Anchimeric Assisted Unprecedented S_Ni-Type Cleavage of Cyclic Sulfite: Application in the Synthesis of the Calcium Channel Blocker Diltiazem†

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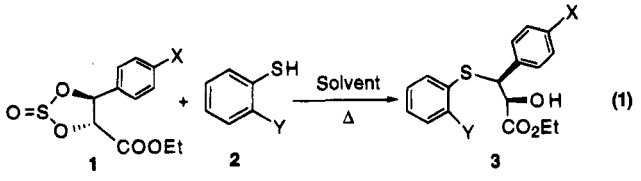
With the new synthetic developments of chiral cyclic sulfites and cyclic sulfates, their stereoselective transformations are of contemporary interest.[1] Much of the known chemistry of cyclic sulfites[2] and cyclic sulfates[3] with nucleophiles proceeds *via* a S_N2 pathway with inversion at the reacting stereogenic center. We anticipated that, with the help of neighboring group participation, the stereoselectivity of the nucleophilic attack could be altered so that the nucleophile could approach from the same face as the leaving group of the cyclic sulfite, resulting in net retention of configuration (eq 1). Such an effect is unknown in the chemistry of cyclic sulfites.[1]



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a) X = OMe b) X = H; a) Y = NH_2 b) Y = H; a) X = OMe; Y = NH_2 b) X = OMe; Y = H

To probe the anchimerically assisted cleavage of cyclic sulfites, we examined the reaction of cyclic sulfites **1a** (X = OCH_3) and **1b** (X = H) with 2-aminothiophenol (**2a**) and thiophenol (**2b**). When a mixture of **1a** and thiophenol (**2b**) was heated at *ca.* 110 °C in toluene for 12 h, only 10% yield of a product was isolated, the structure of which has been assigned as ethyl 2-hydroxy-3-(phenylthio)-3-(*p*-methoxyphenyl)propionate (**3b**), along with 15% of ethyl (*p*-methoxybenzoyl)acetate. Control experiments showed that cyclic sulfite decomposes extensively when heated under argon in toluene at *ca.* 110 °C for 4 h. In contrast, when cyclic sulfite **1b** was treated with either 2-aminothiophenol (**2a**) or thiophenol (**2b**) under identical experimental conditions, only decomposition of **1b** was observed. This result suggested that anchimeric assistance of the *p*-methoxyphenyl group was facilitating the nucleophilic opening of **1a** (such an anchimeric effect of OMe *vs* H in aromatic ring is well documented in the literature).[4]

In contrast, heating a mixture of **1a** and **2a** in refluxing toluene for 3–4 h afforded 60% yield of optically active ethyl 2(*S*)-hydroxy-3(*S*)-[(*o*-aminophenyl)thio]-3-(*p*-methoxyphenyl)propionate (**3a**) as the major product.[5] The improved yield of **3a** (*vs* **3b**) clearly points out that in addition to the anchimeric assistance from the *p*-methoxyphenyl group in the stereoselective opening of **1a**, the NH_2 group of 2-aminothiophenol plays a crucial role in enhancing the reactivity as well as the selectivity of the reaction. Thus, it appears that 2-aminothiophenol not only acts as a nucleophile but also provides H-bonding with the cyclic sulfite (Scheme 1).

To support this mechanistic surmise, we carried out ^1H NMR experiments to show the possible importance of H-bonding in facilitating the nucleophilic opening of the cyclic sulfite. The ^1H NMR (200 MHz) of dioxathiolane **1a** in $CDCl_3$ showed the presence of a mixture of diastereomers (60:40) arising due to diastereotopicity of the sulfoxide lone pair. The doublets at δ 6.1 (J = 10.8 Hz) and 4.77 (J = 10.8 Hz) belong to one diastereomer and were assigned to H^5 and H^4 protons, respectively. Similarly doublets at δ 5.53 (J = 10.8 Hz) and 5.16 (J = 10.8 Hz) belong to the H^5 and H^4 protons of the other diastereomer. Treatment of **1a** separately with 1-equiv of **2a** and **2b** was followed by ^1H NMR. Interestingly, the signals corresponding to H^5 and H^4 remained virtually unaffected in the presence of thiophenol, whereas in the presence of 2-aminothiophenol upfield chemical shifts of these protons were observed in both diastereomers by Δ 0.2–δ 0.1 ppm. ^1H NMR spectra of thiophenol and 2-aminothiophenol were also recorded separately in $CDCl_3$. Whereas the signal due to SH (3.05 ppm) in **2b** remained unaffected in the presence or absence of dioxathiolane **1a** or **1b**, a significant shift was observed for both SH and NH_2 (Δ 0.6 ppm) protons of **2a** in the presence of dioxathiolane **1a**. These experiments clearly suggest association of **2a** with **1a**. Such association of **2a** was not observed with **1b**. Thus, the nature of the H-bonding is also a function of the structure of the cyclic sulfite. In case of **1a**, where O–S=O bond polarization is not assisted due to the absence of the OMe group, no significant H-bonding was observed, at least at the NMR time scale. The importance of such weak forces is well documented to play a crucial role in determining the reactivity and selectivity of reactions in biological systems.[6]

To further validate the importance of H-bonding, we examined the effect of solvents on the reaction. Polar solvents (DMSO, DMF, MeCN, EtOH) which can solvate the carbocation showed a deleterious effect on the nucleophilic opening of cyclic sulfites (several unidentified products were observed in TLC). Nonpolar solvents such as toluene and xylene were found to be more suitable for the reaction. We also examined the effect of temperature and found that the best yield can be obtained by heating

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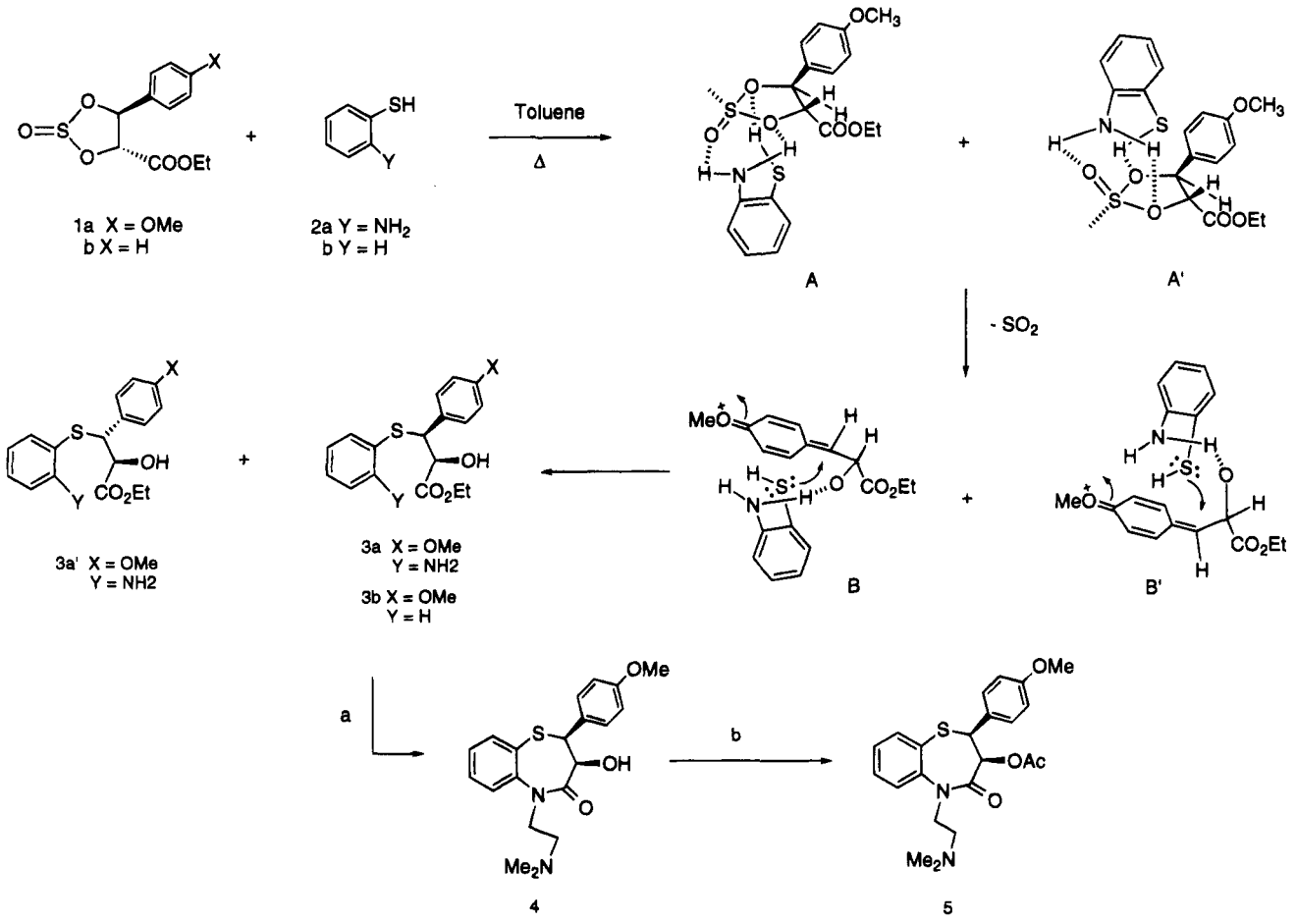
Scheme 1. Mechanism of Stereoselective Reaction of Dioxathiolanes with Aminothiophenol[a]



[a] Key: (a) (i) PTS, toluene, Δ or Δ, 170 °C, (ii) $ClCH_2CH_2NMe_2HCl$, K_2CO_3, moist EtOAc, Δ, 12 h; (b) Ac_2O, Et_3N, CH_2Cl_2.

a premixed solution in a bath at *ca.* 110 −120 °C for 3−4 h. Thus, we assume that the initial step in this reaction involves the formation of weak H-bonded transition state species **A/A'**, which undergoes subsequent rearrangement at elevated temperatures by extrusion of SO_2 to form **B/B'** (Scheme 1). The intermediate **B/B'** can undergo nucleophilic S_Ni type attack by "S" lone pair of the aminothiophenol from the same face or opposite face, resulting in overall retention or inversion of configuration at the reacting stereogenic center. Examination of the crude reaction mixture by ^1H NMR indicates the presence of a mixture of products. Upon cooling to room temperature and allowing to stand overnight, the product (2*S*,3*S*)-**3a** crystallized out. The preferential formation of (2*S*,3*S*)-**3a** may be attributed to the preferential association of **1a** with **2a** as shown in the transition state **A** rather than sterically hindered transition state **A'** which subsequently led to **B** and **B'**, respectively, after extrusion of SO_2. These two transition states **B/B'** can undergo intramolecular nucleophilic attack as shown in Scheme 1 to afford **3a/3a'**.

Finally, we utilized this strategy for a short and stereoselective synthesis of the key intermediate (2*S*,3*S*)-**3a** (X = OMe; Y = NH_2) in the synthesis of diltiazem, a cardiovasodilating agent used for hypertension[7a] and calcium channel blocker.[7b] This drug has been the target of synthesis by a number of groups either in racemic[8] or in optically active form.[9] The ester (2*S*,3*S*)-**3a** (X = OMe; Y = NH_2) was finally converted into diltiazem hydrochloride by a known procedure[9d] (Scheme 1).

Experimental Section

Thiophenol and 2-aminothiophenol were purchased from Aldrich and were freshly distilled. Toluene, xylene, DMSO, CH_3-

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CN, and EtOH were dried and freshly distilled. Flash chromatography was performed using silica gel, EM Science (230–400 mesh). Melting points are uncorrected. Stereochemical assignments are based on comparison with known compounds.

Preparation of Ethyl *threo*-3-(*p*-Methoxyphenyl)-2(*R*),3-(*S*)-dihydroxypropionate. Ethyl (*p*-methoxyphenyl)propionate was dihydroxylated to furnish a 90% yield of optically active *threo*-ethyl 3-(*p*-methoxyphenyl)-2(*R*),3(*S*)-dihydroxypropionate using bis-dihydroquinine terephthalate ester (DHQ_2-TP)–OsO_4 as catalyst and $K_3[Fe(CN)_6]$–K_2CO_3 as cooxidant in *t*-BuOH–H_2O (1:1) (94% ee).[10a] The diol was recrystallized from toluene to furnish optically pure material in 85% yield: mp 68–70 °C; $[\alpha]^{25}_D = +5.0°$ (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.3 (t, J = 8.6 Hz, 3H), 2.65 (bs, 1H, D_2O exchangeable), 3.1 (bs, 1H, D_2O exchangeable) 3.80 (s, 3H), 4.25 (q, J = 8.6 Hz, 2H), 4.35 (bs, 1 H), 4.95 (bs, 1 H) 6.91 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H); IR (KBr)ν_{max} 3467, 1703 cm^{-1}.

Preparation of Ethyl *threo*-3-Phenyl-2(*R*),3(*S*)-dihydroxypropionate. Ethyl 3-phenylpropionate was dihydroxylated to furnish a 92% yield of optically active *threo*-ethyl 3-phenyl-2(*R*),3(*S*)-dihydroxypropionate using bisdihydroquinine terephthlate ester (DHQ_2-TP)–OsO_4 as catalyst and $K_3[Fe(CN)_6]$–K_2CO_3 as cooxidant in *t*-BuOH–H_2O (1:1) (95% ee).[10] The diol was recrystallized from toluene to furnish optically pure material in 88% yield: mp 70–72 °C; $[\alpha]^{25}_D = +10.4°$ (*c* 1.08, $CHCl_3$);[10a] ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 8.5 Hz, 3H), 2.8 (d, J = 6.5 Hz, 1H, D_2O exchangeable), 3.15 (d, J = 6.5 Hz, 1H, D_2O exchangeable), 4.25 (q, J = 8.5 Hz, 2H), 4.33 (bs, 1 H), 5.0 (bs, 1 H) 7.4 (m, 5H); IR (KBr)ν_{max} 3455, 1700 cm^{-1}.

Preparation of 4(*S*)-(*p*-Methoxyphenyl)-5(*R*)-(carboxyethyl)-1,3-dioxathiolane 2-Oxide (1a). Ethyl *threo*-3-(*p*-methoxyphenyl)-2(*R*),3(*S*)-dihydroxypropionate (2.88 g, 12 mmol) was dissolved in dry pyridine (20 mL) under argon. The reaction mixture was cooled to 0 °C, and freshly distilled thionyl chloride (1.56 g, 950 μL, 13 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and poured onto crushed ice containing dilute HCl. The reaction mixture was extracted with ether (3 × 20 mL), washed with dilute HCl (15%, 20 mL), aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a pale yellow oil which was chromatographed over silica gel to furnish 3.35 g (98%) of the cyclic sulfite **1a**: $[\alpha]^{25}_D = -113.3°$ (*c* 9.0, EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.7 Hz, 3H), 3.82 (s, 3H) 4.28 (m, 2H), 4.77 (d, J = 10.8 Hz), 5.16 (d, J = 10.8 Hz), 5.53 (d, J = 10.8 Hz), 6.1 (d, J = 10.8 Hz) (mixture of diastereomers, 2H), 6.9 (d, J = 12 Hz, 2H) 7.41 (dd, J = 12.0, 10.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 55.1, 62.3, 62.5, 80.6, 82.7, 83.2, 87.8, 114.1, 114.2, 128.4, 129.1, 160.3, 160.5, 165.8, 166.6; MS m/z (relative intensity) 287 (M^+ + 1, 3); IR ($CHCl_3$) ν_{max} 1760, 1256, 1214 cm^{-1}.

Preparation of 4(*S*)-Phenyl-5(*R*)-(carboxyethyl)-1,3-dioxathiolane 2-Oxide (1b). This compound was prepared according to the above procedure using ethyl *threo*-3-phenyl-2(*R*),3(*S*)-dihydroxypropionate (0.98 g, 5 mmol), triethylamine (1.3 g, 13 mmol), and thionyl chloride (0.72 g, 6.0 mmol) in CH_2Cl_2 (20 mL) at *ca.* 0 °C to furnish quantitative yield of cyclic sulfite **1b** (1.2 g, 94%) as a pale yellow syrup: ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J = 8.0 Hz, 3H), 4.26 (d, J = 8.0 Hz, 2 H), 4.74 (d, J = 10.8 Hz), 5.15 (d, J = 10.8 Hz), 5.54 (d, J = 10.8 Hz), 6.1 (d, J = 10.8 Hz) (mixture of diastereomers, 2H), 7.41 (m, 5H).

Reaction of Cyclic Sulfite (1a) with 2-Aminothiophenol (2a). A flame-dried two-necked 25 mL round bottom flask was charged with cyclic sulfite **1a** (286 mg, 1 mmol) and dry toluene (1 mL) and stirred under a constant flush of argon. Freshly distilled 2-aminothiophenol (112.5 mg, 96 μL, 0.9 mmol) was added dropwise, and the reaction mixture was allowed to stir for 5 min at rt. The reaction mixture was heated gently in a preheated oil bath at *ca.* 110 °C with stirring and refluxed until all the starting material disappeared (4 h). The reaction mixture was allowed to stand overnight at rt. The product was crystallized out as a pale yellow solid (110 mg) which was filtered, washed, and dried over P_2O_5. The mother liquor was chromatographed using a mixture of ethyl acetate/petroleum ether (1:4) to get the ethyl 2(*S*)-hydroxy-3(*S*)-[(*O*-aminophenyl)thio]-3-(*p*-methoxyphenyl)propionate (**3a**) (200 mg, 60%) in >96% ee: mp 112–113 °C; $[\alpha]^{25}_D = +249.8°$ (*c* 0.45, EtOH) (lit.[11] $[\alpha]^{25}_D = +266.0$ (*c* 1.23, EtOH)); IR (KBr) ν_{max} 3450, 3370, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, J = 7.7 Hz, 3H), 3.8 (s, 3H), 4.0 (m, 4H), 4.3 (b, 1H), 4.48 (s, 2H), 6.65 (m, 2H), 6.82 (d, J = 8.1 Hz, 2H), 7.1 (m, 2H), 7.34 (d, J = 7.3 Hz, 2H); MS m/z (relative intensity) 347 (M^+, 3). Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.2; H, 6.09, N, 4.03. Found: C, 61.84; H, 6.01, N, 4.38.

Reaction of Cyclic Sulfite 1a with Thiophenol 2a. A mixture of **1a** (135 mg, 0.5 mmol) and **2b** (55 mg, 0.5 mmol) in dry toluene (5mL) was placed in an oil bath, previously heated at *ca.* 110 °C under argon and refluxed. The reaction was monitored by TLC. After 12 h, a considerable amount of unreacted thiophenol was observed. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to furnish 15 mg (10%) of a compound, the structure of which has been assigned as ethyl 2-hydroxy-3-(phenylthio)-3-(*p*-methoxyphenyl)propionate (**3b**): ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (t, J = 8.0 Hz, 3H), 3.8 (s, 3H), 4.0 (m, 4H), 4.29 (b, 1H), 6.82 (d, J = 8.1 Hz, 2H), 7.3 (m, 5H), 7.34 (d, J = 8.0 Hz, 2H); IR (KBr) ν_{max} 3450, 1725 cm^{-1}; along with a 15% yield (16 mg) of ethyl *p*-methoxybenzoylacetate.

^1H NMR Evidence in Support of the H-Bonding between Cyclic Sulfite 1a with 2-Aminothiophenol (2a). In an NMR tube was placed **1a** (14 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL), the ^1H NMR was recorded, and then 6 mg of thiophenol **2b** (0.05 mmol) was added and the NMR spectrum was recorded after 1 h intervals. The spectra did not indicate any change in the chemical shift of either the cyclic sulfite **1a** or thiophenol **2b**. A similar result was observed when the experiment was performed on a mixture of **1b** with **2a**. In contrast, when the experiments were repeated with a mixture of **1a** and **2a**, a upfield shift of H^4 and H^5 protons in the ^1H NMR spectrum was observed. The doublets at δ 6.1 (J = 10.8 Hz) and 4.77 (J = 10.8 Hz) which were assigned to H^5 and H^4 protons of one of the diastereomers shifted by δ 0.2 and δ 0.1 ppm, respectively. A similar upfield shift was observed for the doublets at δ 5.53 (J = 10.8 Hz) and 5.16 (J = 10.8 Hz) belonging to H^5 and H^4 protons, respectively, of the other diastereomer.

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(11) An authentic sample of **3a** was prepared by esterification of optically pure 2(*S*)-hydroxy-3(*S*)-[(*o*-aminophenyl)thio]-3-(*p*-methoxyphenyl)propionic acid obtained from Dr. Reddy's Laboratories, Ltd., Hyderabad 500 138, India.