); HRMS *m/e* calcd for $C_{14}H_9FN_2O$ 240.0699, found 240.0702. Anal. Calcd for $C_{14}H_9FN_2O$: C, 70.00; H, 3.78; N, 11.66. Found: C, 69.73; H, 3.51; N, 11.55.

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Supporting Information Available: Copies of ^{1}H NMR spectra of **4d**, **9a**,**b**, and a mixture of **5** and **6** and ^{19}FNMR spectra of a mixture of **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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