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Study on the α-Sulfenylation of 3-Sulfolenes

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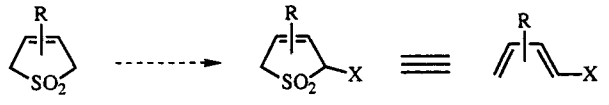
ABSTRACT

The reactions of 3-sulfolenes with PhSCl under basic conditions produce phenyl 1,3-butadienethiosulfonates **7a–d** *in low yields without the formation of 2-sulfenylated 3-sulfolenes* **8**. *Compounds* **7a–d** *can be prepared in high yields from 3-sulfolenes by the sequence of deprotonation, anionic cycloreversion, and phenylsulfenylation reactions.*

Substituted 3-sulfolenes are ideal precursors for the corresponding 1,3-dienes because of their satisfactory stability and the stereospecificity of the extrusion of SO_2 [1]. A general approach toward the synthesis of substituted 3-sulfolenes involves the reaction of an electrophile with a 3-sulfolenyl 2-carbanion generated *in situ* [2]. In this manner, electrophiles bearing carbon [3], silicon [4], and tin [5] can easily be introduced into the 2-position of 3-sulfolenes to give precursors for 1-substituted 1,3-dienes. Since heteroatom substituted 1,3-dienes are useful for the construction of functionalized six-membered carbocycles via Diels-Alder reactions [6], we were interested in investigating the possibility of α-substitution of 3-sulfolenes with heteroatoms such as oxygen, sulfur, and halogens (Equation 1).



1 **2** **3**

There are two general procedures for the α-alkylation of 3-sulfolenes. In one procedure, an electrophile (an alkyl iodide) and a 3-sulfolene are mixed at −78°C at first and a strong base, lithium hexamethyldisilazide (LiHMDS) is then added dropwise to the mixture. Thus, the 3-sulfolenyl-2-anion generated *in situ* can be reacted immediately with the electrophile to avoid anionic cycloreversion [3a]. In the other procedure, the 3-sulfolenyl-2-anion is generated with *n*-BuLi at −105°C, at which temperature the anion remains stable [3b]. The electrophile is then added to react with the anion. The second procedure is especially useful in cases where electrophiles contain acidic protons. However, the reaction of the 3-sulfolenyl anion with N-bromosuccinimide, N-chlorosuccinimide, 1-chlorobenzotriazole, or diphenyl disulfide by either procedure resulted in the recovery of starting materials, indicating that these electrophiles are perhaps not reactive enough. Also, the reaction with iodine, bromine, iodine chloride, MoOPH, or Davis' reagent [7] gave complex mixtures containing no desired product **2**.

The reaction of phenylsulfenyl chloride, PhSCl, with the 3-sulfolenyl-2-anion **5** generated from **4a** at −105°C *in situ* gave a complex mixture from which we could isolate, in addition to a large quantity of PhSSPh, compound **7a** as a meaningful product but in very low yield (Scheme 1). The desired product **8** ($R^1 = R^2 = H$) was not detected. The mass spectrum of **7a** shows no parent peak at *m/z* 226 but gives a distinct peak at *m/z* 162 (loss of SO_2). The absorption bands of the infrared spectrum (1321 and 1128 cm^{-1}) clearly indicate the presence of a $—SO_2—$ functionality. This compound gradually decomposed upon standing so that satisfactory elemental analyses could not be obtained. When PhSCl was reacted with other 3-sulfolenes **4b–d** in the presence of a strong base, similar products were obtained in low yields (Table 1).

The configuration at the $C_1—C_2$ double bond of **7a** was assigned *Z* based on its coupling constant being equal to 10.9 Hz. Presumably, products **7b–d** were formed by the same reaction mechanism,

Dedicated to Professor Yao-Zeng Huang on the occasion of his eightieth birthday.

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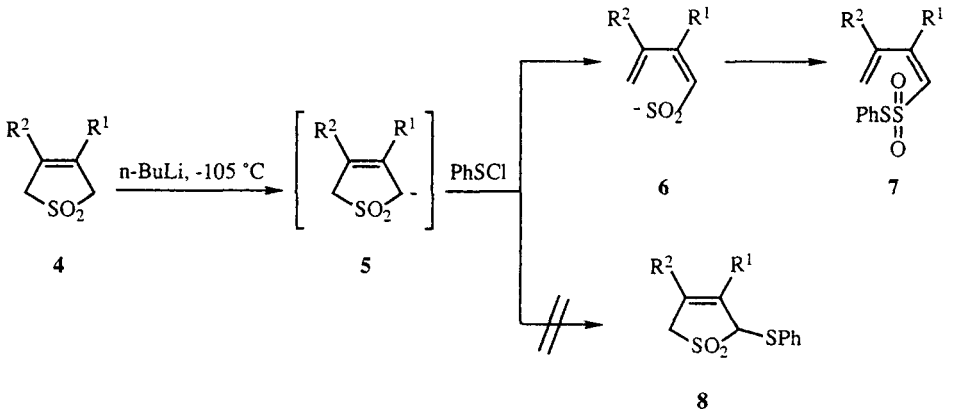


SCHEME 1

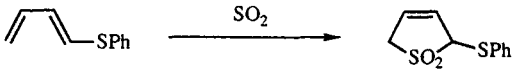
TABLE 1 Reactions of 3-Sulfolenes with PhSCl under Basic Conditions

Entry	*3-Sulfolene*		*Product and Yield*
1	$R^1 = R^2 = H$	**4a**	**7a** (13%)
2	$R^1 = Me$, $R^2 = H$	**4b**	**7b** (16%)
3	$R^1 = Et$, $R^2 = H$	**4c**	**7c** (9%)
4	$R^1 = R^2 = Me$	**4d**	**7d** (9%)

so that they are also assigned the *Z* configuration. This result is consistent with an early report that the anionic cycloreversion of 3-sulfolene at room temperature produces the corresponding Z-1,3-butadienesulfinate stereoselectively [8].

The mode of reaction shown in Scheme 1 giving the thiosulfonyl esters **7a–d** is rather unusual, since anionic cycloreversion has not been observed when 2-substitution reactions are carried out by the two procedures aforementioned [2]. It is speculated that the reaction between the 3-sulfolenyl anion and PhSCl might be very exothermic and that the local temperature in the reaction solution rose over −78°C to induce some cycloreversion. The main reaction products might have undergone rapid secondary reactions which produced diphenyl disulfide and a water-soluble material.

In order to have a better understanding of the stability of the possible primary product, 2-(phenylthio)-3-sulfolene **8** ($R^1 = R^2 = H$), we prepared it via an alternative route. The readily available diene **9** [9] was treated with SO_2 in a sealed tube at room temperature for 24 hours to give **8** in 63% yield (Equation 2). Although compound **8** seemed to be stable during the reaction as a solution in liquid SO_2, it decomposed to a dark-brown colored species within a few hours after chromatographic purification. The decomposition of **8** proceeded even when it was stored under N_2 in a freezer. When compound **8** was treated with the 3-sulfolenyl anion **5a** at −78°C for 10 minutes, no compound other than diphenyl disulfide could be isolated from the mixture. It is quite surprising to find a 3-sulfolene that is apparently less stable than the corresponding diene. These results suggest that compound **8** might have been produced as a primary product when the sulfolenyl anion **5a** was reacted with PhSCl. It is only because compound **8** was so unstable under the reaction conditions that we could not detect its formation.



9 8

Although compounds **7a–d** were produced only in low yields, they are 1-heteroatom substituted, 1,3-dienes, so they should be synthetically useful. It was therefore our aim to explore better procedures for their preparation. When 3-sulfolenes **4a–d** were treated with LiHMDS at room temperature, anionic cycloreversion reactions took place to give lithium butadienesulfinates **6a–d** [10]. It was found that **6a–d** could be treated with PhSCl to afford the desired products **7a–d** in good yields (Table 2).

Although the direct α-substitution of 3-sulfolenes with a sulfur atom did not proceed as we had originally anticipated, we were able to find conditions to prepare 1-heteroatom substituted 1,3-dienes **7a–d** in high yields. This is the first reaction where one could link a thiosulfonyl ester functionality at the 1-position of 1,3-dienes. Moreover, it is noteworthy that while thiosulfonyl esters are generally prepared by reacting metal thiolates with sulfonyl chlorides [12], our procedure illustrates that they can also be prepared by coupling metal sulfinates with sulfenyl chlorides.

TABLE 2 Reactions of Lithium 1,3-Dienylsulfinates with PhSCl

Entry	*Sulfinate*	*Product and Yield*
1	**6a**	**7a** (86%)
2	**6b**	**7b** (90%)
3	**6c**	**7c** (87%)
4	**6d**	**7d** (92%)

EXPERIMENTAL

General Methods

The NMR spectra were determined on a Bruker AC-200 spectrometer as solutions in $CDCl_3$. The IR spectra were determined on a Perkin-Elmer 882 spectrophotometer. Mass spectra were recorded on a VG 70-250S mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer. All reactions were carried out under an atmosphere of dry nitrogen.

Preparation of Butadienesulfonic Acid Phenyl Esters **7a–d**

Method A A hexane solution of *n*-BuLi (2M, 2 mmol) was added dropwise to a solution of 3-sulfolene **4a** (2 mmol) and hexamethylphosphoramide (HMPA, 8 mmol) in THF (10 mL) cooled at −105°C, and the mixture was stirred for 10 minutes. A solution of freshly prepared PhSCl (2 mmol) in THF (0.5 mL) was added slowly and the stirring continued for 10 minutes, whereupon EtOAc (2 mL) was added in one shot. The solvent was evaporated under reduced pressure, and the crude oil was eluted through a silica gel column (hexane/EtOAc, 1:1) to remove HMPA. Further purification by HPLC (LiChrosorb column, hexane/EtOAc, 9:1) afforded **7a**. Compounds **7b–d** were prepared from **4b–d**, respectively, by the same procedure. The yields of **7a–d** thus obtained are summarized in Table 1.

Method B A THF solution of lithium hexamethyldisilazide [LiHMDS (1.1 mmol) freshly prepared from hexamethyldisilazane and *n*-BuLi at 0°C to room temperature in THF (5 mL)] was added dropwise to a solution of **4a** (1 mmol) in THF (10 mL) cooled at −78°C. The reaction mixture was gradually warmed to room temperature and the stirring continued for another 2 hours, giving the sulfinate **6a**. A solution of freshly prepared PhSCl (1.1 mmol) in THF (1 mL) was slowly added, and the resulting mixture was stirred for 30 minutes. The excess of solvent was evaporated under reduced pressure, and the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 9:1) to give **7a**. Compounds **7b–d** were obtained from **4b–d**, respectively, by the same procedure. The yields of **7a–d** thus prepared are summarized in Table 2.

S-Phenyl-1,3-Butadienethiosulfonate **7a**

Colorless oil: IR (neat) 3062, 1621, 1338, 1321, 1128, 999, 938, 875, 747 cm^{-1}; ^1H NMR δ 5.30–5.50(m, 2H), 6.15(d, 2H, J = 10.9 Hz), 6.45–6.78(m, 2H), 7.03–7.52(m, 3H), 7.59–7.70(m, 2H); MS *m/z* 162(M^+—SO_2, 100%), 147, 129, 125, 109, 85. Anal calcd for $C_{10}H_{10}O_2S_2$: C, 53.07; H, 4.45. Found: C, 52.86; H, 4.05.

S-Phenyl-2-Methyl-1,3-butadienethiosulfonate **7b**

Colorless oil: IR (neat) 3041, 1636, 1289, 1124, 1108, 947, 842, 719 cm^{-1}; ^1H NMR δ 1.97 (s, 3H), 5.30(dt, 1H, J = 11.0, 1.0 Hz), 5.48(d, 1H, J = 17.2 Hz), 6.15(s, 1H), 6.86 (ddd, 1H, J = 17.2, 11.0, 0.8 Hz), 7.30–7.52(m, 3H), 7.58–7.67(m, 2H); MS *m/z* 176(M^+—SO_2, 100%), 161, 143, 125, 109, 99, 77. High resolution mass of $C_{11}H_{12}S$ requires 176.0659 found: 176.0665.

S-Phenyl-2-Ethyl-1,3-butadienethiosulfonate **7c**

Colorless oil: IR (neat) 3054, 1619, 1331, 1300, 1125, 938, 839, 745, 685 cm^{-1}; ^1H NMR δ 1.09(t, 3H, J = 7.4 Hz), 2.36(qd, 2H, J = 7.4, 1.0 Hz), 5.28(dt, 1H, J = 11.0, 1.0 Hz), 5.50(d, 1H, J = 17.6 Hz), 6.11(s, 1H), 6.84(ddd, 1H, J = 17.6, 11.0, 0.6 Hz), 7.30–7.51(m, 3H), 7.56–7.69(m, 2H); MS *m/z* 190(M^+—SO_2, 100%), 161, 129, 110, 97, 79. Anal calcd for $C_{12}H_{14}O_2S_2$: C, 56.67; H, 5.55. Found: C, 56.96; H, 5.61.

S-Phenyl-2,3-Dimethyl-1,3-butadienethiosulfonate **7d**

Colorless oil: IR (neat) 3058, 1640, 1598, 1334, 1313, 1124, 910, 827, 794, 748 cm^{-1}; ^{1}NMR δ 1.69(s, 3H), 1.95(s, 3H), 4.42(s, 1H), 4.83(s, 1H), 6.13(s, 1H), 7.40–7.60(m, 3H), 7.63–7.80(m, 2H); MS *m/z* 190(M^+—SO_2, 100%), 175, 157, 113, 79. High resolution mass of $C_{12}H_{14}S$ requires 190.0816; found: 190.0780. Anal. calcd for $C_{12}H_{14}O_2S_2$ = C, 56.67; H, 5.55. Found: C, 56.81; H, 5.76.

Preparation of 2-(Phenylthio)-3-sulfolene **8**

A solution of 1-(phenylthio)-1,3-butadiene **9** (1.3 mmol) [9] and diphenylamine (0.6 mmol) in liquid SO_2 (30 mL), contained in a sealed tube was stirred at room temperature for 24 hours. After the SO_2 was evaporated, saturated $NaHCO_3$ (5 ml) was added. The aqueous solution was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers

were dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 2:1) to give compound **8** in 63% yield as a colorless oil: IR (neat) 3071, 3032, 1576, 1306, 1126, 902 cm^{-1}; ^1H NMR δ 3.50(d, 1H, J = 14.0 Hz), 3.60(d, 1H, J = 14.0 Hz), 4.87(s, 1H), 5.95–6.20(m, 2H), 7.25–7.40(m, 3H), 7.56–7.70(m, 2H). Compound **8** decomposed readily upon standing so that its mass spectrum was not obtained.

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