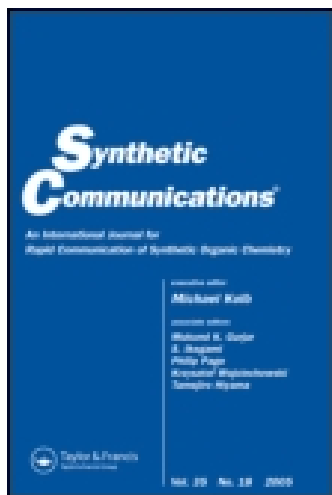


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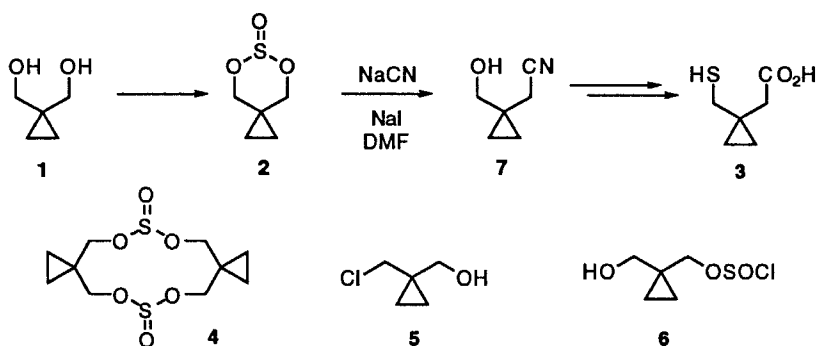
**PREPARATION OF CYCLIC SULFITES BY TRANSESTERIFICATION
OF DIOLS AND DIISOPROPYL SULFITE**

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Abstract: Cyclic Sulfites of 1,2-, 1,3- and 1,4-diols can be prepared in high yield by acid or base catalyzed transesterification with diisopropyl sulfite.

Cyclic sulfites of 1,2- and 1,3- diols have seen increasing use in organic chemistry.¹ This moiety, together with the derived cyclic sulfate, allows selective monofunctionalization by a nucleophile. Recently, we encountered the diol **1** which we wanted to convert to the cyclic sulfite **2** *en route* to the thiol-acid side chain **3** of the LTD₄ antagonist MK-476.² Typical procedures employing thionyl chloride and base led to production of a complicated mixture of **2** and the byproducts **4** and **5**. Although, it was clear that the dimer was thermodynamically disfavored, all attempts to eliminate **4** at high dilution failed. We conjectured that the highly reactive³ sulfonyl chloride intermediate **6** must be responsible for the kinetic dimerization. We thought that it should be possible to prepare **2** by acid or base catalyzed transesterification of diol **1** with a simple sulfite diester (eq. 1).⁴ In this approach, **5** would not be formed due to the absence of chloride; the highly reactive **6** would also be avoided.



Our initial work using 1 mol% methanesulfonic acid as catalyst in toluene showed that the reaction (eq. 1) was viable and that it was necessary to drive the reaction by distilling out the simple alcohol. However, using commercially available dimethyl or diethyl sulfite the equilibrium value was sufficiently unfavorable that it was difficult to push the reaction to completion. Furthermore, byproducts resulting from alkylation by the sulfite complicated the reaction mixture. Since a bulkier R group should favor the formation of the free simple alcohol, we prepared diisopropyl sulfite (DIS).⁵ Using this reagent the reaction was easily driven to completion. The reaction was also considerably cleaner since DIS is a poor alkylating agent. DIS is readily prepared in 95% yield by addition of thionyl chloride to a toluene solution of excess isopropanol followed by concentration to remove HCl, excess isopropanol and toluene.⁶ No formation of isopropyl chloride was observed.

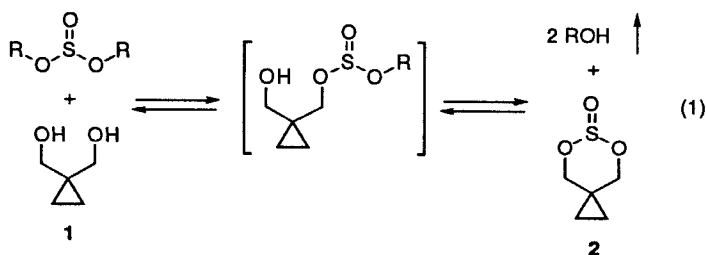

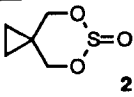

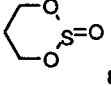

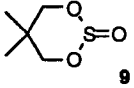
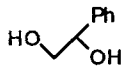
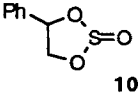
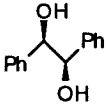
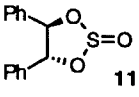

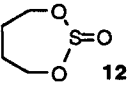


TABLE I: YIELDS OF CYCLIC SULFITE

Diol	Cyclic Sulfite	Transesterification by		Literature ⁹
		Acid	Base	
	 2	92%	91%	NA ^a
	 8	83%		30% ^b
	 9	92%	95%	92% ^c
	 10	98%		62% ^d
	 11	100%		98% ^e
	 12	85%		10% ^b

As shown in Table I the acid catalyzed reaction is quite general.⁷ Five, six, and seven membered sulfites can be prepared. A nonpolar solvent should be used, since attempts to use more polar solvents, such as THF or DMF, were less successful. A sulfonic acid catalyst was necessary since weaker acids such as diphenylphosphoric, trichloroacetic, or trifluoroacetic acid did not induce equilibration. A variety of Lewis acids, including titanium isopropoxide, magnesium bromide, dibutyltin oxide, and zirconium isopropoxide, also failed to induce a reaction. Despite the acidic conditions, the styrene and stilbene derived sulfites were prepared in excellent yields.

The transesterification process also proceeds under base catalyzed conditions. Using diol **1**, we found that the reaction can be run in most solvents using catalytic quantities of lithium or sodium *t*-butoxide. Weaker bases such as DMAP, triethylamine, DBU, tetramethylguanidine, or sodium phenoxide showed only trace amounts of product. Surprisingly, zinc, calcium, or magnesium alkoxides also gave no reaction.

A particular advantage of the base catalyzed process is that it can be run in dipolar aprotic solvents necessary for nucleophilic substitution chemistry. For our synthesis of the thiol-acid **3** we chose to use DMF as solvent. After converting diol **1** to cyclic sulfite **2** in 91% yield, direct addition of NaCN (1.1 equivalents) and a catalytic amount of NaI (0.2 equivalents) to the crude reaction mixture led to production of the hydroxynitrile **7** in 78-83% overall yield from the diol **1**.⁸

The base catalyzed transesterification proved to be far less general than the acid catalyzed reaction. Of the diols in Table I, only 1,1-bis(hydroxymethyl)cyclopropane and neopentyl glycol gave high yields. Other diols, which contain protons β to the incipient sulfite, led to elimination products and low yields.

In summary, acid or base catalyzed transesterification of diisopropyl sulfite and a diol is a synthetically useful alternative for the preparation of cyclic sulfites and is amenable to large scale synthesis.

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 5. Bristow, P.A.; Tillet, J.G. *J. Chem. Soc. (C)* **1968**, 684. Di-*t*-butyl sulfite cannot be easily prepared due to the spontaneous decomposition of the intermediate, *t*-butyl chlorosulfite.
 6. Diisopropyl Sulfite: Toluene (500 mL) and isopropanol (240 g, 306 mL, 4.00 mol) were combined under nitrogen in a 2 L flask equipped with a dropping funnel. Thionyl chloride (119 g, 73 mL, 1.00 mol) was added from the dropping funnel over 30 min maintaining the reaction temperature at 15-25 °C. Some HCl evolution is noted as the reaction proceeds. When the addition was complete, the reaction mixture is put under vacuum to remove HCl. The pressure is slowly lowered. When gas evolution ceases the mixture is concentrated to remove toluene and excess isopropanol. The yield is 157 g (95%). Triethylamine (1 mL) is added to remove residual HCl and the incipient precipitate is filtered away.
 7. Acid Catalyzed Transesterification - Typical Procedure: 1,4-Butanediol (10.1 g, 112 mmol) was suspended in toluene (300 mL) and DIS (19.4 g, 117 mmol). Methanesulfonic acid (0.07 mL, 1.1 mmol) was added and the mixture was distilled at 50 °C/95 torr. After 100 mL was collected, the

reaction was complete and several drops of triethylamine were added to neutralize the catalyst. The solvent was removed and the product was distilled at 80 °C/3 torr to yield 13.0 g (85%) of **12** as a clear liquid. NMR data for the cyclic sulfites (compounds **2**, **8-12**), taken in CDCl₃ using a 250 MHz instrument are given as follows in δ (ppm):

- 2) ¹H-NMR: 5.24 (d, J=11.2 Hz, 2H), 3.04 (d, J=11.7 Hz, 2H), 0.84 (dd, J=8.0, 6.8 Hz, 2H), 0.47 (dd, J=8.8, 6.6 Hz, 2H). ¹³C-NMR: 64.7, 18.0, 12.9, 7.0.
- 8) ¹H-NMR: 4.89 (m, 2H), 3.82 (m, 2H), 2.49 (m, 1H), 1.61 (m, 1H). ¹³C-NMR: 57.3, 25.9.
- 9) ¹H-NMR: 4.59 (d, J=11 Hz, 2H), 3.38 (d, J=11 Hz, 2H), 1.27 (s, 3H), 0.83 (s, 3H). ¹³C-NMR: 66.4, 31.6, 22.5, 22.4).
- 10) diastereomer A: ¹H-NMR: 7.40 (m, 5H), 5.92 (t, J=6.9 Hz, 1H), 4.93 (dd, J=8.5, 6.5 Hz, 1H), 4.19 (dd, J=8.5, 7.4 Hz, 1H). ¹H-NMR: diastereomer B: 7.40 (m, 5H), 5.41 (dd, J=10.6, 6.5 Hz, 1H), 4.74 (dd, J=9.2, 6.5 Hz, 1H), 4.46 (dd, J=10.6, 9.2 Hz, 1H). ¹³C-NMR for diastereomers A and B: 134.5, 133.9, 129.6, 129.5, 129.1, 127.6, 126.7, 85.6, 81.0, 73.6, 71.4.
- 11) ¹H-NMR: 7.39 (m, 8H), 7.25 (m, 2H), 5.71 (d, J=9.8 Hz, 1H), 5.23 (d, J=9.8 Hz, 1H). ¹³C-NMR: 133.3, 132.2, 129.7, 129.4, 129.0, 127.6, 127.2, 91.3, 86.0.
- 12) ¹H-NMR: 4.45 (m, 2H), 3.95 (M, 2H), 1.82 (m, 4H). ¹³C-NMR: 64.1, 28.3.
8. Base Catalyzed Transesterification and Sulfite Displacement: A solution of 1,1-bis(hydroxymethyl)cyclopropane (25.5 g, 250 mmol) in DMF (250 mL) was prepared and 25 mL was distilled at 70 °C/50 torr to dry the solution. NaO*t*Bu solution (2M in THF, 2.0 mL, 4.0 mmol) was added and isopropanol was removed by vacuum distillation (35 - 70 °C/50 torr). The

base catalyst slowly decomposed during the reaction, so a NaOtBu solution (1.0 mL, 2.0 mmol) was added and the distillation was continued until GC assay showed that less than 0.5 % diol remained and $^1\text{H-NMR}$ showed that less than 2 mol% IPA remained in the reaction mixture. When the mixture had cooled to room temperature, NaCN (13.5 g, 275 mmol) and NaI (7.5 g, 50 mmol) were added. The heterogeneous mixture was slowly warmed over 1 h to 70 °C and aged with vigorous stirring. The reaction was followed by GC and was stopped after 36 h when there was less than 2% cyclic sulfite **2** remaining. The reaction was worked up by adding toluene (400 mL) slowly at 70 °C. Water (6 mL) was then added dropwise over 30 min. The water addition causes precipitation of large amounts of light yellow solid which was filtered away. The product **7** was obtained as a solution in 77% (21.4 g by GC assay) yield from diol **1**. For **7**: $^1\text{H-NMR}$ (CDCl_3 , 250 MHz) δ (ppm): 3.54 (s, 2H), 2.57 (s, 2H), 0.63 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 62 MHz) δ (ppm): 118.6, 67.3, 22.5, 19.3, 9.8.

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