Electrolytic Partial Fluorination of Organic Compounds. 23.[1] Regioselective Anodic Difluorination of Sulfides Using Novel Fluorine Source $Et_4NF{\cdot}4HF$

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Received July 9, 1997

Introduction

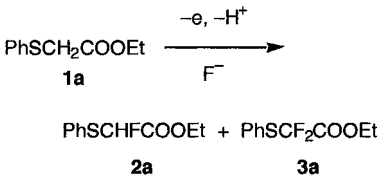
Selective fluorination of organic molecules has attracted much interest because a number of partially fluorinated organic molecules are reported to show unique chemical and physical properties and, in some cases, biological activities.[3−7] Among them, difluoromethylene compounds attract interest because the structure is isopolar and isosteric with an ether oxygen which is contained in many biologically active compounds.[3] The difluoromethylene group is prepared from the corresponding compound using various reagents such as molybdenum hexafluoride,[8] selenium tetrafluoride,[9] sulfur tetrafluoride,[10] and (dimethylamido)sulfur trifluoride (DAST).[11] However, these reagents are highly toxic and their use requires severe reaction conditions. Recently, oxidative fluorodesulfurization of dithioacetals such as 1,3-dithiolanes was successfully conducted using chemical oxidants[12−14] or electrochemical oxidation[15,16] in the presence of fluoride ion. Even in these methods, a large amount of hazardous oxidant is required for the reactions[12−14] or the structure of starting dithioacetal is limited.[15,16] Recently, we successfully conducted highly regioselective anodic monofluorinations of organo chalcogen compounds in acetonitrile using $Et_3N{\cdot}3HF$ as a fluorine source and a supporting electrolyte.[17] We also attempted direct difluorination of these compounds. Difluorination occurred regioselectively, but current efficiencies were extremely low due to competitive oxidation of $Et_3N{\cdot}3HF$ and a monofluorinated product.[17] Recently, Momota et al. reported the anodic fluorination of benzene using a novel molten salt $Et_4NF{\cdot}4HF$ as a fluorine source and a solvent.[18] Even benzene, which has high oxidation potential (> 2.0 V vs SCE), can be fluorinated anodically in $Et_4NF{\cdot}4HF$. This result prompted us to conduct direct anodic difluorination of sulfides using $Et_4NF{\cdot}4HF$ as a fluorine source.

Table 1. Effect of Supporting Electrolytes on Anodic Difluorination of Ethyl α-(Phenylthio)Acetate

run	supporting electrolyte	anodic potential, V vs Ag/Ag^+	charge passed F/mol	product yield % **2a**	**3a**
1	$Et_3N{\cdot}3HF$[a]	2.2	20.7	4	52
2	$Et_4NF{\cdot}4HF$[b]	1.4−2.0	4.0	11	6
3	$Et_4NF{\cdot}4HF$	1.6−1.9	4.0	4	52
4	$Bu_4NF{\cdot}3H_2O$	*c*	2.0	0	0
5	$PhCH_2NMe_3{\cdot}HF_2$	2.4	3.4	0	0

[a] Starting material is a monofluoro derivative **2a**. [b] No solvent; $Et_4NF{\cdot}4HF$ (30 mL). [c] Constant current (10 mA/cm^2) electrolysis.

Scheme 1



Results and Discussion

Anodic difluorination of ethyl α-(phenylthio)acetate (**1a**) was investigated under several conditions as shown in Table 1. As we reported previously,[17] under conventional anodic monofluorination conditions (0.37 M $Et_3N{\cdot}3HF$ in acetonitrile), a large excess amount of electricity (20.7 F/mol) was required in order to complete the fluorination despite using monofluorinated sulfide **2a** as a starting material (run 1).

Next, anodic difluorination of **1a** was conducted using $Et_4NF{\cdot}4HF$ as a fluorine source and a solvent (same conditions as the anodic fluorination of benzene[18]) (run 2). The starting sulfide and monofluorinated product were almost consumed (GC-mass analysis) after 4 F/mol of charge, theoretical amount for difluorination, was passed. This result suggested that the current efficiency should be improved by using $Et_4NF{\cdot}4HF$ compared to the case of using $Et_3N{\cdot}3HF$ (run 1) as a fluorine source. However, the yield of the desired difluorinated product **3a** was very low (6%). The ^{19}F NMR spectrum of the crude product was complicated and indicated that the nonregioselective polyfluorination occurred, i.e., fluorination at the aromatic ring as well as at the α-position to the sulfur atom. The detection of diphenyl disulfide and its oxidation products by GC-mass analysis, suggested that oxidative cleavage of a carbon−sulfur bond also occurred. From these results, it is considered that fluorinating ability of $Et_4NF{\cdot}4HF$ is too high to fluorinate **1a** regioselectively in the conditions of run 2.

To conduct anodic difluorination under milder conditions, acetonitrile was added as a solvent. Anodic difluorination of **1a** in 0.2 M $Et_4NF{\cdot}4HF/CH_3CN$ proceeded smoothly without passivation of the anode to give a satisfactory result (run 3). It is notable that the current efficiency increased five times. The yield of difluorinated

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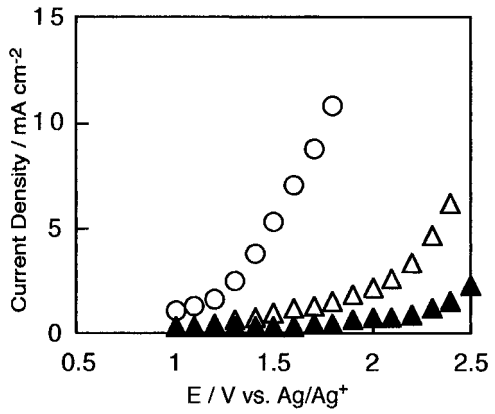


Figure 1. Current-potential curves: 0.37 M $Et_3N{\cdot}3HF$/MeCN (Δ), 0.1 M PhSCHFCOOEt in 0.37 M $Et_3N{\cdot}3HF$/MeCN (○), 0.2 M $Et_4NF{\cdot}4HF$/MeCN (▲).

Table 2. Anodic Difluorination of Sulfides Bearing Electron-Withdrawing Substituents

	sulfide			anodic potential,	charge passed,	product yield, %	
run	no.	R	EWG	V vs Ag/Ag^+	F/mol	**2a**	**3a**
1	**1a**	Ph	COOEt	1.6−1.9	4.0	4	52
2	**1b**	Ph	COOBn	1.5−1.9	4.0	2	52
3	**1c**	Ph	$PO(OEt)_2$	1.8−2.1	4.0	0	50
4	**1d**	Ph	CN	1.8−2.0	4.0	30	30
5	**1e**	C_7H_{15}	COOEt	1.9−2.3	4.6	2	53

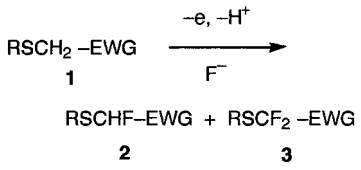
product **3a** was reasonable considering the lack of efficient methods for direct difluorination of a methylene group. Anodic fluorination using other fluorine sources and supporting electrolytes were not effective as shown in Table 1 (runs 4 and 5). In these cases, electrolysis gave a complex mixture containing oxygenated products detected by GC-mass analysis, and fluorinated products were not detected by ^{19}F NMR at all. The best yield and current efficiency of **3a** were obtained using $Et_4NF{\cdot}4HF$ as a supporting electrolyte and acetonitrile as a solvent.

This improvement by using $Et_4NF{\cdot}4HF$ instead of $Et_3N{\cdot}3HF$ is well explained by considering current−potential relationships of electrolytes (Figure 1). As anodic potential was increased, the oxidation of $Et_3N{\cdot}3HF$ started around 1.2 V vs Ag/Ag^+ at which potential monofluorinated sulfide **2a** is oxidized considerably. On the other hand, $Et_4NF{\cdot}4HF$ is almost stable even at the potential of 2.0 V vs Ag/Ag^+. Figure 1 clearly shows that the current efficiency of anodic difluorination increases markedly when oxidation potentials of supporting electrolytes are high enough. Thus, in the electrolyte containing $Et_4NF{\cdot}4HF$, anodic oxidation of monofluorinated product took place preferably.

It is also notable that, in this anodic difluorination, the addition of acetonitrile as a solvent resulted in improvement of the yield of the desired difluorinated product. This is sharp contrast to the case of anodic fluorination of benzene: i.e., the addition of acetonitrile resulted in decrease of both the yield and the current efficiency of fluorination.[19]

The results of anodic difluorinations of several sulfides having electron-withdrawing groups were summarized in Table 2. In all cases, anodic difluorination takes place α to the sulfur atom regioselectively. For example, neither aromatic fluorination nor benzylic fluorination

Scheme 2



was observed in the fluorination of benzyl α-(phenylthio)-acetate (**1b**) (run 2). It is remarkable that anodic difluorination proceeded with such a high regioselectivity despite higher anodic potential required for difluorination compared to monofluorination. Phosphonate derivative **1c** was also difluorinated in fairly good yield, and the difluorinated product **3c** should be a promising building block for biologically interested difluoromethylenephosphonates[20] (run 3). The yield of difluorinated product from cyano derivative **1d** was rather low (run 4). Anodic difluorination of aliphatic sulfide **1e** also occurred as efficiently as phenyl sulfides (run 5). It is noteworthy that these fluorinations could all be conducted in an undivided cell because reduction of protons of hydrogen fluoride took place at the cathode predominantly, and fluorinated products were not reduced under these conditions.

In conclusion, direct anodic difluorination of sulfides having electron-withdrawing groups at α to the sulfur atom was successfully carried out with high current efficiencies and in reasonable yields using a novel molten salt $Et_4NF{\cdot}4HF$ as a supporting electrolyte and a fluorine source in acetonitrile. Furthermore, biologically interesting difluoromethylenephosphonate could be obtained directly from nonfluorinated methylenephosphonate in good yield by this method.

Experimental Section

Caution: $Et_4NF{\cdot}4HF$ is toxic, and contact with skin causes serious burns. $Et_3N{\cdot}3HF$ is much less aggressive. However, proper safety precautions should be taken at all times. It is therefore recommended to refer to an authoritative paper[21] for treatment of HF and related compounds.

^1H NMR and ^{19}F NMR spectra were recorded at 270 or 90 MHz using $CDCl_3$ as a solvent. The chemical shifts for ^1H and ^{19}F NMR are given in δ (ppm) downfield from internal Me_4Si and 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.

Anodic Difluorination of Sulfides. Typical anodic difluorination conditions are as follows. Electrolysis was conducted with a platinum anode and cathode [6 cm^2 (2 × 3 cm)] in 0.2 M $Et_4NF{\cdot}4HF/CH_3CN$ (30 mL) containing 3.0 mmol of sulfides using a cylindrical undivided cell made of PFA resin at ambient temperature. After the starting sulfide and monofluorinated intermediate were almost consumed (monitored by silica gel TLC and GC-mass spectra), the electrolysis solution was passed through a short column of silica gel (CH_2Cl_2) to yield an almost pure difluorinated product.

Ethyl α,α-difluoro-α-(phenylthio)acetate (3a): ^1H NMR δ 1.25 (t, 3H, J = 7.0 Hz), 4.22 (q, 2H, J = 7.0 Hz), 7.0−7.8 (m, 5H); ^{19}F NMR δ −3.3 (s); IR 3010, 1785, 1480, 1450, 1380, 1300, 1135, 1120, 1075, 1025, 980, 760, 695 cm^{-1}; MS *m/e* 232 (M^+), 159 (M^+ − COOEt), 109 (PhS^+), 77 (Ph^+). Anal. Calcd for $C_{10}H_{10}F_2O_2S$: C, 51.72; H, 4.34. Found: C, 51.75; H, 4.51.

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Benzyl α,α-difluoro-α-(phenylthio)acetate (3b): ^{1}H NMR δ 5.21 (s, 2H), 7.2−7.5 (m, 8H), 7.5−7.6 (m, 2H); ^{19}F NMR δ −3.3 (s); IR 3065, 3040, 2960, 1765, 1500, 1475, 1455, 1445, 1285, 1105, 990, 750, 690 cm^{-1}; MS *m/e* 294 (M^+), 159 ($M^+ - COOCH_2Ph$), 109 (PhS^+), 91 ($PhCH_2^+$), 77 (Ph^+); calcd for $C_{15}H_{12}F_2O_2S$ *m/e* 294.0526, found 294.0518.

Diethyl α,α-difluoro-α-(phenylthio)methylphosphonate (3c): ^{1}H NMR δ 1.38 (t, 6H, J = 7.1 Hz), 4.30 (m, 4H), 7.4−7.5 (m, 3H), 7.6−7.7 (m, 2H); ^{19}F NMR δ −6.7 (d, 1F, J = 145 Hz), −7.1 (d, 1F, J = 145 Hz); IR 3080, 2960, 1275, 1117, 1036, 912, 750 cm^{-1}; MS *m/e* 296 (M^+), 214 ($PhPO(OEt)_2$), 159 ($M^+ - PO(OEt)_2$), 109 (PhS^+), 77 (Ph^+); calcd for $C_{11}H_{15}F_2O_3PS$ *m/e* 296.0447, found 296.0464.

α,α-difluoro-α-(phenylthio)acetonitrile (3d): ^{1}H NMR δ 7.3−7.8 (m); ^{19}F NMR δ 8.6 (s); IR 3065, 2930, 2190, 1462, 1446, 1135, 940, 752, 700 cm^{-1}; MS *m/e* 185 (M^+), 109 (PhS^+), 77 (Ph^+); calcd for $C_8H_5F_2NS$ *m/e* 185.0111, found 185.0117.

Ethyl α,α-difluoro-α-(heptylthio)acetate (3e): ^{1}H NMR δ 0.89 (t, 3H, J = 5.7 Hz), 1.2−1.9 (m, 12H), 2.87 (t, 2H, J = 7.0 Hz), 4.36 (q, 2H, J = 7.2 Hz); ^{19}F NMR δ −3.3 (s); IR 2932, 2862, 1771, 1468, 1373, 1296, 1102, 1017, 986, 723 cm^{-1}; MS *m/e* 254 (M^+), 181 ($M^+ - COOEt$), 131 ($C_7H_{15}S^+$), 97 ($C_7H_{13}^+$); calcd for $C_{11}H_{20}F_2O_2S$ *m/e* 254.1152, found 254.1146.

Acknowledgment. We are grateful to Dr. Kunitaka Momota of Morita Chemical Industries Co. Ltd. for his generous gift of $Et_4NF\cdot4HF$.

Supporting Information Available: ^{1}H NMR one-dimensional spectra for compounds **3b**−**e** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971248I