Reactions of 4-chloromethyl-1,3,2-dioxathiolane 2-oxides with sodium phenoxide. A reinvestigation

*Z. A. Bredikhina, A. V. Pashagin, and A. A. Bredikhin**

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center of the Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420088 Kazan, Tatarstan, Russian Federation. Fax: +7 (843 2) 75 2253. E-mail: baa@iopc.kcn.ru

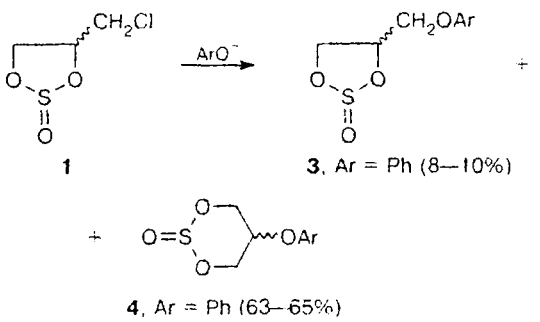
The reactions of 4-chloromethyl-1,3,2-dioxathiolane 2-oxides with PhONa in EtOH are accompanied by ring opening under the action of the ethoxide ion rather than leading to a rearrangement of the starting molecule as has been assumed previously. Under conditions precluding competition with other nucleophiles, the phenoxide anion smoothly replaces the chlorine atom in chloromethyl-substituted cyclic sulfites.

Key words: cyclic sulfites, nucleophilic substitution, sodium phenoxide, ethoxide anion.

In 1988, it was demonstrated[1] that cyclic esters of sulfurous and sulfuric acids (cyclic sulfites and sulfates, CSS) behave analogously to epoxides. The study cited was followed by a large number of investigations of the properties and applications of CSS (for reviews, see Refs 2—5). However, 4-chloromethyl-1,3,2-dioxathiolane 2-oxide (**1**) and 2,2-dioxide (**2**), which can be considered as synthetic equivalents of epichlorohydrin, are poorly studied. Apparently, this is due to the anomalous behavior ascribed to chloromethylsulfite **1** in reactions with nucleophiles.

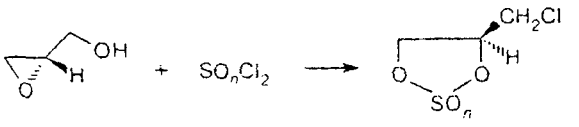
Previously, it has been reported[6] that the reaction of sulfite **1** with the phenoxide anion was accompanied by a rearrangement leading to a mixture of phenoxy-substituted cyclic sulfites **3** and **4** with symmetrical six-membered sulfite **4** substantially predominating (Scheme 1).

Scheme 1



In the reviews of the chemistry of CSS[2—4] with reference to the original study,[6] this anomaly was particularly emphasized because the final product prevailing in this process has lost the chirality inherent in starting compound **1**. As a result, this reaction holds no promise in enantioselective synthesis.

Recently, we have developed a new procedure for the preparation of cyclic sulfites **1** and sulfates **2** from scalemic glycidol with retention of the configuration of the starting chiral center in the final products.[7]



1 (n = 1)
2 (n = 2)

Hence, we decided to return to the previous study[6] and to reveal the scope of the reaction shown in Scheme 1.

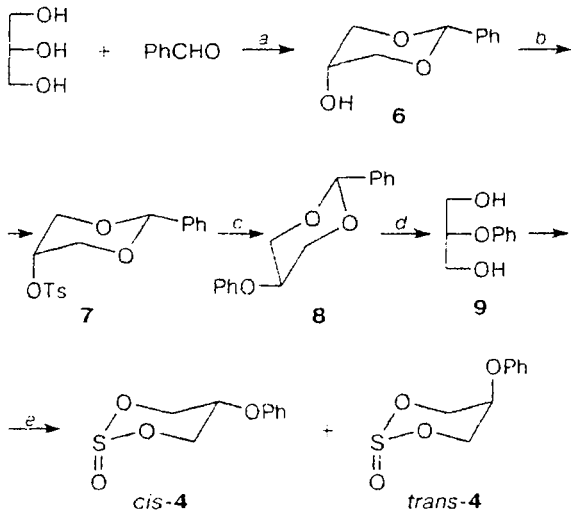
When reproducing the reaction conditions reported in the study cited[6] (the reaction of a mixture of diastereomers of *rac*-**1** with sodium phenoxide in anhydrous EtOH), we did not detect 1,3,2-dioxathiane **4** at all and obtained *rac*-3-phenoxypropane-1,2-diol (**5**) as the major product (~45%). In addition, we identified diethyl sulfite (~20%), glycidol, phenol, the starting sulfite **1**, and traces of phenoxymethylsulfites **3** in a complex mixture of reaction products. A mixture of diastereomers of *rac*-**3** was obtained from diol **5** and $SOCl_2$. Both the physical properties of the final product and its IR spectrum (see the Experimental section) differ from those reported previously[6] for sulfite **3**.

To draw an unambiguous conclusion, we synthesized diastereomeric sulfites **4** according to Scheme 2.

Published in *Izvestiya Akademii Nauk, Seriya Khimicheskaya*, No. 10, pp. 1774—1777, October, 2000.

1066-5285/00/4910-1753 $25.00 © 2000 Kluwer Academic/Plenum Publishers

Scheme 2



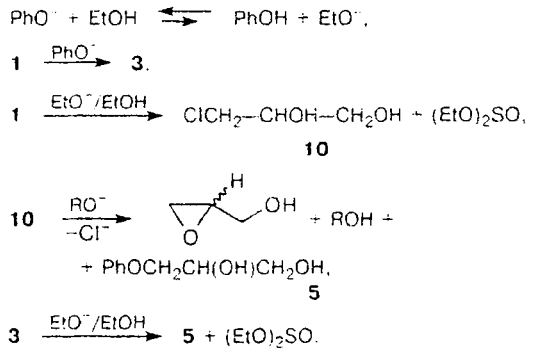
Reagents: *a*. H^+; *b*. TsCl, Py; *c*. PhOH, KOH/H_2O, MeCN; *d*. H^+, H_2O; *e*. $SOCl_2$, CH_2Cl_2.

The structures of the resulting six-membered sulfites **4** were confirmed by X-ray diffraction analysis. Both the individual isomers **4** and their mixture are crystalline compounds (rather than liquids, as has been reported previously[6]). The IR spectra of these compounds are also inconsistent with those reported previously.

All the aforesaid gave grounds to state that the data[6] presented in Scheme 1 and cited in the reviews (Refs. 2—4) are erroneous and the reaction of chloromethylsulfite **1** with the phenoxide anion is not accompanied by a rearrangement.

It should be noted that at least two nucleophiles, *viz.*, PhO^- and EtO^-, are present simultaneously in the reaction mixture under the conditions used in the paper cited.[6] (Apparently, free EtOH and PhOH may be ignored because a control experiment, *viz.*, prolonged refluxing of *rac*-**1** in pure EtOH or in EtOH containing dissolved PhOH, was not accompanied by noticeable losses of the starting sulfite.) A detailed study of all reactions proceeding under these conditions was not the aim of the present study. However, the products identified in the resulting mixture suggest that the reaction of the PhO^- anion with the substrate (the starting sulfite **1** and its derivatives) involves attacks predominantly on the C atom of the terminal chloromethyl fragment, while the harder EtO^- anion attacks predominantly the S atom of the sulfite fragment in the initial sulfite **1** and the newly formed sulfite **3**. In the presence of RO^- as bases, 3-chloropropane-1,2-diol (**10**) produced in the former reaction is converted into glycidol, whereas the irreversible consumption of alkoxides in this process is responsible for the appearance of free PhOH and the retention of the initial sulfite **1** (Scheme 3).

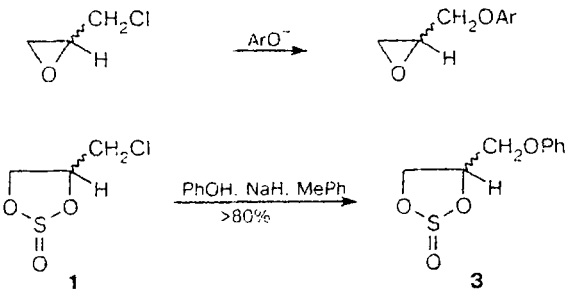
Scheme 3



To avoid the above-mentioned complications, we carried out the reaction of chloromethylsulfite **1** with PhONa under conditions precluding the presence of other reactive nucleophiles. The reaction was performed in toluene. Phenoxide was generated from phenol under the action of metallic Na or NaH. In both cases, phenoxymethylsulfite **3** was isolated as the only reaction product. The reaction performed with the use of sodium hydride afforded the final product with a higher purity and in substantially higher yield.

Therefore, the assumption of the anomalous behavior of sulfite **1** in reactions with nucleophiles is erroneous. Under appropriate conditions, compound **1** behaves analogously to epichlorohydrin to give replacement products of the Cl atom (Scheme 4).

Scheme 4



Experimental

The IR spectra were recorded on UR-20 and Bruker Vector-22 spectrometers. The NMR spectra were measured on Varian VM-250 (250.2 MHz for ^1H) and Bruker MSL-400 (100.6 MHz for ^{13}C) spectrometers in $CDCl_3$ with Me_4Si as the internal standard. TLC was carried out on Silufol plates.

4-Chloromethyl-1,3,2-dioxathiolane 2-oxides (1). A solution of racemic glycidol (7.47 g, 100 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of $SOCl_2$ (12.0 g, 100 mmol) in dry CH_2Cl_2 (30 mL) at −10 to 0 °C. The reaction

mixture was stirred for 1 h with a gradual increase in the temperature to ~20 °C. Then the mixture was refluxed for 30 min and cooled. The solvent was distilled off under reduced pressure. The residue was twice distilled *in vacuo*. Racemic sulfites **1** were obtained as a mixture of *cis* and *trans* diastereomers in a yield of 13.5 g (89%); b.p. 68—69 °C (1.0 Torr), n_D^{20} 1.4840. Other characteristics were reported previously [7]

Reaction of 4-chloromethyl-1,3,2-dioxathiolane 2-oxide (1) with sodium phenoxide in ethanol. Metallic Na (1.15 g, 50 mg-at.) was added to anhydrous EtOH (25 mL) in such a way as to maintain uniform boiling of the mixture. A solution of freshly distilled PhOH (4.7 g, 50 mmol) in toluene was added to the resulting solution of EtONa at ~100 °C. Then sulfite **1** (7.9 g, 50 mmol) was added dropwise with stirring and the reaction mixture was heated for 1 h. The precipitate that formed was immediately filtered off and washed with anhydrous EtOH. The filtrate was concentrated *in vacuo*, the residue was distilled, and the following fractions were collected: 1) 2.3 g, b.p. 45—60 °C (10 Torr), n_D^{20} 1.4250; 2) 1.2 g, b.p. 70—77 °C (10 Torr), n_D^{20} 1.5120; 3) 0.7 g, b.p. 77—85 °C (10 Torr), n_D^{20} 1.4985; and 4) 5.0 g, b.p. 120—122 °C (0.05 Torr), n_D^{20} 1/5250. After repeated fractionation of the first fraction, **diethyl sulfite** was isolated in a yield of 1.4 g (20%), b.p. 50—51 °C (10 Torr), n_D^{20} 1.4160 (*cf.* lit. data[8]: b.p. 53—54 °C (13 Torr), n_D^{25} 1.4130). According to the data from ^{1}H NMR spectroscopy, the second and third fractions contained diethyl sulfite, glycidol, phenol, and sulfite **1**. The fourth fraction crystallized upon storage. After recrystallization from CCl_4, **3-phenoxypropane-1,2-diol (5)** was isolated in a yield of 4.5 g (45%), m.p. 50—51 °C (*cf.* lit. data[9]: m.p. 53—54 °C). ^{1}H NMR ($CDCl_3$), δ: 3.54 (br.s, 1 H, OH); 3.66—3.88 (m, 3 H, C<u>H</u>—C<u>H</u>$_2$OH); 3.95 (d, 2 H, PhOC<u>H</u>$_2$, J = 5.3 Hz); 4.06 (br.s, 1 H, OH); 6.75—7.37 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 63.54 (CH_2); 68.84 (CH_2); 70.45 (CH); 114.44 (*o*-CH); 121.05 (*p*-CH); 129.34 (*m*-CH); 158.30 (*i*-C). IR, ν/cm^{-1}: 1580, 1590 (Ph), 3070 (C_{Ar}—H), 3300 (OH).

4-Phenoxymethyl-1,3,2-dioxathiolane 2-oxides (3). *A.* A solution of $SOCl_2$ (2.2 g, 18.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise with stirring and cooling (−30 °C) to a solution of diol **5** (3.1 g, 18.4 mmol) in CH_2Cl_2 (25 mL). Then the reaction mixture was stirred for 30 min and the temperature was gradually increased to ~20 °C. The solvent was removed *in vacuo* and the residue was distilled. Isomeric sulfites **3** (according to the NMR data, the *trans* : *cis* ratio was ~1 : 1) were isolated in a yield of 3.5 g (90%), b.p. 112—114 °C (0.07 Torr), n_D^{20} 1.5390. The mixture crystallized upon storage, m.p. 59—64 °C (*cf.* lit. data[9]: *trans*-**3**, m.p. 66—67 °C; *cis*-**3**, m.p. 57—58 °C). IR, ν/cm^{-1}: 965, 1050, 1180, 1220, 1250 (C—O, S—O, S=O), 1500, 1590, 1600 (Ph), 3050, 3070 (C_{Ar}—H). ^{1}H NMR ($CDCl_3$), δ: 3.88 (d, ~1 H, C<u>H</u>$_2$OPh, *trans*-**3**, J = 6 Hz); 4.15—4.77 (m, ~3.5 H, CH_2OS, CH_2OPh-*cis*-**3**, CH-*cis*-**3**); 4.83—5.18 (m, ~0.5 H, CH-*trans*); 6.83—7.40 (m, 5 H, Ph). ^{13}C NMR (CCl_4), δ: 66.27 (<u>C</u>H$_2$OPh, *trans*-**3**); 67.98 (OCH_2, *trans*-**3**); 68.36 (<u>C</u>H$_2$OPh, *cis*-**3**); 69.18 (CH_2O, *cis*-**3**); 77.71 (CHO, *trans*-**3**); 79.85 (CHO, *cis*-**3**); 114.54 (*o*-CH); 121.45 (*p*-CH); 129.34 (*m*-CH); 157.82 (*i*-C) (*cf.* Ref. 10).

B. A solution of phenol (1.88 g, 20 mmol) in toluene (4 mL) was added dropwise with stirring to a warm suspension of NaH (0.48 g, 20 mmol) in toluene (4 mL) and the mixture was refluxed for 30 min. A solution of sulfite **1** (3.13 g, 20 mmol) in toluene (4 mL) was added to the resulting paste. The mixture was stirred for 1 h with heating and kept overnight. Then the precipitate was filtered off and washed with toluene. The combined filtrates were concentrated *in vacuo* and the residue was distilled to give a mixture of sulfites **3** in a yield of 3.42 g (80%), b.p. 105—107 °C (0.05 Torr), n_D^{20} 1.5370. The spectral characteristics are identical with those reported previously.

C. Metallic Na (0.23 g, 10 mg-at.) was added to a solution of phenol (0.94 g, 10 mmol) in toluene (50 mL) and the mixture was refluxed until the precipitate dissolved completely. Then sulfite **1** was added (1.58 g, 10 mmol) and the mixture was refluxed for 1 h. Sulfite **3** was isolated as described in procedure *B* in a yield of 0.9 g (42%), b.p. 105—107 °C (0.05 Torr), n_D^{20} 1.5380.

***cis*-5-Hydroxy-2-phenyl-1,3-dioxane (6)** was prepared according to a procedure reported previously,[11] m.p. 81—82 °C (*cf.* lit. data[11]: m.p. 83 °C).

***cis*-2-Phenyl-5-(*p*-toluenesulfonyloxy)-1,3-dioxane (7)** was prepared according to a procedure reported previously,[11] m.p. 124—125 °C (*cf.* lit. data[11]: m.p. 125.5—126.5 °C).

***trans*-5-Phenoxy-2-phenyl-1,3-dioxane (8).** A solution of powdered KOH (5.9 g, 105 mmol) in a minimum amount of water was added to a solution of phenol (8.5 g, 90 mmol) in anhydrous MeCN (35 mL) and the reaction mixture was heated to boiling. Then tosylate **7** (10 g, 30 mmol) was added and the mixture was refluxed for ~40 h until the tosylate was completely consumed (TLC control). After removal of the solvent *in vacuo*, the residue was partitioned between a 2 : 1 ether+CH_2Cl_2 mixture and water. The organic phase was washed three times with 2 *M* NaOH and dried with Na_2SO_4. Then the mixture was concentrated. The residue that crystallized was washed with methanol and dioxane **8** was obtained in a yield of 4.5 g (60%), m.p. 83—84 °C. Found (%): C, 74.73; H, 6.03. $C_{16}H_{16}O_3$. Calculated (%): C, 75.0; H, 6.25. ^{1}H NMR ($CDCl_3$), δ: 3.67—4.06 (m, 2 H, CH_2); 4.43—4.70 (m, 3 H, $CHCH_2$); 5.57 (s, 1 H, CHPh); 6.93—7.57 (m, 10 H, Ph).

2-Phenoxypropane-1,3-diol (9). A suspension of dioxane **8** (1.2 g, 4.7 mmol) in 1 *M* HCl (10 mL) was stirred at 80 °C for 1 h, crystals of **8** being completely dissolved. The mixture was cooled to ~20 °C, neutralized with NH_4OH, and extracted with an ether+CH_2Cl_2 mixture. The extract was dried with $MgSO_4$, the solvent was removed, and the remaining oil was dissolved in a minimum amount of CCl_4 with heating. After cooling, propanediol **9** precipitated in a yield of 0.6 g (77%); m.p. 71—72 °C. ^{1}H NMR ($CDCl_3$), δ: 2.60 (s, 2 H, OH); 3.88 (br.d, 4 H, CH_2, J = 4 Hz); 4.33—4.53 (m, 1 H, CH); 6.77—7.40 (m, 5 H, Ph).

5-Phenoxy-1,3,2-dioxathiane 2-oxides (4). A solution of $SOCl_2$ (0.3 g, 2.5 mmol) in CH_2Cl_2 (2 mL) was added with stirring to a solution of diol **9** (0.4 g, 2.4 mmol) in CH_2Cl_2 (10 mL) at −30 °C. The reaction mixture was stirred for 30 min and warmed to ~20 °C. The solvent was removed *in vacuo*. Isomeric sulfites **4** were isolated with a *cis* : *trans* ratio of 1 : 3 in a yield of 0.5 g (97%), m.p. 49—56 °C. Found (%): C, 52.63; H, 4.72; S, 15.97. $C_9H_{10}O_4S$. Calculated (%): C, 52.94; H, 4.90; S, 15.69. Column chromatography on silica gel (40/100 μ) (column 180×20 mm, a 15 : 1 heptane—CH_2Cl_2 mixture as the eluent) of the mixture of diastereomers (0.2 g) gave *cis*-**4** (R_f 0.49, CH_2Cl_2) in a yield of 20 mg, m.p. 63 °C. IR (CCl_4), ν/cm^{-1}: 994, 1203, 1236 (C—O, S—O, S=O), 1493, 1551, 1600 (Ph), 2895, 2928, 2961, 3050 (C—H). ^{13}C NMR ($CDCl_3$), δ: 59.18 (CH_2); 65.75 (CH); 115.36 (*o*-CH); 122.19 (*p*-CH); 129.52 (*m*-CH); 155.80 (*i*-C). ^{1}H NMR ($CDCl_3$), δ: 4.12—4.20 (m, 1 H, CH); 4.63—4.78 (m, 4 H, CH_2); 6.90—7.34 (m, 5 H, Ph). Further elution afforded *trans*-**4** (R_f 0.38, CH_2Cl_2) in a yield of 110 mg, m.p. 72 °C. IR (CCl_4), ν/cm^{-1}: 1020, 1120, 1194, 1239 (C—O, S—O, S=O), 1495, 1599 (Ph), 2900, 2949, 3043 (C—H). ^{13}C NMR ($CDCl_3$), δ: 57.53 (CH_2); 68.29 (CH); 116.20 (*o*-CH); 122.12 (*p*-CH); 129.57 (*m*-CH); 155.62 (*i*-C).

^{1}H NMR ($CDCl_3$), δ: 3.92 (dt, 2 H, CH_2, J = 12.0 and 1.4 Hz); 4.14 (pseudoquint, 1 H, CH, J = 1.4 Hz); 4.88 (dd, 2 H, CH_2, J = 12.0 and 1.4 Hz); 6.76—7.22 (m, 5 H, Ph).

We thank O. N. Kataeva, A. T. Gubaidullin, and I. A. Litvinov for performing X-ray diffraction studies of some compounds reported in this work.

References

1. Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538.
2. G. W. Fischer and T. Zimmermann, in *Comprehensive Heterocyclic Chemistry*, Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, vol. **6**, p. 851.
3. B. B. Lohray, *Synthesis*, 1992, 1035.
4. B. B. Lohray and V. Bhushan, *Adv. Heterocyclic Chem.*, 1997, **68**, 89.
5. H. C. Kolb, M. S. Van Nieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
6. D. Ben-Ishay, *J. Org. Chem.*, 1958, **23**, 2013.
7. (a) A. A. Bredikhin, S. N. Lazarev, A. V. Pashagin, and Z. A. Bredikhina, *Mendeleev Commun.*, 1999, **9**, 236; (b) A. A. Bredikhin, A. V. Pashagin, Z. A. Bredikhina, S. N. Lazarev, A. T. Gubaidullin, and I. A. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1586 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 1575 (Engl. Transl.)].
8. *Beilst.*, **1** (4), 1324.
9. C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 1975, 190.
10. G. W. Buchanan and D. G. Hellier, *Can. J. Chem.*, 1976, **54**, 1428.
11. O. E. Van Lohuizen and P. E. Verkade, *Rec. Trav. Chim.*, 1959, **78**, 460.

Received February 16, 2000;
in revised form May 6, 2000