Electrolytic Partial Fluorination of Organic Compounds. 47.[1] Highly Regioselective Anodic Monofluorination of 2-Thiadiazolyl, 2-Oxadiazolyl, and 2-Triazolyl Sulfides

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Received March 19, 2001

Introduction

Recently, unique chemical and biological properties of organofluorine compounds have captured intense attention of chemists and biochemists.[2] In fact, a number of fluorine-substituted pharmaceuticals, agrochemicals, dyes, and polymers have already been commercialized.[3] On the other hand, many heterocyclic compounds have unique biological activities.[3] Therefore, introduction of fluorine atom(s) into the heterocyclic compounds is expected to markedly enhance or dramatically change their biological activities.

From a synthetic point of view, chemical fluorination is straightforward provided that the suitable fluorinating agents are available. However, the control of the regioselectivity of fluorination is often difficult to be achieved. Furthermore, many of the reagents which are currently used for direct chemical fluorination are expensive, toxic, corrosive, and sometimes explosive. On the other hand, an anodic partial fluorination strategy for the introduction of fluorine atom(s) into organic compounds represents an attractive alternative methodology.[4,5] The method is often synthetically more elegant and allows the fluorination to be performed with high regioselectivity. However, limited examples of selective anodic partial fluorination of heterocycles have been reported:[6] these processes are limited to only nitrogen- and oxygen-containing hererocycles and, other than our work, the yields are generally quite low.[7]

We have developed a convenient selective anodic partial fluorination of various organic compounds including different heterocyclic compounds to introduce fluorine atom(s) into the heterocyclic ring or their side chain.[7] In this work, we have studied comparatively anodic fluorination of various five-membered heterocyclic sulfides **1**−**3** such as 2-thiadiazolyl, 2-oxadiazolyl, and 2-triazolyl sulfides.

Results and Discussion

Preparation of Heterocyclic Sulfides. The starting heterocyclic sulfides **1**−**3** were synthesized in good yields by the reaction of the 2-mercapto derivatives of heterocyclic compounds with α-halogeno ester, ketone, nitrile, or methyl iodide in boiling THF containing potassium carbonate according to the reported procedures.[8]

Oxidation Potentials of Heterocyclic Sulfides. To investigate the effects of electron-withdrawing groups and ring systems on the oxidation potentials of sulfides **1**−**3**, the anodic peak potentials of **1**−**3** were measured in anhydrous acetonitrile containing $Bu_4N{\cdot}BF_4$ (0.1 M) by cyclic voltammetry. The CV curves were obtained with a three-electrode system using a platinum disk as the working electrode, a platinum wire as the counter electrode, and a 1 M NaCl calomel electrode (SSCE) as a reference electrode. All these sulfides showed irreversible anodic waves; the first oxidation peak potentials E_p^{ox} of the heterocyclic sulfides **1**−**3** are given in Table 1.

It was found that sulfides **1**−**3** having an electron-withdrawing group (EWG) were oxidized at more positive potentials than sulfides **1**−**3** devoid of an EWG owing to the electron-withdrawing effect exerted by the substituents (EWG). This clearly indicates that the polar effect of the substituent (EWG) plays a significant role in the electron-transfer step from the sulfur atom regardless of the ring systems of these sulfides.

It is noted that the oxidation potentials of 2-thiadiazolyl sulfides **1** are similar to those of 2-oxadiazolyl sulfides **2** while 2-triazolyl sulfides **3** are more easily oxidized than **1** and **2**.

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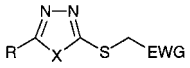
10.1021/jo010300e CCC: $20.00
Published on Web 07/06/2001

Table 1. Oxidation Potentials (Peak Potentials, E_p^{ox}) of Heterocyclic Sulfides

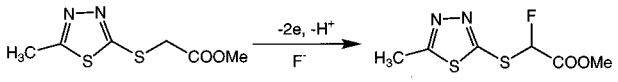


1,2,3

substrate[a]				
no.	X	R	EWG	E_p^{ox} V vs SSCE
1a	S	CH_3	$COOCH_3$	2.16
1b	S	CH_3	$COCH_3$	2.06
1c	S	CH_3	CN	2.31
1d	S	CH_3	H	2.00
2a	O	Ph	$COOCH_3$	2.11
2b	O	Ph	$COCH_3$	2.08
2c	O	Ph	CN	2.26
2d	O	Ph	H	2.02
3a	NH	H	COOEt	1.68
3b	NCH_3	H	$COCH_3$	1.72
3c	NCH_3	H	H	1.54
3d	NPh	Ph	COOEt	1.76

[a] Substrate (1 mmol) in 0.1 M $Bu_4N{\cdot}BF_4$/MeCN. Sweep rate: 100 mV/s.

Table 2. Anodic Monofluorination of Methyl α-[2-(5-Methyl-1,3,4-thiadiazolyl)thio]acetate (1a) under Various Electrolytic Conditions



1a 4a

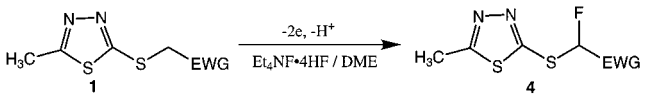
run	supporting electrolyte	solvent	charged passed (F/mol)	product yield (%)[a]
1	$Et_4NF{\cdot}4HF$	MeCN	8	15
2	$Et_4NF{\cdot}4HF$	DME	8	88 (78)
3	$Et_3N{\cdot}3HF$	DME	8	34
4	$Et_3N{\cdot}4HF$	DME	8	50
5	$Et_3N{\cdot}5HF$	DME	9	55
6	$Et_3N{\cdot}3HF$	MeCN	8	14
7	$Et_4NF{\cdot}3HF$	DME	9	73
8	$Et_4NF{\cdot}3HF$	MeCN	9	13

[a] Determined by ^{19}F NMR and isolated yield is indicated in parentheses.

Anodic Monofluorination of 2-(1,3,4-Thiadiazolyl) Sulfides 1. Anodic monofluorination was investigated in detail using methyl α-[2-(5-methyl-1,3,4-thiadiazolyl)-thio]acetate (**1a**) as a model compound. The fluorination was carried out at platinum plate electrodes in anhydrous acetonitrile or dimethoxyethane (DME) containing various fluoride salts as the supporting electrolyte and fluoride ion source using an undivided cell. A constant current was passed until the starting sulfide was completely consumed. The results are summarized in Table 2.

As shown in Table 2, anodic fluorination of **1a** in DME proceeded to give the corresponding α-monofluorinated product **4a.** Among the supporting electrolytes used, $Et_4NF{\cdot}4HF$ gave the best result. Other supporting electrolytes such as $Et_3N{\cdot}nHF$ (n = 4, 5) and $Et_4NF{\cdot}3HF$ gave lower product yields, and $Et_3N{\cdot}3HF$ was not effective due to the formation of a nonconductive polymer deposited on the anode surface (anode passivation). When acetonitrile was used instead of DME, strong anode passivation was observed during the electrolysis regardless of the supporting fluoride salts. On the contrary, the use of $Et_4NF{\cdot}4HF$/DME did not cause any passivation and gave the highest yield of **4a**. Thus, $Et_4NF{\cdot}4HF$/DME was found to be a suitable electrolytic solution for the anodic monofluorination of **1a**.

Table 3. Anodic Monofluorination of 2-(5-Methyl-1,3,4-thiadiazolyl) Sulfides 1

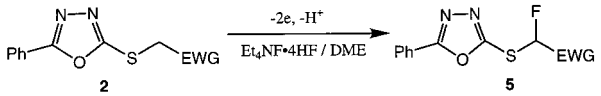


1 4

run	sulfide no.	sulfide EWG	charge passed (F/mol)	product	yield (%)[a]
1	**1a**	COOMe	8	**4a**	88 (78)
2	**1b**	COMe	8	**4b**	70 (62)
3	**1c**	CN	11	**4c**	52 (34)
4	**1d**	H	9	**4d**	58 (48)

[a] Determined by ^{19}F NMR; isolated yields are indicated in parentheses.

Table 4. Anodic Monofluorination of 2-(5-Phenyl-1,3,4 oxadiazolyl) Sulfides 2



2 5

run	sulfide no.	sulfide EWG	charge passed (F/mol)	product	yield (%)[a]
1	**2a**	COOMe	8	**5a**	40 (32)
2	**2b**	COMe	8	**5b**	38 (30)[c]
3	**2c**	CN	9	**5c**	10[b]
4	**2d**	H	9	**5d**	26[c]

[a] Determined by ^{19}F NMR; isolated yields are indicated in parentheses. [b] A large amount of the starting material **2c** was recovered. [c] A complex mixture of unidintified fluorinated products was detected by ^{19}F NMR.

Next, the fluorination reaction was extended to various 2-thiadiazolyl sulfides bearing other electron-withdrawing groups, **1b**,**c**. The monofluorination proceeded well regardless of the electron-withdrawing substituents. A fluorine atom was introduced exclusively into the position α to both the sulfur atom and the electron-withdrawing group to afford the products **4b**,**c** in good yields as shown in Table 3.

Moreover, we successfully carried out anodic monofluorination of 2-methylthio-5-methyl-1,3,4-thiadiazole (**1d**) devoid of an electron-withdrawing group. Although **1d** has a methyl group at the thiadiazole ring, the fluorination took place predominantly at the *S*-methyl group. Therefore, it is noted that the anodic fluorination is highly regioselective.

Anodic Monofluorination of 2-(1,3,4-Oxadiazolyl) Sulfides 2. As a comparative study with the foregoing results, anodic monofluorination of 2-(1,3,4-oxadiazolyl) sulfides **2** as an oxygen analogue to 2-(1,3,4-thiadiazolyl)-sulfides **1** was carried out under the same electrolytic conditions. The results are shown in Table 4.

At the beginning, we expected that 2-oxadiazolyl sulfides **2** would give the same results of anodic fluorination as 2-thiadiazolyl sulfides **1** because of the similarity in the values of the oxidation potentials. However, 2-oxadiazolyl sulfides **2** afforded α-monofluorination products **5** in much lower yields than the corresponding 2-thiadiazolyl sulfides **1**. Our pervious study also showed that the anodic fluorination of benzothiazolyl sulfides[9] proceeded much more efficiently than that of benzoxazolyl sulfides.[10] This trend is quite similar to the results in the present work. From these results, it can be stated

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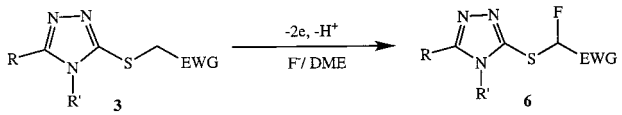
Table 5. Anodic Monofluorination of 2-(1,3,4-Triazolyl) Sulfides 3



run	sulfide no.	R	R′	EWG	supporting electrolyte	charge passed (F/mol)	product	yield (%)[a]
1	**3a**	H	H	COOEt	$Et_4NF{\cdot}4HF$	12	**6a**[c]	2
2	**3b**	H	CH_3	$COCH_3$	$Et_3N{\cdot}3HF$	18	**6b**[d]	4
3	**3c**	H	CH_3	H	$Et_4NF{\cdot}4HF$	12	**6c**[e]	5
4	**3d**	Ph	Ph	COOEt	$Et_4NF{\cdot}4HF$	11	**6d**	18[b]

[a] Determined by ^{19}F NMR; most of the starting material **3** was recovered. [b] Isolated yield: 16%. [c] **6a**: ^{19}F NMR −86.66 (d, J = 50.16 Hz); MS m/z 161 (M^+), 115 (M^+ − EtOH). [d] **6b**: ^{19}F NMR −85.06 (d, J = 51.19 Hz); MS m/z 189 (M^+), 127 (M^+ − MeCOF). [e] **6c**: ^{19}F NMR −113.23 (t, J = 47.98 Hz); MS m/z 147 (M^+).

that the ring system affects significantly the anodic fluorination as well as oxidation potentials.

Anodic Monofluorination of 2-(1,3,4-Triazolyl) Sulfides 3. Finally, we have examined the anodic monofluorination of some 2-triazolyl sulfides **3** under the same electrolytic conditions. The results are shown in Table 5.

In sharp contrast to the cases of **1** and **2**, 2-triazolyl sulfides **3** gave extremely low yields of the fluorinated products **6** in comparison with the corresponding 2-thiadiazolyl and 2-oxadiazolyl sulfides **1** and **2**. Particulary, *N*-unsubstituted derivative **3a** and *N*-methyl derivatives **3b**,**c** provided α-fluorinated products **6a**−**c** in extremly low yields and most of the starting materials were recovered although a large excess amount of electricity was passed. Since **3a**−**c** are rather basic, **3a**−**c** should be protonated in a strongly acidic electrolysis solution. Therefore, they were not oxidized at the anode; they were reduced at the cathode (namely proton reduction) to generate the corresponding starting material, which would be immediately protonated again and the cycle continued. This seems to consume a large excess amount of electricity. In fact, it was confirmed that **3a**−**c** formed the corresponding salts with strong acids such as picric acid. In the case of *N*-phenyl derivative **3d**, the anodic monofluorination proceeded to give the corresponding α-monofluorinated product **6d** in higher yield than the other *N*-unsubstituted and *N*-methyl derivatives **3a**−**c** probably owing to the low basicity of **3d** due to the electron-withdrawing effect of the phenyl substitution, which decreases the tendency to salt formation. In all cases of **3**, severe anode passivation was observed during the electrolysis. This seems to be another reason for extremely low yields of the fluorinated products **6**.

Conclusion

In conclusion, highly regioselective anodic monofluorination of five-membered nitrogen-containing heterocyclic sulfides has been successfully carried out. It was found that the fluorination efficiency is greatly affected by the ring system of the starting sulfides. 2-Thiadiazolyl sulfides **1** afforded the α-monofluorinated products in high yields, while the corresponding oxygen analogues 2-oxadiazolyl sulfides **2** gave moderate to lower yields. In sharp contrast, anodic fluorination of 2-triazolyl sulfides **3** resulted in extremely low yields due to the salt formation of **3** and the anode passivation.

Experimental Section

Caution! $Et_4NF{\cdot}4HF$ and $Et_3N{\cdot}5HF$ were obtained from Morita Chemical Co. Ltd. They are toxic and may cause serious burns if they come in contact with unprotected skin. $Et_4NF{\cdot}3HF$ and $Et_3N{\cdot}3HF$ are much less aggressive. However, proper safety precautions should be taken at all times.[11] It is therefore recommended that hand protection be used.

Anodic Fluorination of the Heterocyclic Sulfides 1−3. A typical procedure for the anodic fluorination of the heterocyclic sulfides is as follows. Anodic oxidation of **1**−**3** (1 mmol) was carried out with platinum-plate electrodes (2 × 2 cm^2) in DME and/or MeCN (15 mL) containing 0.3 M $Et_4NF{\cdot}4HF$ using an undivided cell under a nitrogen atmosphere at room temperature. Constant current (5 mA/cm^2) was passed until the starting material was almost consumed (checked by TLC or GC-MS). After electrolysis, the electrolytic solution was passed through a short chromatographic silica gel column using ethyl acetate to remove fluoride salts. The eluent was evaporated under reduced pressure, and the residue was further purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) as eluent. The results are shown in Tables 2−5.

Methyl α-fluoro-α-[2-(5-methyl-1,3,4-thiadiazolyl)thio]-acetate (4a): mp 50 °C;^1H NMR δ 2.80 (s, 3 H); 3.86 (s, 3 H), 6.57 (d, 1 H, J = 50.48 Hz); ^{19}F NMR δ −85.50 (d, J = 50.50 Hz); MS m/z 222 (M^+), 190 (M^+ − MeOH), 163 (M^+ − COOMe); HRMS m/z calcd for $C_6H_7FN_2O_2S_2$ 221.9914, found 221.9933. Anal. Calcd for $C_6H_7O_2N_2FS_2$: C, 32.42; H, 3.17; N, 12.60; S, 28.85. Found: C, 32.26; H, 3.24; N, 12.46; S, 28.66.

1-Fluoro-1-[2-(5-methyl-1,3,4-thiadiazolyl)thio]-2-propanone (4b): yellow oil; ^1H NMR δ 2.41 (s, 3 H), 2.79 (s, 3 H), 6.50 (d, 1 H, J = 50.15 Hz); ^{19}F NMR δ −80.84 (d, J = 50.15 Hz); MS m/z 206 (M^+), 144 (M^+ − MeCOF); HRMS m/z calcd for $C_6H_7FN_2OS_2$ 205.9958, found 205.9984. Anal. Calcd for $C_6H_7FN_2OS_2$: C, 34.94; H, 3.42; N, 13.58. Found: C, 35.19; H, 3.60; N, 13.58.

α-Fluoro-α-[2-(5-methyl-1,3,4-thiadiazolyl)thio]acetaonitrile (4c): yellow oil;^1H NMR δ 2.85 (s, 3 H); 6.90 (d, 1H, J = 48.50 Hz); ^{19}F NMR δ −85.33 (d, J = 48.50 Hz); MS m/z 189 (M^+); 162 (M^+−HCN); HRMS m/z Calcd for $C_5H_4FN_3S_2$ 188.9806, found 188.9831. Anal. Calcd for $C_5H_4FN_3S_2$: C, 31.73; H, 2.13; N, 22.21; S, 33.89. Found: C, 31.98; H, 2.39; N, 22.12; S, 33.70.

2-Fluoromethylthio-5-methyl-1,3,4-thiadiazole (4d): yellow oil; ^1H NMR: δ 2.79 (s, 3 H), 6.9 (d, 1 H, J = 50.81 Hz).^{19}F NMR: δ −108.46 (t, J = 50.81 Hz); MS m/z 164 (M^+); 144 (M^+ − HF); HRMS m/z calcd for $C_4H_5FN_2S_2$ 163.9869, found 163.9878. Anal. Calcd for $C_4H_5FN_2S_2$ C, 29.25; H, 3.07; N, 17.06; S, 39.05. Found: C, 29.46; H, 3.12; N, 16.70; S, 38.67.

Methyl-α-fluoro-α-[2-(5-phenyl-l,3,4-oxadiazolyl)thio]acetate (5a): yellow oil; ^1H NMR δ 3.94 (s, 3 H); 6.66 (d, 1H, J = 50.15 Hz); 7.50 (m, 3 H); 8.04 (d, 2H, J = 7.26 Hz); ^{19}F NMR δ −85.50 (d, J = 50.15 Hz); MS m/z 268 (M^+), 236 (M^+ − MeOH), 209 (M^+ − COOMe); HRMS m/z calcd for $C_{11}H_9FN_2O_3S$ 268.0251, found 268.0318. Anal. Calcd for $C_{11}H_9FN_2O_3S$: C, 49.25; H, 3.38; N, 10.44; S. 11.95. Found: C, 49.53; H, 3.68; N, 10.35; S, 11.63.

1-Fluoro-1-[2-(5-phenyl-1,3,4-oxadiazolyl)thio]-2-propanone (5b): yellow oil; ^1H NMR δ 2.49 (s, 3 H); 6.63 (d, 1 H, J = 50.15 Hz); 7.53 (m, 3 H); 8.03 (d, 2H, J = 7.26 Hz); ^{19}F NMR δ −85.50 (d, J = 50.15 Hz); MS m/z 252 (M^+); HRMS m/z calcd for $C_{11}H_9FN_2O_2S$ 252.0312, found 252.0364. Anal. Calcd for $C_{11}H_9FN_2O_2S$: C, 52.37; H, 3.60; N, 11.10; S, 12.71. Found: C, 52.60; H, 3.70; N, 10.99; S, 12.86.

α-Fluoro-α-[2-(5-phenyl-1,3,4-oxadiazolyl)thio]acetaonitrile (5c): yellow oil; ^1H NMR δ 6.90 (d, 1H, J = 48.50 Hz); 7.53 (m, 3 H); 8.03 (d, 2H, J = 7.26 Hz); ^{19}F NMR δ −85.33 (d, J = 48.50 Hz); MS m/z 235 (M^+), 208 (M^+ − HCN). Anal. Calcd for $C_{10}H_6FN_3OS$: C, 51.06; H, 2.57; N, 17.86. Found: C, 51.32; H, 2.46; N, 17.55.

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2-Fluoromethylthio-5-phenyl-1,3,4-oxadiazole (5d): yellow oil; ^{1}H NMR δ 6.06 (d, 2 H, J = 50.47 Hz); 7.40 (m, 3 H); 7.99 (d, 2H, J = 7.26 Hz); ^{19}F NMR δ −114.32 (t, J = 50.47 Hz); MS m/z 210 (M^+). Anal. Calcd for $C_9H_7FN_2OS$: C, 51.42; H, 3.36; N, 13.33; S, 15.25. Found: C, 51.58; H, 3.28, N, 13.06; S, 14.98.

Ethyl α-fluoro-α-[2-(5-diphenyl-1,3,4-triazolyl)thio]acetate (6d): yellow oil; ^{1}H NMR δ 1.22 (t, 3 H, J = 6.93 Hz); 4.21 (q, 2 H, J = 6.93 Hz); 6.50 (d, 1H, J = 50.13 Hz); 7.21−7.43 (m, 10 H).^{19}F NMR δ −83.60 (d, J = 50.13 Hz); MS m/z 357 (M^+), 311 (M^+ − EtOH), 284 (M^+ − COOEt); HRMS m/z calcd for $C_{18}H_{16}FN_3O_2S$ 357.0949, found 357.0947.

Acknowledgment. This work was supported by a Grant-in Aid for scientific research (No. 12555252) from the Ministry for Education, Science, Sports, and Culture of Japan and the Kato Foundation.

Supporting Information Available: ^{1}H NMR spectra of **4d** and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010300E