

Short Communication

Nucleophilic Ring Opening of Cyclic Sulfites – a Convenient Method for Selective Functionalisation of 1,2-Diols

Kirsten Nymann and John S. Svendsen

University of Tromsø, Institute of Mathematical and Physical Sciences, Department of Chemistry, N-9037 Tromsø, Norway

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The vicinal diol functionality is gaining increasing importance owing to new methods for the synthesis of chiral diols with high optical purity. Most of these methods are based on asymmetric dihydroxylation of alkenes, where several methods for stoichiometric transformations exist,^{1–6} but of greater synthetic importance is catalytic asymmetric dihydroxylation,^{7–9} a reaction which is capable of producing chiral diols with high optical purity from a wide range of mono-, di- and tri-substituted alkenes.¹⁰

Following this development there is a growing demand for reactions that can transform vicinal diols into synthetically more useful intermediates. Approaches in this direction have been based on selective sulfonylation¹¹ and haloacetoxylation,¹² but the most successful method seems to be the transformation of diols into cyclic sulfates.¹³ The synthesis of cyclic sulfates takes place in two steps: first the diol is converted into a cyclic sulfite by treatment with thionyl chloride, and then the sulfite is catalytically oxidised to the corresponding sulfate with ruthenium tetroxide. Many substrates, however, have functional groups that do not tolerate the oxidation conditions, or alternatively, the cyclic sulfates formed may be too reactive to be isolated, as is the case with the cyclic sulfate from 1-phenyl-1,2-ethanediol (**1a**).¹⁴ In the cases where the sulfates are unstable or have limited stability, the corresponding sulfites themselves may have sufficient reactivity to undergo nucleophilic displacement. It is reported that certain cyclic sulfites may be ring opened by some nucleophiles,^{15–18} but only in very few cases has the reaction been of any synthetic value.^{19–21} We wanted to investigate the synthetic potential and some of the limitations of cyclic sulfites appropriately activated for bimolecular nucleophilic substitution.

Results and discussion

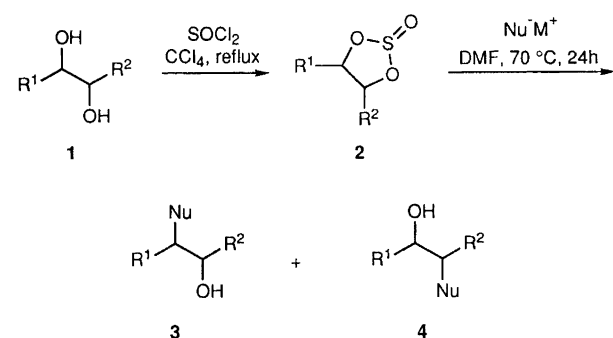
The cyclic sulfites **2a–d** are easily accessible in good to quantitative yields by treatment of the corresponding di-

ols **1a–d** with a slight excess of thionyl chloride in tetrachloromethane or dichloromethane without further work-up. Two diastereomeric cyclic sulfites are obtained for diols **1a**, **1b** and **1d** where the sulfur atom with four different substituents becomes a new chiral centre. The ratios between the diastereoisomers are usually close to equimolar. The cyclic sulfites are usually sufficiently stable to be stored for months at ca. 0°C without deterioration.

The cyclic sulfite functionality has three centres capable of reacting with nucleophiles: the two activated carbon atoms and the sulfite sulfur atom. We wished to develop reaction conditions where nucleophilic substitution takes place at the carbon atoms, and minimise the amount of nucleophilic addition to the sulfur. The nucleophilic displacement reaction can be performed by heating the cyclic sulfites in dimethylformamide (DMF) or acetonitrile in the presence of a nucleophile as shown in Scheme 1.

The results from the reactions are summarized in Table 1. All cyclic sulfites investigated undergo nucleophilic substitution with various nucleophiles in good to excellent yields. Notable exceptions to the general trend are reactions with thiophenolate which give very modest yields (ca. 20%) of the products. When fluoride ion, methyl lithium or methylmagnesium bromide were employed, only the starting diols were isolated. These disappointing findings indicate that, at least for these nucleophiles, the addition takes place preferentially to the sulfite sulfur, rather than to carbon (*vide supra*).^{22,23} The possibility of nucleophilic addition to the sulfite sulfur instead of nucleophilic substitution at carbon clearly limits the types of nucleophile amenable to the reaction and hence the synthetic utility of the reaction.

As shown in Table 1 the regioselectivity in the reactions is usually excellent with the nucleophile adding, as expected, to the activated carbon. An interesting variation in the selectivity scheme occurs for cyanide, where the nucleophile substitutes on the primary rather than the



1, 2, 3, 4	R ¹	R ²
a	Ph	H
b	Ph	Me
c	Ph	Ph
d		H

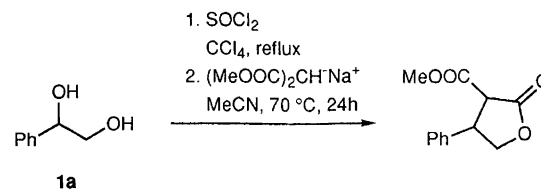
Scheme 1.

benzylic carbon of sulfite **2a**. The selective addition of nucleophiles to the sulfites breaks down when chloride ions are employed, and two products are formed from all cyclic sulfites. For sulfite **2a** the two products were the regioisomers **3a-Cl** and **4a-Cl**, corresponding to chloride substitution at the benzylic or primary carbon, respectively. As shown in Table 1 the regioselectivity was only marginally affected by variation of the cation. For sulfites **2b** and **2c** the two products were not regioisomers, but diastereoisomers. The proton NMR spectrum of the product mixture from **2c** is also in accordance with a diastereoisomer mixture reported in the literature.²⁴

Table 1. Yields and regioselectivity in reactions of various cyclic sulfites, **2a-d**, with different nucleophiles.

2	Nu ⁻	M ⁺	Yield(%)	3:4	
a	Cl ⁻	Li ⁺	90	35:65	
		Na ⁺	80	36:64	
		Cs ⁺	46	52:48	
		TEBA ⁺	93	46:54	
		N ₃ ⁻	Na ⁺	93	100:0
		CN ⁻	TEA ⁺	65	0:100
b	Cl ⁻	Li ⁺	62 ^a	100:0	
		TEBA ⁺	68 ^a	100:0	
		N ₃ ⁻	Na ⁺	98	100:0
c	Cl ⁻	Li ⁺	26 ^a	—	
		TEBA ⁺	56 ^a	—	
		N ₃ ⁻	Na ⁺	99	—
d	Cl ⁻	TEBA ⁺	80	30:70	
		N ₃ ⁻	Na ⁺	90	100:0

^a Two diastereomeric products formed.



Scheme 2.

The activation of chiral diols in the form of the corresponding cyclic sulfites shows promising results: they are readily available in good yields and the compounds available from cyclic sulfites are important synthetic intermediates. The chlorohydrins are easily transformed into epoxides, but, perhaps more importantly, the azidoalcohols should give immediate access to chiral 1,2-amino alcohols which are important pharmaceutical intermediates.²¹ In addition, hydroxy cyanides as **4a-CN**, can be transformed into the corresponding 1,3-amino alcohols, or alternatively into 3-hydroxy acids. Finally, the addition of sodium dimethyl malonate to sulfite **2a** constitutes a very convenient synthesis of chiral γ -lactones as shown in Scheme 2.

We are currently investigating the use of alternative nucleophiles and the application of this method in natural product synthesis.

Experimental

NMR spectra were recorded on a Jeol FX 90Q (89.55 MHz) or a Jeol PMX 60SI (60 MHz) spectrometer using CDCl₃ as the solvent. The multiplicity of the ¹³C NMR spectra was assigned using the DEPT²⁵ pulse sequence.

Gas chromatography was performed on a Varian 3400 gas chromatograph equipped with a Supelco SPB 5 capillary column (30 m × 0.32 mm ID).

Combined gas chromatography–mass spectrometry was carried out on a Hewlett Packard 5890 gas chromatograph with a Supelco SPB 5 (25 m × 0.25 mm ID) column connected to a VG Analytical Tribid mass spectrometer. The mass spectra were recorded using EI ionisation (70 eV) and the ion source temperature was 220 °C.

General procedure for the preparation of cyclic sulfites. Thionyl chloride (1.2–1.5 equiv.) was added to a solution of the diol in tetrachloromethane (4 ml per mmol of diol) and the solution was refluxed for 1 h. After being cooled to ambient temperature, the reaction mixture was washed twice with saturated sodium bicarbonate solution and brine. The organic phase was dried and evaporated under reduced pressure to give the cyclic sulfite.

Preparation of 1-phenyl-1,2-ethanediol cyclic sulfite (4-phenyl-1,3,2-dioxathiolan-2-one) (2a). Compound **2a** was prepared in 95% yield from diol **1a** employing the general

procedure. The diastereomeric cyclic sulfites were formed in a 58:42 ratio.

^1H NMR (90 MHz): δ 7.35 (m, 5 H), 5.87 and 5.36 [(dd, J 7.25 and 6.66 Hz) and (dd J 10.50 and 6.53 Hz), 1 H total], 5.0–4.0 (m, 2 H), ^{13}C NMR (22.5 MHz): δ 134.7 (q), 134.1 (q), 129.4 (d), 129.3 (d), 129.0 (d), 127.4 (d), 126.5 (d), 85.5 (d), 80.9 (d), 73.4 (t), 71.4 (t). MS [m/z (% rel. int.)]: 184 (14), 154 (94), 126 (29), 105 (91), 91 (100).

Preparation of 1-phenyl-1,2-propanediol cyclic sulfite (4-methyl-5-phenyl-1,3,2-dioxathiolan-2-one) (2b). Compound **2b** was prepared in 92% yield from diol **1b** employing the general procedure. The diastereomeric cyclic sulfites were formed in a 69:31 ratio.

^1H NMR (60 MHz): δ 7.34 (m, 5 H), 5.37 and 4.9–4.1 (d, J 9.0 Hz and m, 2 H total), 1.6–1.3 (m, 3 H). ^{13}C NMR (22.5 MHz): δ 134.0, 133.2, 129.7, 129.4, 129.1, 127.6, 127.1, 91.1, 85.8, 85.6, 80.9, 17.7, 15.2. MS [m/z (% rel. int.)]: 198 (6), 154 (96), 126 (74), 105 (100), 92 (46).

Preparation of 1,2-diphenyl-1,2-ethanediol cyclic sulfite (4,5-diphenyl-1,3,2-dioxathiolan-2-one) (2c). Compound **2c** was prepared in 76% yield from diol **1c** employing the general procedure.

^1H NMR (60 MHz): δ 7.28 (m, 10 H), 5.78 (d, J 9.0 Hz, 1 H), 5.17 (d, J 9.0 Hz, 1 H). ^{13}C NMR (22.5 MHz): δ 133.5, 132.5, 129.7, 129.3, 129.0, 127.6, 127.2, 91.3, 86.0, MS [m/z (% rel. int.)]: 179 (6), 167 (11), 154 (100), 126 (34), 105 (78).

Preparation of (4S),(E)-ethyl 4,5-dihydroxy-2-pentenoate cyclic sulfite (2d). Compound **2d** was prepared in 85% yield from diol **1d** employing the general procedure. The diastereomeric cyclic sulfites were formed in a 57:43 ratio.

^1H NMR (90 MHz): δ 7.1–6.6 (m, 1 H), 6.13 and 6.08 [$2 \times$ dd (J 15.8 and -1.1 Hz), 1 H total], 5.6–4.0 (m, 5 H), 1.20 (t, J 7.0 Hz, 3 H). ^{13}C NMR (22.5 MHz): δ 164.0, 138.7, 138.2, 125.2, 124.3, 80.3, 77.2, 69.9, 68.8, 59.9, 13.1, MS [m/z (% rel. int.)]: 176 (5), 161 (7), 142 (4), 133 (6), 112 (41), 97 (90), 83 (88), 69 (100).

General procedure for nucleophilic ring openings of cyclic sulfites. The nucleophile (4 mmol) was added to a solution of the cyclic sulfite (2 mmol) in DMF or acetonitrile (3 ml), and the reaction mixture was heated to 70 °C for 24 h. After being cooled to ambient temperature, the reaction was quenched by addition of 20% sulfuric acid (5 ml), and the resulting mixture was extracted with ethyl acetate (2×10 ml). The combined organic phases were washed with dilute sulfuric acid, water, saturated sodium bicarbonate and brine. The resulting organic phase was dried and evaporated under reduced pressure before the products were isolated by column chromatography.

Preparation of 2-chloro-2-phenylethanol (3a-Cl) and 2-chloro-1-phenylethanol (4a-Cl). Compounds **3a-Cl** and **4a-Cl** were obtained in 90% yield starting with cyclic sulfite **2a** in DMF using lithium chloride as the nucleophile.

3a-Cl: The ^1H NMR, ^{13}C NMR and mass spectral data were in accordance with the literature.^{26,27}

4a-Cl: ^1H NMR (90 MHz): δ 7.26 (m, 5 H), 4.83 (dd, J 8.95 and 3.27 Hz, 1 H), 3.68 (m, J 3.27 and -11.23 Hz, 1 H), 3.60 (m, J 8.95 and -11.23 Hz, 1 H), 2.75 (s, 1 H). The ^{13}C NMR spectrum was in accordance with the literature.²⁸ MS [m/z (% rel. int.)]: 158 (3), 156 (11), 107 (100), 91 (17), 79 (83), 77 (71).

Preparation of 2-azido-2-phenylethanol (3a-N₃). Compound **3a-N₃** was obtained in 93% yield starting with cyclic sulfite **2a** in DMF using sodium azide as the nucleophile.

3a-N₃: The ^1H NMR and ^{13}C NMR spectra were in accordance with the literature.^{29,30} MS [m/z (% rel. int.)]: 132 (35), 104 (71), 77 (100).

Preparation of 3-hydroxy-3-phenylpropanenitrile (4a-CN). Compound **4a-CN** was obtained in 65% yield starting with cyclic sulfite **2a** in DMF using tetraethylammonium cyanide as the nucleophile.

The ^1H NMR spectrum was in accordance with the literature.³¹ ^{13}C NMR (22.5 MHz): δ 140.1 (s), 127.9 (d), 127.8 (d), 124.5 (d), 69.2 (d), 26.9 (t). MS [m/z (% rel. int.)]: 147 (1), 129 (100), 107 (46), 77 (51).

Preparation of methyl 2-oxo-4-phenyltetrahydrofuran-3-carboxylate (3a-malonate). Compound **3a-malonate** was obtained in 23% yield by treating the cyclic sulfite **2a** in acetonitrile with dimethyl malonate and sodium hydride.

^1H NMR (90 MHz): δ 7.30 (m, 5 H), 4.7 (m, 1 H), 4.25 (m, 2 H), 3.80 (s, 3 H), 3.73 (d, J 5.4 Hz, 1 H). ^{13}C NMR (22.5 MHz): δ 171.1 (s), 167.5 (s), 137.0 (s), 129.3 (d), 128.2 (d), 126.9 (d), 72.4 (t), 53.3 (d), 53.1 (q), 45.2 (d).

Preparation of (S,R*)- and (R*,R*)-1-chloro-1-phenyl-2-propanol [(S*,R*)-3b-Cl and (R*,R*)-3b-Cl].* Compounds **(S*,R*)-3b-Cl** and **(R*,R*)-3b-Cl** were obtained in 62% yield starting with cyclic sulfite **2b** in DMF using lithium chloride as the nucleophile. The diastereoisomers were separated by column chromatography using silica gel. The compounds were eluted using 10% ethyl acetate in heptane followed by 20% ethyl acetate in heptane.

First-eluting compound: ^1H NMR (60 MHz): δ 7.28 (s, 5 H), 4.68 (d, J 7.0 Hz, 1 H), 4.12 (m, J 7.0 and 6.2 Hz, 1 H), 2.32 (br s, 1 H), 1.10 (d, 6.2 Hz, 3 H). ^{13}C NMR (22.5 MHz): δ 138.7, 128.7, 127.8, 72.0, 71.1, 19.5. MS [m/z (% rel. int.)]: 172 (4), 170 (12), 135 (23), 128 (93); 126 (54), 125 (88), 91 (54).

Second-eluting compound: ^1H NMR (90 MHz): δ 7.31 (s, 5 H), 4.79 (d, J 5.6 Hz, 1 H), 4.10 (m, J 6.0 and 5.6 Hz, 1 H), 2.40 (br s, 1 H), 1.29 (d, J 6.0 Hz, 3 H). ^{13}C NMR (22.5 MHz): δ 138.1, 128.6, 128.1, 71.8, 68.3,

19.1. The mass spectrum was identical with the first-eluting compound.

Preparation of (S,R*)-1-azido-1-phenyl-2-propanol [(S*,R*)-3b-N₃].* Compound (S*,R*)-3b-N₃ was obtained in 98% yield starting with cyclic sulfite 2b in DMF using sodium azide as the nucleophile.

(S*,R*)-3b-N₃: ¹H NMR (60 MHz): δ 7.28 (s, 5 H), 4.42 (d, *J* 5.6 Hz, 1 H), 3.90 (m, *J* 6.0 and 5.6 Hz, 1 H), 2.46 (br s, 1 H), 1.14 (d, *J* 6.0 Hz, 3 H). ¹³C NMR (22.5 MHz): δ 136.4, 128.8, 128.5, 127.9, 71.6, 70.6, 18.6. MS [*m/z* (% rel. int.)]: 159 (1), 133 (25), 104 (100), 77 (87).

Preparation of (S,R*)- and (R*,R*)-2-chloro-1,2-diphenylethanol [(S*,R*)-3c-Cl and (R*,R*)-3c-Cl].* Compounds (S*,R*)-3c-Cl and (R*,R*)-3c-Cl were obtained in equimolar ratio in 26% total yield starting with cyclic sulfite 2c in DMF using lithium chloride as the nucleophile.

The ¹H NMR and mass spectral data were in accordance with those reported for a diastereomeric mixture.²⁴

Preparation of (R,S*)-2-azido-1,2-diphenylethanol [(R*,S*)-3c-N₃].* Compound (S*,R*)-3b-N₃ was obtained in 99% yield starting with cyclic sulfite 2b in DMF using sodium azide as the nucleophile.

The ¹H NMR and mass spectral data were in accordance with the literature.³² ¹³C NMR (22.5 MHz): δ 139.7, 136.0, 128.6, 128.3, 128.2, 128.1, 127.1, 77.0, 71.3.

Preparation of (E)-ethyl-4-chloro-5-hydroxy-2-pentenoate (3d-Cl) and (E)-ethyl-5-chloro-4-hydroxy-2-pentenoate (4d-Cl). Compounds 3d-Cl and 4d-Cl were obtained in a 30:70 ratio in 80% total yield starting with cyclic sulfite 2d in DMF using benzyltriethylammonium chloride as the nucleophile.

3d-Cl: ¹³C NMR (22.5 MHz): δ 166.1, 145.0, 123.0, 70.7, 60.7, 48.3, 14.2.

4d-Cl: The ¹H NMR spectrum was in accordance with the literature.³³ ¹³C NMR (22.5 MHz): δ 165.7, 142.6, 124.7, 66.0, 60.9, 60.7, 14.2.

Preparation of (E)-ethyl-4-azido-5-hydroxy-2-pentenoate (3d-N₃). Compound 3d-N₃ was obtained in 90% yield starting with cyclic sulfite 2d in DMF using sodium azide as the nucleophile.

¹H NMR (60 MHz): δ 6.80 (dd, *J* 15.0 and 6.0 Hz, 1 H), 6.09 (dd, *J* 15.0 and -1.8 Hz, 1 H), 4.25 (q, *J* 7.0 Hz, 2 H), 4.5-3.4 (m, 3 H), 2.83 (br s, 1 H), 1.28 (t, *J* 7.0 Hz, 3 H). ¹³C NMR (22.5 MHz): δ 165.8, 141.2, 127.4, 64.4, 64.1, 60.9, 14.2. MS [*m/z* (% rel. int.)]: 157 (4), 154 (2), 140 (9), 126 (30), 112 (6), 98 (49), 82 (100).

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