

Anodic *gem*-Difluorination of Dithioacetals¹⁾

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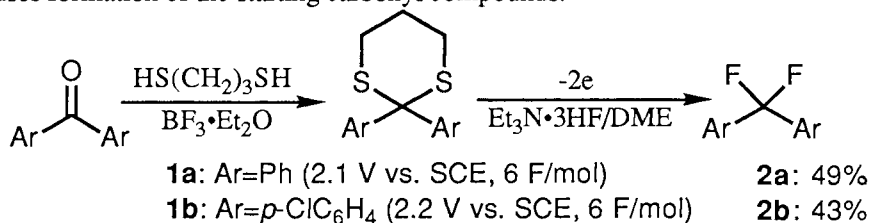
Anodic desulfurization of dithioacetals of ketones in the presence of $\text{Et}_3\text{N}\cdot 3\text{HF}$ provided the corresponding *gem*-difluorocompounds while dithioacetals of aromatic and aliphatic aldehydes gave *gem*-difluoro thioethers and monofluoro thioether, respectively.

Organic compounds containing a difluoromethylene group have been of much interest in biological chemistry since the difluoromethylene group is isopolar and isosteric with an ether oxygen.²⁾ The difluoromethylene group is prepared from the corresponding compound using various reagents such as molybdenum hexafluoride,³⁾ selenium tetrafluoride,⁴⁾ sulfur tetrafluoride,⁵⁾ and (diethylamino) sulfur trifluoride (DAST).⁶⁾ However, these reagents are highly toxic and their use requires severe reaction conditions. Recently, oxidative fluorodesulfurization of dithioacetals such as 1,3-dithiolanes and 1,3-dithianes using N-halo compounds and pyridinium poly (hydrogen fluoride),⁷⁾ $\text{Bu}_4\text{N}\cdot\text{H}_2\text{F}_3$,⁸⁾ or 4-methyl (difluoroiodo) benzene⁹⁾ has been shown to be alternative synthetic methods.

In contrast to these chemical methods, anodic partial fluorination can be carried out under the safe conditions without any oxidizing reagents.¹⁰⁾ From this point, anodic fluorodesulfurization seems to be one of promising methods of the difluoromethylene group.¹¹⁾

By the way, Steckhan *et al.* reported that 1,3-dithiane protecting group could be removed effectively by indirect anodic oxidation.¹²⁾ In their reaction, a small amount of water hydrolyzes anodically generated carbocation intermediates leading to deprotected carbonyl compounds.

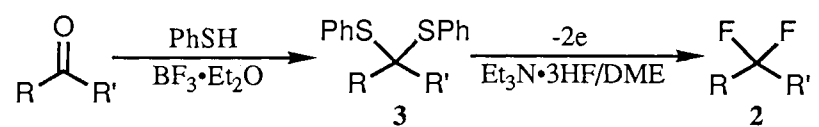
With these points in mind, we first attempted the anodic oxidation of 1,3-dithianes together with 1,3-dithiolanes in the presence of fluoride ions instead of hydroxide ions to provide *gem*-difluorinated compounds.¹³⁾ Expectedly, 1,3-dithianes **1** gave the corresponding *gem*-difluorinated products **2** in reasonable yields (Scheme 1) although 1,3-dithiolanes were difluorinated in extremely low yields (less than 10%). It was also found that acetonitrile was not suitable for this difluorination because acetonitrile easily contains water which causes formation of the starting carbonyl compounds.

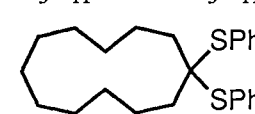


Scheme 1.

Next, anodic difluorination of acyclic dithioacetals of ketones was similarly attempted and the results are summarized in Table 1. Aromatic ketone-derived dithioacetals **3** underwent anodic difluorination smoothly to provide *gem*-difluorinated products in moderate to good yields although the fluorination of aliphatic ketone-derived dithioacetals resulted in unsatisfactory yields (runs, 7 and 8). It was found that the difluorination was strongly affected by the substituents on the benzene ring: Electron-withdrawing groups markedly promoted this anodic difluorination (runs, 2-4) while electron-donating groups significantly interfered with the difluorination (runs, 5 and 6). This substituent effect can be rationalized as due to the electrophilicity of anodically generated benzylic cations.

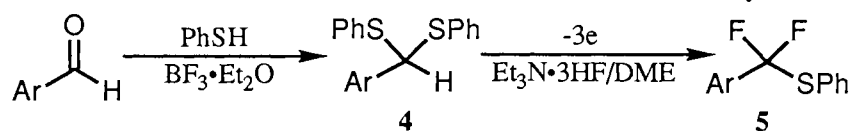
Table 1. Anodic Difluorination of Dithioacetals of Ketones

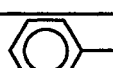
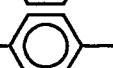
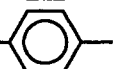


Run	R	R'	Anodic potential V vs. SSCE	Charge passed X 96480 C·mol ⁻¹	Yield of 2/% ^{a)}
1	C ₆ H ₅ -	C ₆ H ₅ -	2.6	11	44(53) ^{b)}
2	<i>p</i> -ClC ₆ H ₄ -	<i>p</i> -ClC ₆ H ₄ -	2.8	15	58
3	<i>p</i> -FC ₆ H ₄ -	<i>p</i> -FC ₆ H ₄ -	2.6	16	79
4	<i>p</i> -FC ₆ H ₄ -	C ₆ H ₅ -	2.6	14	70
5	<i>p</i> -MeC ₆ H ₄ -	<i>p</i> -MeC ₆ H ₄ -	3.2	12	31(52) ^{b)}
6	<i>p</i> -MeOC ₆ H ₄ -	<i>p</i> -MeOC ₆ H ₄ -	2.6	10	30
7	<i>n</i> -C ₅ H ₁₁ -	<i>n</i> -C ₅ H ₁₁ -	2.5	14	23
8			2.6	12	15

a) Isolated yield. b) Determined by ¹⁹F NMR.

Table 2. Anodic Difluorination of Dithioacetals of Aromatic Aldehydes

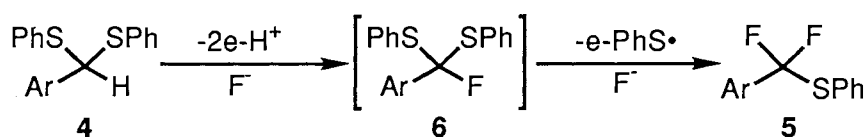


Run	Ar	Anodic potential V vs. SSCE	Charge passed x96480 C·mol ⁻¹	Yield of 5/% ^{a)}
1		2.6	11	20
2	MeO- 	2.8	16	7
3	O ₂ N- 	3.0	14	57

a) Determined by ¹⁹F NMR.

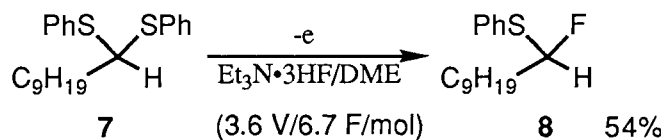
Contrary to the dithioacetals of ketones, dithioacetals of aldehydes showed quite different anodic behavior. Thus, aromatic aldehyde-derived dithioacetals **4** were converted into sulfides containing a difluoromethylene group (Table 2).¹⁴⁾ It was also found that an electron-withdrawing nitro group markedly accelerated the difluorinating reaction while an electron-donating methoxy group significantly interfered with the reaction. In addition, a large amount of diphenyl disulfide was formed in all cases.

Since monofluoro dithioacetal intermediates **6** were detected by ¹⁹F NMR and MS in the course of the reactions,¹⁵⁾ this reaction may proceed *via* **6** as shown in Scheme 2. These results are notable since anodic α -fluorination of simple benzyl phenyl sulfide did not proceed at all.¹⁶⁾



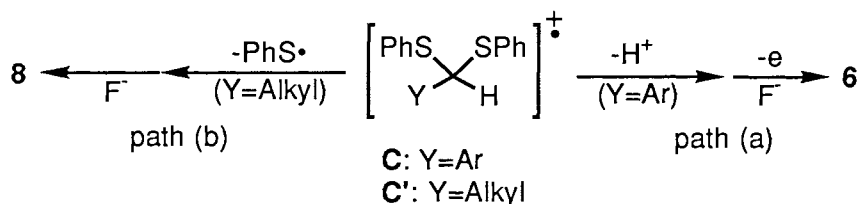
Scheme 2.

On the other hand, aliphatic aldehyde-derived dithioacetal **7** underwent C-S bond cleavage selectively and monofluorinated sulfide **8** was formed solely when the starting **7** was completely consumed (Scheme 3).¹⁷⁾



Scheme 3.

Thus, it is quite interesting that aromatic dithioacetals **4** showed different anodic behavior from that of aliphatic dithioacetal **7**. This can be explained as follows. As shown in Scheme 4, deprotonation of cation radicals **C** derived from aromatic dithioacetals **4** seems to be easier than that of **C'** from alkyl dithioacetal **7** since the former α -hydrogen is more acidic than the latter one. This is consistent with the fact that an electron-withdrawing group remarkably promoted the fluorination and *vice versa* (Table 2, runs 2 and 3). Therefore, it is reasonable that **4** underwent α -fluorination [path (a)] while **7** underwent desulfurization-fluorination [path (b)] at the first step.



Scheme 4.

In summary, we successfully carried out anodic *gem*-difluorination of dithioacetals, and found that this fluorination was greatly affected by their molecular structures. Such trend has never been observed in chemically oxidative fluorodesulfurization.

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- 11) So far, only one paper has been reported on anodic fluorodesulfurization: T. Brigaud and E. Laurent, *Tetrahedron Lett.*, **31**, 2287 (1990).
- 12) M. Platen and E. Steckhan, *Tetrahedron Lett.*, **21**, 551 (1980).
- 13) In a typical anodic difluorination, constant potential electrolysis was carried out with platinum electrodes (3x4 cm) at room temperature in 0.1 M Et₃N•3HF/dimethoxyethane (DME) (20 ml) containing 2 mmol of dithioacetal using a divided cell with anion-exchange membrane (ACH-45T, Tokuyama Soda). After the starting substrate was almost consumed (monitoring by TLC and/or MS), the electrolysis solution was neutralized with saturated NaHCO₃ aq. solution, and extracted with CH₂Cl₂. The combined extracts were dried over anhydrous MgSO₄, and then concentrated under reduced pressure. The residue was purified by silica gel (hexane/dichloromethane, mainly 10: 1) to provide difluorinating products.
- 14) Similar new type *gem*-difluorinated sulfides have been prepared: M. Kuroboshi and T. Hiyama, *Chem. Lett.*, **1992**, 827.
- 15) For example, **6** (Ar=*p*-NO₂C₆H₄): ¹⁹F NMR (CDCl₃, ext CF₃COOH) δ -25.7 (s) ; MS (35 eV) *m/z* (rel intensity) 371 (M⁺, trace), 262 (M⁺-SPh, 100).
- 16) T. Fuchigami, M. Shimojo, A. Konno, and K. Nakagawa, *J. Org. Chem.*, **55**, 6074 (1990).
- 17) The monofluorinated sulfide **8** could be converted into 1,1-difluorodecane although the yield was low (13%).

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