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Nucleophilic Addition to Cyclic 1,2-Sulfites

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Addition of heteroatom nucleophiles has been shown to attack at either the C_5- or the S-atom sites in 4-(benzyloxymethyl)-1,3-dioxa-2-thiolane 2-oxide. No C_4-reactivity was observed. The regioselectivity depended on the type of nucleophile.

Derivatives of glycerol such as glycidol and glycerol acetonides are versatile C_3-synthons that have found widespread use in syntheses of racemic as well as optically active products.[1] Introduction of substituents into the C_3-unit can be accomplished, e.g., by nucleophilic addition to glycidol derivatives or by selective derivatization of suitably substituted glycerols. Recently several workers, particularly from the Sharpless group, have reported reinvestigations of formation and reactions of 1,2-cyclic sulfates and have also put this reactivity into the framework of modern synthetic chemistry.[2]

In a synthetic study towards chiral, bioactive molecules derived from glycerol, we found that cyclic sulfate chemistry is potentially useful for the introduction of substituents into the C_3-framework by nucleophilic substitution. Cyclic sulfates are usually synthesized from the corresponding sulfites by a Ru-catalyzed oxidation procedure.[3] However, in our experience it is often difficult to obtain the pure sulfates and thus also the corresponding addition products. Losses during work-up were a troublesome aspect as well. For the purpose of reducing the number of reaction steps and to avoid the problems associated with sulfate formation, we decided to investigate the potential of the chemistry of cyclic sulfites.[4] Reports dealing with the same concept for 1,2-diols have recently appeared in the literature.[5] We now report the results of an investigation of nucleophilic addition reactions with the cyclic sulfite, **3**, derived from 3-benzyloxy-1,2-propanediol, **2**,[6] which was easily obtained from benzyloxymethyl-2,2-dimethyl-1,3-dioxolane, **1**.[7]

According to literature procedures, cyclic sulfites have usually been synthesized by reacting diols with thionyl chloride in a refluxing inert solvent such as dichloromethane or tetrachloromethane.[8] However, the reaction

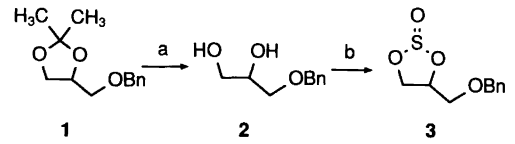

Fig. 1. a, 0.75 M H_2SO_4; b, $SOCl_2$–CH_2Cl_2, −78 °C.

of **2** with thionyl chloride at room temperature resulted in the formation of a multitude of products as indicated by GLC analysis. We observed in the present study, that virtually pure cyclic sulfite **3** could be obtained by reacting **2** with thionyl chloride in dichloromethane at low temperature (−78 °C). Under these conditions an essentially quantitative yield of the pure sulfite was obtained as a colorless oil. An alternative procedure was investigated involving the direct conversion of the acetonide **1** by the action of thionyl chloride in the presence of trace amounts of water and BF_3, but the yields here never exceeded 60%, and we therefore decided to use the two-step diol procedure. The product **3** was isolated as a 38:62 mixture of diastereomers. The composition was deduced from GLC and NMR measurements. However, GLC analyses of samples taken from the reaction mixture at −78 °C revealed a 49:51 mixture.

The sulfite **3** was then reacted with a series of nucleophiles in *N*,*N*-dimethylformamide, DMF, at room temperature according to the reaction in Fig. 2. The results are compiled in Table 1.

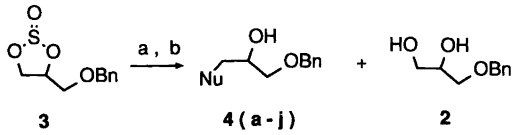

Fig. 2. a, Nu^-Na^+–DMF, r.t.; b, HCl–H_2O.

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Table 1. Reactions of the cyclic sulphite **3** with nucleophiles.

Entry	Nucleophile	Ratio **2**:**4**[a]	Product (s)	Yield (%) of **4**[b]
a	PhO^-Na^+	0:100	**4a**	81
b	$PhCH_2O^-Na^+$	1:6	**4b** + **2**	82
c	$PhNH^-Na^+$	3:1	**4c** + **2**	37[c]
d	$PhCH_2NH^-Na^+$	9:1	**4d** + **2**	32[c]
e	PhS^-Na^+	0:100	**4e**	86
f	$PhCH_2S^-Na^+$	1:18	**4f** + **2**	83
g	NaN_3–NH_4Cl	0:100	**4g**	86
h	NaCN–Bu_4NCl	0:100	**4h**	82
i	$PhCH_2NH_2$[d]	0:100	**4d**	84
j	$(CH_3)_2CHNH_2$[d]	0:100	**4j**	78

[a] The ratio was determined by GLC. [b] Isolated yield. [c] Combined yield of **4** + **2**. [d] Reaction in refluxing CH_3CN for 12 h.

Nucleophiles may attack at any of three different positions, at C_2 and C_3 or at the sulfite S atom. The reactions were worked up under acidic conditions, (0.1 M HCl). This caused hydrolysis of the sulfinate esters, resulting in the formation of the products **4** and **2**. The proportion of **2** in the product mixtures reflected the degree of *S*-attack by the nucleophile only, not the amount of unchanged **3**, as this compound was found to be stable under the hydrolytic conditions used. Products corresponding to C_2 attack were not detected. Thus, it appeared that the nucleophiles used in this study attack exclusively at the C_3 or the sulfite positions.

Reactions between **3** and the sodium salts of phenol and thiophenol, sodium azide and sodium cyanide in DMF at room temperature, in all cases, resulted in the exclusive formation of the C_3-addition products, with no noticeable formation of **2**. To ensure full conversion with azide and cyanide to **4g** and **4h**, the presence of ammonium chloride and tetrabutylammonium chloride, respectively, was required. The addition of the anions corresponding to aniline and the non-conjugated anions of the benzylic nucleophiles gave only moderate yields of the *C*-addition products together with varying amounts of product **2**, corresponding to an initial nucleophilic attack at the sulfite S-atom (Table 1, entries **c** and **d**). A high yield of **4d** was, however, obtained upon reacting benzylamine with **3** in refluxing acetonitrile (Table 1 entry **i**). The isopropylamine adduct **4j** was obtained in good yield after reaction under similar conditions. Interestingly, the same reaction involving aniline gave only a 45% conversion of **3**, and formation of a product mixture containing **4c** and **2** in a 4:1 ratio. The differences in reactivity of the nucleophiles in Table 1 may be rationalized in terms of the HSAB concept. Since polarizability is considered intrinsically associated with chemical softness, the observed regioselectivities may well be due to changes in softness because of reduced polarizability. The harder, less polarizable anions, will display an increased reactivity towards the harder sulfite S-atom site relative to the softer C_3-carbon.

The identities of the addition products **4** were confirmed by comparison of IR and NMR spectroscopic and chromatographic properties with those of authentic samples, prepared either as previously reported in the literature or by known standard procedures. Thus, compound **4a–f** were prepared by addition of the appropriate nucleophiles to 1-benzyloxy-2,3-epoxypropane, using the standard procedure earlier applied by Takano *et al.*[9] The epoxide was prepared according the procedure described by Nelson *et al.*[10]

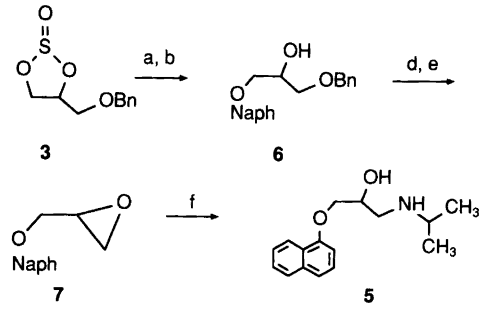

Fig. 3. a, 1-Naph-ONa–DMF, r.t.; b, 0.1 M HCl (61%); c, H_2/Pd–C (83%); d, 36% HBr–AcOH (93%); e, NaOH–CH_3OH, 0 °C (88%); f, iso-$PrNH_2$–H_2O (94%).

The value of **3** as a synthon was further explored in the synthesis of the β-adrenergic blocking agent propranolol, **5**, which is an important drug. The synthesis of **5** was accomplished according to Fig. 3. The key step in this synthesis is the transformation of **3** into the naphthyloxy adduct **6**. In this step, the general procedure described above for addition of nucleophiles to **3** was applied. Further elaboration of **6** to **5** via the epoxide **7** was performed using a modification of the procedure earlier described by Iriuchijima *et al.*[11] and others.[12] The properties of the intermediate products were similar to those described in Ref. 11. The overall yield of propranolol based on the sulfite **3** was 35%.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-100 NMR spectrometer, or on a JEOL JNM-EX400 FT NMR SYSTEM, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. IR spectra were obtained on a Nicolet 20-SXC FT-IR spectrophotometer. Mass spectra were recorded on a AEI MS-902 spectrometer at 70 eV (IP) and 180 °C inlet temperature. GC measurements were made on a Varian 3700 gas chromatograph equipped with a BP-1 capillary column (24 m). Preparative TLC was performed on 20×20 cm^2 glass plates covered with 1 mm Merck silica gel $60F_{254}$.

4-(Benzyloxymethyl)-1,3-dioxa-2-thiolane 2-oxide, **3**. A solution containing 0.30 g (1.6 mmol) of 3-benzyloxy-1,2-propanediol, **2**, in 10 ml of dichloromethane was cooled to −78 °C in dry ice–acetone bath. Thionyl chloride (0.24 g, 2.0 mmol) was then added over a 10 min period, and the resulting reaction mixture was allowed to stand

for another 30 min. The mixture was then warmed to room temperature and the solvent evaporated off under reduced pressure, leaving behind an essentially quantitative yield of the desired product, **3**, which was shown by GLC to be of better than 97% purity. The crude product was used in the subsequent reactions without further purification. The GLC chromatogram showed two clearly separated signals in a 38:62 ratio due to the presence of two diastereomers, which was also confirmed by the NMR spectra. GLC analyses of samples taken from the reaction mixture at −78 °C revealed a 49:51 mixture.

IR (KBr): 3064, 3031, 2903, 2867, 1734, 1497, 1453, 1209, 1105, 1052, 1028, 965, 848, 742, 699 cm^{-1}. MS [*m/z* (% rel. int.)]: 228 (M^+, 5), 164 (3), 135 (2), 134 (2), 122 (2), 107 (22), 105 (6), 92 (10), 91 (100), 77 (3), 65 (9), 58 (4), 43 (4), 41 (4). ^1H NMR (400 MHz, $CDCl_3$, TMS) (main diastereomer): δ 3.54 and 3.61 (ABX-pattern, 2 H), 4.57 (s, 2 H), 4.30 and 4.68 (m, 2 H), 5.06 (m, 1 H); (minor diastereomer): δ 3.77 and 3.86 (ABX-pattern, 2 H), 4.53 (m, 2 H), 4.60 (s, 2 H), 5.06 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS) (main diastereomer): δ 67.2, 69.2, 73.4, 78.6, 128.1, 128.3, 128.9, 137.4; (minor diastereomer): δ 67.8, 70.3, 73.7, 81.2, 128.1, 128.3, 128.9, 137.6.

Reactions of **3** *with nucleophiles: general procedure.* A solution of the appropriate anionic nucleophile was prepared by stirring a mixture of 5 mmol of the reagent and 0.135 g (5.5 mmol) of sodium hydride in 5 ml of dry DMF. A solution of 1.15 g (5 mmol) of **3** in 3 ml of DMF was added and the resulting reaction mixture stirred at room temperature overnight. 25 ml of ether were then added and the mixture treated with 5 ml of 0.1 M hydrochloric acid. The ether phase was then extracted with another three portions of hydrochloric acid, 0.1 M sodium hydroxide and brine, dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure, yielding the crude product, **4** (and **2**) which was further purified by recrystallization or flash chromatography. The identities of the products were confirmed by comparison of the chromatographic and spectroscopic properties with those of authentic samples.

3-Azido-1-benzyloxy-2-propanol, **4g**. This product was obtained using the general procedure described above from 0.20 g (0.88 mmol) of **3**, and 0.29 g (4.5 mmol) of sodium azide in 10 ml of DMF except that ammonium chloride (0.10 g, 1.7 mmol) was added to the reaction mixture. The yield of pure **4g** was 86%.

1-Benzyloxy-3-cyano-2-propanol, **4h**. Tetrabutylammonium chloride, 0.29 g (2.6 mmol) and 0.13 g (2.6 mmol) of sodium cyanide were stirred in 10 ml of dry DMF for 15 min and then **3** (0.20 g, 0.88 mmol) in 3 ml of DMF was added. The resulting mixture was stirred at room temperature for 32 h and then worked up as described in the general procedure. **4h** was isolated as a colorless oil in 82% yield.

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