

Nucleophilic Ring Opening of Cyclic 1,2-Sulfites with Nitrogen Nucleophiles. A Route to Enantiopure Benzylic Amino Alcohols

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The reaction between cyclic 1,2-sulfites and two imide and two sulfonamide nucleophiles has been investigated in order to develop a procedure for the enantioselective preparation of *N*-protected vicinal amino alcohols. The results show that both imide and sulfonamide anions react with cyclic sulfites, yielding the desired products. In some cases the regioselectivities are low, and for the sulfonamides products originating from nucleophilic addition to the sulfite sulfur are observed.

Chiral 1,2-amino alcohols are important substructures of many biologically active substances, and their preparation has attracted considerable attention. Among the multitude of reactions leading to enantiopure, vicinal amino alcohols, asymmetric aminohydroxylation (AA) is a recent important synthetic development.^{1–5} The asymmetric induction in the AA process exhibits the same stereochemical sense and facial selectivity as the asymmetric dihydroxylation (AD) process, indicating that the transfer of chirality occurs by a similar pathway proceeding through a *syn*-addition to the alkene. As is the case with the AD process, AA only gives satisfactory enantioselectivities when *trans*-alkenes are employed as substrates.

In our work the Sharpless AD process is used to prepare enantiopure 1,2-diols which are further transformed into cyclic sulfites with retention of chirality. A nucleophilic S_N2 displacement with inversion of chirality of the cyclic sulfites thus formed gives access to amino alcohols with stereochemistry representing an overall *anti*-addition to the starting *trans*-alkene. The amino alcohols thus formed are diastereomers of the Sharpless *syn*-amino alcohols, and the two-step reaction sequence therefore represents a complement to the AA process.

The reaction between azide anion and a cyclic sulfite forming an azidohydrin is well known.^{6–10} We have also previously described¹¹ that the reaction between cyclic sulfite **2a** and azide anion proceeds only in the benzylic position and in excellent yield. This azidohydrin should, after reduction, give access to chiral 1,2-amino alcohols.

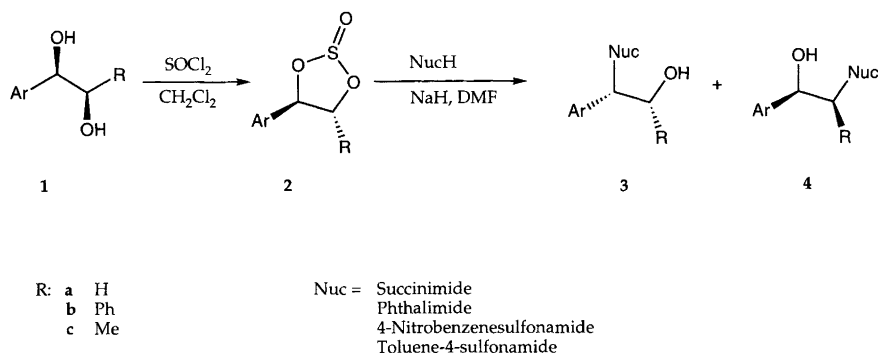
In this work we wanted to explore the reaction of sulfonamides and of imide anions with cyclic sulfites in order to gain direct access to suitably protected benzylic amino alcohols. The sulfonamide anions tested as nucleophiles were toluene-4-sulfonamide and 4-nitrobenzene-sulfonamide anions giving directly *N*-Tos- and *N*-Nos¹²-protected amino alcohols, whereas phthalimide and succinimide anions were used as representatives for the imide anions.

Results and discussion

The cyclic sulfites **2a–c** were prepared in almost quantitative yields by treatment of the corresponding diols **1a–c** with thionyl chloride in dichloromethane (Scheme 1). No epimerisation of the chiral carbon atoms could be detected during the reaction. The nucleophilic displacement reactions are performed by heating the cyclic sulfites in *N,N*-dimethylformamide (DMF) in the presence of the nucleophile as shown in Scheme 1. The nucleophiles were generated by treating the sulfonamide or imide with NaH in DMF. Benzyl carbamate anion did not react with the cyclic sulfite **2a**.

Chemoselectivity. In the cyclic sulfite both the two carbon atoms and the sulfite sulfur atom are capable of reacting with nucleophiles. Soft nucleophiles have a larger propensity to react with the carbon atoms while harder nucleophiles react rather with the sulfite sulfur atom. When a hard nucleophile reacts at the sulfite sulfur a sulfonate ester is formed, which upon hydrolysis gives the diol and the sulfonate.¹³ The phthalimide and succinimide anions behave as soft nucleophiles towards cyclic sulfites, as

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Scheme 1.

they react almost quantitatively (Table 1) at the carbon atoms, producing the expected imide protected amino alcohols **3** and **4** as shown in Scheme 1. On the other hand, the products obtained after the reactions with 4-nitrobenzenesulfonamide and toluene-4-sulfonamide anions indicate that sulfonamide anions behave like harder nucleophiles with a higher degree of sulfur nucleophilicity, since the reaction mixture contains not only the expected amino alcohol products **3** and **4**, but also, in almost the same amount, the diol **1** (Table 1).

Regioselectivity. The results show that when R = H (compound **2a**) the regioselectivity of the nucleophilic attack on carbon is low and products **3** and **4** are formed in equal amounts or with attack at the non-benzylic carbon predominating. This trend is valid for both the imide and the sulfonamide anions, and is in remarkable contrast with the corresponding reaction with the azide anion, which gives only the product corresponding to a reaction at the benzylic carbon.¹¹ When R = Me and Ph, the reactions were slow and not quantitative, and were performed only with the imide anions. In compound **2c** where R = Me, only the products with substitution in the benzylic position **3** were formed. The finding that the secondary carbon competes less favourably with the benzylic carbon in **2c** is expected from normal S_N2 reactivity.

Table 1. Yields and regioselectivity in nucleophilic reactions of various cyclic sulfites with nitrogen nucleophiles.

Substrate	Reagent	Yield of			
		1 (%)	2 (%)	3 + 4 (%)	3 : 4
a (S)	4-Nitrobenzenesulfonamide	32	6	49	1 : 1
a (S)	Toluene-4-sulfonamide	25	—	37	2 : 5
a (S)	Phthalimide	—	—	100	1 : 1
a (S)	Succinimide	—	—	86	2 : 3
b (R,R)	Phthalimide	—	8	81	—
b (R,R)	Succinimide	6	23	62	—
c (R,R)	Phthalimide	—	24	76	100 : 0
c (R,R)	Succinimide	—	33	67	100 : 0

Stereoselectivity. Since two chiral carbon centers are present in compounds **2b** and **2c** where R = Ph or Me, any loss of optical purity during the reaction will give rise to diastereomers. Only one diastereomer is formed in the reactions with these substrates, hence the nucleophilic displacement is stereochemically clean, at least for the imide anions. The reactions with phthalimide or succinimide anions are by analogy supposed to be stereospecific for compound **2a**, where no external chiral center will indicate any loss of stereochemical integrity. The stereoselectivities of the reactions between the cyclic sulfites and sulfonamide nucleophiles were determined by the enantiomeric purity of the products (**3a**,4-Me) and (**4a**,4-Me) by ¹H NMR spectroscopy using Eu(hfc)₃ as a chiral shift reagent and (²H₆)benzene as the solvent. The racemic products were used as references, and the enantiomeric purity was found to be better than 95% (the limit of analyses).

The results from this study show that the synthetically useful imide and sulfonamide anions work as nucleophiles towards cyclic sulfites. In all cases the reactions proceed with clean inversion, albeit with low regioselectivity if the cyclic sulfite contains both a benzylic and a primary carbon.

Experimental

General. Proton NMR spectra were recorded on a Jeol Eclipse 400 (399.65 MHz) spectrometer and CDCl₃ was used as the solvent unless otherwise stated.

Gas chromatography was performed on a Varian 3400 gas chromatograph equipped with a Supelco SPB 5 capillary column (15 m × 0.32 mm ID).

Combined gas chromatography–mass spectrometry was carried out on either a VG Analytical Tribid mass spectrometer or a Quattro VG mass spectrometer connected to a Hewlett Packard 5890 Series II gas chromatograph. The gas chromatograph was equipped with either a Supelco SPB 5 (25 m × 0.25 mm ID) or a Supelco β-cyclodextrin (enantiomeric purity determination) (50 m × 0.25 mm ID) column. Mass spectrometry was performed either using EI ionisation (70 eV) with ion source temperature 180 °C, or CI ionisation with

isobutane as the reactant gas and ion source temperature 150 °C.

Preparation of diols 1a–c. The diols **1a–c** were prepared in yields ranging from 70 to 80% from the corresponding alkenes according to literature procedures¹⁴ using (DHQD)₂-PHAL (to give *Re* selective addition) or (DHQ)₂-PHAL (to give *Si* selective addition) as chiral ligand. The enantiomeric purities were in all cases better than 99.9% (GC).

Preparation of cyclic sulfites 2a–c. The cyclic sulfites **2a–c** were prepared in yields ranging from 76 to 99% from the corresponding diols according to literature procedures.¹⁵

Reaction of cyclic sulfites with imide anion or sulfonamide anion: general procedure. The reaction was performed under nitrogen. Sodium hydride (0.36 g of a 20% suspension, 3.0 mmol) was washed four times with pentane. Dry DMF (4 ml) was added and the resulting slurry was cooled on an ice bath before the nucleophile (3.0 mmol) was added. The reaction was stirred until all gas evolution ceased. The cyclic sulfite (1.0 mmol) was added and the reaction mixture was stirred with heating (70–80 °C) and monitored by GC. The reaction was quenched by addition of sulfuric acid (20%, 5 ml). The resulting mixture was extracted with ethyl acetate (2 × 10 ml) and the combined organic phases were washed with sulfuric acid (20%, 5 ml), water (2.5 ml), saturated sodium hydrogencarbonate solution (2 × 2.5 ml) and brine (5 ml) before being dried (MgSO₄). The products were separated by flash chromatography (SiO₂; mixtures of EtOAc in dichloromethane).

Reaction of cyclic sulfite S-2a with 4-nitrobenzenesulfonamide anion. The reaction was performed as described in the general procedure and the reaction time was 5 h. A 1 : 1 regioisomer mixture of *N*-[(1*R*)-2-hydroxy-1-phenylethyl]-4-nitrobenzenesulfonamide (**3a,4-NO₂**) and *N*-[(2*S*)-2-hydroxy-2-phenylethyl]-4-nitrobenzenesulfonamide (**4a,4-NO₂**) was isolated.

3a,4-NO₂: ¹H NMR: δ 1.24 (1 H, s), 3.76 (1 H, dd, *J* = 6.6, 11.4 Hz), 3.85 (1 H, dd, *J* = 4.4, 11.3 Hz), 4.56 (1 H, m), 5.65 (1 H, d, *J* = 6.6 Hz), 7.06–7.25 (5 H, m), 7.78 (2 H, d, *J* = 9.2 Hz), 8.11 (2 H, d, *J* = 9.2 Hz). MS [*m/z*, (% rel. int.)]: 291 (100), 275 (2), 245 (2), 186 (17), 156 (5), 122 (40), 104 (21).

4a,4-NO₂: ¹H NMR: δ 3.10 (1 H, m), 3.33 (1 H, m), 4.84 (1 H, dd, *J* = 3.7, 8.0 Hz), 5.07 (1 H, br s), 5.20 (1 H, br s), 7.25–7.35 (5 H, m), 8.00 (2 H, d, *J* = 9.2 Hz), 8.33 (2 H, d, *J* = 9.2 Hz). MS [*m/z*, (% rel. int.)]: EI, 304 (8), 186 (15), 136 (3), 156 (8), 122 (14), 118 (43), 107 (100).

Reaction of cyclic sulfite S-2a with toluene-4-sulfonamide anion. The reaction was performed as described in the general procedure except that 8 ml of DMF was used.

The reaction time was 4 h and a 2 : 5 regioisomer mixture of *N*-[(1*R*)-2-hydroxy-1-phenylethyl]toluene-4-sulfonamide (**3a,4-Me**) and *N*-[(2*S*)-2-hydroxy-2-phenylethyl]toluene-4-sulfonamide (**4a,4-Me**) was isolated.

3a,4-Me: ¹H NMR: δ 1.24 (1 H, s), 2.38 (3 H, s), 3.74 (2 H, m), 4.37 (1 H, m), 5.15 (1 H, br d), 7.09–7.23 (7 H, m), 7.61 (2 H, d, *J* = 8.4 Hz). MS [*m/z*, (% rel. int.)]: EI, 262 (46), 155 (31), 104 (79), 91 (100). CI, 292 (2, *M* + H). The enantiomeric purity was better than 95% as determined by ¹H NMR spectroscopy using Eu(hfc)₃ as chiral shift reagent and (²H₆)benzene as the solvent.

4a,4-Me: ¹H NMR: δ 1.31 (1 H, s), 2.42 (3 H, s), 3.03 (1 H, ddd, *J* = 4.4, 8.8, 13.2 Hz), 3.25 (1 H, ddd, *J* = 3.6, 8.0, 13.2 Hz), 4.79 (1 H, dd, *J* = 3.6, 8.8 Hz), 4.83 (1 H, m), 7.21–7.37 (7 H, m), 7.72 (2 H, d, *J* = 8.4 Hz). MS [*m/z*, (% rel. int.)]: EI, 273 (1), 184 (5), 136 (4), 118 (6), 107 (100), 91 (85). CI, 292 (2, *M* + H). The enantiomeric purity was better than 95% as determined by ¹H NMR spectroscopy using Eu(hfc)₃ as chiral shift reagent and (²H₆)benzene as the solvent.

Reaction of cyclic sulfite S-2a with phthalimide anion. The reaction was performed as described in the general procedure and the reaction time was 3 h. A 1 : 1 regioisomeric mixture of 2-[(1*R*)-2-hydroxy-1-phenylethyl]isoindole-1,3-dione (**3a,phthal**) and 2-[(2*S*)-2-hydroxy-2-phenylethyl]isoindole-1,3-dione (**4a,phthal**) was isolated.

3a,phthal: ¹H NMR: δ 4.24 (1 H, dd, *J* = 5.1, 11.7 Hz), and 4.64 (1 H, dd, *J* = 8.8, 11.7 Hz), 5.47 (1 H, dd, *J* = 5.1, 8.8 Hz), 7.27–7.36 (5 H, m), 7.44 (2 H, m), 7.72 (2 H, m). MS [*m/z*, (% rel. int.)]: EI, 249 (1), 237 (65), 236 (100), 130 (58), 105 (34), 104 (32), 102 (38), 77 (26), 76 (45). CI, 268 (100, *M* + H).

4a,phthal: ¹H NMR: δ 3.94 (1 H, dd, *J* = 3.7, 14.3 Hz), 4.02 (1 H, dd, *J* = 8.4, 14.3 Hz), 5.06 (1 H, dd, *J* = 3.7, 8.4 Hz), 7.27–7.36 (5 H, m), 7.44 (2 H, m), 7.72 (2 H, m). MS [*m/z*, (% rel. int.)]: 267 (2, *M*), 249 (0.5), 161 (100), 132 (7), 105 (9), 104 (38), 77 (48), 76 (43). CI, 268 (5, *M* + H).

3a,phthal and 4a,phthal mixture: ¹³C NMR (100.4 MHz): δ 45.84, 57.62, 62.48, 72.75, 123.5–134.4, 167.2–168.8.

Reaction of cyclic sulfite S-2a with succinimide anion. The reaction was performed as described in the general procedure and the reaction time was 4 h. A 2 : 3 regioisomeric mixture of 1-[(1*R*)-2-hydroxy-1-phenylethyl]pyrrolidine-2,5-dione (**3a,succ**) and 1-[(2*S*)-2-hydroxy-2-phenylethyl]pyrrolidine-2,5-dione (**4a,succ**) was isolated.

3a,succ: ¹H NMR: δ 2.70 (4 H, s), 4.08 (1 H, dd, *J* = 5.1, 11.7 Hz), 4.56 (1 H, dd, *J* = 9.2, 11.7 Hz), 5.28 (1 H, dd, *J* = 5.1, 9.2 Hz), 7.28–7.38 (5 H, m). ¹³C NMR (100.4 MHz): δ 28.21, 58.2, 61.9, 125.8–128.8, 136.2, 178.0. MS [*m/z*, (% rel. int.)]: EI, 219 (1, *M*), 201 (7),

189 (100), 161 (10), 160 (14), 133 (2), 132 (16), 106 (34), 104 (18). CI, 220 (100, $M+H$).

4a,succ: $^1\text{H NMR}$: δ 2.70 (4 H, s), 3.73 (1 H, dd, $J=3.3, 13.9$ Hz), 3.86 (1 H, dd, $J=8.8, 13.9$ Hz), 4.96 (1 H, dd, $J=3.3, 8.8$ Hz), 7.28–7.38 (5 H, m). $^{13}\text{C NMR}$ (100.4 MHz): δ 28.20, 46.51, 72.18, 125.8–128.8, 141.0, 177.94. MS [m/z , (% rel. int.)]: EI, 219 (4, M), 201 (8), 120 (55), 113 (100), 107 (60). CI, 220 (6, $M+H$).

Reaction of cyclic sulfite R,R-2b with phthalimide anion. The reaction was performed as described in the general procedure and the reaction time was 12 h. 2-[(1*S*,2*R*)-1,2-Diphenyl-2-hydroxyethyl]isoindole-1,3-dione (**3b**, phthal) was isolated.

3b,phthal: $^1\text{H NMR}$ [($^2\text{H}_6$)DMSO]: δ 5.42 (1 H, d, $J=10.3$ Hz), 5.78 (1 H, dd, $J=5.9, 10.3$ Hz), 5.86 (1 H, d, $J=5.9$ Hz), 7.1–7.7 (14 H, m). MS [m/z , (% rel. int.)]: EI, 325 (100), 237 (86), 236 (33), 178 (93), 167 (37), 166 (27), 130 (15), 105 (63), 104 (40), 77 (60), 76 (38).

Reaction of cyclic sulfite R,R-2b with succinimide anion. The reaction was performed as described in the general procedure and the reaction time was 24 h. 1-[(1*S*,2*R*)-1,2-Diphenyl-2-hydroxyethyl]pyrrolidine-2,5-dione (**3b**, succ) was isolated.

3b,succ: $^1\text{H NMR}$: δ 2.39 (4 H, s), 2.73 (1 H, s), 5.38 (1 H, d, $J=8.8$ Hz), 5.87 (1 H, d, $J=8.8$ Hz), 7.08–7.69 (10 H, m). MS [m/z , (% rel. int.)]: 277 (3), 189 (100), 161 (42), 160 (52), 132 (42), 107 (78), 105 (65), 104 (50), 79 (70), 77 (82).

Reaction of cyclic sulfite R,R-2c with phthalimide anion. The reaction was performed as described in the general procedure and the reaction time was 27 h. 2-[(1*S*,2*R*)-2-Hydroxy-1-phenylpropyl]isoindole-1,3-dione (**3c**,phthal) was isolated.

3c,phthal: $^1\text{H NMR}$: δ 1.29 (3 H, d, $J=6.2$ Hz), 4.99 (1 H, quintet, $J=6.2, 6.6$ Hz), 5.10 (1 H, d, $J=7.0$ Hz), 7.29–7.87 (9 H, m). MS [m/z , (% rel. int.)]: EI, 281 (0.5, M), 263 (0.5), 237 (100), 236 (40), 219 (30), 130 (50), 104 (68), 102 (7), 77 (51), 76 (49). CI, 282 (100, $M+H$).

Reaction of cyclic sulfite R,R-2c with succinimide anion. The reaction was performed as described in the general procedure and the reaction time was 24 h. 1-[(1*S*,2*R*)-2-Hydroxy-1-phenylpropyl]pyrrolidine-2,5-dione (**3c**,succ) was isolated.

3c,succ: $^1\text{H NMR}$: δ 1.21 (3 H, d, $J=6.2$ Hz), 2.69 (4 H, s), 4.80 (1 H, quintet, $J=6.2$ Hz), 4.95 (1 H, d, $J=6.2$ Hz), 7.3–7.6 (5 H, m). MS [m/z , (% rel. int.)]: EI, 215 (0.5), 189 (100), 161 (28), 160 (45), 132 (30), 106 (26), 104 (39). CI, 234 (100, $M+H$).

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