

고리 설파이트의 친핵성 치환반응

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Nucleophilic Substitution Reactions of Cyclic Sulfites

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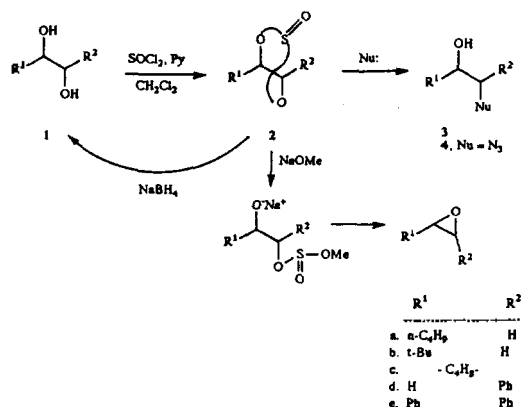
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Although the chemistry of cyclic sulfites has been known a long time¹, the synthetic utility of these compounds has not been studied extensively unlike the corresponding sulfates and sulfonates². Recently, the addition of nucleophiles to cyclic sulfites has proven to be a useful method for the synthesis of chiral molecules and natural products³. Among this nucleophilic reaction of azide with cyclic sulfite is perhaps the most commonly studied and well known for its high selectivity⁴. However the reactivity of other nucleophiles at varying conditions has not been studied. Now we wish to report nucleophilic reaction of various nucleophiles with representative cyclic sulfites (Scheme 1). And a simple method for the synthesis of amino alcohols from azido alcohols with borohy-

dride exchange resin (BER) nickel acetate and BER copper sulfate was also mentioned⁵.

RESULTS AND DISCUSSION

The cyclic sulfites prepared in quantitative yield by the reaction of vicinal diols with thionyl chloride in dichloromethane^{1c,6}, undergo facile nucleophilic reaction with sodium azide in dimethylformamide (DMF) to afford 78~92% yield of azido alcohols (Table 1, entry 1, 6, 13 and 18). In the case of the cyclic sulfite derived from 1-phenylethane-1,2-diol, the nucleophilic attack occurs at the benzylic position giving to 2-amino-2-phenylethanol and 2-iodo-2-phenylethanol (Table 1, entry 13 and 14). Whereas the cyclic sulfites prepared from 1,2-hexandiol and 3,3-dimethyl-1,2-butandiol furnishes 1-azido-2-hexanol and 1-azido-3,3-dimethyl-2-butanol respectively. Nucleophilic opening of cyclic sulfite with LiI in refluxing DMF gives iodo alcohol 4 in 39~59% yield (Table 1, entry 2, 7, 14, and 19). However cyclic sulfite of 1,2-cyclohexandiol is resistant to the nucleophiles such as LiI, NaN₃, NaCN, and NaOMe at refluxing in DMF for twenty four hours. This implies the secondary position of this cyclic sulfite is stable to the nucleophilic attack. Reaction of aliphatic cyclic sulfites 2a and 2b with NaCN give corresponding diol 1a and 1b in 70~73% yield respectively (Table 1, entry 3 and 8), whereas aromatic cyclic



Scheme 1.

Table 1. Reaction of cyclic sulfites with nucleophiles^a

Entry	Cyclic sulfites	Reaction conditions	Product	Isolated yield, % ^b
1	2a	NaN ₃ , DMF, reflux, 3 h	3	82
2	2a	LiI, DMF, reflux, 24 h	4	59 ^c
3	2a	NaCN, DMF, reflux, 24 h	1	70
4	2a	NaOMe, THF, RT, reflux, 3 h	1	90
5	2a	NaBH ₄ , THF, RT, 2 h	1	83
6	2b	NaN ₃ , DMF, reflux, 3 h	3	80
7	2b	LiI, DMF, reflux, 24 h	4	39 ^{c,d}
8	2b	NaCN, DMF, reflux, 8 h	1	73 ^e
9	2b	NaOMe, THF, reflux, 3 h	1	67
10	2b	NaBH ₄ , THF, RT, 2 h	1	80
11	2c	NaN ₃ , NaCN, LiI, NaOMe, reflux, DMF, 24 h	NR	
12	2c	NaBH ₄ , THF, RT, 3 h	1	62 ^e
13	2d	NaN ₃ , DMF, reflux, 3 h	3	78
14	2d	LiI, DMF, reflux, 24 h	4	45 ^e
15	2d	NaCN, DMF, reflux, 24 h	NR	
16	2d	NaOMe, THF, reflux, 3 h	Styrene oxide	21 ^e
17	2d	NaBH ₄ , THF, RT, 2 h	1	90
18	2e	NaN ₃ , DMF, reflux, 3 h	3	92
19	2e	LiI, DMF, reflux, 4 h	3	40 ^{e,f}
20	2e	NaCN, DMF, reflux, 24 h	NR	
21	2e	NaOMe, THF, reflux, 10 h	Stilbene oxide	50 ^h
22	2e	NaBH ₄ , THF, RT, 2 h	1	93
23	2e	LiAlH ₄ , THF, RT, 2 h	1	85

^aA nucleophile (4 eq) was added to a solution (0.25 M) of a cyclic sulfite in solvent and the mixture was stirred under the given reaction conditions. ^bThe yields are the isolated yields after column chromatography. ^cUnreacted cyclic sulfite was recovered. ^dThe yield of product was 34% in THF. ^eCyclic sulfite (21%) and phenyl-1,2-ethanediol (52%) were recovered. ^fUnreacted 55% of cyclic sulfite was recovered. ^gThe product was obtained in 30% yield when NaI was used as nucleophile. ^hHydrobenzoin (43%) was produced.

sulfites **2d**, **2e** and cyclic sulfite of 1,2-cyclohexanediol **2c** do not react with NaCN at DMF refluxing condition. Reaction of cyclic sulfites **2d** and **2e** with sodium methoxide give the mixture of epoxide and diol suggesting that the methoxide ion attack at sulfur site. Lohray reported that cyclic sulfite of ethylene glycol with sodium methoxide gave ethylene oxide, whereas phenolate reacted with the same cyclic sulfite yielded aryl 2-hydroxyethyl ether^{1a}. Interestingly, using sodium borohydride as hydride nucleophile, all of the examined cyclic sulfites gave only diols in high yields at mild reaction condition (Table 1, entry 5, 10, 12, 17 and 22). This indicates the hydride nucleophile can be used deprotect the cyclic sulfite to the correspon-

ding diol.

Amino alcohols containing terminal amino group are known to be otherwise difficult to prepare. However, treatment of α -azido alcohol **3** with BER-Ni(OAc)₂ and BER-CuSO₄ in methanol produces α -amino alcohol in 60~85% yield (Table 2, entry 1-4). Since the reduction of azides to amines is an important reaction in organic synthesis, many reagents have been reported suitable for this purpose⁹. However BER-Ni(OAc)₂ and BER-CuSO₄ system is a reagent of choice for the reduction of azides to amines because of its good yields and simple work-up procedure for the isolation of product¹².

Table 2. Preparation of α -amino alcohol from α -azido alcohol with BER-Ni(OAc)₂ and BER-CuSO₄ in methanol at room temperature^a

Entry	α -Azido alcohol	Isolated yield of α -amino alcohol, %	
		BER-Ni(OAc) ₂	BER-CuSO ₄
1	4a	74	70
2	4b	85	75
3	4d	76	60
4	4e	79	76

^a α -Azido alcohol (5 mmol) was added to the mixture of BER (25 mmol) and Ni(OAc)₂ (0.5 mmol) or CuSO₄ (0.5 mmol) in methanol. The reaction mixture was then stirred at room temperature for 1 h.

EXPERIMENTAL

¹H-NMR spectra were recorded with a Varian EM-390, XL-200, or Jeol GX-400 instruments with TMS as internal standard. IR spectra were recorded with Hitachi 270-30 spectrophotometer. Anion Exchange resin (Amberlite IRA-400[20~50 mesh]) was used for supporting polymer of BER. All of the organic compounds utilized in this study were commercial products of the highest purity. Some compound were prepared using standard synthetic methods. Borohydride Exchange Resin was prepared according to the literature procedure¹⁰.

General procedure for preparation of cyclic sulfite. The preparation of cyclic sulfite from 1,2-diphenyl-1,2-ethanediol is representative. An oven-dried 150 ml three necked flask equipped with a reflux condenser and dropping funnel, was placed 3.67 g (17.1 mmol) of 1,2-diphenyl-1,2-ethanediol in 40 ml of methylene chloride, and 5.6 ml (68.5 mmol) of pyridine was added at room temperature. To this was added dropwise 1.5 ml (20.5 mmol) of thionyl chloride. During this period, reaction mixture was stirred vigorously at room temperature. After 4 h, reaction mixture added 5 ml of cold water and the organic layer was extracted with methylene chloride (30 ml \times 3). The extracts were washed with cold 2 M HCl (2 \times 20 ml), followed by brine and dried over anhydrous magnesium sulfate, filtered and concentrated to dryness on

a rotary evaporator. The crude solid product was recrystallized from *n*-hexane and 1,2-diphenyl-1,2-ethane cyclic sulfite was obtained in 96% yield (4.281 g): mp. 125~127°C; ¹H-NMR(CDCl₃), 6.86~6.89(d, 2), 7.12~7.15(m, 10); IR(KBr) 3040, 1456, 1214, 962 cm⁻¹.

Reaction of cyclic sulfite with sodium azide. The preparation of 2-azido-1,2-diphenyl ethanol is representative, a 50 ml oven-dried flask, equipped with a side arm, fitted with a rubber septum, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was cooled down to room temperature under a stream of dry nitrogen. A reaction flask was charged with 1.13 g (4.4 mmol) of 1,2-diphenyl-1,2-ethane cyclic sulfite. To this was added 25 ml of DMF and 1.14 g (17.6 mmol) of NaN₃. After refluxing for 3 h, the mixture was cool down to room temperature. 5 ml of water was added, and extracted with three portions of 20 ml of Et₂O. The organic layer was washed with water and brine, and dried with anhydrous sodium sulfate. The solution was filtered, concentrated, and purified by silica gel column chromatography (Et₂O/*n*-hexane=1/1) to give 872 mg (92%) of 2-azido-1,2-diphenyl ethanol as a colorless oil: bp. 175~178°C; ¹H-NMR(CDCl₃) 2.75~2.85(s, br, 1), 4.75~4.60(d, 1), 4.70~4.73(d, 1), 7.03~7.23(m, 10); IR(film) 3464, 3040, 2108, 1680, 1254 cm⁻¹.

Reaction of 2-phenyl-1,2-ethane cyclic sulfite with sodium borohydride. The reaction of 2-phenyl-1,2-ethane cyclic sulfite is representative. The experimental set up was same as in the previous experiment. Into a clean, pre-dried 100 ml flask was charged with 340 mg (2.0 mmol) of 2-phenyl-1,2-ethane cyclic sulfite in 30 ml of THF. To this was added 75 mg (2.0 mmol) of sodium borohydride at room temperature. After 2 h reaction at room temperature, the reaction mixture was quenched with 5 ml of cold water, followed by 20 ml of 2 M HCl solution. The organic layer was extracted three times with Et₂O (3 \times 50 ml) and washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated. The crude solid was recrystallized from ethanol and 250 mg (90%) of 2-phenyl-1,2-ethanediol was obtained as a

white solid: mp. 64~65°C (lit.¹³, 66~68°C); IR (KBr) 3408, 2963, 1454 cm⁻¹.

General procedure for preparation of α -amino alcohol with BER-Ni(OAc)₂. The reaction of 1-amino-3,3-dimethyl-2-buthanol from 1-azido-3,3-dimethyl-2-buthanol is representative. To the solution of 0.13 g (0.5 mmol) of Ni(OAc)₂·4H₂O in methanol (5 ml) was added 8.1 g (25 mmol) of BER with vigorous stirring at room temperature. After 1 min, 750 mg (5 mmol) of 1-azido-3,3-dimethyl-2-buthanol was added to the reaction flask and the mixture was stirred at room temperature for 1 h. Then the resin was removed by filtration. The methanol was evaporated and purified by silica gel column chromatography (*n*-hexane/Et₂O = 3/2) to afford 510 mg (85%) of 1-amino-3,3-dimethyl-2-buthanol as a white solid: mp. 69~71°C; ¹H-NMR(CDCl₃) 0.83~0.98(s, 9), 1.68~1.71(s, 1), 2.48~2.56(dd, 1), 2.85~2.89(dd, 1), 3.12~3.20(dd, 1); IR(KBr) 3299, 2964, 1596, 1478, 1350 cm⁻¹.

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