New Mechanistic Aspects of Anodic Monofluorination of Halogenoalkyl and Alkyl Phenyl Sulphides

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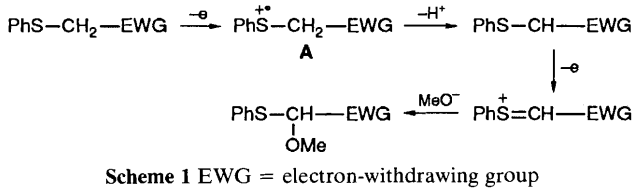
A unique Pummerer type mechanism *via* fluorosulphonium ions for anodic monofluorination of sulphides is established by comparing the anodic monofluorination of partially halogenated ethyl phenyl sulphides (**1**, $PhSCH_2R$; R = CF_3, CF_2H, CFH_2, CF_2Cl, $CClH_2$) with their anodic methoxylation; simple alkyl phenyl sulphides **2** bearing no electron-withdrawing group could be monofluorinated anodically in satisfactory yields for the first time when tetrahydrofuran was used as a solvent.

Fluoro-organic compounds have specific chemical and physical properties. A great deal of recent interest has been focused on partially fluorinated compounds because of their potential biological activities.[1] However, methods for their synthesis are limited in many cases.[2] Most recently, we[3] and Laurent *et al.*[4] have reported the anodic fluorination of sulphides at the α-position to sulphur in the presence of the $Et_3N{\cdot}3HF$ complex which is rather stable to air and moisture; this fluorination can be carried out in normal laboratory glassware. Although this fluorination method has high synthetic value, the anodic monofluorination of sulphides was strongly suppressed unless the carbon α to the sulphur atom was substituted by an electron-withdrawing group.[3,4] It is self-evident that in view of the synthetic utility, application of the anodic monofluorination to simple alkyl sulphides devoid of an electron-withdrawing substituent is desirable.†



Scheme 1 EWG = electron-withdrawing group

In this communication, we report the first example of the successful anodic monofluorination of simple alkyl phenyl sulphides devoid of an electron-withdrawing substituent and interesting features of the anodic monofluorination of halo-

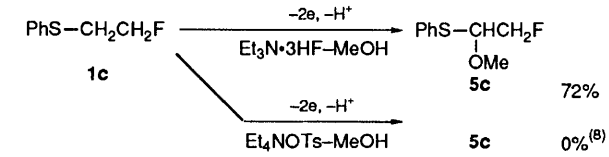
† So far, few successful examples of anodic α-substitution reactions of sulphides are known.[5] For example, anodic α-methoxylation is also markedly promoted by strong electron-withdrawing groups such as trifluoromethyl and cyano.[5–7]

Table 1 Anodic monofluorination of halogenoethyl phenyl sulphides **1** and alkyl phenyl sulphides **2**

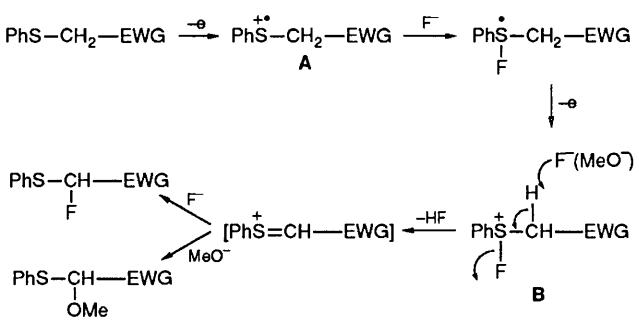
$$\underset{\textbf{1a–e, 2a, b}}{PhSCH_2R} \xrightarrow[Et_3N\cdot 3HF\text{–}MeCN]{-2e,\ -H^+} \underset{\textbf{3a–e, 4a, b}}{PhSCHFR}$$

Run	R	E_p^{ox}/V *vs.* SCE[a]	Anodic potential/V *vs.* SSCE	Charge passed, F/mol	Product (Yield, %[b])
1	CF_3 (**1a**)	+1.78	+1.9	3.2	**3a** (62)[c]
2	CF_2H (**1b**)	+1.69	+2.3	4.0	**3b** (53)
3	CFH_2 (**1c**)	+1.58	+2.1	2.7	**3c** (60)
4	CF_2Cl (**1d**)	+1.80	+2.0	5.0	**3d** (43)
5	$CClH_2$ (**1e**)	+1.62	+1.8	3.0	**3e** (30)
6	H (**2a**)	+1.51	+1.6	4.0	**4a** (27)
7	H (**2a**)[d]		+3.0	4.0	**4a** (50)
8	CH_3 (**2b**)	+1.48	+1.8	4.0	**4b** (18)
9	CH_3 (**2b**)[d]		+3.3	6.0	**4b** (45)

[a] Measured by cyclic voltammetry in 0.1 mol dm^{-3} Et_4NBF_4–MeCN. Anode and cathode: Pt, sweep rate: 0.1 V s^{-1}. SCE and SSCE = standard and standard sodium calomel electrode, respectively. [b] Isolated yield. [c] Ref. 3. [d] Tetrahydrofuran was used as a solvent.



Scheme 2 Ts = *p*-$MeC_6H_4SO_2$



Scheme 3

genoalkyl phenyl sulphides; we propose a novel Pummerer-type mechanism for the anodic fluorination.

Halogenoalkyl groups, especially fluoroalkyl are appropriate electron-withdrawing groups to investigate the effects of such substituents on the fluorination because the electron-withdrawing ability can be gradually increased by successive substitution of hydrogen with halogen without significant changes in steric effects. The more the electron-withdrawing ability of halogenoalkyl groups is increased, the higher is the oxidation peak potential showed by the corresponding sulphide, as expected (Table 1).‡

A typical anodic fluorination was carried out as follows. The halogenoalkyl phenyl sulphide **1** (5.0 mmol) was subjected to controlled-potential electrolysis in a simple one-compartment cell using Pt electrodes (3 × 4 cm) as anode and cathode in the presence of 1.0 mol dm^{-3} $Et_3N\cdot 3HF$ complex in acetonitrile (50 ml). Electricity was passed until **1** had been completely consumed. The results are summarized in Table 1.

For the fluoroalkyl sulphides **1a–c**, anodic fluorination proceeded to afford the corresponding α-monofluorinated products **3a–c** in good yields. The electron-withdrawing ability of the fluoroalkyl groups, therefore, did not affect the efficiency of anodic monofluorination. These results are quite different from those for their anodic methoxylation.[8] It is remarkable that **1c** and **1e** which have only one halogen atom could be anodically monofluorinated (runs 3 and 5) because the anodic methoxylation of **1c** did not take place at all.[8] In the case of anodic methoxylation of halogenated sulphides, the decrease in the electron-withdrawing ability of the halogenoalkyl group resulted in a substantial decrease in the yield of the α-methoxylation process and many complicated side reactions including methoxylation on the aromatic ring were observed instead.[8]

It is notable that the promotion effect of a fluorine atom on the anodic fluorination is much more pronounced than that of a chlorine atom although the electronegativities of these atoms are similar (runs 1, 4 and runs 3, 5). Therefore, the effect of a fluorine atom is quite specific.

The ECEC mechanism is well established for anodic methoxylation of amines and carbamates.[9] We have recently clarified that the anodic methoxylation of fluoroalkyl sulphides proceeds similarly (Scheme 1).[5,8] Laurent *et al.* also proposed a mechanism for anodic fluorination in line with this ECEC mechanism.[4] However, the differences between the anodic fluorination and anodic methoxylation suggest that the mechanism for anodic fluorination may differ from the ECEC mechanism.

In order to clarify the reaction mechanism, the anodic fluorination of **1c** was carried out in methanol instead of acetonitrile. Interestingly, the α-methoxylated product **5c** rather than the α-fluorinated product **3c** was obtained in a yield as high as 72% (Scheme 2).§ As reported previously,[8] **5c** was not obtained under conventional anodic methoxylation conditions and this is attributed to the very slow deprotonation of cation radical intermediates due to the weak electron-withdrawing ability of the CFH_2 group. This remarkable promotion effect of $Et_3N\cdot 3HF$ on the α-methoxylation of **1c** could not be explained by the conventional ECEC mechanism.

We propose a Pummerer-type mechanism *via* the fluorosulphonium cation **B** for the anodic fluorination (Scheme 3).[10] In this mechanism, the cation radical **A** of the sulphide is trapped by a fluoride ion and this step should suppress side reactions from the cation radical **A** (such as dimerization and nucleophilic attack on an aromatic ring) even when deprotonation of **A** is slow. Since fluoride ions are much weaker nucleophiles than methoxide, it is reasonable that the methoxylation

‡ Good linear relationships between oxidation peak potentials of halogenoalkyl phenyl sulphides **1** and Taft's σ* values of the halogenoalkyl group have been obtained.[8]

§ ^1H NMR and ^{19}F NMR spectra were recorded at 60 MHz on JEOL JNM-PMX 60 and Hitachi R-24F NMR spectrometers, respectively. The chemical shifts for ^1H and ^{19}F are given in δ (ppm) downfield from $SiMe_4$ and downfield from external CF_3CO_2H, respectively.

Selected spectroscopic data for **3b**: ^1H NMR ($CDCl_3$) δ 5.67 (dtd, 1H, J_{HCF} 50.4, J_{HCCF} 8.2, J_{HCCH} 4.0 Hz, CHF), 5.77 (tdd, 1H, J_{HCF} 54.0, J_{HCCF} 4.0, J_{HCCH} 4.0 Hz, CHF_2) and 7.2–7.8 (m, 5H, C_6H_5); ^{19}F NMR δ −46.7 [dddd, $J(F^aCF^b)$ 300, J_{FCH} 54.0, J_{FCCF} 22.5, J_{FCCH} 8.2 Hz, CF^aF^bH] −48.7 [dddd, $J(F^bCF^a)$ 300, J_{FCH} 54.0, J_{FCCF} 19.6, J_{FCCH} 8.2 Hz, CF^aF^b] and −86.7 [dddd, J_{FCH} 50.4, $J(FCCF^a)$ 22.5, $J(FCCF^b)$ 19.6, J_{FCCH} 4.0 Hz, CFH).

For **3c**: ^1H NMR ($CDCl_3$) δ 4.50 (ddd, 1H, J_{HCF} 46.0, J_{HCCF} 16.0, J_{HCCH} 6.5 Hz, CH^aH^bF), 4.53 (ddd, 1H, J_{HCF} 46.0, J_{HCCF} 19.0, J_{HCCH} 4.0 Hz, CH^aH^bF), 5.80 [dddd, 1H, J_{HCF} 51.0, J_{HCCF} 15.0, $J(HCCH^a)$ 6.5, $J(HCCH^b)$ 4.0 Hz, CHF] and 7.1–7.8 (m, 5H, C_6H_5); ^{19}F NMR δ −78.0 [dddd, J_{FCH} 51.0, J_{FCCF} 22.3, $J(FCCH^b)$ 19.0, $J(FCCH^a)$ 16.0 Hz, CFH) and −139.8 (m, CFH_2).

For **4b**: ^1H NMR ($CDCl_3$) δ 1.67 (dd, 3H, J_{HCCF} 22.0, J_{HCCH} 6.2 Hz, CH_3), 5.90 (dq, 1H, J_{HCF} 56.0, J_{HCCH} 6.2 Hz, CHF) and 7.1–7.7 (m, 5H, C_6H_5); ^{19}F NMR δ −59.2 (dq, J_{FCH} 56.0, J_{FCCH} 22.0 Hz).

For **5c**: ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H, OCH_3), 3.9–5.0 [m, 3H, $CH(OMe)CH_2F$] and 7.2–7.6 (m, 5H, C_6H_5); ^{19}F NMR δ −133.0 (td, J_{FCH} 48.0, J_{FCCH} 14.0 Hz).

predominated in methanol; thus efficient α-fluorination in acetonitrile and α-methoxylation in methanol of **1c** in the presence of $Et_3N{\cdot}3HF$ can both be explained by assuming a common intermediate **B**. Furthermore, the facts that aromatic ring fluorination was not observed even when the aromatic ring of **1a** was substituted by electron-donating groups such as methyl and methoxy,[3]¶ and that this fluorination is characteristic of sulphides only (amines and ethers, their nitrogen and oxygen analogues, which had been anodically methoxylated not being fluorinated at all under these anodic fluorination condtions), also support this mechanism.

The results showing that even weak electron-withdrawing groups promote anodic fluorination encouraged us to investigate the anodic fluorination of simple alkyl phenyl sulphides **2** lacking an electron-withdrawing group. The sulphides **2** underwent fluorination under the same electrolytic conditions to provide monofluorosulphides **4**, although the yields are not satisfactory (runs 6 and 8). The yields of **4**, however, were approximately doubled when tetrahydrofuran instead of acetonitrile was used as a solvent (runs 7 and 9). The products **4** are known to be useful building blocks for the preparation of monofluorovinyl sulphides.[11] Although the details of this unusual solvent effect remain to be clarified,‖ these findings should lead to extensive applications of anodic fluorination to the syntheses of partially fluorinated organic compounds.

¶ Anodic α-methoxylation of such fluorosulphides was accompanied by aromatic ring methoxylation.[8]

‖ Recently, a similar improvement in the yields of anodic α-monofluorination of arylacetates was reported.[12] In this case, the use of sulpholane instead of acetonitrile as a solvent greatly suppressed side reactions such as anodic acetamidation. In our case, however, the solvent (tetrahydrofuran) affected the anodic fluorination differently because acetamidation of **2** was not observed when electrolysis was conducted in acetonitrile (runs 6 and 8).

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