Journal of the Korean Chemical Society
1994, *Vol. 38, No. 6*
Printed in the Republic of Korea

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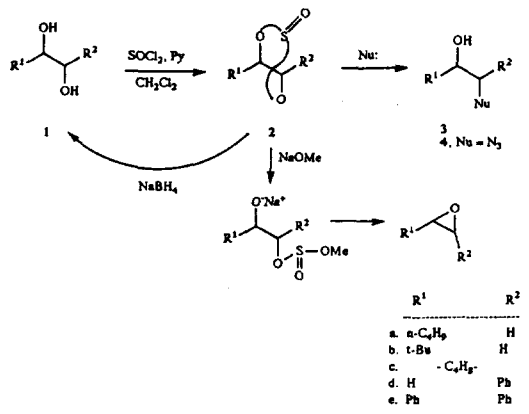
고리 설파이트의 친핵성 치환반응

景永洙* · 全完植
강릉대학교 자연과학대학 화학과
(1994. 1. 14 접수)

Nuclephilic Substitution Reactions of Cyclic Sulfites

Young Soo Gyoung* and Wan Sik Jeon
Department of Chemistry, Kangnung National University, Kangnung 210-702, Korea
(Received January 14, 1994)

Although the chemistry of cyclic sulfites has been known a long time[1], the synthetic utility of these compounds has not been studied extensively unlike the corresponding sulfates and sulfonates[2]. Recently, the addition of nucleophiles to cyclic sulfites has proven to be a useful method for the synthesis of chiral molecules and natural products[3]. Among this nucleophilic reaction of azide with cyclic sulfite is perhaps the most commonly studied and well known for its high selectivity[4]. 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 borohydride exchange resin (BER) nickel acetate and BER copper sulfate was also mentioned[5].



Scheme 1.

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). Whearas 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 nuclephiles such as LiI, NaN_3, 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

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**	$NaBH_4$, TF, 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[c]
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[c]
13	**2d**	NaN_3, DMF, reflux, 3 h	**3**	78
14	**2d**	LiI, DMF, reflux, 24 h	**4**	45[c]
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[f,g]
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

[a]A 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. [b]The yields are the isolated yields after column chromatography. [c]Unreacted cyclic sulfite was recovered. [d]The yield of product was 34% in THF. [e]Cyclic sulfite (21%) and phenyl-1,2-ethanediol (52%) were recovered. [f]Unreacted 55% of cyclic sulfite was recovered. [g]The product was obtained in 30% yield when NaI was used as nucleophile. [h]Hydrobenzoin (43%) was produced.

sulfites **2d**, **2e** and cyclic sulfite of 1,2-cyclohexandiol **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 corresponding 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-$CuSO_4$ 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 purpose[9]. However BER-$Ni(OAc)_2$ and BER-$CuSO_4$ 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 product[12].

Table 2. Preparation of α-amino alcohol from α-azido alcohol with BER-$Ni(OAc)_2$ and BER-$CuSO_4$ 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 $CuSO_4$ (0.5 mmol) in methanol. The reaction mixture was then stirred at room temperature for 1 h.

EXPERIMENTAL

^{1}H-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 procedure[10].

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 m*l* 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 m*l* of methylene chloride, and 5.6 m*l* (68.5 mmol) of pyridine was added at room temperature. To this was added dropwise 1.5 m*l* (20.5 mmol) of thionyl chloride. During this period, reaction mixture was stirred vigorously at room temperature. After 4 h, reaction mixture added 5 m*l* of cold water and the organic layer was extracted with methylene chloride (30 m*l*×3). The extracts were washed with cold 2 *M* HCl (2×20 m*l*), 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℃ ; ^{1}H-NMR($CDCl_3$), 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 m*l* 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 m*l* of DMF and 1.14 g (17.6 mmol) of NaN_3. After refluxing for 3 h, the mixture was cool down to room temperature. 5 m*l* of water was added, and extracted with three portions of 20 m*l* of Et_2O. 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 (Et_2O/*n*-hexane=1/1) to give 872 mg (92%) of 2-azido-1,2-diphenyl ethanol as a colorless oil: bp. 175~178℃ ; ^{1}H-NMR($CDCl_3$) 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 m*l* flask was charged with 340 mg (2.0 mmol) of 2-phenyl-1,2-ethane cyclic sulfite in 30 m*l* 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 m*l* of cold water, followed by 20 m*l* of 2 *M* HCl solution. The organic layer was extracted three times with Et_2O (3×50 m*l*) 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℃ (lit.[13], 66~68℃); 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 $Ni(OAc)_2 \cdot 4H_2O$ 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/Et_2O= 3/2) to afford 510 mg (85%) of 1-amino-3,3-dimethyl-2-buthanol as a white solid: mp. 69~71℃; ^{1}H-NMR($CDCl_3$) 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}.

ACKNOWLEDGEMENT

This work was supported by NON DIRECTED RESEARCH FUND, Korea Research Foundation, 1992.

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