Facile and Efficient Sulfenylation Method Using Quinone Mono-*O,S*-Acetals under Mild Conditions

Masato Matsugi,[†] Kenji Murata,[†] Kentoku Gotanda,[†] Hisanori Nambu,[†] Gopinathan Anilkumar,[†] Keita Matsumoto,[‡] and Yasuyuki Kita*[,†]

Graduate School of Pharmaceutical Sciences, Osaka University, 1−6 Yamada-oka, Suita, Osaka 565-0871, Japan, and Research Center, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Omiya, Saitama 330-8530, Japan

kita@phs.osaka-u.ac.jp

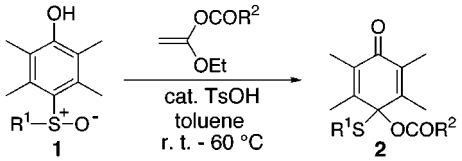
Received December 5, 2000

A novel sulfenylation method induced by aromatization of quinone mono-*O,S*-acetals is described. These sulfenylation reagents readily react with silyl enolethers or electron rich aromatic compounds to give sulfenylation products under mild conditions. In particular, *O,S*-acetal **2j**, which possesses a pentafluorophenylthio function, is the most effective reagent from the standpoint of the adaptability for various substrates.

Introduction

It is important to effectively introduce sulfur into organic compounds, since many biologically active compounds contain sulfur functions.[1] Furthermore, the sulfur function has great versatility as a foothold for the construction of various target molecules.[2] Many sulfenylation methods have been studied to date[3] that include electrophilic substitution with sulfur-containing electrophiles such as sulfenyl chloride, sulfenylamines, thiosulfonates, disulfides, nucleophilic substitution of aryl halides with metal mercaptides, replacement reactions via diazonium intermediates, and coupling reactions via a radical cation. However, these approaches usually require basic, acidic, or heating conditions during the sulfenylation process except for in limited cases,[3q] and until now, a mild sulfenylation reaction under neutral conditions was not readily available.

Table 1. Preparation of Quinone Mono-*O,S*-acetals 2



O,S-acetal	R^1	R^2	yields(%)
2a	Me	Me	86
2b	Ph	//	70
2c	//	CH_2Cl	90
2d	*p*-$MeOC_6H_4$	//	86
2e	*p*-$NO_2C_6H_4$	//	75

We have already reported that various quinone mono-*O,S*-acetals **2**, which are intermediates in the aromatic Pummerer-type rearrangement, could be easily isolated in high yields,[4] and recent preliminary communications[5] showed that these quinone mono-*O,S*-acetals **2** readily aromatize by reaction with some nucleophiles giving sulfenylation products under mild conditions. In this paper, we present the full account of these studies along with the efficient sulfenylation of various substrates. The starting quinone mono-*O,S*-acetals **2a**−**j** were readily prepared from the corresponding sulfoxides **1** by the reported method[4] using 1-ethoxy vinylesters (Table 1).[6,7]

Result and Discussion

We first examined the ability of quinone mono-*O,S*-acetals **2a**−**e** to undergo sulfenylation of cyclic silyl enol

* To whom correspondence should be addressed.
[†] Osaka University.
[‡] Taisho Pharmaceutical Co., Ltd.

(1) For recent reviews, see: (a) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223−269.

(2) (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363−382. (b) Akai, S.; Takeda, Y.; Iio, K.; Takahashi, K.; Fukuda, N.; Kita, Y. *J. Org. Chem.* **1997**, *62*, 5526−5536. (c) Kita, Y.; Iio, K.; Kawaguchi, K.; Fukuda, N.; Takeda, Y.; Ueno, H.; Okunaka, R.; Higuchi, K.; Tsujino, T.; Fujioka, H.; Akai, S. *Chem. Eur. J.* **2000**, *6*, 3897−3905. (d) Akai, S.; Morita, N.; Iio, K.; Nakamura, Y.; Kita, Y. *Org. Lett.* **2000**, *2*, 2279−2282.

(3) For examples: (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887−4902. (b) Scholz, D. *Synthesis* **1983**, 944−945. (c) Bischoff, L.; David, C.; Martin, L.; Meudal, H.; Roques B.-P.; Fournié-Zaluski, M.-C. *J. Org. Chem.* **1997**, *62*, 4848−4850. (d) Foray, G.; Peñéñory, A. B.; Rossi, R. A. *Tetrahedron Lett.* **1997**, *38*, 2035−2038. (e) Tanaka, T.; Azuma, T.; Fang, X.; Uchida, S.; Iwata, C.; Ishida, T.; In, Y.; Maezaki, N. *Synlett* **2000**, 33−36. (f) Bottino, F.; Fradullo, R.; Pappalardo, S. *J. Org. Chem.* **1981**, *46*, 2793−2795. (g) Criatau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892−894. (h) Oae, S.; Shinhana, K.; Kim, Y. H. *Chem. Lett.* **1979**, 939−942. (i) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480−481. (j) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567−569. (k) Bates, D. K.; Tafel, K. A. *J. Org. Chem.* **1994**, *59*, 8076−8080. (l) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 733−737. (m) Franco, F.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 1682−1688. (n) Hocker, J.; Ley, K.; Merten, R. *Synthesis* **1975**, 334−335. (o) Hartke, K.; Teuber, D.; Gerber, H.-D. *Tetrahedron* **1988**, *44*, 3261−3270. (p) Pagnoni, U. M.; Pinetti, A. *J. Heterocyclic Chem.* **1993**, *30*, 617−621. (q) Kita, Y.; Takada, T.; Mihara, S.; Whelen, B. A.; Tohma, H. *J. Org. Chem.* **1995**, *60*, 7144−7148.

(4) Kita, Y.; Takeda, Y.; Matsugi, M.; Iio, K.; Gotanda, K.; Murata, K.; Akai, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1529−1531.

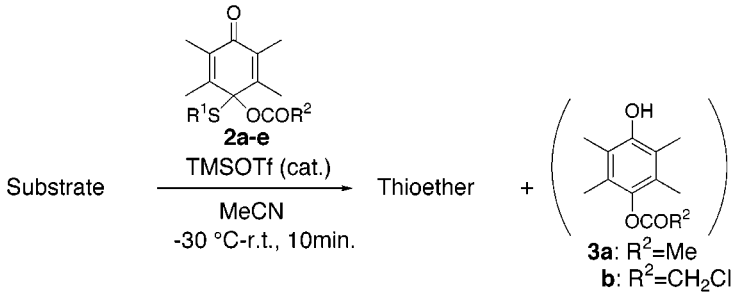
(5) (a) Matsugi, M.; Gotanda, K.; Murata, K.; Kita, Y. *Chem. Commun.* **1997**, 1387−1388. (b) Matsugi, M.; Murata, K.; Nambu, H.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 1077−1080.

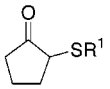
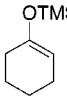
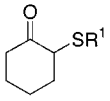
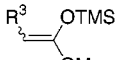
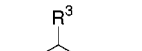
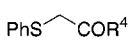
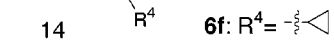
(6) (a) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2999−3005. (b) Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 303−310.

(7) Quinone mono-*O,S*-acetals (**2a**−**j**) are stable for several months during storage in a refrigerator.

10.1021/jo001710q CCC: $20.00
Published on Web 03/15/2001

Table 2. Sulfenylation of Silyl Enol Ethers Using Quinone Mono-*O,S*-acetals 2a−e



Entry	Substrate	*O,S*-Acetal	Thioether	Yield(%)[a]
1	 **4a**	**2a**	 **5a**: R^1=Me	94
2	//	**2b**	**5b**: R^1=Ph	98
3	//	**2c**	//	99
4	//	**2d**	**5c**: R^1=*p*-$MeOC_6H_4$	99
5	//	**2e**	**5d**: R^1=*p*-$NO_2C_6H_4$	100
6	 **4b**	**2a**	 **5e**: R^1=Me	94
7	//	**2c**	**5f**: R^1=Ph	95
8	//	**2d**	**5g**: R^1=*p*-$NO_2C_6H_4$	96
9	 **6a**: R^3=H	**2c**	 **7a**	99
10	**6b**: R^3=Me	**2c**	**7b**	100
11	**6c**: R^3=Ph	**2c**	**7c**	98
12	**6d**: R^3=OMe	**2c**	**7d**	99
13	 **6e**: R^4=Ph	**2c**	 **7e**	96
14	**6f**: R^4= 	**2c**	**7f**	81

ethers (**4a**, **b**) and found that **2a**−**e** were excellent sulfenylating reagents which produce the α-sulfenylcycloalkanone (**5a**−**g**) in quantitative yields (Table 2, entries 1−8). We used **2c** as the reagent to examine other sulfenylation reactions because of its facile preparation (Table 1). Acyclic silyl enol ethers (**6a**−**f**) were similarly reacted with **2c** to give the corresponding α-phenylthioketones (**7a**−**f**) in high yields (Table 2, entries 9−14).

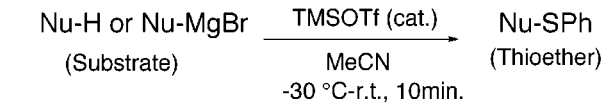
The sulfenylating reagent also reacted with electron-rich aromatic compounds (**8a**−**g**), and the corresponding thioethers (**9a**−**g**) were regioselectively obtained (Table 3, entries 1−7). It should be noted that no other regio isomers were obtained in these reactions. In these cases, the electron density of the substrates strongly influenced the yield of the sulfenylation products. Electron-rich aromatic compounds gave the sulfenylation products in quantitative yields (Table 3, entries 1−3). However, the less electron-rich aromatic compounds gave the corresponding products in lower yields (Table 3, entries 4−7). Benzene itself did not react at all with **2c** (Table 3, entry 8). However, for such cases, the problem has been solved by using Grignard reagents (**8i**−**l**). This approach gave the corresponding thioethers (**9h**−**k**) in moderate yields (Table 3, entries 9−12). It is noteworthy that the use of Grignard reagents could introduce the sulfenyl function even when the significant electron deficient aromatic such as trifluorobenzene was used (Table 3, entry 12).

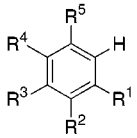
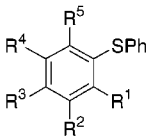
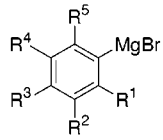
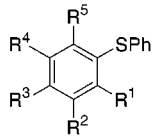
Furthermore, heteroaromatic compounds such as the indole, pyrrole, or thiophene derivatives (**10a**−**h** and **12a**−**e**) also reacted similarly with **2c** to give regioselectively the corresponding thioethers (**11a**−**h** and **13a**−**e**) (Table 4).

On the other hand, unexpected results were obtained when certain electron-rich aromatics were used. Thus, the reaction of 1,2,3-trimethoxybenzene (**8m**) with **2c** gave an unexpected desulfurization product exclusively, the structure of which was assigned as **14a** based on the following chemical transformation and spectral and analytical data (Table 5, entry 1). Treatment of **14a** with $NaBH_4$ followed by heating under acidic condition gave the biaryl compound **15** in 93% yield (Scheme 1). Similarly, **8n**, **o**, and **p** predominantly afforded the addition products **14b**, **c**, and **e** (Table 5, entries 2, 3, 5). When using **8g**, the reaction afforded both the sulfenylation product (**9g**) and the C−C bond formation product (**14d**) (Table 5, entry 4). Neither the sulfenylation nor the C−C bond formation product was produced in the case of mesitylene (**8q**) (Table 5, entry 6).

The quinone mono-*O,S*-acetal **2c** was useful for the sulfenylation of standard organic compounds involving

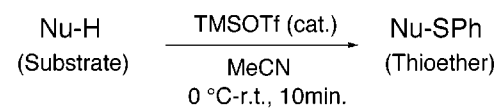
Table 3. Sulfenylation of Aromatic Compounds Using Quinone Mono-*O,S*-acetal 2c

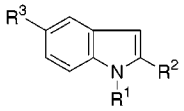
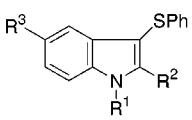
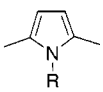
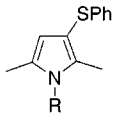
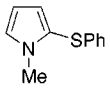
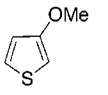
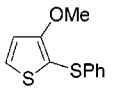
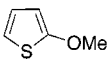
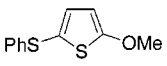


Entry	Substrate		R^1	R^2	R^3	R^4	R^5	Thioether		Yield(%)[a]
1		**8a**	H	OMe	OMe	H	OMe		**9a**	99
2		**8b**	OMe	H	OMe	H	OMe		**9b**	99
3		**8c**	OMe	H	OMe	H	Me		**9c**	99
4		**8d**	Me	H	OMe	H	Me		**9d**	67
5		**8e**	H	H	NMe_2	H	H		**9e**	64
6		**8f**	H	Me	OMe	H	OMe		**9f**	47[b]
7		**8g**	OMe	H	OMe	H	H		**9g**	31[b]
8		**8h**	H	H	H	H	H		—	0[b]
9[c]		**8i**	H	H	H	H	H		**9h**	87
10[c]		**8j**	OMe	H	H	H	H		**9i**	68
11[c]		**8k**	H	H	F	H	H		**9j**	83
12[c]		**8l**	H	F	F	F	H		**9k**	85

[a] Isolated yield. Phenol derivative (**3b**) was formed as a byproduct, but it is readily removed by shaking with aqueous $NaHCO_3$ solution. [b] Diphenyl disulfide and tetramethylquinone were formed as byproducts. [c] These reactions were performed in Et_2O without TMSOTf.

Table 4. Sulfenylation of Heteroaromatic Compounds Using Quinone Mono-*O,S*-acetal 2c



Entry	Substrate		R^1	R^2	R^3	Thioether		Yield(%)[a]
1		**10a**	H	Me	OMe		**11a**	99
2		**10b**	H	Me	H		**11b**	99
3		**10c**	H	Me	Me		**11c**	99
4		**10d**	H	Ph	H		**11d**	94
5		**10e**	H	H	OMe		**11e**	61
6		**10f**	H	H	H		**11f**	69
7		**10g**	Me	Ph	H		**11g**	81
8		**10h**	Me	Me	H		**11h**	74
9		**12a**	R=H				**13a**	82
10		**12b**	R=Me				**13b**	76
11		**12c**					**13c**	43[b]
12		**12d**					**13d**	30[b]
13		**12e**					**13e**	18[b]

[a] Isolated yield. Phenol derivative (**3b**) was formed as a byproduct, but it is readily removed by shaking with aqueous $NaHCO_3$ solution. [b] Diphenyl disulfide and tetramethylquinone were formed as byproducts.

Scheme 1. The Formation of the Biaryl Compound 15

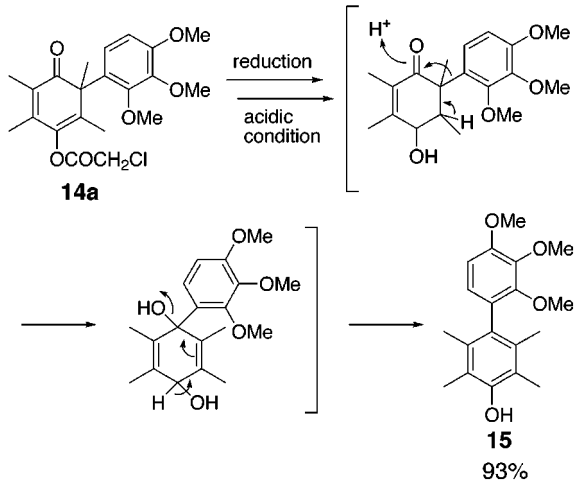
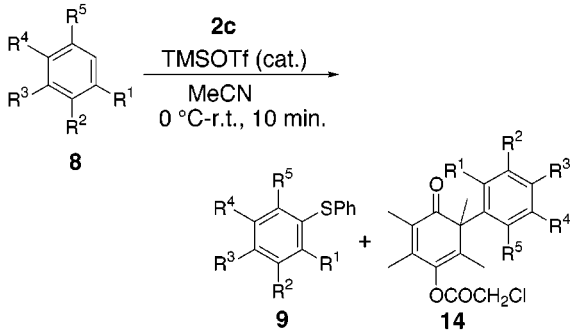


Table 5. Reaction of Some Methoxybenzenes with Quinone Mono-*O,S*-acetal 2c



Entry		Substrate R^1	R^2	R^3	R^4	R^5	Yield (%)[a] 9		14	
1	**8m**	OMe	OMe	OMe	H	H	–		**14a**	45
2	**8n**	H	OMe	OMe	H	H	–		**14b**	34
3	**8o**	OMe	H	H	OMe	H	–		**14c**	20
4	**8g**	OMe	H	OMe	H	H	**9g**	31	**14d**	16
5	**8p**	H	H	OMe	H	H	–		**14e**	11
6	**8q**	Me	H	Me	H	Me	–		–	

[a] Isolated yield. Phenol derivative (**3b**) was formed as a byproduct.

silyl enol ethers and electron-rich aromatic compounds (Scheme 2, route a), whereas unexpected desulfenylation products (**14**) were observed in some very electron-rich aromatic compounds such as the di- and trimethoxybenzenes (**8m**−**p**) in fair yields without the formation of the expected sulfenylation products (Scheme 2, route b). In this way, we found that quinone mono-*O,S*-acetals reacted with a nucleophile on the sulfur atom or on the carbon atom depending on the structural difference in the substrate. The reason for the difference in the reactivity of substrates is not completely known. We think that not only the electron density but also the steric hindrance of substrates influence the route of the reactions. For example, **8c** is a good substrate for sulfenylation (Table 3, entry 3). On the other hand, **8g** gave the sulfenylation product (**9g**) and the C−C bond formation product (**14a**) (Table 5, entry 4). It is thought that less hindered aromatic substrates tend to attack the β-carbon of the acetal part of **2c**.

Next, we investigated a more general method for the chemoselective sulfenylation of aromatics because sulfur functionalities on the aromatic ring as well as in aliphatic compounds are quite useful for synthetic transformations. For example, the sulfur functional group on aromatics could be easily converted to an oxygen functional group by the aromatic Pummerer-type rearrangement[2b,c] and also *ipso* substitution of the sulfur functional group by carbon substituents through a ligand exchange reaction.[2d] We aimed to avoid the side reaction, i.e., the formation of **14**, and planned the use of tuned *O,S*-acetals which have more activated sulfur atoms than **2c** for nucleophilic attack. Thus, the newly synthesized quinone mono-*O,S*-acetals (**2f**−**j**) bearing the electron-withdrawing group on an aryl thio moiety,[7] which were obtained in 60−85% yields from the corresponding sulfoxides,[4] were examined for the sulfenylation reaction of **8m**. The results of the reaction of these *O,S*-acetals (**2f**−**j**) with **8m** are summarized in Table 6. Both the thioether product **16** and compound **14a** were obtained in the reaction of **8m** with quinone mono-*O,S*-acetals (**2g**, **h**, **e**, **i**) bearing a moderately strong electron-withdrawing group on the aromatic ring (Table 6, entries 3−6). On the other hand, we found that the reaction of **8m** with **2j** bearing a pentafluorophenyl group on the sulfur atom afforded only the sulfenylation product (**16e**) in 81% yield (Table 6, entry 7). Replacement of a trifluorophenyl group by a pentafluorophenyl group in **2j** makes the sulfur atom more electrophilic, thus allowing the chemoselective sulfenylation reaction to predominate.

Similarly, we could produce various types of pentafluorophenylthio compounds (**16f**, **e**, **g**−**j**) in high yields from the corresponding mono-, di-, and trimethoxybenzenes (**8i**, **m**−**o**, **g**, **p**) (Table 7, entries 1−6). When mesitylene (**8q**) was used as the substrate, the sulfenylation product (**16k**) was obtained in 96% yield (Table 7, entry 7). 2-Methoxynaphthalene (**8r**) also afforded the thioether product (**16l**) in quantitative yield (Table 7, entry 8). The present sulfenylation reagent **2j** was quite effective for the sulfenylation of indole (**10f**), indole derivatives (**10a**, **b**, **e**, **i**−**m**), and various heteroaromatics (**12a**−**c**, **12f**−**i**) (Table 7, entries 9−24). In contrast, **2c** did not react at all with **8q**, the *N*-tosylated indole (**10i**), and some heteroaromatics (**12f**−**i**).

We performed the calculation of the steric structure for every quinone mono-*O,S*-acetal **2** using PM3.[8] The steric structure of **2c** as the typical example is shown in Figure S1. It is assumed that the dienone moiety of **2** is located between the aromatic ring and carbonyl group of the ester function. It is suggested that an orbital interaction exists between the dienone moiety and the aromatic ring. The stereo environment of the sulfur atom of **2** is generally less hindered than the β-carbon of the acetal part of **2**. Therefore, most nucleophiles predominantly attack the sulfur atom rather than the β-carbon of the acetal part.

In fact, the X-ray structure of the quinone mono-*O,S*-acetals **2d** and **2j** were almost identical to the PM3 calculation result (Figure 1). And because NOE between the α-methyl proton of acetal carbon and the proton *o*-position to the sulfur atom in **2d** was observed, it is

(8) MO calculations were performed by SPARTAN (Ver. 3.1.2) using the PM3 Hamiltonian.

Scheme 2. Sulfenylation or Nucleophilic Addition to the β-position of Acetal Carbon

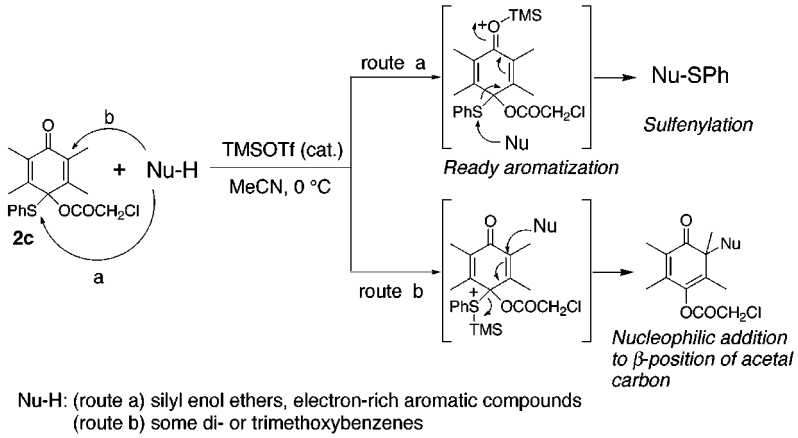
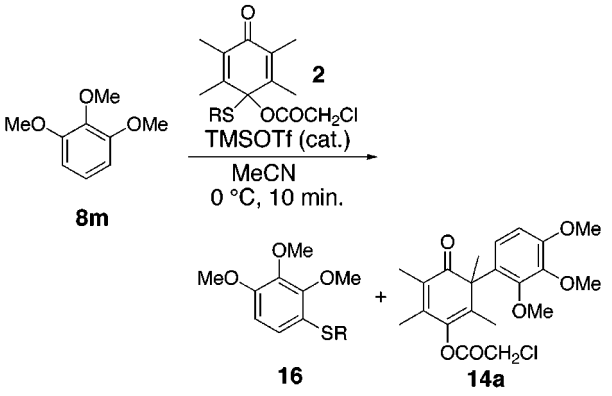


Table 6. Reaction of Quinone Mono-*O*,*S*-acetals 2 with 1,2,3-Trimethoxybenzene 8m



Entry		R	Yield (%)[a] 16		14a
1	**2c**	Ph		N. D.	45
2	**2f**	*p*-Cl-Ph		N. D.	46
3	**2g**	*p*-F-Ph	**16a**	16	25
4	**2h**	*p*-CF_3-Ph	**16b**	24	28
5	**2e**	*p*-NO_2-Ph	**16c**	76	20
6	**2i**	$C_6H_2F_3$	**16d**	79	13
7	**2j**	C_6F_5	**16e**	81	N. D.

[a] Isolated yield.

thought that the conformation of **2** in solution is similar to that in crystal. The dienone moiety is sandwiched between the aromatic ring and the ester carbonyl function. Especially, the aromatic part of the quinone mono-*O*,*S*-acetal **2j** is closest to the dienone moiety in every **2**. Therefore, it is postulated that nucleophiles could not attack at all the β-carbon of the acetal part. In addition, the pentafluorophenyl group is quite effective due to the higher electrophilicity on the sulfur atom.

Conclusion

As already described, we have succeeded in developing some novel sulfenylating reagents by taking advantage of their activation on the sulfur atom due to the driving force of their aromatizations. The advantages of this methodology are as follows: (1) The sulfenylation reactions are complete within 10 min below room temperature, (2) The dihydroquinone side product is easily removed by treatment with weak aqueous alkali, and (3) The corresponding thioethers are obtained in good yields. When the side reaction, in which the substrates attacked the β-position of acetal carbon in **2c**, occurred, the **2j**-bearing pentafluorophenylthio group was quite effective for the sulfenylation reaction. It gave the corresponding thioethers in good yield even in the case of indole derivatives bearing an electron-withdrawing group. Besides, we confirmed that the pentafluorophenylthio group works similar to a phenylthio group for oxidation and the pentafluorophenyl sulfinyl group also behaves similar to a phenyl sulfinyl group in the Pummerer-type rearrangement on aromatics and syn elimination in aliphatics.[9] These reagents might be applied to the synthesis of biologically active substances having sulfur functionalities and labile functional groups which are sensitive to basic or acidic conditions.

Experimental Section

Melting points are uncorrected. Infrared (IR) absorption spectra were recorded as a KBr pellet. The ^{1}H NMR spectra were measured in $CDCl_3$ on 200, 270, 300, and 500 MHz spectrometers with $SiMe_4$ as the internal standard. The ^{19}F NMR spectra were measured in $CDCl_3$ on a 188 MHz spectrometer with C_6F_6 as the internal standard. Mass spectra were obtained at 70 eV via GC-MS coupling. High-resolution mass spectra were obtained by EI. Column chromatographic purifications were performed using silica gel with either a 70−230 or 200−400 mesh size. The enolsilyl ethers (**6a**−**d**)[10] were prepared by a reported method. Diphenyl disulfide and tetramethylquinone were identified with commercially available compounds.

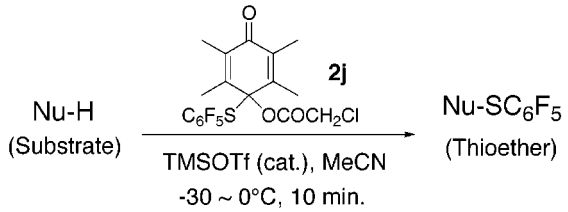
General Procedure for the Preparation of 2. Under a nitrogen atmosphere, to a stirred suspension of **1c**[2b] (274 mg, 1.00 mmol) and 1-ethoxyvinyl 2-chloroacetate[6] (492 mg, 3.00 mmol) in dry toluene (30 mL) was added *p*-TsOH (8.5 mg, 0.05 mmol). The reaction mixture was stirred at 60 °C for 1 h and cooled to room temperature. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1) to give **2c** (305 mg, 87% yield).

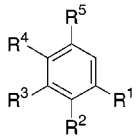
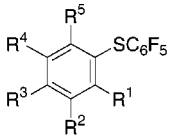
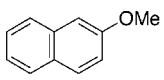
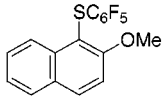
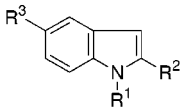
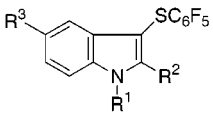
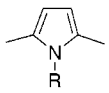
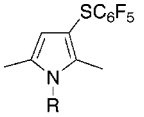
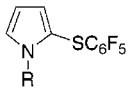
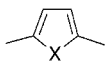
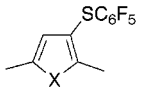
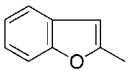
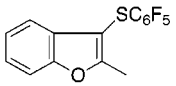
2,3,5,6-Tetramethyl-4-oxo-1-phenylthiocyclohexa-2,5-dienyl 2-Chloroacetate 2c. 90%; pale yellow crystals; mp 132−133 °C (dec) (AcOEt−hexane). IR 1776, 1662, 1630 cm^{-1}. ^{1}H NMR δ: 1.64 (d, 6H, J = 1.0 Hz), 2.01 (d, 6H, J = 1.0 Hz),

(9) Both cyclic and acyclic α-pentafluorophenylthioalkanones are readily obtained in quantitative yield by the reaction of **2j** and the corresponding trimethylsilyl enol ethers under standard conditions.

(10) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, 4311−4314.

Table 7. Sulfenylation of Various Aromatic Compound Using Quinone Mono-*O,S*-acetals 2j



Entry	Substrate		R^1	R^2	R^3	R^4	R^5	Thioether	Yield (%)[a]
1		**8i**	OMe	H	OMe	H	OMe		**16f** 99
2		**8m**	OMe	OMe	OMe	H	H		**16e** 81
3		**8n**	H	OMe	OMe	H	H		**16g** 94
4		**8o**	OMe	H	H	OMe	H		**16h** 60
5		**8g**	OMe	H	OMe	H	H		**16i** 83
6		**8p**	H	H	OMe	H	H		**16j** 70
7		**8q**	Me	H	Me	H	Me		**16k** 96
8		**8r**							**16l** 99
9		**10a**	H	Me	OMe				**17a** 99
10		**10b**	H	Me	H				**17b** 99
11		**10e**	H	H	OMe				**17c** 78
12		**10f**	H	H	H				**17d** 83
13		**10i**	Ts	H	H				**17e** 88
14		**10j**	Ac	H	H				**17f** 75
15		**10k**	H	CO_2Et	H				**17g** 80
16		**10l**	H	H	CN				**17h** 84
17		**10m**	H	H	NO_2				**17i** 78
18		**12a**	R =H						**18a** 82
19		**12b**	R =Me						**18b** 88
20		**12c**	R =Me						**18c** 77
21		**12f**	R =H						**18d** 49
22		**12g**	X = S						**18e** 78
23		**12h**	X = O						**18f** 78
24		**12i**							**18g** 88

[a] Isolated yield. Phenol derivative (**3b**) was formed as a byproduct in in all cases, but it is readily removed by shaking with aqueous $NaHCO_3$ solution.

4.16 (s, 2H), 7.01 (brd, 2H, J = 7.5 Hz), 7.21 (brt, 2H, J = 7.5 Hz), 7.38 (brt, 1H, J = 7.5 Hz). HRMS Calcd for $C_{18}H_{19}ClO_3S$: 350.0742. Found: 350.0727. Anal. Calcd for $C_{18}H_{19}ClO_3S$: C, 61.62; H, 5.46. Found: C, 61.61; H, 5.32.

1-(2,3,4,5,6-Pentafluorophenylthio)-2,3,5,6-tetramethyl-4-oxocyclohexa-2,5-dienyl 2-Chloroacetate 2j. 76%; colorless crystals; mp 137−138 °C (Et_2O−hexane). IR 1782, 1634 cm^{-1}. ^1H NMR δ: 1.72 (s, 6H), 2.02 (s, 6H), 4.18 (s, 2H). ^{19}F NMR δ: −161.40 (m, 2F), −145.66 (m, 1F), −130.62 (m, 2F). HRMS (FAB) Calcd for $C_{18}H_{14}ClF_5O_3S$ (M^++1): 441.0350. Found 441.0352. Anal. Calcd for $C_{18}H_{14}ClF_5O_3S$: C, 49.05; H, 3.20. Found: C, 49.30; H, 3.29.

General Procedure of Sulfenylation with 2. Under a nitrogen atmosphere, to a stirred solution of **4a** (176 mg, 1.00 mmol) and **2c** (351 mg, 1.00 mmol) in dry MeCN (5 mL) was added TMSOTf (10 mg, 0.05 mmol) at 0 °C. After 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 4:1) to give **5b** (183 mg, 99% yield).

2-Phenylthiocyclopentanone 5b.[11] 99%; colorless oil. IR 1710 cm^{-1}. ^1H NMR δ: 1.62−2.38 (m, 7H), 2.91 (m, 1H), 3.84 (t, 1H, J = 6.0 Hz), 7.20−7.45 (m, 5H). MS 206 (M^+, 68), 110 (100).

(11) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159−161.

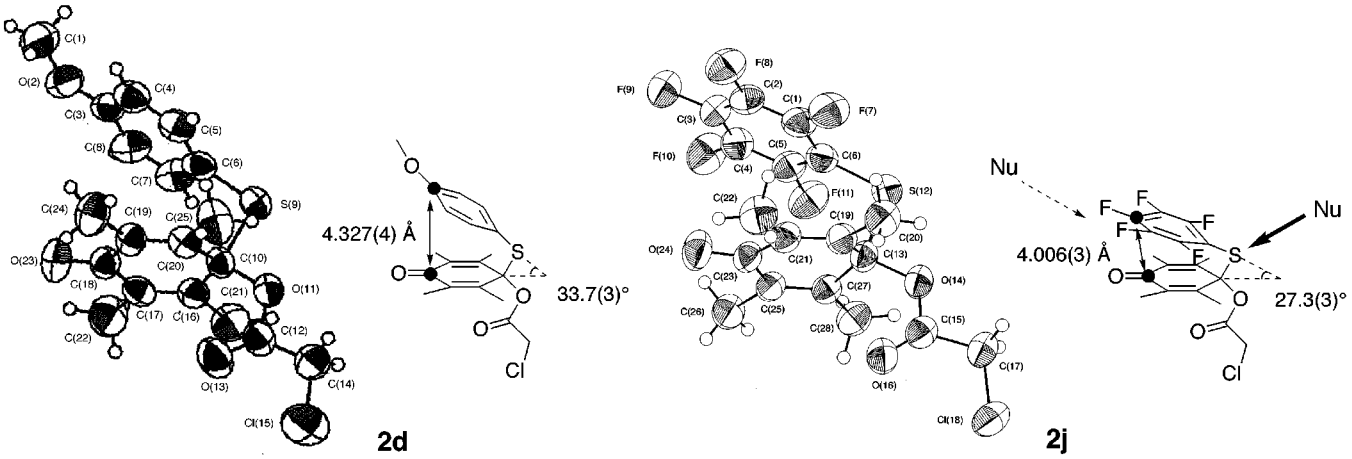


Figure 1. ORTEP drawing of **2d** and **2j**. Selected interatomic distances [Å] and dihedral angles between the aromatic plane and the dienone plane [deg]. **2d**: C(3)−(18), 4.327(4); dihedral angle, 33.7(3). **2j**: C(3)−C(23), 4.006(3); dihedral angle, 27.3(3).

Phenylthioacetic Acid Methyl Ester 7a.[12] 99%; colorless oil. IR 1740 cm^{-1}. ^1H NMR δ: 3.65 (s, 2H), 3.72 (s, 3H), 7.20−7.42 (m, 5H). MS 182 (M^+, 89), 109 (100).

1,2,4-Trimethoxy-5-phenylthiobenzene 9a. 99%; colorless oil. ^1H NMR δ: 3.78 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 6.60 (s, 1H), 6.95 (s, 1H), 7.10−7.26 (m, 5H). MS 276 (M^+, 100). Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84; S, 11.60. Found: C, 64.85; H, 5.81; S, 11.58.

5-Methoxy-2-methyl-3-phenylthioindole 11a.[13] 99%; colorless crystals; mp 132−133 °C (AcOEt−hexane) (lit.[13] 129−130 °C). IR 3395 cm^{-1}. ^1H NMR δ: 2.48 (s, 3H), 3.79 (s, 3H), 6.83 (dd, 1H, J = 8.5, 2.5 Hz), 6.99−7.25 (m, 7H), 8.18 (bs, 1H). MS 269 (M^+, 100).

2,5-Dimethyl-3-phenylthiopyrrole 13a.[14] 98%; colorless oil. IR 3395 cm^{-1}. ^1H NMR δ: 2.25 (s, 6H), 5.90 (d, 1H, J = 2.5 Hz), 7.00−7.26 (m, 5H), 7.86 (bs, 1H). MS 203 (M^+, 100).

4-(4-Fluorophenylthio)-1,2,3-trimethoxybenzene 16a. 16%; colorless crystals; mp 195 °C (AcOEt−hexane). ^1H NMR δ: 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 6.43 (d, 1H, J = 8.5 Hz), 6.93 (d, 2H, J = 7.0 Hz), 7.00 (d, 1H, J = 8.5 Hz), 7.28 (d, 2H, J = 7.0 Hz). MS 294 (M^+, 100). HRMS. Calcd for $C_{15}H_{15}FO_3S$: 294.0726. Found 294.0720.

General Procedure of Sulfenylation with 2c and Grignard Reagents. Under a nitrogen atmosphere, to a stirred suspension of Mg (24 mg, 1.0 mmol) in dry Et_2O (4 mL) was added dibromoethane (2 mg, 0.10 mmol) at room temperature. After 10 min, 2-bromoanisol (150 mg, 0.8 mmol) was added to the solution and the mixture was stirred for 15 min at the same temperature. The solution was added to **2c** (70 mg, 0.20 mmol) in dry Et_2O at −30 °C and the mixture was stirred for 10 min at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt, 10:1) to give **9i** (15 mg, 62% yield).

1-Methoxy-2-phenylthiobenzene 9i.[15] 62%; colorless oil. ^1H NMR δ: 3.87 (s, 3H), 6.89, (t, 2H, J = 8.0 Hz), 7.08 (d, 1H, J = 8.0 Hz), 7.24−7.37 (m, 6H). MS 216 (M^+, 100).

General Procedure for S_N2' Reaction of 2c with 8. Under a nitrogen atmosphere, to a solution of **2c** (301 mg, 0.855 mmol) and **8m** (200 mg, 0.570 mmol) in dry MeCN (10 mL) was added TMSOTf (20 mg, 0.090 mmol) and the mixture was stirred at room temperature. After 10 min, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1) to give **14a** (105 mg, 45%).

2,3,5,6-Tetramethyl-5-(2,3,4-trimethoxyphenyl)-4-oxocyclohexa-1,2-dienyl 2-Chloroacetate 14a. 45%; colorless crystals; mp 106−108 °C (AcOEt−hexane). IR 1775, 1761, 1646 cm^{-1}. ^1H NMR δ: 1.38 (s, 3H), 1.49 (s, 3H), 1.97 (s, 3H), 2.00 (s, 3H), 3.62 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 4.25 (s, 2H), 6.65 (d, 1H, J = 9.0 Hz), 7.05 (d, 1H, J = 9.0 Hz). MS 410 (M^+ + 2, 5), 408 (M^+, 15), 283 (100). Anal. Calcd for $C_{21}H_{25}ClO_6$: C, 61.69; H, 6.16; Cl, 8.67. Found: C, 61.60; H, 6.08; Cl, 8.51.

Formation of the Biaryl Compound 15. To a solution of **14a** (100 mg, 0.26 mmol) in EtOH (5 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was diluted with MeCN (4 mL), KI (60 mg, 0.35 mmol), TMSCl (38 mg, 0.35 mmol), and $NaBH_4$ (10 mg, 0.26 mmol) were added, and the mixture was stirred for 12 h at room temperature. Saturated aqueous $Na_2S_2O_3$ solution was added to the above reaction mixture and extracted with AcOEt. The extract was then washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was diluted with toluene (1 mL), treated with *p*-TsOH (45 mg, 0.26 mmol), and the mixture was stirred for 3 h under reflux. The resulting reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1) to give **15** (81 mg, 93% yield).

4-(2,3,4-Trimethoxyphenyl)-2,3,5,6-tetramethylphenol 15. 93%; colorless crystals; mp 165−167 °C (AcOEt−hexane). IR 3500 cm^{-1}. ^1H NMR δ: 1.95 (s, 6H), 2.21 (s, 6H), 3.58 (s, 3H), 3.91 (s, 6H), 4.65 (brs, 1H), 6.66 (d, 1H, J = 8.0 Hz), 6.72 (d, 1H, J = 8.0 Hz). MS 316 (M^+, 92), 73 (100). HRMS. Calcd for $C_{19}H_{24}O_4$: 316.1674. Found 316.1673.

General Procedure of Sulfenylation with 2j. Under a nitrogen atmosphere, to a stirred solution of **8m** (40.0 mg, 0.238 mmol) and **2j** (105 mg, 0.238 mmol) in dry MeCN (2 mL) was added TMSOTf (3 mg, 0.012 mmol) at 0 °C. After 10 min, it was quenched with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 5:1) to give **16e** (70.6 mg, 81% yield).

4-(2,3,4,5,6-Pentafluorophenylthio)-1,2,3-trimethoxybenzene 16e. 78%; pale yellow crystals; mp 43−44 °C (AcOEt−hexane). ^1H NMR δ: 3.84 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 6.61 (d, 1H, J = 9.0 Hz), 7.04 (d, 1H, J = 9.0 Hz). ^{19}F NMR δ: −162.34 (m, 2F), −153.89 (m, 1F), −133.79 (m, 2F). MS 366 (M^+, 100). HRMS. Calcd for $C_{15}H_{11}F_5O_3S$: 366.0365. Found 366.0349.

(12) Yoshimura, T.; Motoyama, A.; Morishige, A.; Tsukurimichi, E.; Shimasaki, C.; Hasegawa, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 174−180.

(13) Hamel, P.; Zajac, N.; Atkinson, J. G.; Girard, Y. *J. Org. Chem.* **1994**, *59*, 6372−6377.

(14) Jeng, H.-J.; Fang, J.-M. *J. Chin. Chem. Soc.* **1994**, *41*, 803−811.

(15) Nagata, T.; Fujimori, K.; Yoshimura, T.; Furukawa, N.; Oae, S. *J. Chem. Soc., Perkin. Trans. 1* **1989**, 1431−1435.

3-(2,3,4,5,6-Pentafluorophenylthio)-5-methoxy-2-methylindole 17a. 99%; colorless crystals; mp 149−150 °C (AcOEt−hexane). IR 3389 cm^{-1}. ^1H NMR δ: 2.60 (s, 3H), 3.87 (s, 3H), 6.79 (dd, 1H, J = 9.0, 2.0 Hz), 7.10−7.17 (m, 2H), 8.12 (brs, 1H). ^{19}F NMR δ: −162.35 (m, 2F), −154.82 (t, 1F, J = 21 Hz), −134.26 (m, 2F). MS 359 (M^+, 100). Anal. Calcd for $C_{16}H_{10}F_5NOS$: C, 53.48; H, 2.81; N, 3.90. Found: C, 53.55; H, 2.88; N, 3.91.

3-(2,3,4,5,6-Pentafluorophenylthio)-2,5-dimethylpyrrole 18a. 82%; colorless oil. IR 3375 cm^{-1}. ^1H NMR δ: 2.16 (s, 3H), 2.34 (s, 3H), 5.91 (s, 1H), 7.70 (brs, 1H). ^{19}F NMR δ: −162.68 (m, 2F), −155.52 (t, 1F, J = 21 Hz), −134.92 (m, 2F). MS 293 (M^+, 100). HRMS Calcd for $C_{12}H_8F_5NS$: 293.0298. Found: 293.0297.

Supporting Information Available: Characterization data for compounds not included in the Experimental Section, calculated structure for **2c**, crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **2d** and **2j**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001710Q