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Fluoride Ion Promoted Anodic Substitutions of Chalcogeno Compounds. 1.[†] Regioselective Anodic Alkoxylation of Sulfides

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Summary: Anodic α-alkoxylation of sulfides was remarkably promoted in the presence of fluoride ions: When $Et_3N{\cdot}3HF$ was used as a supporting electrolyte, simple alkyl phenyl sulfides and sulfides bearing weak electron-withdrawing groups underwent anodic alkoxylation via fluorosulfonium ions as key intermediates in a unique Pummerer-type mechanism with reasonable or high yields for the first time.

Anodic substitution is characteristic of organic electrochemical reactions.[1] The anodic methoxylation of organo nitrogen compounds has been well-established and is quite useful for organic synthesis.[2] However, the analogous methoxylation of organo sulfur compounds has been undeveloped mainly because the anodic oxidation of simple sulfides usually results in the formation of sulfoxide and/or cleavage of C–S bonds.[3] Therefore, very few successful examples of anodic α-substitution reactions,[4,5] particularly anodic α-methoxylation of sulfides,[6–9] have been known so far.

Recently, we have reported that anodic α-methoxylation of sulfides was markedly promoted by strong electron-withdrawing groups (EWG's) such as the trifluoromethyl group.[6,10,11] The reaction is notable because nucleophilic substitution at the position α to the trifluoromethyl group is usually quite difficult to achieve.[12] Moreover, this methoxylation has a highly synthetic value to serve versatile trifluoromethylated building blocks.[10]

However, the reaction is severely limited. For example, the anodic methoxylation of a para-substituted phenyl 2,2,2-trifluoroethyl sulfides was drastically suppressed by electron-donating substituents.[11] In addition, a less strong electron-withdrawing difluoromethyl group or weak electron-withdrawing monofluoromethyl and β-trifluoromethyl groups did not promote the methoxylation well or at all.[11]

Therefore, the development of efficient and more widely applicable methods for the anodic methoxylation of sulfides is desirable in electroorganic fluorine chemistry. Reported herein are the first successful examples of anodic methoxylation of sulfides bearing weak EWG's and simple alkyl phenyl sulfides devoid of EWG in the presence of fluoride ions.

In the course of our broad program of anodic substitutions of fluoro organic compounds,[6,10,11,13] most recently we have found anodic α-fluorination of 2,2,2-trifluoroethyl sulfides in acetonitrile containing $Et_3N{\cdot}3HF$ as a supporting electrolyte and a fluorine source.[14]

Even the sulfides bearing α-difluoro- and α-monofluoromethyl groups underwent the anodic fluorination with moderate efficiency.[15] It is known that the nucleophilicity of fluoride ions is greatly affected by solvents. In our efforts to increase the efficiency of the anodic fluorination by changing solvents, we have made the quite interesting observation that highly efficient and regioselective anodic methoxylation resulted instead of anodic fluorination when anodic oxidation of the sulfides bearing the α-monofluoromethyl group was carried out in methanol instead of acetonitrile (Scheme I).

Scheme I

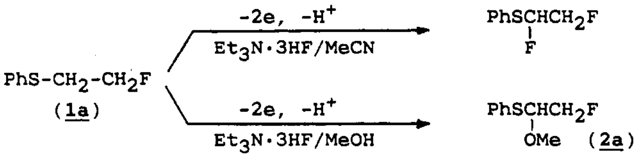

Table I. Fluoride Ion Promoted Anodic Methoxylation of Sulfide 1a

$$\underset{\textbf{1a}}{PhSCH_2CH_2F} \xrightarrow[F^-/MeOH]{-2e,\ -H^+} \underset{\textbf{2a}}{PhSC(OMe)HCH_2F}$$

run	supporting electrolyte[a]	charge passed (F/mol)	product yield, %
1	$Et_3N{\cdot}3HF$	3.5	63
2	$Et_3N{\cdot}3HF$ (1 equiv)	3.5	42
3	$Bu_4NF{\cdot}3H_2O$	3.5	50
4	NaF	3.5	trace
5	Et_4NBr	3.5	0
6	Bu_4NCl	7.2	0

[a] A 10:1 ratio with sulfide **1a** was used.

Then, the anodic methoxylation was investigated in detail using 2-monofluoroethyl sulfide **1a** as a model compound. Anodic oxidation of **1a** was carried out in methanol using various fluorides as supporting electrolytes.[16]

[†] A part of this work is "Electrolytic Reactions of Fluoro Organic Compounds. Part 9."

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Table II. Fluoride Ion Promoted Anodic Alkoxylation of Sulfides 1

$$\underset{\mathbf{1}}{\text{ArSCH}_2\text{–EWG}} \xrightarrow[\text{Et}_3\text{N·3HF (A) or Et}_4\text{NOTs (B)/ROH}]{-2e,\ -H^+} \text{ArSC(OR)H–EWG}$$

2: R = Me
3: R = Et

run	no.	sulfide Ar	EWG	supporting electrolyte[a]	solvent R	charge passed (F/mol)	product (yield, %)
1	**1a**	Ph	CH_2F	A	Me	3.5	**2a** (63)
2	**1a**	Ph	CH_2F	B	Me	3.5	**2a** (0)
3	**1a**	Ph	CH_2F	A	*a*	3.5	**2a** (51)[b]
4	**1a**	Ph	CH_2F	A	Et	7.2	**3a** (83)
5	**1b**	Ph	CHF_2	A	Me	5.1	**2b** (98)
6	**1b**	Ph	CHF_2	B	Me	10	**2b** (19)
7	**1c**	*p*-$MeOC_6H_4$	CF_3	A	Me	3.5	**2c** (81)
8	**1c**	*p*-$MeOC_6H_4$	CF_3	B	Me	10	**2c** (13)
9	**1d**	Ph	COOEt	A	Me	3.5	**2d** (84)
10	**1d**	Ph	COOEt	B	Me	6.3	**2d** (52)
11	**1e**	Ph	$CONEt_2$	A	Me	4.7	**2e** (63)
12	**1e**	Ph	$CONEt_2$	B	Me	10	**2e** (24)
13	**1e**	Ph	$CONEt_2$	A	Et	5.8	**3e** (73)
14	**1f**	Ph	CH_2CF_3	A	Me	3.5	**2f** (74)
15	**1f**	Ph	CH_2CF_3	B	Me	10	**2f** (trace)
16	**1g**	Ph	H	A	Me	4.0	**2g** (29)[c]
17	**1g**	Ph	H	B	Me	10	**2g** (0)

[a] Acetonitrile containing methanol (10:1 with **1a**) was used as a electrolytic solvent. [b] α-Monofluorinated product was also formed in 25% yield. [c] α-Monofluorinated product was also formed in 3% yield.

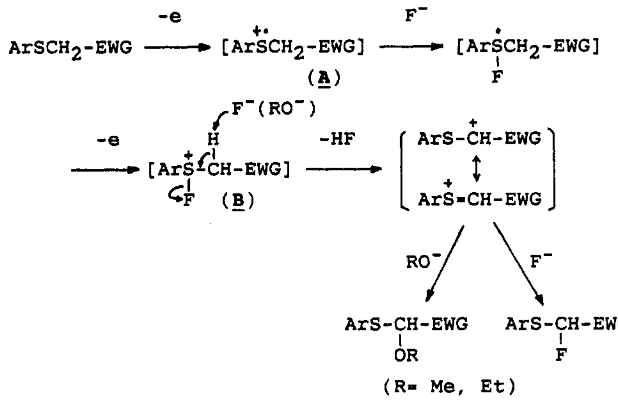
As shown in Table I, among the fluorides, $Et_3N·3HF$ was the most effective. Even if the amount of $Et_3N·3HF$ was reduced to one-tenth (equimolar amount), the reaction still proceeded to provide the methoxylation product in reasonable yield (run 2). It is notable that $Bu_4NF·3H_2O$ was also effective although it contains water. On the contrary, sodium fluoride was not effective.

Next, the reaction was successfully extended to various sulfides **1b**, **1d**, and **1e** bearing other EWG's such as difluoromethyl, ester, and amide. The yields of the desired α-methoxylated products were much higher than those obtained under conventional conditions (B)[6,7,10,11] using Et_4NOTs as a supporting electrolyte regardless of EWG's.

It should be noted that a methoxy group was selectively introduced α to the sulfur atom of **1e** (run 11) although anodic methoxylation of amides usually occurs α to the nitrogen atom.[17] Therefore, this anodic methoxylation is highly regioselective. In addition, the yield of the methoxylated product of *p*-methoxyphenyl 2,2,2-trifluoroethyl sulfide (**1c**) was greatly improved by this method although electron-donating groups on the benzene ring strongly retarded anodic methoxylation and caused side reactions.[11]

Furthermore, the α-methoxylation of sulfide **1f** bearing a β-trifluoromethyl group was also successful (run 14), although this sulfide failed to give α-methoxylated product **2f** in the absence of fluoride ions.[10] The product **2f** seems to be a useful building block as a 3,3,3-trifluoropropionaldehyde equivalent. The result showing that even a weak EWG promotes anodic methoxylation prompted us to investigate the anodic methoxylation of a simple alkyl phenyl sulfide devoid of an EWG. It was found that methyl phenyl sulfide **1g** underwent methoxylation to provide an α-methoxylated sulfide in reasonable yield (run 16). This seems to be the first successful example of anodic α-methoxylation of a simple sulfide to the best of our knowledge. It should be noted that the electricity required for consumption of a starting sulfide in this method was much less compared to that required by the conventional method.

Scheme II



In our previous work,[11] we clarified that the anodic methoxylation of fluoroalkyl para-substituted phenyl sulfides proceeds via cation radicals of sulfides in a typical ECEC mechanism. The methoxylation is greatly affected by both fluoroalkyl and substituent groups. However, such an effect was not observed in the presence of fluoride ions.

The current–potential curves of the sulfides in the presence of fluoride ions suggest that the anodic methoxylation is initiated by the direct oxidation of a sulfide. In addition, it is known that electrofluorination of sulfides in anhydrous hydrogen fluoride gives hypervalent sulfur compounds.[18] From these results and facts, this novel anodic methoxylation may proceed via fluorosulfonium cation B in a Pummerer-type mechanism (Scheme II). In this mechanism, the cation radical A of the sulfide is trapped by a fluoride ion, and this step should suppress

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(16) A typical procedure is as follows. The electrolysis of 1 (1.5 mmol) was carried out at platinum electrodes (2 × 2 cm) at 17 °C in 0.33 M $Et_3N·3HF$ in methanol (15 mL). After a constant current (25 mA) was passed until 1 was almost consumed (monitored by GC column: PEG 20M or silicone OV17), the electrolyte solution was neutralized with 12% aqueous ammonia. The solution was extracted repeatedly with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel TLC (hexane/AcOEt, mainly 5:1) to provide α-methoxylated products **2**.

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side reactions from the cation radical A (such as dimerization and nucleophilic attack on an aromatic ring) even when deprotonation of A is slow due to the weak EWG's or electron-donating substituents on the benzene ring.

Since fluoride ions are much weaker nucleophiles compared to methoxide, it is reasonable that the methoxylation predominated in methanol. In support of this, more strongly nucleophilic ethanol gave higher yields (Table II, runs 4 and 13) compared to the results with methanol; reduction of the amount of methanol to 10:1 equivalents with a sulfide resulted in the formation of the fluorinated sulfide in addition to the methoxylated one (formation ratio, 33:67; Table II, run 3). Contrary to our cases, Shono and Matsumura et al. reported that bromosulfonium ions derived from sulfides and anodically generated positive bromonium ions can be used as so-called mediators for indirect anodic oxidation of alcohols.[19] However, they have never observed the formation of alkoxylated sulfides. In fact, our experiments, chloride and bromide ions other than fluoride ions did not promote the methoxylation at all (Table I, runs 5 and 6).

Thus, it was illustrated for the first time that fluoride ions remarkably promoted anodic substitution of the sulfides. This method has a wide applicability to various sulfides. Utilization of this novel electrochemical method for other synthetic applications is under investigation.

Acknowledgment. We thank Dr. Kokoro Iio of Industrial Products Research Institute for obtaining the high-resolution mass spectra.

Registry No. **1a**, 33740-59-9; **1b**, 134024-36-5; **1c**, 2262-07-9; **1d**, 7605-25-6; **1e**, 53136-40-6; **1f**, 102687-64-9; **1g**, 100-68-5; **2a**, 136764-65-3; **2b**, 134024-37-6; **2c**, 108200-49-3; **2d**, 136764-66-4; **2e**, 136764-67-5; **2f**, 129265-01-6; **2g**, 13865-50-4; **3a**, 136764-68-6; **3e**, 136764-69-7; MeOH, 67-56-1; EtOH, 64-17-5.

Supplementary Material Available: ^{1}H NMR, IR, MS, and high-resolution MS data for all new compounds (2 pages). This material is contained in many 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 for ordering information.

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An Improved Synthesis of Chiral Oxazolidine-2-selones: Highly Sensitive ^{77}Se NMR Reagents for the Detection and Quantitation of Chirality

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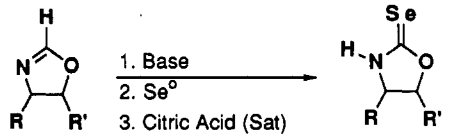
Summary: The synthesis of the title compounds from readily available oxazolines has been accomplished in one step in high yield. These chiral reagents exhibit extraordinary ^{77}Se chemical shift sensitivity and are useful for the detection and quantitation of chirality at remotely disposed chiral centers.

There has been considerable interest in the development of new methods and reagents for the determination of enantiomeric excesses[2] and, to a larger extent, the assignment of absolute configuration.[3] We have recently disclosed the application of the extreme chemical shift sensitivity of the ^{77}Se nucleus for the detection and quantitation of chirality at chiral centers distant from the observing nucleus.[4] To explore the scope and limitation of this novel method, a more efficient general synthetic route to a variety of chiral oxazolidine-2-selones is necessary.[5] In this report, we describe significant improvements in the synthesis of multigram quantities of selones (selenocarbonyl compounds) and demonstrate the remarkable chemical shift sensitivity of these chiral auxiliaries vis a vis the diastereomers which result from the coupling of these reagents to (R,S)-2-phenylpropanoyl chloride.

In recent reports, chiral and achiral selones can be constructed via the reaction of commercially available amino alcohols with carbon diselenide and mercury salts in a one-pot process.[6] While the reported yields were modest to fair (31–53%), the major drawback was the use of carbon diselenide, an expensive and hazardous reagent.[7] We envisioned that "selenonylation" of chiral amino alcohols could be accomplished via the reasily accessible intermediate oxazolines shown in Scheme I.[8]

Scheme I



1 a-g **2 a-g**

The chiral oxazolines can be constructed in excellent yield and in enantiomerically pure form by the method of

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[1] Adjunct Professor, Department of Chemistry and Biochemistry, University of South Carolina.

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[7] Carbon diselenide is available from ICN Biomedicals at $184.00/g.

[8] The word "selenonylation" is derived by analogy to carbonylation.