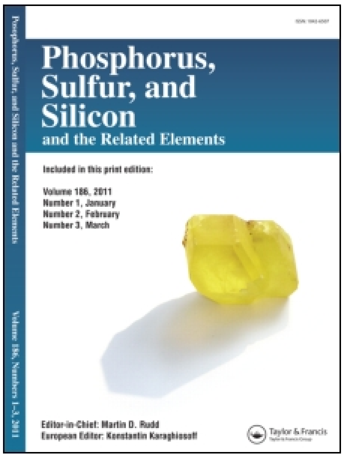

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A NOVEL SYNTHESIS OF THIONO-ESTER S-OXIDES BY SUBSTITUTION OF CHLORINE IN CHLOROSULFINES

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Communication

A NOVEL SYNTHESIS OF THIONO-ESTER S-OXIDES BY SUBSTITUTION OF CHLORINE IN CHLOROSULFINES

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Thiono-ester S-oxides, a rather neglected class of sulfines, can be readily obtained by nucleophilic substitution of chlorine in chlorosulfines by sterically demanding phenolates and alcoholates. The reaction occurs with predominant retention of the configuration of the starting chlorosulfine.

Key words: Chlorosulfines, nucleophilic displacement reactions, thiono-ester S-oxides, 1,3-dipolar cycloaddition reactions, thiadiazoline S-oxides.

INTRODUCTION

For the preparation of sulfines (thione S-oxides) several synthetic pathways are now available.[1,2] The most important routes to these sulfur-centered heterocumulenes are oxidation of thiocarbonyl compounds, alkylidenation of sulfur dioxide with α-silyl carbanions, and dehydrohalogenation of sulfinyl chlorides. With these methodologies a large variety of aromatic and aliphatic sulfines has been obtained.

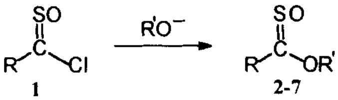
Chlorosulfines can be readily obtained by peracid oxidation of the corresponding thioacyl chlorides.[3,4] These substrates bearing a leaving group at the sulfine carbon atom are prone to give nucleophilic displacement reactions,[5,6] in particular the reaction with thiophenol leads to displacement of chlorine by a phenylthio substituent with predominant retention of configuration.[3]

RESULTS AND DISCUSSION

We report in this paper the preparation of sulfines derived from thiono-esters by substitution of the chlorine substituent in chlorosulfines by sterically demanding phenolates and *tert*-alcoholates. Recently, Metzner *et al.*[7] described the synthesis of sulfines by peracid oxidation of methyl thiono-esters. The methoxy sulfines thus obtained turned out to be rather unstable at room temperature, as they readily lose sulfur to give the corresponding carboxylic methyl esters. As a consequence, these sulfines were not obtained in the pure state, but admixed with the corresponding methyl carboxylates.

Three different chlorosulfines were used in this study. Phenyl-chlorosulfine **1a**,[3,8] phenylthio-chlorosulfine **1b**[3,9] and mesityl-chlorosulfine **1c**[4] were readily obtained by oxidation of the corresponding thioacyl chlorides with mCPBA.[10]

All displacement reactions were performed first by making the alkoxide or phenolate from the corresponding alcohol or phenol by treatment with *n*-butyllithium.



Then, the chlorosulfines **1** were added at −20°C. After 0.5 h of reaction, the products **2–7** were isolated by passing the crude reaction mixture through a short column of celite. Chromatography on silica gel or alumina was not always possible due to the limited stability of the products. The structure of the products could readily be deduced from IR, NMR and mass spectral data. The Z:E ratio of the sulfines was determined by ^{1}H NMR and LIS experiments, thereby relying on the configurational assignment of the related arylthio-sulfines derived from dithioesters.[3,12] The yields of the new oxysulfines and the ratio of Z and E isomers are compiled in Table I.

The substitution reaction of the Z and E isomers of phenyl-chlorosulfine **1a** with mesitol gave products **2-Z** and **2-E** in a ratio 7:1 and 1:9, respectively. This observation implies that the geometrical configuration of the starting chlorosulfine is predominantly retained during this displacement reaction. Attempted purification by

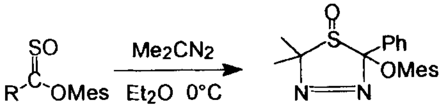
TABLE I

Chlorosulfine	Configuration of **1**	R^1	R	Thionoester S-Oxide	Yield (%)	*Z*/*E*
1a	*Z*	Mes$^{(a)}$	Ph	**2**	> 95	7/1
1a	*E*	Mes$^{(a)}$	Ph	**2**	> 95	1/9
1a	*Z*	t-Bu	Ph	**3**	83	3/1
1a	*E*	t-Bu	Ph	**3**	83	1/3
1b	*Z*	t-Bu	PhS	**4**	84	1/5$^{(c)}$
1b	*Z*	Mes$^{(a)}$	PhS	**5**	35	1/2$^{(c)}$
1c	*Z*/*E*=4/1	t-Bu	Mes	**6**	> 95	n. d.$^{(b)}$
1c	*Z*/*E*=4/1	Ph	Mes	**7**	79	n.d.$^{(b)}$

(a) 2,4,6-Trimethylphenyl.
(b) Not determined.
(c) See ref. 11

chromatography gave isomerization and considerable decomposition. After three days exposure to light at room temperature product **2** was partially degraded to the corresponding carboxylic ester.

Sulfine **2** reacted with 2-diazopropane to give the thiadiazoline **8** albeit in low yield (20%). This reaction substantiates the sulfine structure because such cycloaddition is typical for sulfines.[13] The low yield must be attributed to severe steric hindrance by the O—Mes group.



2 **8**

Similarly, the reaction of Z-**1a** and E-**1a** with *tert*-butyl alcohol gave product **3** with predominant retention of configuration. The reaction of Z-**1b** with *t*-butyl alcohol and with mesitol gave the expected products **4** and **5** in 84 and 35% yields, respectively. Also in this case the geometry of the starting sulfine is predominantly retained in the products.[11]

An isomeric mixture of **1c** was used in the reaction with *tert*-butyl alcohol and phenol to give products **6** and **7** whose configuration could not be assigned. Attempts were also made to react **1a,b,c** with lithium methoxide. This reaction did not give the methoxy sulfines, but in all cases the main product isolated was the corresponding carboxylic ester. We suggest that the initially formed methoxy sulfines readily lose sulfur.[7]

In conclusion, the reaction of chlorosulfines with phenol, mesitol and *tert*-butyl alcohol provides an easy access to new substituted oxysulfines. Kinetic stabilization by sterically demanding groups is clearly a prerequisite. It should be noted that these oxysulfines are much less stable than the corresponding sulfines derived from dithioesters. These results indicate that the displacement at sp^2 carbon atom in the chlorosulfine occurs with predominant retention of configuration. Such substitution reactions at a sp^2 center are not frequently encountered.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian Gemini 200 (200 MHz, FT) spectrometer with chloroform or TMS as internal standard. The LIS experiments were performed with $Eu(fod)_3$. IR spectra were recorded on a Perkin-Elmer mod 257 spectrophotometer. For mass spectroscopy a VG 7070 E spectrometer was used. Dry solvents were prepared as follows: diethy ether was pre-dried on calcium chloride and then distilled from calcium hydride, THF was distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride. BuLi was used as a stock solution of 1.6 M in hexane or in ether. All alcohols used as nuchleophiles were purified by distillation prior to use. The reactions were all carried out under an inert atmosphere of argon.

General Procedure

To a solution of phenol or alcohol (0.6 mmol) in THF, BuLi (0.6 mmol) was added at −40°C under protection from light. After stirring for 30 minutes the chlorosulfines **1a–c** (0.6 mmol) were added at −20°C. The temperature was lowered to −30°C and the reaction mixture was stirred for one hour. After concentration of the mixture the product was passed through celite with ether to remove the salts. Concentration of the solution gave the products **2–7**. The yields of the products are summarized in the table. The physical and spectral data of these compounds are as follows:

2-(Z): yellow oil; IR (CCl_4) 1060 (CSO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, *p*-Mes—CH_3, 3H), 2.32 (s, *o*-Mes-CH_3, 6H), 6.82 (s, Mes—H, 2H), 7.35–7.65 (m, Ph—H, 5H); δ (C_6D_6) 2.04 (s, *p*-Mes—CH_3, 3H), 2.25 (s, *o*-Mes-CH_3, 6H), 6.62 (s, Mes—H, 2H), 6.85–7.05 (m, Ph—H, 3H); MS (EI^+): m/e 272 (M^+), 256 (M^+-O), 240 (M^+-S), 135, (OMes), 105, 77. **2**-(E): yellow oil ^1H NMR ($CDCl_3$) δ 2.25 (s, *o*-Mes—CH_3, 6H), 2.30 (s, *p*-Mes—CH_3, 3H), 6.91 (s, Mes—H, 2H), 7.40–7.65 (*m*, (*m* + *p*)-Ar—H, 3H), 8.44–8.53 (dd, *J* = 8 Hz, 1.5 Hz, *o*-Ar—H, 2H). LIS experiment ($CDCl_3$ + Eu(fod)$_3$): **2**-(Z): ^1H NMR δ 2.39 (s, *o*-Mes—CH_3, 6H) $\Delta\delta$ = 0.07 ppm; **2**-(E): ^1H NMR δ 2.27 (s, *o*-Mes—CH_3, 6H) $\Delta\delta$ = 0.02 ppm

3-(Z), **3**-(E): yellow oil; IR (CCl_4) 3000–2850, 1370, 1140 (CSO) cm^{-1}. **3**-(Z): ^1H NMR ($CDCl_3$) δ 1.19 (s, $OC(CH_3)_3$, 9H), 7.15–7.60 (m, ArH, 5H). **3**-(E): ^1H NMR ($CDCl_3$) δ 1.44 (s, $OC(CH_3)_3$, 9H), 7.15–7.60 (m, ArH, 5H). MS (EI^+): m/e 210 (M^+), 194 (M^+-O), 153 (M^+-C_4H_9), 139, 121, 105, 89;

4-(Z), **4**-(E): yellow oil; IR (CCl_4) 3100–2850, 1330, 1130, 1080 (CSO), 1020 (CSO) cm^{-1}. **4**-(Z): ^1H NMR ($CDCl_3$) δ 1.36 (s, $OC(CH_3)_3$, 9H), 7.15–7.60 (m, ArH, 5H). **4**-(E): ^1H NMR ($CDCl_3$) δ 1.42 (s, $OC(CH_3)_3$, 9H), 7.15–7.60 (m, ArH, 5H). MS (EI^+): m/e 242 (M^+), 224 (M^+-O), 185 (M^+-C_4H_9), 170, 154, 134, 121, 109. LIS experiment ($CDCl_3$ + Eu(fod)$_3$): **4**-(Z): ^1H NMR δ 1.42 (s, $OC(CH_3)_3$, 9H) $\Delta\delta$ = 0.07 ppm; **4**-(E): ^1H NMR δ 1.62 (s, $OC(CH_3)_3$, 9H) $\Delta\delta$ = 0.21 ppm.

5-(Z), **5**-(E): yellow oil; IR (CCl_4) 1080, 1020 (CSO) cm^{-1}. **5**-(Z): ^1H NMR ($CDCl_3$) δ 2.10–2.38 (m, Mes CH_3, 9H), 6.85–6.90 (m, Mes H, 2H), 7.00–7.75 (m, ArH, 5H). **5**-(E): ^1H NMR ($CDCl_3$) δ 2.10–2.38 (m, Mes CH_3, 9H), 6.78–6.83 (m, Mes H, 2H), 7.00–7.75 (m, ArH, 5H). MS (EI^+): m/e 304 (M^+), 224 (M^+-O), 185 (M^+-C_4H_9), 153, 135, 119, 109.

6: yellow oil; IR (CCl_4) 3000–2840, 1610, 1370, 1140, 1070 (CSO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, $C(CH_3)_3$, 9H), 2.20–2.40 (m, $MesCH_3$, 9H), 6.70–6.90 (bs, MesH, 2H); MS (EI^+): m/e 236 (M^+-O), 179 (M^+-O-C_4H_9), 163, 147, 119. The presence of only one signal for the *t*-Butyl group reveals that only one product is formed. No configuration assignment was possible.

7: yellow oil; IR (CCl_4) 3050–2840, 1340, 1180, 1150, 1070 (CSO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19–2.50 (m, $MesCH_3$, 9H), 6.79–7.33 (m, ArH, 7H); MS (EI^+): m/e 256 (M^+-O), 239 (M^+-O-CH_3-2H), 225 (M^+-SO), 192, 163, 147. No LIS experiment was performed and the ^1H-NMR spectrum was too complicated to obtain the E:Z ratio.

8: A large excess of freshly prepared 2-diazopropane (dissolved in ether) was added to **2** (263 mg, 0.97 mmol). This mixture was kept at 0°C. When no gas escaped anymore from the mixture, this was put in the refrigerator overnight. The reaction mixture was filtered and concentrated in vacuo. The crude was purified by chromatography (Fluorisil, petroleum ether:ether 1:2) giving **8** (67 mg, 0.195 mmol, 20%). IR ($CHCl_3$) 1080 (CSO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, CH_3, 3H), 2.00 (s, CH_3, 3H), 2.42 (s, *o*-Mes—CH_3, 6H), 6.64 (s, Mes—H, 2H), 7.10–7.30 (*m*, (*m* + *p*) Ar-H, 3H), 7.40–7.45 (d, *J* = 8.5 Hz, *o*-ArH, 2H); MS (EI^+): m/e 342 (M^+), 294 (M^+-SO), 266 (M^+-SO-N_2), 136 (MesOH), 131, 129, 121, 105, 91.

Exposure of (Mesitoxy)phenylsulfine **2** *to light*: In situ prepared **2** (0.58 mmol) was exposed to light of a normal lamp for three days. The mixture was separated by chromatography (petroleum ether:ether 9:1) yielding the corresponding ester (mesitylbenzoate, 32.5 mg, 25%) mesitol (12 mg, 16%) and the unreacted sulfine (E and Z mixture).

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10. ^{1}H NMR analyses of **1b** showed that only one stereoisomer is present, but it is not possible to establish with certainty which isomer, E or Z, is present (Reference 9). On the basis of the results obtained by us in the reactions of **1b** with RO^- which yield mostly the E isomers (see in the text), we suggest the Z configuration for **1b** (Reference 11).
11. Note that in these products, because of the priority rules, the E configuration corresponds with the Z configuration of the starting material.
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