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Anodic fluorination of β,β-bis(methylthio)vinyl phenyl ketone

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Carbonyldesulfurization and fluorodesulfurization proceeded as well as the 1,2-rearrangement of a methylthio group to provide three kinds of fluoro products in the anodic fluorination of β,β-bis(methylthio)vinyl phenyl ketone.

An electrochemical method for the introduction of fluorine into organic compounds is an attractive alternative new methodology.[1–6] The method is often synthetically more elegant compared with conventional chemical methods, and allows the fluorination to be performed with high regioselectivity under safe conditions. On the other hand, the introduction of fluorine into enone compounds has attracted a great deal of attention due to its biologically and synthetically interesting products. For example, α-fluoro-β-halogeno enone derivatives could be used as intermediates in the synthesis of fluoro enynes and fluoro retinal analogues.[7] Moreover, optically active 2,2-difluoro-3-hydroxycarboxylates, which were prepared from the difluoroketene acetal, are versatile intermediates for the synthesis of fluorinated peptides, which were used as protease inhibitors mimicing the transition state for hydrolytic amide bond cleavage.[8] Actually, anodic fluorination of β-thio-α,β-unsaturated carbonyl compounds has been carried out to provide the α-monofluorinated product.[9] It was also reported that β,β-bis(methylthio)vinyl carbonyl compounds reacted with amine-HF and $Hg(OCOCF_3)_2$ to give β,β-difluoro-β-(methylthio)carbonyl compounds.[10] However, the reaction needs very long times.

Previously, monofluorination of 1,3-dithiolane-2-one took place at the α-position of the sulfur atom. In contrast, in the case of 1,3-dithiolane-2-thione, the oxidative fluorodesulfurization of the C=S group took place to give the corresponding *gem*-difluoro products.[11] These results prompted us to consider what would happen in the anodic fluorination of *gem*-bis(alkylthio)vinyl compounds [$RCOC{=}C(SR)_2$]. With these facts in mind, in this work, the anodic fluorination of β,β-bis(methylthio)vinyl phenyl ketone was investigated under various electrolytic conditions.

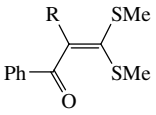
Starting β,β-bis(methylthio)vinyl phenyl ketones **1** were prepared according to a published procedure.[12] At first, the oxidation potentials were measured by cyclic voltammetry using a divided cell with a platinum disk electrode (φ = 1 mm) in 0.1 M Bu_4NClO_4/MeCN. The compounds chosen showed irreversible oxidation waves. The first peak oxidation potentials are summarised in Table 1. It was found that the substitution (R) at the α-position of the enones affected the oxidation potential significantly. α-Methoxyl derivative **1c** exhibited significantly lower oxidation potentials than non-substituted ketone **1a** owing to the electron-donating effect of a methoxyl group. In addition, it was shown that the electron-donating effect of the methyl group of **1b** also caused a little decrease in the oxidation potential. On the other hand, derivative **1d** with an α-cyano substituent was oxidised at a much more positive potential than **1a** owing to the strongly electron-withdrawing effect of the cyano group. The calculated values of the HOMO energies of these compounds agree well with their first oxidition potentials.

Next, the anodic fluorination of **1a** was carried out at platinum electrodes in anhydrous dimethoxyethane (DME) and acetonitrile (MeCN) under a constant current. Fluoride salts were used as both the supporting electrolyte and the fluorine source. The results of the anodic fluorination under various electrolytic conditions are summarised in Table 2.

As shown in Table 2, mono- and difluoro-1,3-diketone derivatives **2a~4a**† were formed. Regardless of electrolytic conditions, 2,2-difluoro-1,3-diketone **2a** was mainly formed.

In order to avoid the possible cathodic reduction of starting compound **1a** and fluorinated products **2a~4a** with an easily reducible activated double bond and carbonyl group, a divided cell was used to give difluoro product **2a** in 31% yield (Table 2, entry 2). Et_3N–3HF was found to be less effective than Et_4NF–4HF for the anodic fluorination of **1a** (Table 2, Entry 3). One of the reasons seems to be as follows. Owing to the much lower

Table 1 Oxidation potentials (E_p^{ox}) of β,β-bis(methylthio)vinyl phenyl ketones.[a]

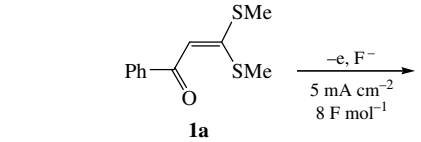


1a–d

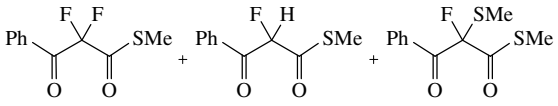
Substrate		E_p^{ox}/V *vs.* SCE	HOMO[b]/eV
Compound	R		
1a	H	1.53	–8.476
1b	Me	1.50	–8.184
1c	OMe	1.23	–8.164
1d	CN	1.90	–8.746

[a]In 0.1 M Bu_4NClO_4/MeCN, sweep rate: 100 mV s^{-1}. [b]Calculated with MOPAC 2000 program using AM1.

Table 2 Anodic fluorination of β,β-bis(methylthio)vinyl phenyl ketone **1a**.



1a



2a **3a** **4a**

Entry	Cell[a]	Solvent	Supporting electrolyte (1 M)	Yield[b] (%)		
				2a	**3a**	**4a**
1	U	DME	Et_4NF–4HF	10	3	8
2	D	DME	Et_4NF–4HF	31	trace	trace
3	D	DME	Et_3N–3HF	24	trace	trace
4	D	DME	Et_3N–5HF	15	6	2
5	D	MeCN	Et_4NF–4HF	3	0	trace
6	U	—	Et_4NF–4HF	trace	0	trace

[a]U – undivided cell; D – divided cell. [b]Determined by ^{19}F NMR.

† **2a**: yellow oil; ^1H NMR ($CDCl_3$) δ: 2.46 (s, 3H), 7.49–8.11 (m, 5H), ^{19}F NMR ($CDCl_3$) δ: –28.23 (s). ^{13}C NMR ($CDCl_3$) δ: 29.62, 111.19, 128.70, 129.35 (t, *J* 93.77 Hz), 131.11, 134.81, 181.11, 184.10. MS, *m/z*: 230 (M^+), 187 (M^+ – SMe), 156 (M^+ – CH_2SCO), 105 ($PhCO^+$). HRMS, *m/z*: found, 230.0221; calc. for $C_{10}H_8F_2O_2S$, 230.0213.

3a: yellow oil. ^1H NMR ($CDCl_3$) δ: 2.05 (s, 3H), 6.07 (d, 1H, *J* 49.1 Hz), 7.48–8.06 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: –114.0 (d, *J* 49.1 Hz). MS, *m/z*: 212 (M^+), 165 (M^+ – SMe), 138 (M^+ – CH_2SCO), 105 ($PhCO^+$). HRMS, *m/z*: found, 212.0310; calc. for $C_{10}H_9FO_2S$, 212.0307.

4a: yellow oil. ^1H NMR ($CDCl_3$) δ: 2.24 (s, 3H), 2.40 (s, 3H), 7.44–8.14 (m, 5H). ^{19}F NMR ($CDCl_3$) δ: –57.61 (s). ^{13}C NMR ($CDCl_3$) δ: 29.64, 31.87, 105.01, 128.36, 129.26 (d, *J* 127.29 Hz), 132.09, 134.09, 181.49, 185.20. MS, *m/z*: 258 (M^+), 183 (M^+ – MeSCO), 105 ($PhCO^+$). HRMS, *m/z*: found, 258.0184; calc. for $C_{11}H_{11}FO_2S_2$, 258.0184.

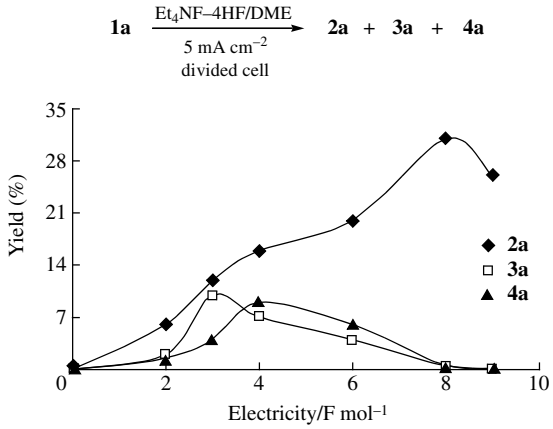


Figure 1 Relationships of electricity and yields of fluoro products.

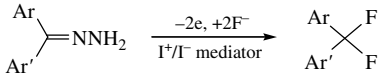
oxidation potential of Et_3N–3HF compared with Et_4NF–4HF, the former salt can be easily oxidised during the anodic fluorination of **1** to cause a decrease of the yield of difluoro product **2a**. On the other hand, the fluorination using Et_3N–5HF gave much lower yield of **2a**, however, the yield of the monofluoro product **3a** was increased appreciably (Table 2, Entry 4). In contrast to DME, MeCN was unsuitable for the fluorination (Table 2, Entry 5). The fluorination of **1a** scarcely proceeded under solvent-free conditions.

Monofluoro products **3a** and **4a** could not be obtained in high yields regardless of electrolytic conditions. Particularly when difluoro product **2a** was obtained in reasonable yield, only trace amounts of **3a** and **4a** were formed (Table 2, entries 2 and 3). These facts suggest that the monofluoro products **3a** and **4a** may be precursors of difluoro product **2a** and their further oxidation would give **2a**. In support of this hypothesis, the relationships between electricity and the yields of fluoro products were investigated under the electrolytic conditions of entry 2 (Table 2).

As shown in Figure 1, three fluoro products **2a~4a** were formed even at the early stage of the anodic fluorination. The yield of difluoro product **2a** increased with an increase of electricity, and the maximum yield of **2a** was obtained at 8 F mol^{-1}, and then the yield decreased with the amount of electricity. In contrast, when 3 F mol^{-1} of electricity was passed, the yield of monofluoro product **3a** reached the maximum, and then decreased to almost 0% with an increase of electricity. Dependency of the yield of another monofluoro product **4a** on electricity was quite similar to the case of **3a**. This can be explained in terms of further oxidation of **3a** and **4a** to provide **2a** during the electrolysis.

It was found that anodic *gem*-difluorination of hydrazone derivatives was successfully carried out by using I^+/I^- as a mediator in the presence of a fluoride salt (Scheme 1).[13] The indirect anodic fluorination of dithioacetals using a Br^+/Br^- redox mediator in the presence of fluoride ions proceeded with high current efficiencies to provide *gem*-difluorodesulfurization products (Scheme 2).[14]

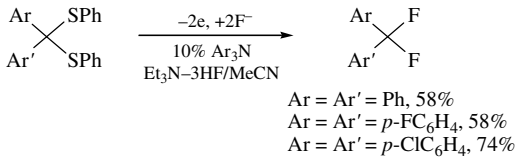
These facts prompted us to attempt the indirect fluorination of substrate **1a** using Et_4NI as the I^- source in the presence of a fluoride salt. However, unexpectedly, iodinated derivative **5a**‡



Ar = Ar′ = Ph, 60%
Ar = Ar′ = *p*-FC_6H_4, 44%
Ar = Ar′ = *p*-ClC_6H_4, 34%

Scheme 1

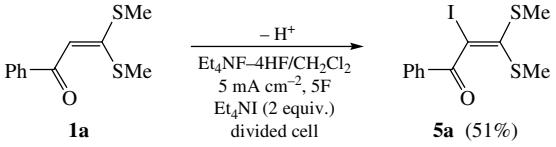
‡ **5a**: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.13 (s, 3H), 2.48 (s, 3H), 7.45–7.98 (m, 5H). MS, *m/z*: 350 (M^+), 335 (M^+ – Me), 303 (M^+ – MeSCO), 223 (M^+ – I), 105 ($PhCO^+$). HRMS, *m/z*: found, 349.9296; calc. for $C_{11}H_{11}IOS_2$, 349.9296.



Ar = Ar′ = Ph, 58%
Ar = Ar′ = *p*-FC_6H_4, 58%
Ar = Ar′ = *p*-ClC_6H_4, 74%

Scheme 2

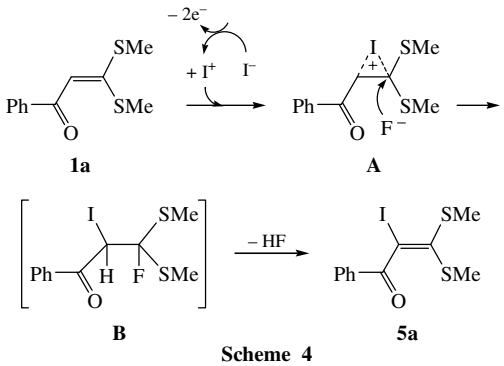
was obtained instead of the expected *gem*-difluoro product as shown in Scheme 3.



1a **5a** (51%)

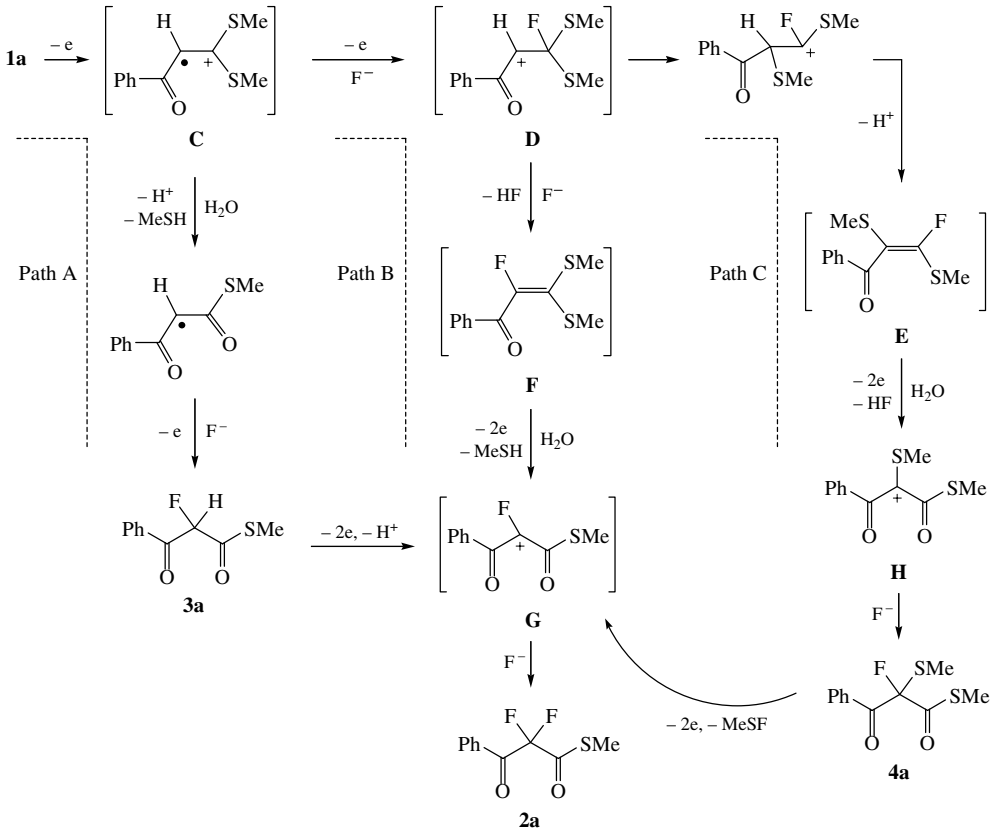
Scheme 3

This can be explained as shown in Scheme 4. Anodically generated 'I$^+$' reacted with **1a** to form intermediate **A**, followed by an attack with a fluoride ion to provide intermediate **B**. Product **5a** may be readily formed from **B** by elimination of HF since the α proton is rather acidic owing to the benzoyl group in the presence of F^- as the base. Actually, it has been reported that bromofluorination of the double bond of β,β-bis(methylthio)-α,β-unsaturated carbonyl compounds took place to produce the corresponding fluorobrominated product when 1,3-dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromosuccinimide (NBS) was used as the oxidant.[15]



Scheme 4

Generally, an ECEC mechanism is widely accepted for electrochemical nucleophilic substitution reactions. Moreover, it was shown that the water contaminated in the solution would take part in the nucleophilic reaction.[11] Since the α-substituents affected the oxidation potentials of **1** significantly, as shown in Table 1, the initial electron transfer of anodic oxidation seems to take place at an olefin moiety to generate radical cation **C**, which reacts with water followed by elimination of methylthiol to form the carbonylated radical intermediate (Scheme 5, Path A). This radical is immediately further oxidised and then attacked with a fluoride ion to give monofluoro product **3a**. Furthermore, difluoro product **2a** could be formed from **3a** by further oxidation, deprotonation and fluorination in sequence, as shown in Path A. On the other hand, radical cation **C** also reacts with a fluoride ion, followed by oxidation to generate unstable cation intermediate **D**. Sequentially, monofluorinated intermediate **F** could be formed by deprotonation followed by the elimination of β-fluorine atom of α,β-difluoro compound due to its α-acidic proton in the presence of F^- as the base, which was once formed by the reaction of the fluoride ion with **D**. A similar elimination of HF has been reported by Andres *et al.*[9] Since the fluorine substitent at the olefin moiety should decrease the oxidation potential of **F**, intermediate **F** could be further oxidised immediately to form the radical cation, which reacted with water contaminated in the solution, followed by desulfurization to generate the α-cation intermediate of 1,3-diketone derivative **G** (Path B). *gem*-Difluoro product **2a** seems to be formed directly from this intermediate **F**.



Scheme 5

The formation of monofluoro product **4a** is attributable to the intramolecular rearrangement of a methylthio group. Hara *et al.*[16] reported interesting fluorination by accompanying with a ring expansion reaction of cycloalkylidene acetates to provide the *gem*-difluoro product due to the rearrangement of an unstable carbocation, whose structure is quite similar to that of intermediate **D**. Namely, unstable cation **D** undergoes 1,2-rearrangement of a methylthio group to form a more stable intermediate, followed by deprotonation to give another type of monofluoro product **E**. This product should be easily oxidised owing to two methylthio groups and a fluorine atom at the double bond, followed by raction with water and dehydrofluorination to generate α-cation intermediate **H**. Thus, monofluoro product **4a** is readily produced *via* Path C. Moreover, monofluoro product **4a** has an easily oxidisable methylthio group; therefore, **4a** could be readily subjected to oxidative fluorodesulfurization to form *gem*-difluoro product **2a** as shown in Path C (Scheme 5).

In conclusion, the anodic fluorination of β,β-bis(methylthio)-vinyl phenyl ketones was carried out to provide a *gem*-difluoro-1,3-diketone derivative as the major product. Moreover, the monofluoro-1,3-diketone derivative and/or another type of a monofluoro-1,3-diketone derivative due to the 1,2-rearrangement of a methylthio group were also formed simultaneously. By the investigation of relationships between the electricity and yield of each product, it was found that the difluoro product was produced from both of the monofluoro products with an increase of electricity. On the other hand, in the anodic fluorination using I^+/I^- as a mediator, the iodinated product was obtained instead of the expected fluorodesulfurization product.

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