Pergamon

Tetrahedron Letters 40 (1999) 7819–7822

TETRAHEDRON
LETTERS

Electrolytic partial fluorination of organic compounds. Part 37: Selective electrolytic fluorination of dimethoxyethane, diethylene glycol dimethyl ether, and crown ethers[1]

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Received 19 July 1999; revised 18 August 1999; accepted 20 August 1999

Abstract

The anodic fluorination of dimethoxyethane (DME) and diethylene glycol dimethyl ether in acetonitrile containing a fluoride salt provided moderate yields of the corresponding monofluoromethyl ethers. The anodic fluorination of crown ethers resulted in carbon–carbon bond cleavage which led to the selective production of α,ω-difluoro products with high yields. © 1999 Elsevier Science Ltd. All rights reserved.

Fluoroorganic compounds have attracted a great deal of interest due to their considerable biological and physical importance.[2] Direct fluorination is the simplest way to prepare organofluorine compounds. However, chemically direct fluorination usually requires hazardous and/or costly fluorinating reagents. An alternative, electrochemically partial fluorination, is an ideal method for direct fluorination.[3] Quite recently, we demonstrated that dimethoxyethane (DME) electrolytic solvent markedly enhances anodic fluorination.[4] We also found that the DME was simultaneously fluorinated during this anodic fluorination process. This finding suggested a study of anodic fluorination of DME, its homolog, and crown ethers.

A typical procedure used for the anodic fluorination of DME (**1a**) is as follows. Anodic oxidation of **1a** (1 mmol) was carried out using platinum plate electrodes (2×2 cm^2) in 0.4 M $Et_3N\cdot5HF$ (20 equiv. of F^- to **1a**)[5]/CH_3CN (10 ml) and an undivided cell under a nitrogen atmosphere at 20°C. A 10 mA/cm^2 constant current was applied. After the electrolysis, the electrolyte was removed by silica gel short column chromatography. The structure of fluorinated product **2a**[6] was identified by comparison with ^{19}F NMR, ^1H NMR, and MS spectral data of independently synthesized **2a** by halogen exchange of 2-methoxyethoxymethyl chloride with KF.

As shown in Table 1, anodic fluorination of **1a** produced the corresponding monofluorinated product **2a** in moderate yields regardless of the supporting electrolytes used. Among the electrolytes used by this work, $Et_3N\cdot5HF$ gave the best result, and $Et_4NF\cdot4HF$ also gave **2a** with almost the same yield. On the

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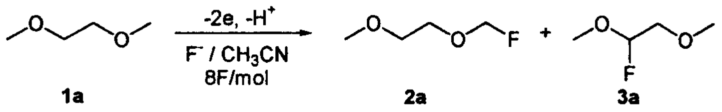
PII: S0040-4039(99)01627-5

Table 1
Anodic fluorination of dimethoxyethane

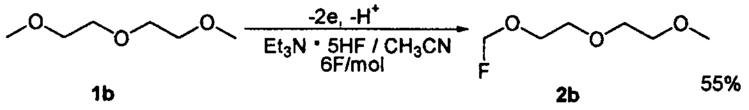


run	Supporting Electrolyte	Yield of **2a** (%)	Yield of **3a** (%)
1	$Et_3N \cdot 3HF$	31	24
2	$Et_3N \cdot 5HF$	62	14
3	$Et_4NF \cdot 3HF$	49	11
4	$Et_4NF \cdot 4HF$	59	19

other hand, use of $Et_3N \cdot 3HF$ electrolyte resulted in a much lower **2a** yield. Of the electrolytes used by this work, $Et_3N \cdot 3HF$ is most easily oxidized.[7]

Since the oxidation peak potential of the **1a** starting material is extremely high (2.72 V versus SCE: measured by cyclic voltammetry using a Pt anode at 500 mV/s scan rate), these electrolytic results clearly indicate that the stability of the supporting electrolyte against anodic oxidation greatly affects the fluorinated product yield. In all cases, the methylene group was also to some extent fluorinated thereby producing **3a**.[8]

Next, the anodic fluorination technique was extended to a DME homolog, diethylene glycol dimethyl ether (**1b**), using $Et_3N \cdot 5HF$ as a supporting electrolyte as illustrated in Scheme 1.

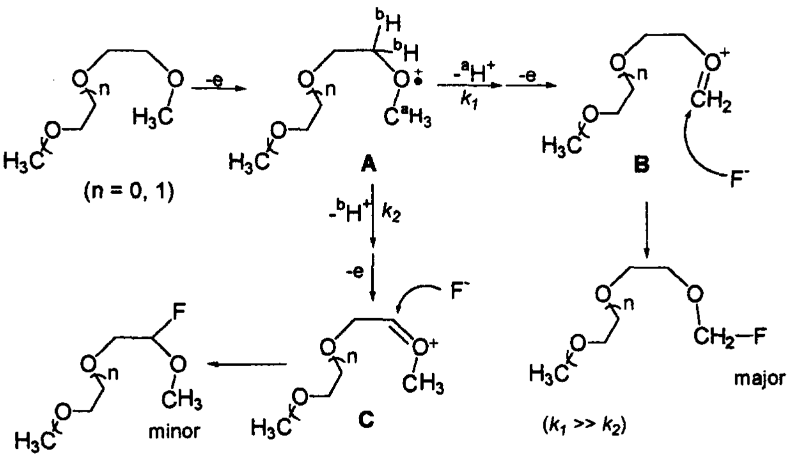


Scheme 1.

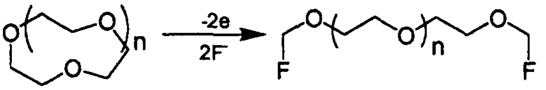
Similarly, to the case of **1a**, a fluorine atom was predominantly introduced into a methyl group and **2b**[9] was formed in a moderate yield. In this case, a trace amount of a regioisomeric monofluorinated product was detected by ^{19}F NMR; however, the fluorination position could not be determined due to its low yield. Although carbon–carbon bond cleavage commonly takes place in the anodic oxidation of 1,2-diols and their ethers[10], such a bond cleavage reaction does not seem to occur during the anodic fluorination of **1b**.[11]

The regioselectivity in this fluorination can be explained as shown in Scheme 2. Since the oxygen atom is most easily oxidized, the anodic oxidation takes place at the oxygen atom selectively to generate the radical cation intermediate **A**. Then deprotonation takes place. In this step, the regioselectivity seems to be governed by the deprotonation rate (k_1, k_2), that is, the kinetic acidity[12] difference between ^aH and ^bH (not thermodynamically controlled) because the major product was derived from the least stable intermediate **B**. This is the first successful selective anodic fluorination of ether compounds. Although Gambaretto et al. reported anodic partial fluorination of *N*-substituted morpholine derivatives, the monofluorinated product yield was as low as 28% due to the formation of many polyfluorinated products.[13] Chemically partial fluorination of ethers has not been reported either to date.

Finally, we also examined anodic fluorination of 15-crown 5-ether (**1c**) and 18-crown 6-ether (**1d**) as shown in Scheme 3.[14]



Scheme 2.



1c, 1d

2c, 2d

1c: n = 3; electricity: 6 F/mol; yield of **2c**: 90%
1d: n = 4; electricity: 8 F/mol; yield of **2d**: 74%

Scheme 3.

Interestingly, preferential carbon–carbon bond cleavage took place with fluorine insertion at both the α- and ω-carbon sites resulting in predominantly α,ω-difluorinated products with high yields. In these cases, the corresponding monofluorinated crown ethers which might be expected to form were not observed. This is in sharp contrast to the open-chain ether cases of **1a** and **1b**. This anodic fluorination can be explained as follows. The crown ethers **1c** and **1d** have only methylene protons while open-chain ethers **1a** and **1b** have methyl protons. Therefore, deprotonation of the crown ether cation radicals is much slower than that of the cation radicals **A**. Consequently, the carbon–carbon bond cleavage seems to take place predominantly prior to the deprotonation in the case of the crown ethers, **1c** and **1d**. This is the first report of such anodic carbon–carbon bond cleavage leading to α,ω-difluorination.

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5. When the concentration of fluoride ions decreased, the yields of **2a** and **3a** decreased as follows: **2a** (56%), **3a** (15%) in 0.2 M $Et_3N \cdot 5HF$/MeCN; **2a** (28%), **3a** (8%) in 0.1 M $Et_3N \cdot 5HF$/MeCN.
6. Ethylene glycol fluoromethyl methyl ether (**2a**): ^1H NMR δ 3.39 (s, 3H), 3.59 (t, 2H, J=4.0 Hz), 3.86 (t, 2H, J=4.0 Hz), 5.31 (d, 2H, J=56.4 Hz); ^{19}F NMR δ –74.16 (t, J=56.1 Hz). MS m/e 108 (M^+, trace), 88 (M^+–HF).
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8. 1-Fluoro-1,2-dimethoxyethane (**3a**): ^{19}F NMR δ –56.06 (dt, J=66.4, 14.0 Hz).

9. Diethylene glycol fluoromethyl methyl ether (**2b**): ^{1}H NMR δ 3.38 (s, 3H), 3.71 (m, 8H), 5.30 (d, 2H, *J*=56.1 Hz); ^{19}F NMR δ −74.32 (t, *J*=56.5 Hz). MS m/e 152 (M^+, trace), 133 (M^+−F).
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11. If the carbon–carbon bond cleavage followed by fluorination takes place, one of the expected products would be **2a**. However, **2a** was not detected from the electrolytic solution of **1b** by ^{19}F NMR spectrometry.
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14. Pentaethylene glycol difluoromethyl ether (**2c**): ^{1}H NMR δ 3.69 (m, 20H), 5.31 (d, 4H, *J*=56.41 Hz); ^{19}F NMR δ −74.07 (t, *J*=56.1 Hz). MS m/e 302 (M^+, trace), 282 (M^+−HF). Tetraethylene glycol difluoromethyl ether (**2d**:) ^{1}H NMR δ 3.70 (m, 20H), 5.31 (d, 4H, *J*=56.4 Hz); ^{19}F NMR δ −74.05 (t, *J*=56.1 Hz). MS m/e 272 (M^+, trace), 252 (M^+−HF).