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Electrolytic partial fluorination of organic compounds. Part 43: Highly regioselective anodic mono- and difluorination of propargyl sulfides and preparation of α-fluoroallenyl sulfides†

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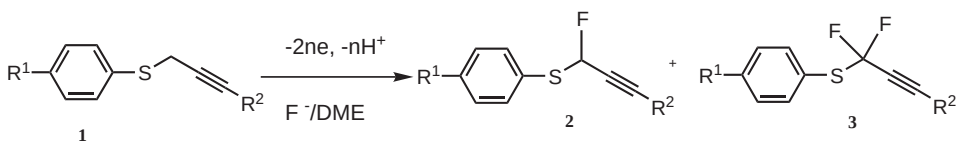
Abstract—The anodic fluorination of aryl propargyl sulfides in DME containing a fluoride supporting electrolyte using an undivided cell provided the corresponding α-mono- and α,α-difluorinated sulfides selectively, depending on the amount of electricity passed. The α-monofluorinated sulfides were readily converted into the corresponding α-fluoroallenyl sulfides in good to moderate yields.

Selective direct fluorination of organic molecules is of much importance in various fields such as medicinal chemistry and material science.[2–6] Among organofluorine compounds, difluoromethylene compounds attract much interest because the difluoromethylene group is isopolar and isosteric with an ether oxygen, and recent work has revealed that difluoromethylene compounds have a wide range of biological activities such as anticancer agent gemcitabine,[7] HIV-1 protease inhibitors,[8] and phosphotyrosine mimetics.[9] However, the construction of a difluoromethylene group is not so easy and very often requires a large amount of oxidizing, toxic or costly reagents.[10] On the other hand, very recently, the first synthesis and synthetic application of α-fluoroallenyl phosphonate have been reported.[11] α-Fluoroallenyl

Table 1. Anodic mono- and difluorination of aryl propargyl sulfides **1a–d**



Run	Sulfide			Supporting electrolyte	Charge passed (F/mol)	Yield (%)	
	No.	R^1	R^2			**2**	**3**
1	**1a**	H	H	$Et_4NF·4HF$	2	43	5
2	**1a**	H	H	$Et_4NF·4HF$	4	64	13
3[a]	**1a**	H	H	$Et_4NF·4HF$	4	70	0
4	**1a**	H	H	$Et_3N·5HF$	4	77	17
5	**1a**	H	H	$Et_4NF·4HF$	8	22	70
6	**1a**	H	H	$Et_4NF·4HF$	10	0	55
7	**1a**	H	H	$Et_3N·3HF$	8	21	75
8	**1b**	Cl	H	$Et_3N·3HF$	8	5	72
9	**1c**	H	Ph	$Et_3N·3HF$	10	0	65

[a] Constant potential electrolysis.

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sulfides should be useful as a fluorobuilding block. However, there has been no report on α-fluoroallenyl sulfides so far. Previously, we have found that an electron-withdrawing group markedly facilitated anodic α-fluorination of sulfides.[12] An acetylenic group is an electron-withdrawing group; however, to the best of our knowledge, no anodic partial fluorination of sulfides having an acetylenic group has been reported.

In this paper, we report the first successful regioselective anodic mono- and difluorination of aryl propargyl sulfides **1** using various fluoride salts in DME and the transformation of monofluoropropargyl sulfides to α-fluoroallenyl sulfides.

At first, we carried out the anodic fluorination of phenyl propargyl sulfide **1a** using constant current electrolysis under various conditions.[13] The results are summarized in Table 1.

Although MeCN was not suitable for the fluorination (the yield of **2a** was up to 25%) due to anode passivation, DME was found to be very effective irrespective of the supporting fluoride salts. When twice the theoretical amount of electricity (4F/mol) was passed in DME, α-monofluorinated sulfide **2a** was selectively formed in good yield (run 4). A fluorine atom was regioselectively introduced into the position α to the sulfur atom. Fluorination at the acetylenic group or phenyl ring did not take place at all. However, α,α-difluorinated sulfide **3a** was also formed as a by-product. On the other hand, constant potential anodic oxidation of **1a** at 1.5 V versus SSCE provided **2a** predominantly in good yield (run 3).[14]

In order to obtain α,α-difluorinated product **3a** selectively, a large excess amount of electricity was passed. As shown in Table 1, **3a** was formed as a main product (runs 5 and 7).[15] Longer electrolysis resulted in exclusive formation of **3a** although the yield decreased (run 6). Previously, we found that $Et_4NF{\cdot}4HF$/MeCN was effective for α,α-difluorination of sulfides having various electron-withdrawing groups but $Et_3N{\cdot}3HF$/MeCN was not suitable.[16] In contrast, only poor yield (14%) of **3a** was obtained in $Et_4NF{\cdot}4HF$/MeCN but the use of $Et_3N{\cdot}3HF$/DME provided **3a** in good yield of 75%. Consequently, MeCN electrolytic solutions were not suitable for the formation of **2a** and **3a**. On the other hand, DME was suitable because it did not cause anode passivation although excess amount of electricity is necessary due to the simultaneous oxidation of DME during electrolysis. Therefore, a solvent effect of DME on the anodic fluorination is notable.

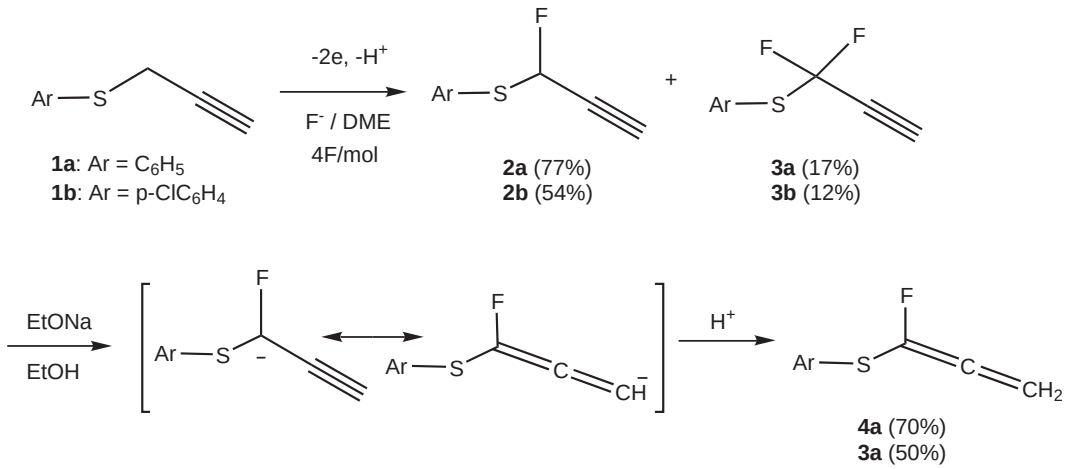
We extended this anodic fluorination to other derivatives **1b**,**c**. In all cases, α,α-difluorinated sulfides **3b**,**c** were predominantly (run 8) or exclusively (run 9) formed. The difluorinated products **3b**,**c** were readily isolated by column chromatography.[17] In the case of **1c**, neither phenyl fluorination nor acetylenic fluorination occurred and α,α-difluorinated product **3c** was obtained exclusively. Therefore, this fluorination is highly regioselective.

Although α-monofluorinated sulfide **2a** was formed in good yield, its complete isolation was unsuccessful due to its instability. Therefore, we attempted to convert **2a** into a more stable derivative. Thus, a solution of a crude product **2a** was basified by addition of an ethanol solution of sodium ethoxide, and the resulting stable α-fluoroallenyl sulfide **4a**[18] was easily isolated in good yield as shown in Scheme 1. *p*-Chlorophenyl derivative **4b** was similarly obtained in moderate yield from **1b**.

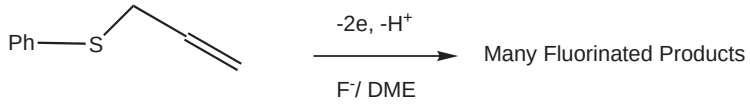
Since α-fluoroallenyl sulfides **4** have multifunctional groups, they may be highly useful building blocks similarly to α-fluoroallenyl phosphonates.[10]

In order to disclose the role of an acetylenic group, anodic fluorination of allyl phenyl sulfide was attempted. However, many complicated fluorinated products were formed. Therefore, a strongly electron-withdrawing acetylenic group is essential for this regioselective anodic fluorination (Scheme 2).

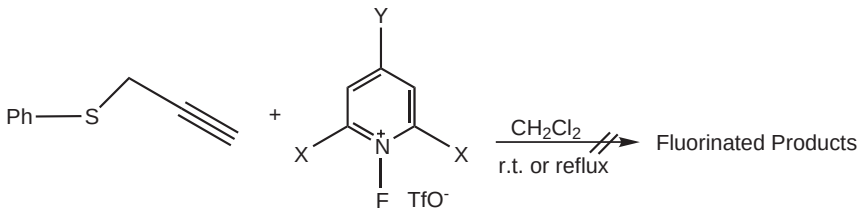
N-Fluoropyridinium salts are known to be good fluorinating reagents.[19] The chemical fluorination of phenyl propargyl sulfide **1a**, as a model compound, was also attempted. However, treatment of **1a** with various *N*-fluoropyridinium triflates in dichloromethane at either room temperature or under refluxing resulted in no



Scheme 1.



Scheme 2.



Scheme 3.

formation of fluorinated products as shown in Scheme 3.[20] Therefore, electrochemical fluorination proved to be superior to the conventional chemical method.

In summary, we have successfully carried out for the first time selective anodic mono- and difluorination of aryl propargyl sulfides, and the monofluorinated products were readily transformed into stable α-fluoroallenyl sulfides. Further studies of the synthetic application of allenes are in progress. The fluorinated products obtained here are proposed to be highly useful building blocks.

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13. Constant current electrolysis (5 mA/cm^2) of **1a** (1 or 5 mmol) was carried out at platinum electrodes (3×3 cm^2) at ambient temperature in DME (30 or 60 ml) containing 0.37 M fluoride salt using an undivided cell under a nitrogen atmosphere. After electrolysis, the supporting electrolyte was removed by silica gel short column chromatography. The yields of the products **2a** and **3a** were estimated by ^{19}F NMR spectroscopy. Compound **2a** was converted to α-fluoroallenyl sulfide **4a**, which was easily isolated by silica gel preparative thin-layer chromatography.
14. After electrolysis, the electrolytic solution was passed through silica gel short column chromatography using ethyl acetate and the eluent was concentrated to give **2a**. Compound **2b** was obtained similarly. Compound **2a**: yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.03 (dd, 1H, J=4.6, 2.3 Hz), 6.41 (dd, 1H, J=53.8, 2.3 Hz), 7.3–7.6 (m, 5H); ^{19}F NMR ($CDCl_3$, 254 MHz) δ −62.82 (dd, J=55, 5 Hz); MS (m/z) 166 (M^+). HRMS calcd for C_9H_7FS: 166.0253. Found: 166.023.
15. Compound **3a**: pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.98 (t, 1H, J=4.3 Hz), 7.2–7.6 (m, 5H); ^{19}F NMR ($CDCl_3$, 254 MHz) δ 16.7 (d, J=4.6 Hz); MS (m/z) 184 (M^+). HRMS calcd for $C_9H_6F_2S$: 184.0157. Found: 184.0158.
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17. Compound **3b**: pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.03 (t, 1H, J=4.3 Hz), 7.3 (d, 2H, J=8 Hz), 7.6 (d, 2H, J=8 Hz); ^{19}F NMR ($CDCl_3$, 254 MHz) δ 16.7 (d, J=4.3 Hz); MS (m/z) 218 (M^+). Anal. calcd for $C_9H_5ClF_2S$: C, 49.44; H, 2.30. Found: C, 49.11; H, 2.70. Compound **3c**: yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.3–7.7 (m, 10H); ^{19}F NMR ($CDCl_3$, 254 MHz) δ 18.5 (s) MS (m/z) 260 (M^+). Anal. calcd for $C_{15}H_{10}F_2S$: C, 69.21; H, 3.87. Found: C, 69.19; H, 4.18.
18. Compound **4a**: yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.09 (t, 2H, J=3 Hz), 7.2–7.5 (m, 5H); ^{19}F NMR ($CDCl_3$, 254 MHz) δ −40.05 (t, J=3 Hz); MS (m/z) 166 (M^+). HRMS calcd for C_9H_7FS: 166.0253. Found: 166.0239.
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