Electrolytic Partial Fluorination of Organic Compounds. Part 41:[1] Highly Selective Electrolytic Fluorination of Dimethoxyethane, its Homologues, and Crown Ethers

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Abstract—The anodic fluorination of dimethyoxyethane (DME), and diethylene glycol dimethyl ether in acetonitrile containing a fluoride salt as a supporting electrolyte and a fluoride ion source using an undivided cell provided the corresponding monofluoromethyl ethers as a main product in good yields. On the other hand, 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. A carbon anode as well as a platinum anode was found to be effective for the electrolytic fluorination when $Et_3N \cdot 5HF$ was used as the supporting electrolyte. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Fluoroorganic compounds have attracted a great deal of interest due to their unique physical properties, specific chemical reactivities, and marked potential biological activities.[2] Direct fluorination is the simplest way to prepare organofluorine compounds. However, chemical direct fluorinations usually require hazardous and/or costly fluorinating reagents. An alternative, electrochemical partial fluorination is an ideal method for direct fluorination because the reaction can be carried out under mild conditions using a reactively simple equipment.[3]

Quite recently, we demonstrated that dimethoxyethane (DME) electrolytic solvent markedly enhances anodic fluorination of heterocyclic sulfides.[4] While we studied solvent effects on the electrolytic fluorination in detail,[5] we found that DME solvent was simultaneously fluorinated during the anodic fluorination process. This finding suggested a study of anodic fluorination of DME, its homologues, and crown ethers. There has been no report dealing with anodic partial fluorination of ethers so far.

Results and Discussion

Oxidation potentials of DME, its homologues and crown ethers

The oxidation potentials of DME, its homologues, and crown ethers were measured by cyclic voltammetry in 0.1 M $Bu_4N \cdot BF_4$/anhydrous acetonitrile. The cyclic voltammograms were obtained with a three-electrode system using a platinum disk ($\phi=1$ mm) working electrode, a platinum wire counter electrode, and a saturated NaCl calomel electrode (SSCE) as a reference electrode. When the sweep rate was 500 mV/s, all the compounds chosen in the present study showed irreversible oxidation waves.[6] The first peak oxidation potentials are summarized in Table 1.

Comparing DME and its homologues (**1a**, **1b**, and **1c**) with crown ethers (**1d**, **1e**, and **1f**), it was found that the oxidation potentials of crown ethers are higher than those of open chain ethers (**1a**, **1b**, and **1c**). A similar trend was observed in the cases of DME (**1a**) and dioxane (**1g**). However, the reason is not clear. This may be due to the steric hindrance of the ring and/or ring strain of cyclic ethers, and the oxygen atoms of cyclic ethers become more difficult to be oxidized than those of open-chain ethers. In fact, DME has much higher donor number (23.9) than 1,4-dioxane (14.0).

Table 1. Oxidation potentials (peak potentials, E_p^{ox} of dimethoxyethane, its homologue and crown ethers (In 0.1 M Bu_4NBF_4/CH_3CN. Sweep rate: 500 mV/s)

No	Substrate	E_p^{ox} (V vs. SSCE)
1a	$CH_3OCH_2CH_2OCH_3$	2.72
1b	$(CH_3OCH_2CH_2)_2O$	2.78
1c	$(CH_3CH_2OCH_2CH_2)_2O$	2.80
1d	crown 18-6	2.90
1e	crown 15-5	2.94
1f	crown 12-4	2.90
1g	1,4-dioxane	2.89

Table 2. Anodic fluorination of dimethoxyethane (DME) (constant current electrolysis was carried out)
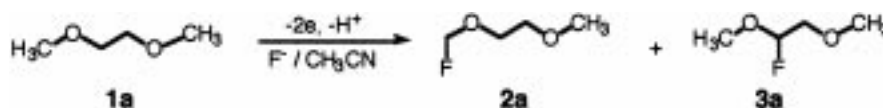
Run	Supporting electrolyte	Concentration of fluoride ion (M)	Charge passed (F/mol)	Yield of 2a (%)	Yield of 3a (%)
1	Et$_3$N·5HF	0.1	8	28	8
2	Et$_3$N·5HF	0.2	8	56	15
3	Et$_3$N·5HF	0.4	8	62	14
4	Et$_3$N·3HF	0.4	8	31	24
5	Et$_4$NF·3HF	0.4	8	49	11
6	Et$_4$NF·4HF	0.4	8	59	19
7	Et$_3$N·5HF	0.4	2	6	Trace
8	Et$_3$N·5HF	0.4	4	17	Trace
9	Et$_3$N·5HF	0.4	6	43	9
10	Et$_3$N·5HF	0.4	10	60	19

Anodic fluorination of DME and its homologues

As shown in Table 2, anodic fluorination of **1a** produced the corresponding monofluorinated product **2a** in moderate yields regardless of the supporting electrolytes used. Among these electrolytes used in this work, Et$_3$N·5HF gave the best result (run 3), and Et$_4$NF·4HF also gave **2a** with almost same yield (run 6). On the other hand, use of Et$_3$N·3HF electrolyte resulted in a much lower **2a** yield (run 4). Et$_3$N·3HF is most easily oxidized while Et$_3$N·5HF and Et$_4$NF·4HF are relatively difficult to be oxidized.[7]

Since the oxidation peak potential of starting material **1a** is extremely high (2.72 V vs. SSCE), these electrolytic results clearly indicated that the stability of the supporting electrolyte against anodic oxidation greatly affects the fluorinated product yield. When the concentration of the supporting fluoride salts (Et$_3$N·5HF) decreased, the yield of **2a** also decreased. Therefore, this fluorination was found to require high concentration of fluoride ions. In all cases, the methylene group was also to some extent fluorinated thereby producing **3a** and trace amount of α,ω-difluorinated product was also detected by ^{19}F NMR.

Next, the anodic fluorination technique was extended to a DME homologue, diethylene glycol dimethyl ether (**1b**). Similarly to the case of **1a**, a fluorine atom was predominantly introduced into a methyl group and **2b** was formed in a moderate yield after 6 F/mol electricity was consumed as shown in Table 3. In this case, a trace amount of a regioisomeric monofluorinated product was detected by ^{19}F NMR; however, the fluorination position could not be deter-

mined due to its extremely low yield. Among the fluoride salts used in this case, Et$_3$N·5HF also gave the best result (run 2). Although the carbon–carbon bond cleavage commonly takes place in the anodic oxidation of 1,2-diols,[8] it is noted that the anodic fluorination of DME and its homologue proceeded preferentially.[9]
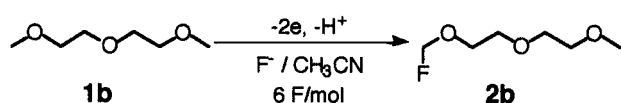
Next, the effect of anode materials on the anodic fluorination was investigated. Anodic fluorination of **1a** and **1b** was carried out using various anode materials as shown in Table 4. The starting **1a** and **1b** were almost consumed when 8 F/mol of electricity was passed respectively using a platinum anode in Et$_3$N·5HF/CH$_3$CN. Therefore, in order to compare the electrolytic results using different anodes, the electrolysis was stopped when 8 F/mol of electricity was passed. The results are summarized in Table 4.

The anodic fluorination proceeded smoothly regardless of anode materials to provide the fluorinated products **2a** and **2b** in moderate yields. A platinum anode was the most suitable for the fluorination. A carbon plate, and carbon felt anodes were also effective for this fluorination. Since carbon anodes are much cheaper than a platinum anode, this finding is quite important from a practical aspect. DSA (dimensionally stable anode) is commercially used for the preparation of chlorine gas. Therefore, DSA was expected to be suitable for anodic fluorination. Though a good product yield was obtained using a DSA anode, the color of the anode surface was greatly changed after the electrolysis. Therefore, DSA was found to be not so stable in such a strongly acidic electrolytic solution containing HF.

An ECEC mechanism is widely accepted for electrochemical nucleophilic substitution reactions.[10] The high

Table 3. Anodic fluorination of diethylene glycol dimethyl ether

Run	Supporting electrolyte	Yield of 2b (%)
1	Et$_4$·3HF	28
2	Et$_3$·5HF	55
3	Et$_4$·3HF	29
4	Et$_4$·4HF	39

Table 4. Effect of electrode materials on anodic fluorination of dimethoxyethane and diethylene glycol dimethyl ether in Et$_3$N·5HF/MeCN

Run	Anode material	Yield of 2a (%)	Yield of 2b (%)
1	PT	62	55
2	carbon plate	51	53
3	carbon sheet	41	20
4	carbon felt	43	48
5	DSA	–	50
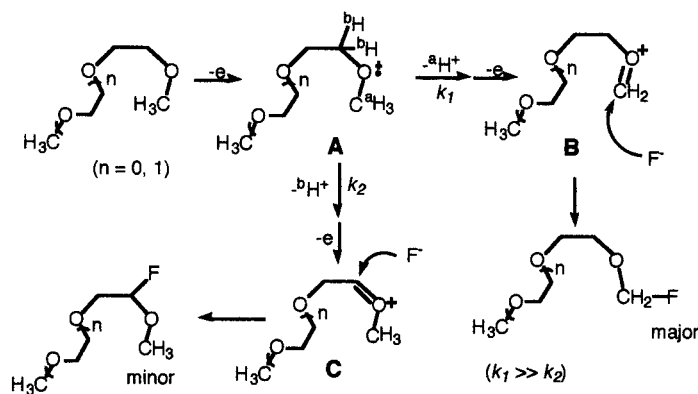
Scheme 1.

regioselectivity in this fluorination can be depicted as shown in Scheme 1.

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, the 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[11] difference between [a]H and [b]H (not thermodynamically controlled) because the major product was derived from the least stable intermediate **B**. It is well known that the deprotonation of methyl proton of *N*-ethyl-*N*-methylamine cation radical is much faster than that of methylene proton.[12] In order to confirm the kinetic acidity-controlled regioselectivity, the electrolytic fluorination of diethylene glycol diethyl ether (**1c**) devoid of a methyl group was studied as shown in Scheme 2. In contrast to the cases of **1a** and **1b**, only trace amount of the corresponding fluorinated product was obtained and complicated products were formed. This suggests that the deprotonation of the methyl protons ([a]H) takes place more easily compared with the methylene protons ([b]H).

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 yield of monofluorinated products was as low as 28% due to the formation of many polyfluorinated products.[13] Quite recently, the chemical partial fluorination
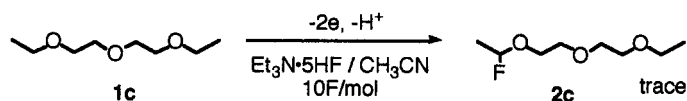
of unsaturated ethers has been reported, however, an excess amount of high-valence metal fluorides such as $KCoF_4$ is required.[14]

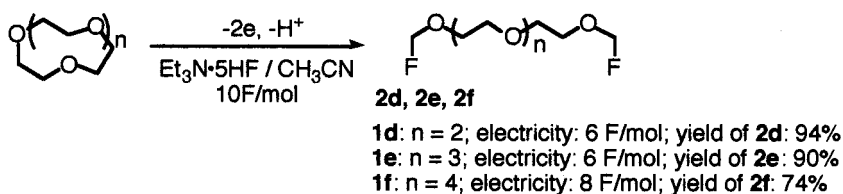**Anodic fluorination of crown ethers**

Finally, this fluorination was successfully extended to crown ethers as shown in Scheme 3. Interestingly, preferential carbon–carbon bond cleavage took place and α,ω-difluorinated products were formed in high yields.

In all cases, the corresponding monofluorinated crown ethers were not observed. This is in sharp contrast to the cases for open-chain ether **1a** and **1b**. This anodic fluorination can be explained as follows. The crown ethers **1d**, **1e**, and **1f** 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** possessing a methyl group. Consequently, the carbon–carbon bond cleavage seems to take place predominantly prior to the deprotonation in the case of the crown ethers, **1d**, **1e**, and **1f**. Such an anodic carbon–carbon bond cleavage leading to α,ω-difluorination is rare. Recently, Yoneda et al. have reported that anodic fluorination of cyclic ketones gave α,ω-difluorinated intermediates.[7]

In summary, anodic partial fluorination of DME and diethylene glycol dimethyl ether was successfully carried

Scheme 2.

1d: n = 2; electricity: 6 F/mol; yield of **2d**: 94%
1e: n = 3; electricity: 6 F/mol; yield of **2e**: 90%
1f: n = 4; electricity: 8 F/mol; yield of **2f**: 74%

Scheme 3.

out in MeCN for the first time to provide the corresponding fluorinated products in good yields. The anodic fluorination of crown ethers resulted in a carbon–carbon bond cleavage leading to α,ω-difluoro products selectively in high yields. This is the first report of the anodic carbon–carbon bond cleavage of cyclic ethers leading to α,ω-difluorination. Such a unique carbon–carbon bond cleavage followed by fluorination reaction will be useful for future electroorganic studies.

Experimental

General

Et$_3$N·3HF was purchased from Aldrich, and Et$_4$NF·nHF (n=3, 4) and Et$_3$N·5HF were obtained from Morita Chemical Industries Co. Ltd. Et$_4$NF·4HF[15] and Et$_3$N·5HF[7] are toxic and may cause serious burns if they come in contract with unprotected skin, while Et$_4$NF·3HF and Et$_3$N·3HF are much less aggressive. However, proper safety precautions should be taken at all times.[16] ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded at 270, 254 and 68 MHz, respectively, in CDCl$_3$ as a solvent. The chemical shifts for ^{19}F NMR were given in δ ppm downfield from external CF$_3$COOH. Cyclic voltammetry was performed with a computer-controlled electrochemical system (BAS 100 W).

Anodic fluorination of DME, its homologues and crown ethers

A typical procedure for the anodic fluorination of DME (**1a**) is as follows. Electrolysis of **1a** (1 mmol) was carried out with platinum plate electrodes (2×2 cm^2) in 0.4 M Et$_3$N·5HF (20 equiv. of F$^-$ to **1a**) / CH$_3$CN (10 ml) using an undivided cell under nitrogen atmosphere at 20°C. Constant current (10 mA/cm^2) was passed. After the electrolysis, the fluorinated product yields were estimated by ^{19}F NMR of the electrolytic solution using monofluoromethylene as a standard substrate. The products were extracted with CHCl$_3$, then evaporated under vacuo. The oily residue was purified using bulb-to-bulb distillation. Since the fluorinated products **2a**, **2b**, and **3a** were very unstable, their structure were confirmed mainly by ^{19}F NMR, ^{1}H NMR, and MS spectra. The molecular ion peaks of **2a**, **2b**, and **3a** were not observed in their high resolution mass spectra (HRMS). The structure of fluorinated product **2a** was identified by comparison with ^{19}F NMR, ^{1}H NMR, and MS spectral data of the authentic sample independently synthesized by halogen exchange of 2-methoxyethoxymethyl chloride with KF in MeCN.

Ethylene glycol fluoromethyl methyl ether (2a). ^{1}H 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).

1-Fluoro-1,2-dimethoxyethane (3a). ^{19}F NMR δ −56.06 (dt, J=66.4, 14.0 Hz) MS m/e 108 (M$^+$, trace).

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).

Pentaethylene glycol di(fluoromethyl) ether (2d). ^{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); HRMS(FAB): m/z calcd for C$_{12}$H$_{25}$F$_2$O$_6$ 303.1619 (M$^+$+H), found 303.1645.

Tetraethylene glycol di(fluoromethyl) ether (2e). ^{1}H NMR δ 3.70 (m, 16H), 5.31 (d, 4H, J=56.4 Hz); ^{19}F NMR δ −74.05 (t, J=56.1 Hz). MS m/e 258 (M$^+$, trace), 238 (M$^+$ −HF); HRMS(FAB): m/z calcd for C$_{10}$H$_{20}$F$_2$O$_5$ 259.1357 (M$^+$+H), found 259.1355.

Triethylene glycol di(fluoromethyl) ether (2f). ^{1}H NMR δ 3.70 (m, 12H), 5.30 (d, 4H, J=56.4 Hz); ^{19}F NMR δ −74.05 (t, J=56.1 Hz). MS m/e 214 (M$^+$, trace), 194 (M$^+$ −HF); HRMS(FAB): m/z calcd for C$_8$H$_{17}$F$_2$O$_4$ 215.1095 (M$^+$+H), found 215.1036.

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