Electrolytic Partial Fluorination of Organic Compounds. 19.[1] A Novel Synthesis of Fluorothieno[2,3-*b*]pyridines Using Anodic Fluorination of Heterocyclic Sulfides as a Key Step

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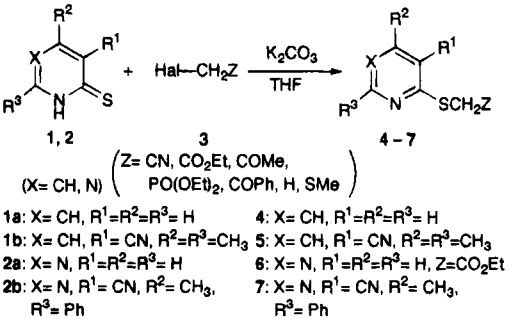
Highly regioselective anodic monofluorination of 2-pyridyl and 4-pyrimidinyl sulfides bearing various electron-withdrawing groups were successfully carried out. The fluorinated sulfides were easily converted into 2-fluorothieno[2,3-*b*]pyridines in good yields.

Introduction

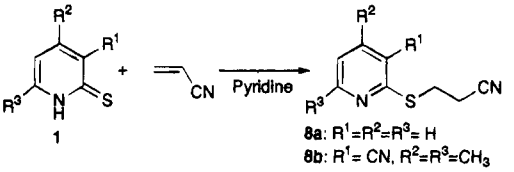
A wide variety of fluorinated heterocyclic compounds have been synthesized and studied as potential enzyme inhibitors and as therapeutic agents.[3–8] Of the possible replacements for hydrogen in carbon–hydrogen bonds, fluorine has the unique advantage of effecting a marked change in electron density distribution and related properties, with minimal change in molecular size or shape. The combination of these properties is proposed to be the basis for the effectiveness of drugs such as fluorouracil and fluorosteroids.[3–8] However, the preparation of fluorinated heterocycles is not always straightforward. In fact, although numerous ring-fluorinated aromatic and heteroaromatic systems have been prepared and studied as biochemicals, there exists no information on ring-fluorinated thienopyridines in which the fluorine atom is attached to the thiophene ring.[5–14]

Recently, we found that sulfides bearing electron-withdrawing groups underwent selective anodic fluorination with good efficiencies.[15,16] We also achieved the anodic monofluorination of simple alkyl phenyl sulfides.[17]

Scheme 1



Scheme 2



These findings prompted us to attempt anodic fluorination of heterocyclic sulfides.

In this paper, we report the highly selective anodic fluorination of 2-pyridyl and 4-pyrimidinyl sulfides **4**–**6**[10] bearing electron-withdrawing groups at the position α to the sulfur atom, together with the novel synthesis of fluorinated fused heterocycles such as thieno[2,3-*b*]pyridines using the anodically fluorinated sulfides as precursors.

Results and Discussion

Preparation of Heterocyclic Sulfides. The starting 2-pyridyl sulfides **4**, **5** and 4-pyrimidinyl sulfides **6**, **7** were prepared in good yields by the reaction of the corresponding 2-thioxopyridines **1** or 4-thioxopyrimidines **2** with α-halogeno compounds **3** in boiling THF in the presence of K_2CO_3 as shown in Scheme 1.[9,10] On the other hand, 2-cyanoethyl 2-pyridyl sulfides **8** were prepared by the reaction of **1** with acrylonitrile as shown in Scheme 2.

Oxidation Potentials of Heterocyclic Sulfides. In order to investigate the effect of heterocyclic rings on the oxidation potential of sulfides, the anodic peak potentials of **4**–**7** and **8** were measured by cyclic voltammetry, using a divided cell with platinum electrodes in 0.1 M $NaClO_4$/anhydrous acetonitrile. These sulfides exhibited irreversible multiple anodic waves. The first peak poten-

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(1) Part 18: Narizuka, S.; Fuchigami, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1293.

(2) UNESCO Research Fellow (1993–1994), on leave from Department of Chemistry, Faculty of Science, Cairo University.

(3) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997 and references therein.

(4) Nagase, S. *Fluorine Chem. Rev.* **1967**, *1*, 77.

(5) Silvester, M. J. *Aldrichim. Acta* **1991**, *24*, 32.

(6) Goldman, P. *Science* **1969**, *164*, 1123.

(7) Weygand, F.; Oettmeier, W. *Russ. Chem. Rev.* **1970**, 290.

(8) Loncrini, D. F.; Filler, R. *Adv. Fluorine Chem.* **1970**, *6*, 43.

(9) Litvinov, V. P.; Rodinovskaya, L. A.; Sharanin, Yu. A.; Shestopalov, A. M. *Sulfur Rep.* **1992**, *13*, 1.

(10) (a) Gewald, K.; Jansch, H.-J. *Ger. Patent (East)* **1974**, *107*, 287; *Chem. Rev.* **1975**, *82*, 140099. (b) Elnagdi, M. H.; Abdelragek, F. M.; Ibrahim, N. S.; Erian, A. W. *Tetrahedron* **1989**, *45*, 3597.

(11) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha and Biomedical: Tokyo, 1982.

(12) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

(13) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishinan, S., Eds.; Wiley: New York, 1991.

(14) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991.

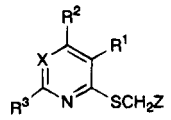
(15) (a) Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6074. (b) Narizuka, S.; Fuchigami, T. *J. Org. Chem.* **1993**, *58*, 4200. (c) Fuchigami, T.; Konno, A.; Nakagawa, K.; Shimojo, M. *J. Org. Chem.* **1994**, *59*, 5937. (d) Konno, A.; Fuchigami, T. *J. Appl. Electrochem.* **1995**, *25*, 173. (e) Fuchigami, T.; Shimojo, T.; Konno, A. *J. Org. Chem.* **1995**, *60*, 3459.

(16) (a) Fuchigami, T.; Konno, A. In *Current Topics in Electrochemistry*; Council of Scientific Research Integration, Ed.; Research Trends: Trivandrum, India, 1993; Vol. 2, pp 155–166. (b) Fuchigami, T. *Rev. Heteroatom. Chem.* **1994**, *10*, 155.

(17) Konno, A.; Nakagawa, K.; Fuchigami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1027.

0022-3263/95/1960-7654$09.00/0

Table 1. Oxidation Potentials (Peak Potentials, E_p^{ox}) of Heterocyclic Sulfides and Phenyl Sulfides[a]



4 ~ 7

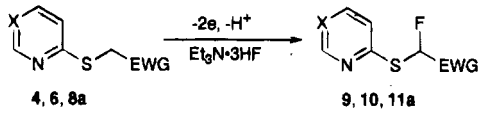
sulfide						E_p^{ox}
no	X	R^1	R^2	R^3	Z	(V vs SSCE)
4a	CH	H	H	H	H	1.74
4b	CH	H	H	H	CN	2.10
4c	CH	H	H	H	CO_2Et	1.83
4d	CH	H	H	H	$PO(OEt)_2$	1.88
5a	CH	CN	CH_3	CH_3	CN	2.35
5b	CH	CN	CH_3	CH_3	CO_2Et	2.0
5c	CH	CN	CH_3	CH_3	$COCH_3$	1.88
5d	CH	CN	CH_3	CH_3	COPh	1.92
5f	CH	CN	CH_3	CH_3	SCH_3	1.64
5g	CH	CN	CH_3	Ph	CN	2.25
5h	CH	CN	CH_3	Ph	CO_2Et	2.15
6	N	H	H	H	CO_2Et	1.92
7a	N	CN	CH_3	Ph	CN	> 2.4
7b	N	CN	CH_3	Ph	CO_2Et	> 2.4
8b	CH	CN	CH_3	CH_3	CH_2CN	2.06
		$PhSCH_3$				1.41[b]
		$PhSCH_2CN$				1.75[b]
		$PhSCH_2CO_2Et$				1.53[b]

[a] In 0.1 M $NaClO_4$ / MeCN. Sweep rate : 100 mV / s. [b] Ref. 15e.

tials, E_p^{ox}, of heterocyclic sulfides and phenyl sulfides are summarized in Table 1.

It was found that heterocyclic rings affected the oxidation potentials of sulfides significantly. The heterocyclic sulfides were oxidized at more positive potentials than the corresponding phenyl sulfides. The 2-pyridyl group caused a considerable increase of E_p^{ox} (*ca.* 0.3 V) when compared to a phenyl group. A strong electron-withdrawing cyano group at the position α to the sulfur atom also greatly increased E_p^{ox} (more than 0.3 V) while other α-electron-withdrawing groups such as ester and phosphate groups cause a slight increase (*ca.* 0.1 V).

Scheme 3



4, 6, 8a 9, 10, 11a

Anodic Fluorination of Heterocyclic Sulfides. Anodic fluorination was carried out at platinum plate electrodes in anhydrous acetonitrile containing $Et_3N{\cdot}3HF$ as both the supporting electrolyte and the fluorine source using an undivided cell. Constant potential electrolysis was performed. In order to avoid deposition of polymerized products on the anode, pulse electrolysis was employed. The results of anodic fluorination of **4**, **6**, and **8a** are summarized in Table 2 and Scheme 3.

As shown in Table 2, anodic fluorination of sulfides **4b–d** bearing electron-withdrawing groups proceeded smoothly to give the corresponding fluorinated products **9b–d** in good yields. In these cases, the α-position to the sulfur atom at **4** was selectively monofluorinated. On the other hand, pyridyl sulfides **8a** bearing a cyano group at the β-position to the sulfur atom gave only trace amounts of a fluorinated product **11a**. In this case, the dehydrofluorination product **11a'** was detected by MS. The fluorination at the β-position to an electron-withdrawing group is generally difficult owing to predominant HF elimination.

Although the 4-pyrimidinyl sulfide **6** has a slightly higher oxidation potential when compared to **4c** and **4d**, a large amount of electricity was required to complete the electrolysis. This seems to be as due to the inevitable passivation of the anode. However, desired selective anodic fluorination of **6** was also successful. It is known that anodic fluorination of simple pyridine takes place at the pyridine ring.[18] We also found anodic fluorination at the pyridine ring of isonicotinic acid ester.[19] Therefore, it should be noted that the fluorination took place exclusively at the α-position to the sulfur atom of heterocyclic sulfides **4**.

In contrast to the cases of **4b–d**, anodic fluorination of simple methyl pyridyl sulfide (**4a**) devoid of an electron-withdrawing group and pyridyl sulfide having a methylthio group **4e** yielded only trace amounts of the desired fluorinated product **9a** and **9e** (Table 2, runs 1 and 5). In these cases, a large amount of **1** due to C–S

Table 2. Anodic Fluorination of 2-Pyridyl and 4-Pyrimidinyl Sulfides Having Electron-Withdrawing Groups

	sulfide			anodic potential	charge passed	product yield
run	no	x	EWG	(V vs SSCE)	(F/mol)	(%)
1	**4a**	CH	H	1.6	5	**9a** (trace)[a,b]
2	**4b**	CH	CN	1.6	5	**9b** (76)
3	**4c**	CH	CO_2Et	1.6	5	**9c** (76)
4	**4d**	CH	$PO(OEt)_2$	1.6	6	**9d** (20)
5	**4e**	CH	SMe	1.6	5	**9e** (trace)[b,c]
6	**6**	N	CO_2Et	2.2	11	**10** (55)
7	**8a**	CH	CH_2CN	1.6	6	**11a** (trace)[d,e]

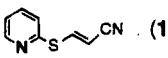
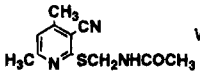
[a] The formation of **9a** was detected by MS: m/e 143 (M^+). [b] Considerable amount of **1a** was detected by MS. [c] MS of **9e**: m/e 189 (M^+), 142 (M^+-SMe). [d] MS of **11a**: m/e 182 (M^+). [e] Considerable amount of HF elimination product  (**11a'**) was detected by MS: m/e 162 (M^+), 110(M^+-CH_2=CHCN).

Table 3. Anodic Fluorination of 2-(3-Cyanopyridyl) Sulfides Having Electron-Withdrawing Groups

run	sulfide no	R	EWG	supporting electrolyte	charge passed (F/mol)	product yield (%)
1	**5a**	CH_3	CN	$Et_3N{\cdot}3HF$	11	**12a** (55)
2	**5a**	CH_3	CN	$Et_3N{\cdot}2HF$	22	**12a** (10)
3	**5a**	CH_3	CN	$Et_4NF{\cdot}4HF$	2	**12a** (0)
4	**5b**	CH_3	CO_2Et	$Et_3N{\cdot}3HF$	11	**12b** (45)
5	**5c**	CH_3	$COCH_3$	$Et_3N{\cdot}3HF$	11	**12c** (20)[a]
6	**5d**	CH_3	COPh	$Et_3N{\cdot}3HF$	11	**12d** (0)
7	**5e**	CH_3	$PO(OEt)_2$	$Et_3N{\cdot}3HF$	11	**12e** (30)
8	**5f**	CH_3	SCH_3	$Et_3N{\cdot}3HF$	11	**12f** (trace)[b,c]
9	**8b**	CH_3	CH_2CN	$Et_3N{\cdot}3HF$	11	**11b** (trace)[d]
10	**5g**	Ph	CN	$Et_3N{\cdot}3HF$	11	**12g** (60)
11	**5h**	Ph	COOEt	$Et_3N{\cdot}3HF$	11	**12h** (50)

[a] By-product  was detected by MS: m/e 235 (M^+), 192 (M^+-$COCH_3$).

[b] MS of **12f**: m/e 242 (M^+), 196 (M^+-SMe). [c] Considerable amount of **1b** was detected by MS. [d] MS of **11b**: m/e 235 (M^+).

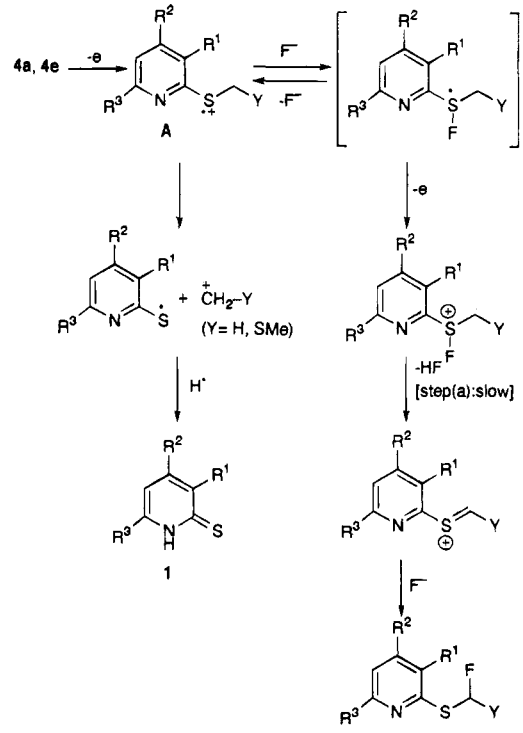
bond cleavage was detected in the electrolytic solution. Previously, we reported that anodic fluorination of simple methyl phenyl sulfide gave a fluorinated sulfide in moderate yield.[15c,17] In this case, the main byproduct was the corresponding sulfoxide while considerable amounts of C–S bond cleavage products were not detected. Therefore, the anodic behavior of methyl pyridyl sulfide (**4a**) is quite different from that of methyl phenyl sulfide. We have already proposed a Pummerer-type mechanism for the anodic fluorination of sulfides. In this mechanism, the trapping of a cation radical intermediate by a fluoride ion should suppress the C–S bond cleavage. However, in the case of methyl pyridyl sulfide **4a**, the C–S bond cleavage took place readily. Owing to lack of an electron-withdrawing group, the dehydrofluorination step (a) is very slow. Therefore, the predominant C–S bond cleavage may take place prior to the trapping of the cation radical intermediate **A** with a fluoride ion as shown in Scheme 4. This assumption is reasonable as follows: Since 2-pyridylsulfenyl radicals (in the cases of **4a** and **4e**) and methylthiomethyl cation (in the case of **4e**) are readily generated, the anodically generated radical cation intermediates of **4a** and **4e** split into 2-pyridylsulfenyl radical and methyl cation (or methylthiomethyl cation) as shown in Scheme 4. Therefore, electron-withdrawing groups are necessary for the efficient anodic fluorination of 2-pyridyl sulfides.

Anodic fluorinations of 2-(3-cyanopyridyl) sulfides **5** were also successful except for **5d** (Scheme 5). The results are summarized in Table 3. In these cases, the quantities of electricity required for anodic fluorination were more than 2-fold those of the corresponding 2-pyridyl sulfides **4** due to the presence of a strong electron-withdrawing cyano group in the pyridine ring of **5**.

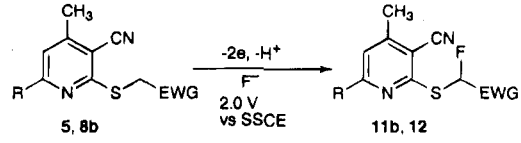
In order to decrease the electricity required, $Et_3N{\cdot}2HF$ and $Et_4NF{\cdot}4HF$ were each employed as a supporting electrolyte and a fluorine source for the anodic fluorination of **5a** as a model compound. However, $Et_3N{\cdot}2HF$ gave a much lower yield (run 2). When $Et_4NF{\cdot}4HF$ was used, the starting **5a** was consumed after passing 2 F/mol of electricity. However, fluorination did not take place, and no isolable product was obtained (run 3). Therefore, $Et_3N{\cdot}3HF$ was found to be suitable for the fluorination of **5**.

6-Phenyl-2-pyridyl sulfides **5g** and **5h** gave somewhat better yields when compared to the corresponding 6-methyl-2-pyridyl sulfides **5a** and **5b**. Anodic fluorination of **5e** resulted in low yield because **12e** was rather unstable

Scheme 4

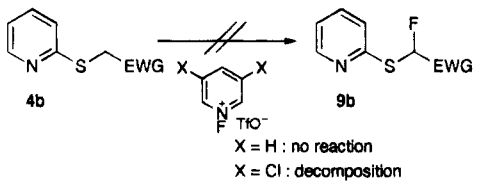


Scheme 5



(18) Ballinger, J. R.; Teare, F. W. *Electrochim. Acta* **1985**, *30*, 1075.
(19) Fuchigami, T.; Shimojo, M.; Konno, A. Unpublished results.

Scheme 6

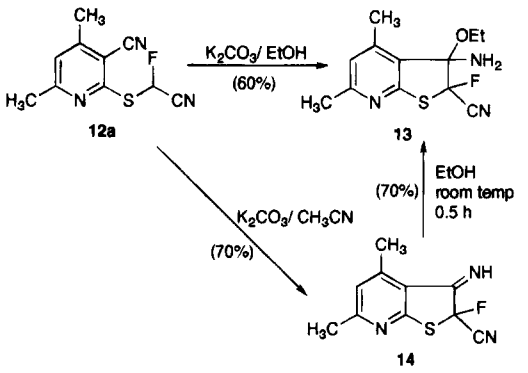


(run 7). In the case of **5c**, anodic acetoamidation took place as a side reaction. This is probably due to the fact that an acetyl cation is readily generated as observed in the anodic fluorination of α,α-diacetylmethyl phenyl sulfide.[15e] On the contrary, (methylthio)methyl sulfide **5f** and 2-cyanoethyl sulfide **8b** gave only a trace amount of fluorinated products (runs 8 and 9). A similar trend was observed in the cases of **4e** and **8a** (Table 2, runs 5 and 7).

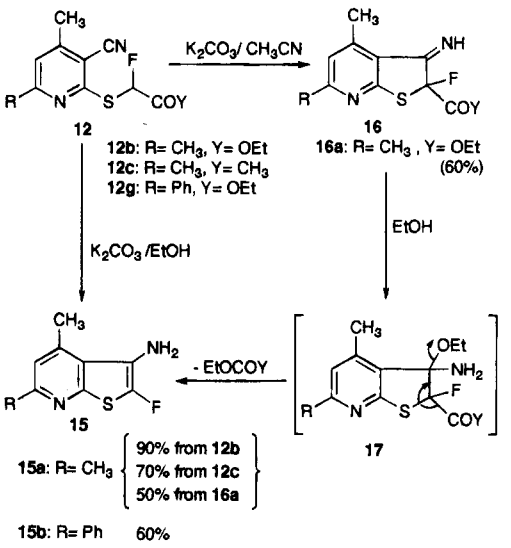
Hitherto known fluorinating reagents are dangerous and/or costly and require Teflon equipment.[14,20-23] In contrast, *N*-fluoropyridinium triflates have been shown to be safe and effective reagents.[24] However, fluorination of **4b** as a model compound with *N*-fluoropyridinium triflate or *N*-fluoro-3,5-dichloropyridinium triflate resulted in no formation of **9b** (Scheme 6). Therefore, the electrochemical fluorination is more advantageous than the chemical method since fluorination can be performed under mild conditions in normal laboratory glassware with little precautions.

Synthetic Utility of Anodically Fluorinated Sulfides. In order to demonstrate the synthetic utility of the fluorinated products, cyclization of **12a** was attempted. We found that treatment of **12a** with potassium carbonate in ethanol at ambient temperature resulted in the formation of an unexpected addition product **13** in a relatively good yield. The structure was established by elemental analyses and spectroscopic methods. The mass spectral data of **13** revealed a molecular formula $C_{12}H_{14}FN_3OS$ (*m/e* = 267). ^1H NMR spectral data showed characteristic triplet and quartet signals at δ = 1.24 and 4.23 ppm for the ethoxy group and a broad band at δ = 8.23 ppm assigned to the NH_2 unit; the latter signal underwent a rapid hydrogen–deuterium exchange and disappeared upon addition of deuterium oxide to the NMR sample. Furthermore, ^{19}F NMR spectral data supported the proposed structure as it revealed a singlet signal for an uncoupled fluorine atom at δ = −50.7 ppm. It is interesting that the product **13** is a single stereoisomer, although its stereochemistry has not been established. On the contrary, cyclization in acetonitrile instead of ethanol provided the corresponding fused heterocyclic product **14** having an imino group in good yield. Since compound **14** was readily converted into **13** by treatment of **14** with ethanol at room temperature, the fluorinated heterocyclic product **13** should be formed *via* **14** as the intermediate (Scheme 7). It was found that the *N,O*-acetal moiety of **13** is quite stable. This unusual stability seems to be due to the strong electron-withdrawing effect of a cyano group and a fluorine atom.[25]

Scheme 7



Scheme 8



On the contrary, it was found that treatment of either **12b** or **12c** with potassium carbonate in ethanol at ambient temperature provided the same product **15a** in good yields. The α-fluoro sulfide **12g** was similarly converted into **15b** in a moderate yield. The product **15** was found to be a fused heteroaromatic compound, 2-fluorothieno[2,3-*b*]pyridine derivative, on the basis of its elemental analysis and compatible spectroscopic data. It was also found that **15a** could be prepared by an independent route involving the cyclization of **12b** with K_2CO_3 in acetonitrile to give the cyclized imine form **16a**, which dissolved in ethanol to directly give the final isolable product **15a**. Therefore, the unexpected formation of fully aromatic fused compound **15** should proceed *via* cyclized intermediates **16** and **17** as shown in Scheme 8. The intermediate **17** was aromatized by loss of diethyl carbonate (**12b**, **12g**) or ethyl acetate (**12c**), respectively.

In summary, this work represents the first successful example of anodic fluorination of heterocyclic sulfides together with a novel synthesis of fluorinated fused heterocycles using anodic fluorination as a key step.

Experimental Section

Caution: $Et_4NF{\cdot}4HF$ is toxic and if in contact with skin causes serious burns. $Et_3N{\cdot}3HF$ and $Et_3N{\cdot}2HF$ are much less aggressive. However, proper safety precautions should be

(20) Yoneda, N. *Tetrahedron* **1991**, *47*, 5329.
(21) Umemoto, T. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 338.
(22) Uneyama, K. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 232.
(23) Kuroboshi, M.; Hiyama, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 1124.
(24) Umemoto, T.; Tomizawa, G. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3625.
(25) We have already shown that a strong electron-withdrawing CF_3 group markedly stabilizes *N,O*-acetals[26] and *O,S*-acetals.[27]
(26) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, *59*, 607.
(27) Fuchigami, T.; Nakagawa, Y.; Yamamoto, K. *J. Org. Chem.* **1991**, *56*, 137.

taken at all times. It is therefore recommended to protect the hands with rubber gloves.

^{1}H NMR and ^{19}F NMR spectra were recorded at 270 MHz using $CDCl_3$ as a solvent. The chemical shifts for ^{1}H and ^{19}F NMR are given in δ ppm downfield from internal Me_4Si and upfield from external CF_3COOH, respectively. High-resolution mass spectra were obtained with a Hitachi M-80B GC-mass spectrometer. Cyclic voltammetric and preparative electrolysis experiments were carried out using a Hokutodenko HA-501 Potentiostat/Galvanostat equipped with a Hokutodenko HF-201 digital coulometer.

Preparation of 2-Pyridyl Sulfides 4 and 5 and 4-Pyrimidinyl Sulfides 6 and 7. *General Procedure* **for 4-7.** To a solution of 2-thioxopyridine **1** or 4-thioxopyrimidine **2** (0.01 mol) in 20 mL of THF containing 1.5 g (0.012 mol) of K_2CO_3 was added α-halogeno compound **3** (0.01 mol). The reaction mixture was heated under reflux for 30 min. The solid product, formed upon dilution by water, was collected by filtration and recrystallized from THF to give the desired 2-pyridyl sulfides **4** and **5** or 4-pyrimidinyl sulfides **6** and **7**.[9,10]

Cyanomethyl 2-pyridinyl sulfide (4b): 70% yield; colorless oil; ^{1}H NMR δ 4.04 (s, 2H), 7.06−8.43 (m, 4H); IR (neat) 3050, 2220 (CN), 1600 cm^{-1}. Anal. Calcd for $C_7H_6N_2S$: C, 55.99; H, 3.99; N, 18.65. Found: C, 56.09; H, 3.92; N, 18.76.

(Ethoxycarbonyl)methyl 2-pyridyl sulfide (4c): 70% yield; colorless oil; ^{1}H NMR δ 1.25 (t, 3H, J = 7.1 Hz), 4.03 (s, 2H), 4.18 (q, 2H, J = 7.1 Hz), 7.06−8.41 (m, 4H); IR (neat) 2950, 1715 (CO), 1600 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.83; H, 5.58; N, 7.10. Found: C, 54.89; H, 5.61; N, 7.18.

Diethyl [(2-pyridylthio)methyl]phosphonate (4d): 60% yield; colorless oil; ^{1}H NMR δ 1.31−1.47 (m, 6H), 4.01 (s, 2H), 4.20−4.41 (m, 4H), 7.09−8.46 (m, 4H); IR (neat) 3000, 2950, 1600 cm^{-1}. Anal. Calcd for $C_{10}H_{16}NO_3PS$: C, 45.99; H, 6.12; N, 5.36. Found: C, 46.20; H, 6.30; N, 5.37.

(Methylthio)methyl 2-pyridyl sulfide (4e): 74% yield; oil; ^{1}H NMR δ 2.94 (s, 3H), 4.02 (s, 2H), 7.06−7.40 (m, 2H), 7.49−7.52 (m, 1H), 8.41−8.46 (m, 1H); IR (neat) 3000, 2950, 1600 cm^{-1}. Anal. Calcd for $C_7H_9NS_2$; C, 49.14; H, 5.26; N, 8.18. Found: C, 49.18; H, 5.30; N, 8.14.

2-(3-Cyano-4,6-dimethyl)pyridyl cyanomethyl sulfide (5a): 85% yield; mp 120.5−121 °C; ^{1}H NMR δ 2.48 (s, 3H), 2.57 (s, 3H), 4.03 (s, 2H), 6.92 (s, 1H); IR (KBr) 2222 (CN), 1600 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3S$: C, 59.13; H, 4.43; N, 20.67. Found: C, 59.30; H, 4.41; N, 20.69.

2-(3-Cyano-4,6-dimethyl)pyridyl (ethoxycarbonyl)methyl sulfide (5b): 80% yield; mp 95 °C; ^{1}H NMR δ 1.25 (t, 3H, J = 7.0 Hz), 2.49 (s, 3H), 2.58 (s, 3H), 4.01 (s, 2H), 4.20 (q, 2H, J = 7.0 Hz), 6.92 (s, 2H); IR (KBr) 2220 (CN), 1715 (CO), 1660 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.61; H, 5.59; N, 11.19. Found: C, 57.65; H, 5.62; N, 11.25.

2-(3-Cyano-4,6-dimethyl)pyridyl acetonyl sulfide (5c): 60% yield; mp 132.5−133 °C; ^{1}H NMR δ 2.46 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 4.01 (s, 2H), 6.95 (s, 1H); IR (KBr) 2219 (CN), 1715 (CO), 1690, 1650 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 60.00; H, 5.45; N, 12.71. Found: C, 59.92; H, 5.31; N, 12.80.

2-(3-Cyano-4,6-dimethyl)pyridyl phenacyl sulfide (5d): 90%; mp 140−141 °C; ^{1}H NMR δ 2.48 (s, 3H), 2.56 (s, 3H), 4.04 (s, 2H), 6.91−7.52 (m, 6H); IR (KBr) 2220 (CN), 1670 (CO), 1660, 1600 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.09; H, 4.96; N, 9.92. Found: C, 68.10; H, 5.12; N, 9.95.

Diethyl {[2-(3-cyano-4,6-dimethylpyridyl)thio]methyl}-phosphonate (5e): 68% yield; yellow solid; mp 129 °C; ^{1}H NMR δ 1.33−1.49 (m, 6H), 2.48 (s, 3H), 2.56 (s, 3H), 4.02 (d, 2H, $J_{H,P}$ = 6.5 Hz), 4.21−4.46 (m, 4H), 6.92 (s, 1H); IR (KBr) 3050, 2950, 2221 (CN), 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_2O_3SP$: C, 49.70; H, 6.04; N, 8.91. Found: C, 49.76; H, 6.09; N, 9.00.

2-(3-Cyano-4,6-dimethyl)pyridyl (methylthio)methyl sulfide (5f): 50% yield; mp 135 °C; ^{1}H NMR δ 2.46 (s, 3H), 2.58 (s, 3H), 2.91 (s, 3H), 4.03 (s, 2H), 6.92 (s, 1H); IR (KBr) 3030, 2219 (CN), 1600 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_2S_2$: C, 53.56; H, 5.35; N, 12.48. Found: C, 53.45; H, 5.40; N, 12.43.

(Ethoxycarbonyl)methyl 4-pyrimidinyl sulfide (6): 65% yield; yellow oil; ^{1}H NMR δ 1.34 (t, 3H, J = 7.2 Hz), 4.01 (s, 2H), 4.35 (q, 2H, J = 7.2 Hz), 7.45−8.02 (m, 3H); IR (KBr) 3050, 2900, 1600 cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.51; H, 5.05; N, 14.13. Found: C, 48.60; H, 5.01; N, 14.20.

4-(5-Cyano-6-methyl-2-phenyl)pyrimidinyl cyanomethyl sulfide (7a): 75% yield; mp 155.5−156 °C; ^{1}H NMR δ 2.61 (s, 3H), 4.04 (s, 2H), 6.90−7.62 (m, 6H); IR (KBr) 2222, 2219 (CN), 1660 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3S$: C, 67.92; H, 4.14; N, 15.83. Found: C, 67.81; H, 4.20; N, 15.80.

4-(5-Cyano-6-methyl-2-phenyl)pyrimidinyl (ethoxycarbonyl)methyl sulfide (7b): 75%; mp 142 °C; ^{1}H NMR δ 1.25 (t, 3H, J = 7.0 Hz), 2.45 (s, 3H), 4.04 (s, 2H), 4.18 (q, 2H, J = 7.0 Hz), 6.91−7.61 (m, 6H); IR (KBr) 1715 (CO), 1660 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.41; H, 5.12; N, 8.97. Found: C, 65.50; H, 5.10; N, 8.94.

General Procedure for ***8a*** *and* ***8b***. To a solution of 2-thioxopyridine **1a** or **1b** (0.01 mol) in 20 mL of pyridine was added 0.04 mol of acrylonitrile. The reaction mixture was heated under reflux for 30 min. The solid product, formed upon dilution by water, was collected by filtration and crystallized from ethanol to give **8a** or **8b**.

2-Cyanoethyl 2-pyridyl sulfide (8a): 75% yield; yellow solid; mp 59.5−60 °C; ^{1}H NMR δ 2.71 (t, 2H), 2.90 (t, 2H), 7.09−7.38 (m, 2H), 7.51−7.60 (m, 1H), 8.43−8.49 (m, 1H): IR (KBr) 3000, 2950, 2219 (CN), 1600 cm^{-1}. Anal. Calcd for $C_8H_8N_2S$: C, 58.56; H, 4.87; N, 17.06. Found: C, 58.71; H, 4.79; N, 17.10.

2-Cyanoethyl 2-(3-cyano-4,6-dimethyl)pyridyl sulfide (8b): 80% yield; pale yellow solid; mp 149 °C; ^{1}H NMR δ 2.49 (s, 3H), 2.55 (s, 3H), 2.72 (t, 2H), 2.91 (t, 2H), 6.90 (s, 1H); IR (KBr) 3000, 2960, 2221, 2219 (CN) cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.85; H, 5.06; N, 19.34. Found: C, 60.79; H, 5.10; N, 19.28.

Anodic Fluorination of Heterocyclic Sulfides. Typical anodic fluorination conditions are as follows. Electrolysis was conducted with a platinum anode and cathode [6 cm^2 (2 × 3 cm)] in 0.37 M $Et_3N{\cdot}3HF/CH_3CN$ (15 mL) containing 1.5 mmol of heterocyclic sulfides using a cylindrical undivided cell at ambient temperature. In order to avoid deposition of polymerized products on the anode, pulse electrolysis [applied potential (90 s)/0 V (10 s)] was performed. After the starting sulfide was completely consumed (silica gel, TLC monitoring), the electrolysis solution was passed through a short column of silica gel (CH_2Cl_2) to yield an almost pure monofluorinated product.

α-Fluorocyanomethyl 2-pyridyl sulfide (9b): ^{1}H NMR δ 7.10−7.19 (m, 2H), 7.36 (d, 1H, J_{HF} = 51.0 Hz), 7.59−7.67 (m, 1H), 8.50 (d, 1H); ^{19}F NMR δ −80.0 (d, J_{HF} = 50.0 Hz); IR (neat) 2170 (CN), 1600 cm^{-1}; MS *m/e* 168 (M$^+$), 78 (M$^+$ − SCHFCN). Anal. Calcd for $C_7H_5FN_2S$: C, 49.99; H, 3.00; N, 16.66. Found: C, 49.78; H, 2.78; N, 16.51.

Ethyl α-fluoro-α-(2-pyridylthio)acetate (9c): ^{1}H NMR δ 1.32 (t, 3H, J = 7 Hz), 4.31 (q, 2H, J = 7 Hz), 7.11 (d, 1H, J_{HF} = 51.5 Hz), 7.04−7.15 (m, 1H), 7.24−7.35 (m, 1H), 7.59−7.65 (m, 1H), 8.36−8.48 (m, 1H); ^{19}F NMR δ −85.5 (d, J_{FH} = 51.5 Hz); IR (neat) 1765 (C=O), 1600 cm^{-1}; MS *m/e* 215 (M$^+$), 142 (M$^+$ − CO_2Et). Anal. Calcd for $C_9H_{10}FNO_2S$: C, 50.22; H, 4.68; N, 6.51. Found: C, 50.14; H, 4.44; N, 6.39.

Diethyl [fluoro(2-pyridylthio)methyl]phosphonate (9d): ^{1}H NMR δ 1.29−1.45 (m, 6H), 4.20−4.41 (m, 4H), 7.10−7.45 (m, 3H), 7.49−7.62 (m, 1H), 8.4−8.45 (m, 1H); ^{19}F NMR δ −98.0 (dd, J_{FP} = 85.6 Hz, J_{FH} = 49.6 Hz); IR (neat) 3000, 2950, 1600 cm^{-1}; MS *m/e* 279 (M$^+$), 142 (M$^+$ − $PO(OEt)_2$). Anal. Calcd for $C_{10}H_{15}FPNO_3S$: C, 43.01; H, 5.41; N, 5.01. Found: C, 43.11; H, 5.36; N, 4.92.

Ethyl α-fluoro-α-(4-pyrimidinylthio)acetate (10): ^{1}H NMR δ 1.32 (t, 3H, J = 7.2 Hz), 4.30 (q, 2H, J = 7.2), 7.32 (d, 1H, J_{HF} = 50.2 Hz), 7.41−7.49 (m, 2H), 7.90−8.02 (m, 1H); ^{19}F NMR δ −88.5 (d, J_{FH} = 50.2 Hz); IR (neat) 3000, 2940, 1790 (C=O), 1590 cm^{-1}; MS *m/e* 216 (M$^+$), 143 (M$^+$ − CO_2Et). Anal. Calcd for $C_8H_9N_2O_2SF$: C, 44.44; H, 4.20; N, 12.96. Found: C, 44.42; H, 4.14; N, 13.10.

α-Fluorocyanomethyl 2-(3-cyano-4,6-dimethyl)pyridyl sulfide (12a): mp 86.5−87 °C; ^{1}H NMR δ 2.51 (s, 3H), 2.59 (s, 3H), 7.02 (s, 1H), 7.59 (d, 1H, J_{HF} = 48.4 Hz); ^{19}F NMR δ −83.0 (d, J_{FH} = 48.4 Hz); IR (KBr) 3000, 2210, 2195 (CN), 1595 cm^{-1}; MS *m/e* 221 (M$^+$), 201 (M$^+$ − HF), 132 (M$^+$ − SCHFCN).

Anal. Calcd for $C_{10}H_8FN_3S$: C, 54.29; H, 3.64; N, 19.00. Found: C, 54.30; H, 3.60; N, 18.88.

Ethyl α-fluoro-α-[2-(3-cyano-4,6-dimethylpyridyl)thio]-acetate (12b): mp 74.5–75 °C; ^{1}H NMR δ 1.34 (t, 3H, J = 7.3 Hz), 2.48 (s, 3H), 2.55 (s, 3H), 4.34 (q, 2H, J = 7.3 Hz), 6.93 (s, 1H), 7.21 (d, 1H, J_{FH} = 50.2 Hz); ^{19}F NMR δ −87.3 (d, 1H, J_{FH} = 50.2 Hz); IR (KBr) 3000–2850, 2210 (CN), 1795 (C=O) cm^{-1}; MS *m/e* 268 (M^+), 195 ($M^+ - CO_2Et$). Anal. Calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44. Found: C, 53.75; H, 4.87; N, 10.26.

α-Fluoroacetonyl 2-(3-cyano-4,6-dimethylpyridyl) sulfide (12c): mp 96 °C; ^{1}H NMR δ 2.46 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 6.85 (d, 1H, J_{HF} = 49.48 Hz), 6.92 (s, 1H); ^{19}F NMR δ −87.93 (d, 1F, J_{FH} = 49.0 Hz); IR (KBr) 2950, 2210 (CN), 1750 (C=O) cm^{-1}; MS *m/e* 238 (M^+), 195 ($M^+ - COCH_3$). Anal. Calcd for $C_{11}H_{11}N_2OSF$: C, 55.46; H, 4.62; N, 11.76. Found: C, 55.46; H, 4.63; N, 11.89.

Diethyl {fluoro[2-(3-cyano-4,6-dimethylpyridyl)thio]-methyl}phosphonate (12e): mp 55 °C; ^{1}H NMR δ 1.29–1.45 (m, 6H), 2.48 (s, 3H), 2.55 (s, 3H), 4.20–4.41 (m, 4H), 7.02 (s, 1H), 7.59 (d, 1H, J_{HF} = 50.1 Hz); ^{19}F NMR δ −98.9 (dd, J_{HF} = 50.1 Hz, J_{FP} = 86.0 Hz); IR (neat) 3000, 2950 (CH_2), 2210 (CN), 1590 cm^{-1}; MS *m/e* 332 (M^+), 195 ($M^+ - PO(OEt)_2$). Anal. Calcd for $C_{13}H_{18}FN_2O_3PS$: C, 46.98; H, 5.42; N, 8.43. Found: C, 46.96; H, 5.41; N, 8.35.

α-Fluorocyanomethyl 2-(3-cyano-4-methyl-6-phenylpyridyl) sulfide (12g): mp 110 °C; ^{1}H NMR δ 2.60 (s, 3H), 7.39 (d, 1H, J_{HF} = 48.5 Hz), 7.42–7.58 (m, 4H), 7.90–8.20 (m, 2H); ^{19}F NMR δ −83.1 (d, J_{FH} = 48.5 Hz); IR (KBr) 2950, 2210, 2195 (CN) cm^{-1}; MS *m/e* 283 (M^+), 193 (M^+ − SCHFCN). Anal. Calcd for $C_{15}H_{10}FN_3S$: C, 63.59; H, 3.56; N, 14.83. Found: C, 63.62; H, 3.54; N, 14.90.

Ethyl α-fluoro-[2-(3-cyano-4-methyl-6-phenylpyridyl)-thio]acetate (12h): mp 101.5–102 °C; ^{1}H NMR δ 1.30 (t, 3H, J = 7.2 Hz), 2.60 (s, 3H), 4.35 (q, 2H, J = 7.2 Hz), 7.25 (d, 1H, J_{HF} = 50.1 Hz), 7.40–7.58 (m, 4H), 7.95–8.15 (m, 2H); ^{19}F NMR δ −88.2 (d, J_{FH} = 50.1 Hz); IR (KBr) 3000 (CH_3), 2210 (CN), 1790 (C=O), 1600 cm^{-1}; MS *m/e* (M^+), 257 ($M^+ - CO_2$-Et), 237 ($M^+ - F - CO_2Et$). Anal. Calcd for $C_{17}H_{15}FN_2O_2S$: C, 61.80; H, 4.58; N, 8.48. Found: C, 61.72; H, 4.57; N, 8.60.

Preparation of 2-Cyano-2-fluoro-3-ethoxy-4,6-dimethyldihydrothieno[2,3-*b*]pyridine (13). A solution of **12a** (0.1 mmol) in ethanol (5 mL) containing potassium carbonate (0.15 mmol) was stirred at room temperature for 1 h. After filtration of insoluble material, the filtrate was evaporated under vacuum at room temperature to yield 60% of **13** in a pure form. **13**: mp 166 °C; ^{1}H NMR δ 1.24 (t, 3H, J = 7.1 Hz), 2.53 (s, 3H), 2.6 (s, 3H), 4.31 (q, 2H, J = 7.1 Hz), 6.86 (s, 1H), 8.23 (br, 2H); ^{19}F NMR δ −50.7 (s); IR (KBr) 3350–3200, 3000, 2220 (CN), 1660 cm^{-1}; MS *m/e* 267 (M^+), 222 (M^+ − OEt). Anal. Calcd for $C_{12}H_{14}FN_3OS$: C, 53.92; H, 5.28; N, 15.72. Found: C, 53.81; H, 5.26; N, 15.84.

Preparation of 2-Cyano-2-fluoro-3-imino-4,6-dimethyldihydrothieno[2,3-*b*]pyridine (14) and 2-(Ethoxycarbonyl)-2-fluoro-3-imino-4,6-dimethyldihydrothieno[2,3-*b*]pyridine (16a). To a solution of **12a** or **12b** (0.1 mmol) in dry acetonitrile (5 mL) was added potassium carbonate (0.15 mmol). The reaction mixture was stirred at room temperature for 1 h. After filtration of insoluble material, the filtrate was evaporated under vacuum at room temperature to yield **14** (70%) or **16a** (60%) in a pure form.

14: mp 144.5–145 °C; ^{1}H NMR δ 2.55 (s, 3H), 2.74 (s, 3H), 6.93 (s, 1H), 10.9 (br, 1H); ^{19}F NMR δ −64.61 (s); IR (KBr) 3300 (NH), 2220 (CN) cm^{-1}; MS *m/e* 221 (M^+), 206 ($M^+ - CH_3$), 195 (M^+ − CN). Anal. Calcd for $C_{10}H_8FN_3S$: C, 54.29; H, 3.64; N, 18.99. Found: C, 54.12; H, 3.52; N, 18.76.

16a: mp 119.5–120 °C; ^{1}H NMR δ 1.34 (t, 3H, J = 7.2 Hz), 2.48 (s, 3H), 2.55 (s, 3H), 4.35 (q, 2H, J = 7.2 Hz), 6.95 (s, 1H), 7.31 (s, 1H); ^{19}F NMR δ −65.72 (s); IR (KBr) 3350, 1795 (C=O) cm^{-1}; MS *m/e* 268 (M^+), 195 ($M^+ - CO_2Et$). Anal. Calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44. Found: C, 53.85; H, 4.64; N, 10.34.

Preparation of 3-Amino-2-fluoro-4,6-dimethylthieno-[2,3-*b*]pyridine (15a) and 3-Amino-2-fluoro-4-methyl-6-phenylthieno[2,3-*b*]pyridine (15b). A solution of **12** (0.1 mmol) in ethanol (5 mL) containing potassium carbonate (0.15 mmol) was stirred at room temperature for 3 h. After filtration of insoluble material, the filtrate was evaporated under vacuum to yield pure **15** (**15a**, 90% yield from **12b**, 70% yield from **12c**; **15b**, 60% yield).

15a: mp 113.5–114 °C; ^{1}H NMR δ 2.51 (s, 3H), 2.62 (s, 3H), 3.50 (br, 2H), 6.87 (s, 1H); ^{19}F NMR δ −77.1 (s); IR (KBr) 3400–3200, 1660 cm^{-1}; MS *m/e* 196 (M^+), 150 ($M^+ - 2CH_3 - NH_2$), 133 (M^+ − CSF), 105 ($M^+ - SC_2H_2NF$). Anal. Calcd for $C_{9H9}FN_2S$: *m/e* 196.0470; C, 55.80; H, 4.62; N, 14.27. Found: C, 55.12; H, 4.61; N, 14.40.

15b: mp 138.5–139 °C; ^{1}H NMR δ 2.2 (s, 3H), 2.75 (s, 2H), 7.39–7.49 (m, 4H), 7.90–8.15 (m, 2H); ^{19}F NMR δ −74.72 (s); IR (KBr) 3400, 3200, 1620 cm^{-1}; MS *m/e* 258 (M^+). Anal. Calcd for $C_{14}H_{11}FN_2S$: C, 65.10; H, 4.29; N, 10.84. Found: C, 65.15; H, 4.23; N, 10.94.

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