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REACTIONS OF γ-SULTINES WITH ELECTROPHILIC REAGENTS. 4*. CHLORINATION OF 5-(4-METHOXYPHENYL)-3-PHENYL-1,2-OXATHIOLANE 2-OXIDE

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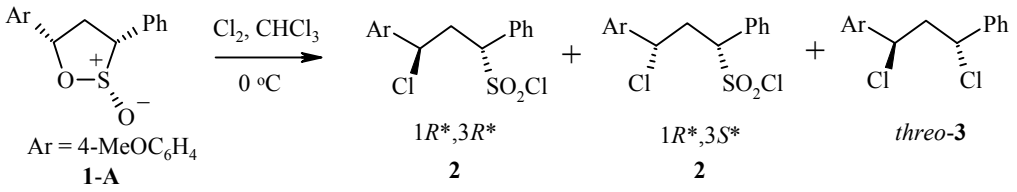
We have studied chlorination of 5-(4-methoxyphenyl)-3-phenyl-1,2-oxathiolane 2-oxide and we discuss possible mechanisms for this reaction.

Keywords: 1,3-diaryl-1,3-dichloropropanes, 1,3-diaryl-3-chloropropanesulfonyl chloride, diastereomers, 1,2-oxathiolane 2-oxides (γ-sultines), diastereoselectivity, chlorination.

We reported earlier [1] on the different behaviors of 3,5-diaryl-1,2-oxathiolane 2-oxides (γ-sultines) under chlorination conditions, depending on the nature of the aryl substituents. In this paper, we report on the results of chlorination of an asymmetrically substituted γ-sultine: 5-(4-methoxyphenyl)-3-phenyl-1,2-oxathiolane 2-oxide (**1**). The reactions of sultine **1** with chlorine and sulfuryl chloride were conducted under the same conditions as in [1]. Sultine **1** was used in the reaction both as a mixture of diastereomers **A-D** and as the pure *cis,cis* diastereomer **A** [2]. The progress of the reaction was monitored and the reaction mixture was analyzed as described in [1].

The reaction of diastereomer **A** of sultine **1** with a chlorine solution in chloroform at 0°C leads to formation of a 95% mixture of diastereomers (1*R**,3*R**):(1*R**,3*S**), 85:15, 3-chloro-3-(4-methoxyphenyl)-1-phenylpropanesulfonyl chloride (**2**) and 5% *threo*-1,3-dichloro-1-(4-methoxyphenyl)-3-phenylpropane (**3**) (see Table 1 and Scheme 1).

Scheme 1



* For Communication 3, see [1].

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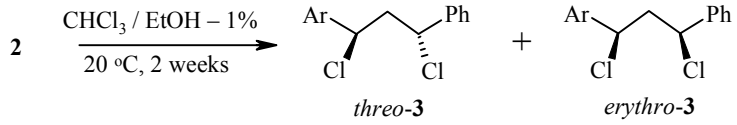
Subsequently holding the reaction mixture in chloroform containing 1% ethanol at 20°C for 2 weeks led to formation of a mixture of diastereomers of dichloride **3** (*threo*:*erythro* = 57:43) (see Scheme 2). Furthermore, in the ^{1}H NMR spectrum we observed signals for 3-chloro-1-ethoxy-1-(4-methoxyphenyl)-3-phenylpropane (**4**), a slight amount of which was formed.

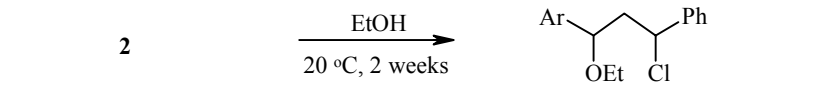
Scheme 2



threo-**3** *erythro*-**3**

Chlorination of the mixture of diastereomers **A-D** of sultine **1** under the same conditions leads to a similar result (see Table 1). Subsequently holding the reaction mixture for 1 week at 0°C led to formation of 88% equimolar mixture of diastereomers of sulfonyl chloride **2** and 12% equimolar mixture of diastereomers of dichloride **3** (Table 1). Holding the diastereomeric mixture of sulfonyl chloride **2** (1*R**,3*R**):(1*R**,3*S**) = 75:25 in ethanol at 20°C for 2 weeks led to an equimolar mixture of diastereomers of 3-chloro-1-ethoxy-1-(4-methoxyphenyl)-3-phenylpropane (**4**) (Scheme 3).

Scheme 3



1*R**,3*R** : 1*R**,3*S** = 75 : 25 1*R**,3*R** : 1*R**,3*S** = 47 : 53

4

From the results obtained it follows that chlorination of sultine **1** occurs stereoselectively. Using a substrate enriched in diastereomer **A** leads to preferential formation of (1*R**,3*R**)-sulfonyl chloride **2**, which is racemized on standing in solution and in this case decomposes to a mixture of diastereomers of dichloride **3**, while in the presence of excess ethanol it goes to ethoxy derivative **4**.

TABLE 1. Chlorination of γ-Sultine **1** by Chlorine and Sulfuryl Chloride at 0°C for 24 h

Diastereomeric composition of sultine **1**, %	Composition of reaction mixture, %	Stereochemical composition of reaction mixture, %
A, 100*	**2**; 95 **3**; 5	1*R**,3*R**:1*R**,3*S**, 85:15 *threo* 100
A:**B**:**C**:**D** = 55:32:11:2*	**2**; 97 **3**; 3	1*R**,3*R** :1*R**,3*S**, 75:25 *threo* 100
A:**B**:**C**:**D** = 55:32:11:2*, *[2]	**2**; 88 **3**; 6	1*R**,3*R**:1*R**,3*S**, 50:50 *threo:erythro*, 50:50
A, 100*[3]	**2**; 94 **3**; 6	1*R**,3*R**:1*R**,3*S**, 50:50 *threo:erythro*, 46:54
A:**B**:**C**:**D** = 86:4:8:2*[3]	**2**; 88 **3**; 12	1*R**,3*R**:1*R**,3*S**, 50:50 *threo:erythro*, 65:35

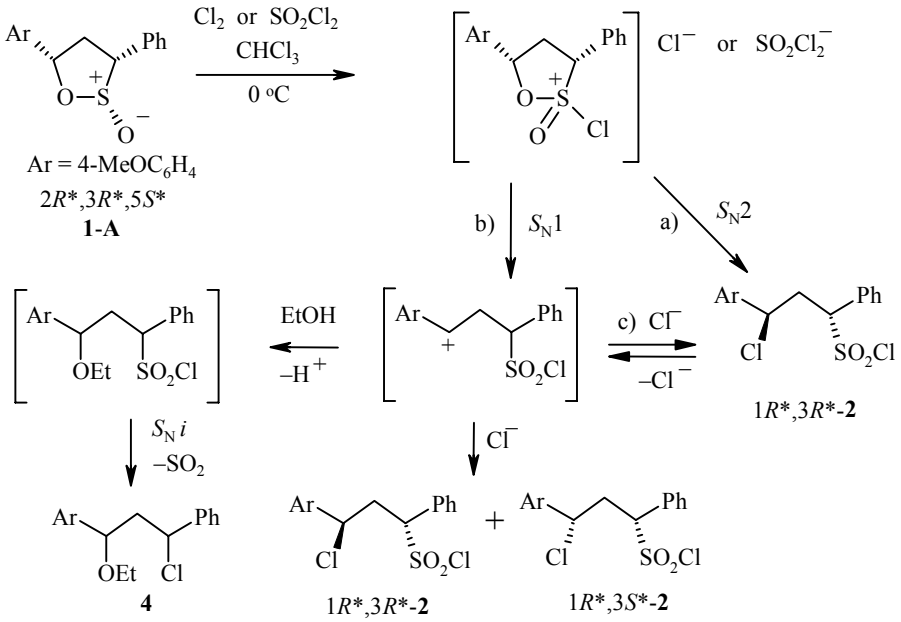
* Reagent = chlorine.

*[2] Reaction time = 1 week.

*[3] Reagent = sulfuryl chloride.

The reaction of sultine **1** with sulfuryl chloride under similar conditions occurs nonstereoselectively, with formation of an equimolar mixture of diastereomers of sulfonyl chloride **2** (see Table 1). The data obtained can be illustrated by Schemes 4 and 5.

Scheme 4



The reaction of sultine **1** with chlorine or sulfuryl chloride begins with electrophilic attack on the lone electron pair of the sulfur atom. The cationic cyclic intermediate formed can undergo nucleophilic attack at the $C_{(5)}$ atom (route *a*) or else ring opening can occur with formation of an open-chain stabilized carbocation of the anisyl type (route *b*). The direction of reaction *a*) suggests formation of sulfonyl chloride **2** with inversion of the configuration of the $C_{(5)}$ atom and retention of the configuration of the $C_{(3)}$ atom of the sultine ring. When diastereomer **A** of sultine **1** is used, which has the relative configuration (2*R**,3*R**,5*S**), direction *a*) leads to formation of the diastereomer (1*R**,3*R**)-**2**, as shown in Scheme 4. The data obtained allow us to hypothesize that the reaction with chlorine occurs stereoselectively along direction *a*), due to the sufficient nucleophilicity of the chloride anion and activity of the anisyl center in the nucleophilic substitution reaction. A fairly small amount of diastereomer (1*R**,3*S**)-**2** is formed, probably as a result of realization of the competing direction of reaction *b*), and also as a result of racemization of the initially formed diastereomer (1*R**,3*R**)-**2** along route *c*).

Scheme 5

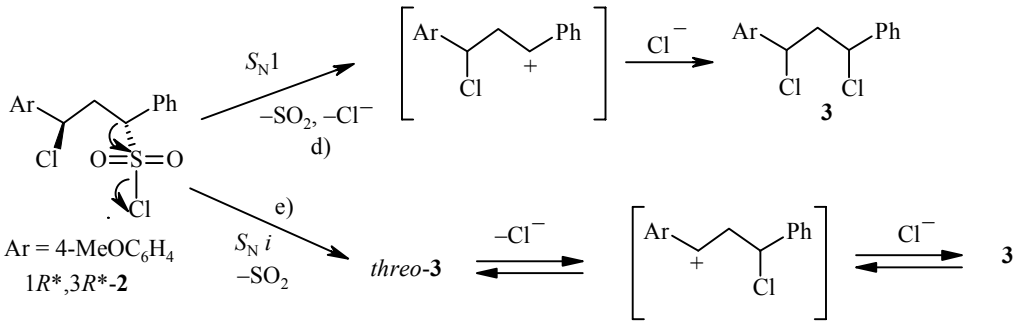


TABLE 2. ^{1}H NMR Spectra of Compounds **2** and **3**

Compound	Chemical shifts, δ, ppm (*J*, Hz)				
	CH_2	CHCl	CHS	CH_3O (3H, s)	CH_{Ar}
(1*R**,3*R**)-**2**	3.16* (1H); 3.35* (1H), $^{2}J_{AB}$ = 14.0	4.69 (1H, dd, $^{3}J_{AM}$ = 10.2, $^{3}J_{BM}$ = 5.8)	4.40 (1H, dd, $^{3}J_{AX}$ = 4.2, $^{3}J_{BX}$ = 10.0)	3.84	6.93 (2H, d); 7.18 (2H, d), ^{3}J = 8.8; 7.30-7.60 (5H, m)
(1*R**,3*S**)-**2**	2.90* (1H); 3.30* (1H), $^{2}J_{AB}$ = 14.4	5.16 (1H, dd, $^{3}J_{AM}$ = 11.6, $^{3}J_{BM}$ = 3.6)	4.55 (1H, dd, $^{3}J_{AX}$ = 2.8, $^{3}J_{BX}$ = 11.2)	3.81	6.90 (2H, d); 7.26 (2H, d), ^{3}J = 8.4; 7.30-7.60 (5H, m)
threo-**3**	2.71*^{2} (2H)	5.20*^{3} (2H)	—	3.82	6.90 (2H, d)
erythro-**3**	2.69*^{2} (1H); 3.00*^{2} (1H), $^{2}J_{AB}$ = 14.2	4.80 (1H, dd, $^{3}J_{AX}$ = 6.8, $^{3}J_{BX}$ = 8.4); 4.85 (1H, dd, $^{3}J_{AY}$ = $^{3}J_{BY}$ = 7.6)	—	3.83	6.92 (2H, d); 7.32 (2H, d); 7.33 (2H, d), ^{3}J = 8.8; 7.35-7.45 (10H, m)

* AB part of the ABMX system.
*^{2} AB part of the ABXY system.
*^{3} XY part of the ABXY system.

TABLE 3. ^{13}C NMR Spectra of Compounds **2** and **3**

Compound	Chemical shifts, δ, ppm					
	CH_2	CHCl	CHS	CH_3O	CH_{Ar}	C_{Ar}
(1*R**,3*R**)-**2**	40.00	58.60	78.71	55.47	114.66, 128.49, 129.51, 130.24, 130.79	129.36, 130.42, 160.37
(1*R**,3*S**)-**2**	39.88	59.64	79.63	55.47	114.39, 128.19, 129.58, 130.27, 130.75	129.09, 131.95, 160.15
3, *threo* + *erythro*	49.53, 49.62	60.22, 60.37, 60.80, 60.92	—	55.44	114.27, 114.32, 127.13, 127.15, 128.43, 128.49, 128.74, 128.82, 128.94, 128.95	132.24, 132.95, 140.29, 140.87, 159.85, 159.93

TABLE 4. ^{1}H NMR Spectra of Compounds **4** and **5**

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	CH_2	CHCl	CHO (**4**), CHS (**5**)	CH_3O	CH_3	CH_2O (**4**), CH_2N (**5**)	CH_{Ar}
(1*R**,3*R**)-**4**	2.31 (2H, m)*	5.23 (1H, dd, $^3J_{AM}$ = 4.0, $^3J_{BM}$ = 10.0)	4.56 (1H, dd, $^3J_{AX}$ = 4.0, $^3J_{BX}$ = 8.8)	3.81 (3H)	1.14 (3H, t, ^3J = 7.0)	3.37 (1H)*^{2}; 3.44 (1H), $^2J_{AB}$ = 9.4, $^3J_{AX}$ = $^3J_{BX}$ = 7.2	6.88 (2H, d); 6.89 (2H, d); 7.20 (2H, d)
(1*R**,3*S**)-**4**	2.25 (1H); 2.70 (1H), $^2J_{AB}$ = 14.4*	4.89 (1H, dd, $^3J_{AM}$ = $^3J_{BM}$ = 7.6)	4.05 (1H, dd, $^3J_{AX}$ = 5.6, $^3J_{BX}$ = 8.4)	3.81 (3H)	1.21 (3H, t, ^3J = 7.0)	3.14 (1H)*^{2}; 3.28 (1H), $^2J_{AB}$ = 9.4, $^3J_{AX}$ = $^3J_{BX}$ = 7.2	7.24 (2H, d); 7.30-7.40 (10H, m)
(1*R**,3*R**)-**5**	2.93 (1H); 3.14 (1H), $^2J_{AB}$ = 14.0*	4.75 (1H, dd, $^3J_{AX}$ = 9.6, $^3J_{BX}$ = 6.4)	3.83 (1H, dd, $^3J_{AM}$ = 4.8, $^3J_{BM}$ = 11.0)	3.82 (3H, s)	0.94 (6H, t, ^3J = 7.2)	2.87 (4H, br. q, ^3J = 7.2)	6.89 (2H, d); 7.19 (2H, d), ^3J = 8.8; 7.30-7.50 (5H, m)
(1*R**,3*S**)-**5**	2.73 (1H); 3.07 (1H), $^2J_{AB}$ = 14.4*^{3}	4.47 (1H, dd, $^3J_{AX}$ = 11.2, ^3J = 4.0); 4.49 (1H, dd, $^3J_{AY}$ = 3.6, $^3J_{BY}$ = 11.2)		3.79 (3H, s)	1.02 (6H, t, ^3J = 7.2)	2.99 (4H, br. q, ^3J = 7.2)	6.85 (2H, d); 7.23 (2H, d), ^3J = 8.8; 7.30-7.50 (5H, m)

* AB part of the ABMX system.
*^{2} AB part of the ABX_3 system.
*^{3} AB part of the ABXY system.

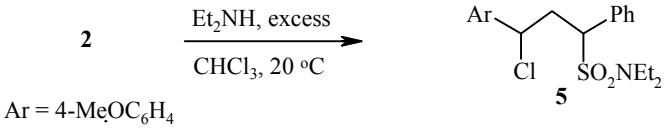
TABLE 5. ^{13}C NMR Spectra of Compounds **4** and **5**

Compound	Chemical shifts, δ, ppm							
	CH_2	CHCl	CHO (**4**) CHS (**5**)	CH_3O	CH_3	CH_2O (**4**) CH_2N (**5**)	CH_{Ar}	C_{Ar}
4 (1*R**,3*R**) + (1*R**,3*S**)	48.25, 48.63	60.33, 60.77	78.16, 78.93	55.40	15.44, 15.54	63.91, 64.32	114.03, 127.18, 127.32, 127.83, 128.00, 128.43, 128.49, 128.74, 128.79	135.55, 134.31, 141.34, 142.02, 159.30, 159.42
5 (1*R**,3*R**) + (1*R**,3*S**)	40.05, 40.37	59.96, 60.68	65.83, 66.35	55.43	14.84	42.52, 42.61	114.17, 114.34, 128.23, 128.61, 128.94, 129.03, 129.22, 129.16, 129.73, 129.88	131.77, 132.69, 133.04, 133.10, 159.83, 159.97

The reaction of sultine **1** with sulfuryl chloride probably preferentially proceeds along route *b*), due to the low nucleophilicity of SO_2Cl^- and facile formation of the carbocation.

Conversion of sulfonyl chloride **2** to dichloride **3** during holding of the solution can occur in two directions (see Scheme 5). Route *e*) is preferred, since it suggests formation of a more stable carbocation and initial formation of dichloride **3** only as the *threo* diastereomer, which was always observed in chlorination of sultine **1**. The presence of a carbocation of the anisyl type is also confirmed by the fact that compound **4** is obtained in the reaction of sulfonyl chloride **2** with ethanol (Scheme 4). We could not isolate sulfonyl chloride **2** individually because of its instability. When treated with excess diethylamine in chloroform at a temperature of 20°C, it was converted to the corresponding N,N-diethylsulfamide **5** as an equimolar mixture of diastereomers (Scheme 6).

Scheme 6



Thus chlorination of compound **1** by chlorine, in contrast to 3,5-bis(4-methoxyphenyl)-1,2-oxathiolane 2-oxide, occurs stereoselectively with formation of the corresponding sulfonyl chloride **2**, as in the case of chlorination of 3,5-diphenyl-1,2-oxathiolane 2-oxide [1]. The reaction of sultine **1** with sulfuryl chloride occurs nonstereoselectively and leads to formation of an equimolar mixture of diastereomers of sulfonyl chloride **2**.

EXPERIMENTAL

The ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were obtained on a Varian VXR 400 in $CDCl_3$ at 30°C. The IR spectra were obtained in a thin film on a UR-20 spectrophotometer.

5-(4-Methoxyphenyl)-3-phenyl-1,2-oxathiolane 2-Oxide (1) was obtained by reaction of the corresponding 1,2-diarylcyclopropane with sulfur dioxide according to the procedure in [2, 3].

Chlorination of Sultine 1 by Chlorine (General Procedure). A saturated solution of chlorine in chloroform was added with stirring to a solution of the sultine (0.3 mol) in chloroform (10 ml), cooled down to 0°C (the reaction time is indicated in Table 1). After the reaction was complete (monitored by TLC, Silufol support, eluent CCl_4–$CHCl_3$–ether, 4:1:1), the reaction mass was evaporated down and the reaction products were analyzed.

Chlorination of Sultine 1 by Sulfuryl Chloride (general procedure). A solution of sulfuryl chloride (1.4 mmol) in chloroform was added with stirring at 0°C to a solution of the sultine (0.7 mmol) in chloroform (10 ml). The reaction mixture was held at 0°C for 24 hours, then the mixture was evaporated down and analyzed.

(1*R,3*R**)/(1*R**,3*R**)-3-Chloro-3-(4-methoxyphenyl)-1-phenylpropanesufonyl Chloride (2)**, yield 88-97%, unstable oil. The ^1H and ^{13}C NMR spectra are given in Tables 2 and 3.

***threo/erythro*-1,3-Dichlo-1-(4-methoxyphenyl)-3-phenylropropane (3).** A solution of sulfonyl chloride **2** in chloroform was held at a temperature of 20°C for 2 weeks. The solvent was evaporated down and the residue was recrystallized from a 1:10 chloroform–pentane mixture. Grayish-white crystals with mp 81-38°C were obtained in 85% yield. Found, %: C 65.52; H 5.45. $C_{16}H_{15}Cl_2O$. Calculated, %: C 65.10; H 5.46. The ^1H and ^{13}C NMR spectra are given in Tables 2 and 3.

(1*R,3*R**)/(1*R**,3*S**)-3-Chloro-1-ethoxy-1-(4-methoxyphenyl)-3-phenylpropane (4).** A solution of sulfonyl chloride **2** in chloroform was mixed with excess ethanol at a temperature of 20°C and held for 2 weeks. After the solvent was removed, compound **4** was isolated as a yellow oil in 80% yield. Found, %: C 71.01; H 7.09. $C_{18}H_{21}ClO_2$. Calculated, %: C 70.93; H 6.94. ^{1}H NMR and ^{13}C NMR spectra are given in Tables 4 and 5.

(1*R,3*R**)/(1*R**,3*S**)-N,N-Diethyl-3-chloro-3-(4-methoxyphenyl)-1-phenylpropanesulfamide (5).** Excess diethylamine was added dropwise at a temperature of 20°C to a solution of sulfonyl chloride **2** in chloroform; this mixture was stirred for 5 h and then poured into cold acidified water and extracted with chloroform. The extract was washed with water until it tested neutral and then dried with $CaCl_2$. After the solvent was removed, compound **5** was isolated by reprecipitation with hexane as a viscous yellow-brown mass in 60% yield. Found, %: C 61.38; H 6.69. $C_{20}H_{26}ClNO_3S$. Calculated, %: C 60.67; H 6.62. IR spectrum (thin film), ν, cm^{-1}: 1333, 1140 (SO_2). The ^{1}H NMR and ^{13}C NMR spectra are given in Tables 4 and 5.

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