Electrolytic Partial Fluorination of Organic Compounds. 1.[†] Regioselective Anodic Monofluorination of Organosulfur Compounds

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Received June 12, 1990

Summary: Regioselective anodic monofluorination of aryl 2,2,2-trifluoroethyl sulfides gave, exclusively, aryl 1,2,2,2-tetrafluoroethyl sulfides, the products of fluorination at the position α to the trifluoromethyl group. The α-monofluorination of sulfides bearing electron-withdrawing substituents other than trifluoromethyl was also successful. Furthermore, the procedure could be applied to the α,α-difluorination of sulfides. The products are versatile building blocks and useful precursors of sulfur-free fluorinated compounds.

Although much attention has been paid to fluoroorganic compounds because of their potential biological activity,[1] methods for their synthesis are limited in number.[2] For example, nucleophilic substitution α to a trifluoromethyl group is rarely observed, due to the strong electron-withdrawing effect of the group.[3,4] Therefore, the development of methods that permit substitution at the α position is one of the most important goals of modern organofluorine chemistry.

Recently, we found that the trifluoromethyl group remarkably promoted anodic methoxylation and acetoxylation of aryl 2,2,2-trifluoroethyl sulfides **1** (Scheme I).[5,6] We also found that these anodic substitutions proceeded via the cationic intermediate A.[6]

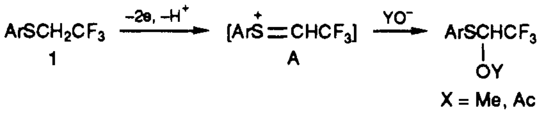
Methods for the partial fluorination of organic molecules are becoming increasingly important. Electrochemical fluorination is attractive because fluorine atoms can be introduced into organic molecules in one step. Although anodic perfluorination is a well-established technique, relatively few studies on anodic partial fluorination have been made.[7]

With these points in mind, we attempted the anodic substitution of the sulfides **1** with fluorine.

α-Monofluorination of aryl 2,2,2-trifluoroethyl sulfides **1** gave the tetrafluoro sulfides **2** in good yield when the constant potential anodic oxidation of **1** was performed in an undivided cell at a platinum anode in an acetonitrile solution of $Et_3N{\cdot}3HF$.[8] The results are summarized in Table I. Fluorine was exclusively introduced at the position α to the trifluoromethyl group. Neither aromatic fluorination nor benzylic fluorination (run 5) was observed. The results are remarkable because nucleophilic substitution at the position α to the trifluoromethyl group is usually quite difficult to achieve.[3,4] Also, the products **2** are difficult to prepare by other methods.

Anodic fluorination of **1** appears to proceed in a manner similar to that of anodic methoxylation (Scheme I). However, the effect of substituents is quite different from that observed for anodic methoxylation. Electron-donating groups on the benzene ring strongly retarded anodic methoxylation,[9] whereas electron-donating methyl and methoxy groups promoted anodic fluorination (runs 2 and 3). Also, anodic methoxylation of benzyl 2,2,2-trifluoroethyl sulfide (**1e**) occurred both at the benzylic position and α to the trifluoromethyl group,[6] whereas anodic fluorination of **1e** occurred exclusively α to the trifluoromethyl group. More study is certainly necessary for clarification of the mechanism of anodic fluorination.

Scheme I



$$\underset{\mathbf{1}}{ArSCH_2CF_3} \xrightarrow{-2e,\ -H^+} \underset{A}{[Ar\overset{+}{S}{=}CHCF_3]} \xrightarrow{YO^-} ArS\underset{OY}{\underset{|}{C}}HCF_3$$

X = Me, Ac

Table I. Anodic Monofluorination of Aryl 2,2,2-Trifluoroethyl Sulfides

$$\underset{\mathbf{1}}{RSCH_2CF_3} \xrightarrow[Et_3N\cdot 3HF]{-2e,\ -H^+} \underset{\mathbf{2}}{RSCHFCF_3}$$

run	$RSCH_2CF_3$ (R)	anodic potential (V vs SSCE)	charge passed (F/mol)	product[a] (yield, %)
1	Ph (**1a**)	+1.9	4.0	**2a** (35)
2	p-MeC_6H_4 (**1b**)	+2.1	8.2	**2b** (51)
3	p-$MeOC_6H_4$ (**1c**)	+1.7	6.0	**2c** (56)
4	p-ClC_6H_4 (**1d**)	+2.0	7.2	**2d** (65)
5	$PhCH_2$ (**1e**)	+2.3	11.5[b]	**2e** (25)[c]

[a] Isolated yield. [b] Electrolysis was incomplete. [c] Based on **1e** consumed (84% conversion).

Furthermore, the α-monofluorination of sulfides bearing electron-withdrawing substituents other than trifluoromethyl was also successful. The desired products were obtained in good yield regardless of the substituent[10] (Table II).

[†] Presented at the 57th meeting of the Electrochemical Society of Japan, Kyoto, April 5-7, 1990.

(1) (a) Carbon-Fluorine Compounds; A CIBA Foundation Symposium; Elsevier: Amsterdam, 1972. (b) Schlosser, M. Tetrahedron **1978**, *34*, 3. (c) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Ed.; Kodansha & Elsevier Biomedicinal: Tokyo, 1983.

(2) For example, see: Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Wiley: New York, 1976.

(3) For example, see: Umemoto, T.; Goto, Y. *J. Fluorine Chem.* **1986**, *31*, 231.

(4) Bonnet-Delpon, D.; Cambillau, C.; Charpenttier-Morize, M.; Jacquot, R.; Mesucur, D.; Ovreritch, M. *J. Org. Chem.* **1988**, *53*, 754.

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(6) Fuchigami, T.; Yamamoto, K.; Nakagawa, Y. *J. Org. Chem.* In press.

(7) (a) Rozhkov, I. N. In *Organic Electrochemistry*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker: New York, 1983; Chapter 24. (b) Laurent, E.; Marquet, B.; Tardivel, R.; Thiebault, H. *Tetrahedron Lett.* **1987**, *28*, 2359. (c) Makino, K.; Yoshioka, H. *J. Fluorine Chem.* **1988**, *39*, 435. (d) Laurent, E.; Marquet, B.; Tardivel, R. *Tetrahedron* **1989**, *45*, 4431.

(8) The electrolysis was performed at a platinum anode and cathode (3 × 4 cm) in 0.37 M $Et_3N{\cdot}3HF/MeCN$ (50 mL) containing 5 mmol of the substrate. During the electrolysis, the temperature was maintained at ca. 20 °C. After the starting material was completely consumed [silica gel, TLC monitering], the electrolysis solution was neutralized with 12% aqueous ammonia. The acetonitrile was then removed by evaporation below 40 °C. The residue was extracted with ether (40 mL, then 20 mL × 4). The extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3/CCl_4$, 1:1 to 4:1) to provide the desired product.

(9) Fuchigami, T.; Yamamoto, K.; Konno, A. *Tetrahedron.* In Press.

(10) Recently, Brigaud and Laurent reported a similar anodic fluorination.[11] They obtained monofluorinated products from ethyl α-(phenylthio)-α-phenylacetate, bis(α-ethoxycarbonyl)methyl sulfide, and α-(phenylthio)acetophenone. A divided cell was used for the fluorination of α-benzoyl sulfide, and an undivided cell was used for the fluorination of α-ethoxycarbonyl sulfide. On the other hand, we found that an undivided cell was effective regardless of the identity of the electron-withdrawing substituents of the sulfide. Thus, our system is experimentally simpler.

(11) Brigaud, T.; Laurent, E. *Tetrahedron Lett.* **1990**, *31*, 2287.

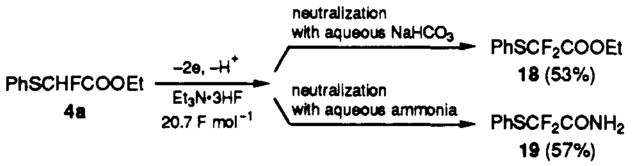
0022-3263/90/1955-6074$02.50/0

Table II. Anodic Monofluorination of Sulfides Bearing Electron-Withdrawing Substituents

run	substrate	anodic potential (V vs SSCE)	charge passed (F/mol)	product[a] (yield, %)
	p-$XC_6H_4SCH_2COOEt$			p-$XC_6H_4SCHFCOOEt$
1	X = H (**3a**)	1.6	2.5	X = H (**4a**) (76)
2	**3a**	*b*	2.4	**4a** (88)
3	X = Me (**3b**)	1.6	2.1	X = Me (**4b**) (78)
4	$PhCH_2SCH_2COOEt$ (**3c**)	2.1	5.0	$PhCH_2SCHFCOOEt$ (**4c**) (44)
5	n-$C_7H_{15}SCH_2COOEt$ (**3d**)	2.1–2.3	16.1	n-$C_7H_{15}SCHFCOOEt$ (**4d**) (70)
6	$PhSCH_2CN$ (**5**)	1.7	5.0	PhSCHFCN (**6**) (75)
7	$PhSCH_2COMe$ (**7**)	1.6–1.8	7.6	PhSCHFCOMe (**8**) (80)
8	$PhS\overline{CH(CH_2)_4C}{=}O$ (**9**)	1.8	2.3	$PhS(F)\overline{C(CH_2)_4C}{=}O$ (**10**) (67)
9	$PhS\overline{CH(CH_2)_2OC}{=}O$ (**11**)	1.8	2.3	$PhS(F)\overline{C(CH_2)_2OC}{=}O$ (**12**) (84)
10	$PhSCH(COOEt)_2$ (**13**)	2.0	15.4	$PhSCF(COOEt)_2$ (**14**) (77)
11	$PhSCH(COMe)_2$ (**15**)	1.7	3.0	PhSCHFCOMe (**8**) (55)
12	$PhSCH_2Ph$ (**17**)	1.6	2.2	PhSSPh (91)[c]

[a] Isolated yield. [b] Constant-current electrolysis (5.8 mA/cm^2). [c] Both benzyl phenyl sulfoxide and benzaldehyde were also detected.

Scheme II



On the other hand, compounds lacking an electron-withdrawing substituent, such as benzyl phenyl sulfide (**17**), failed to give a fluorinated product (run 12). In this case, diphenyl disulfide was the major product, and both benzaldehyde and benzyl phenyl sulfoxide were detected in the electrolysis solution. This result clearly indicated that an electron-withdrawing substituent α to the site of fluorination was necessary. For example, the α-thioesters **3b**, **3c**, and **3d** each have multiple positions susceptible to substitution by a fluorine. However, highly regioselective fluorination took place: fluorine was introduced exclusively α to the ester group. No fluorination of the p-tolyl, benzyl, or n-heptyl groups was observed.

The reaction was successful with the α-(phenylthio)-substituted cyclic ketone **9** and lactone **11** (runs 8 and 9). Fluorination of the malonic ester **13** and diketone **15** was also attempted. Both possessed two electron-withdrawing substituents. The diester **13** provided the expected fluorinated product **14** (run 10). However, the diketone **15** gave the fluorinated ketone **8** instead of the expected fluorinated diketone (run 11).[12] How compound **8** was formed is unclear.

Although some of the sulfides, such as **7**, **9**, and **15**, possessed reducible carbonyl groups, only anodic fluorination occurred, even in an undivided cell. Because the acidic protons of $Et_3N{\cdot}3HF$ were discharged at a relatively early stage of the electrolysis, the carbonyl group was not reduced.

Selective anodic monofluorination could be also achieved by constant-current electrolysis because the fluorinated products had much higher oxidation potentials than the starting materials. Thus, for example, monofluorinated product **4a** was obtained in excellent yield (88%) from ethyl α-(phenylthio)acetate (**3a**) (run 2).[13] This finding, that constant-current electrolysis with an undivided cell was effective for the fluorination, is important from a practical point of view.[10]

The procedure was also applied to the preparation of difluoro derivatives. For example, anodic oxidation of monofluoro ester **4a** at 2.2 V vs SSCE provided the difluoro ester **18** in good yield (Scheme II).[14] In this case, after electrolysis was complete, the electrolysis solution was neutralized with aqueous $NaHCO_3$. If, instead, the solution was neutralized with aqueous ammonia, α,α-difluoro-α-(phenylthio)acetamide (**19**), formed by ammonolysis of the initial product, was isolated.

Traditional methods for the preparation of α-fluoro sulfides require expensive, unstable, or troublesome reagents, such as xenon difluoride,[15] (diethylamino)sulfur trifluoride (DAST),[16] and potassium fluoride.[17,18] N-Fluoropyridinium triflate is also a useful fluorinating reagent.[19] However, fluorination of **3a**, for example, with the latter reagent resulted in only low (38%) yields. In contrast, anodic fluorination does not require any special reagents, the procedure is very simple, and the desired products can be obtained directly in almost pure form.

The fluorinated products are versatile building blocks[20] and, furthermore, desulfurization can be easily achieved with various reducing reagents. Therefore, the present anodic fluorination should prove to be highly useful for the preparation of a variety of fluoroorganic compounds bearing electron-withdrawing substituents.

Acknowledgment. We thank Prof. Tsutomu Nonaka of Tokyo Institute of Technology for helpful discussions. We are also grateful to Prof. Tomoya Kitazume of Tokyo Institute of Technology for obtaining ^{19}F NMR spectra and to Dr. Kokoro Iio of Industrial Products Research Institute for obtaining the high resolution mass spectra.

Supplementary Material Available: Spectroscopic and other analytical data (^1H NMR, ^{19}F NMR, IR, MS, and high resolution MS spectra) for all fluorinated products (5 pages). Ordering information is given on any current masthead page.

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[12] The presence of a trace amount of the fluorinated diketone **16** was established from the mass spectrum of a sample of the electrolysis solution removed during the electrolysis.

[13] For example, the half-peak oxidation potentials of **3a** and **4a** measured at a platinum anode in 0.1 M $NaClO_4$/MeCN (scan rate, 100 mV s^{-1}) were 1.6 V and 1.86 V vs SSCE, respectively.

[14] Difluoro product **18** could also be obtained directly, by anodic fluorination of **3a** at 2.2 V.

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[17] Potassium fluoride is very hygroscopic, and the reaction requires heating in MeCN solution, in the presence of an expensive crown ether, for as long as 4–5 days.[18]

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