

## 수소화붕소 아연에 의한 에폭시케톤의 선택환원

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## Selective Reduction of $\alpha$ , $\beta$ -Epoxy Ketones with Zinc Borohydride

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**요약.** 에폭시케톤을 수소화붕소 아연으로 환원하면 카르보닐기만 선택적으로 환원되어 해당하는 에폭시알코올을 좋은 수득율로 얻을수 있음을 알 수 있었다.

**ABSTRACT.** Reduction of epoxy ketones with zinc borohydride proceeds selectively to the corresponding epoxy alcohols in good yields. Thus we obtained 3, 4-epoxy-4-methyl-2-pentanol (79.8%), *trans*-isophorol oxide (89.5%), *trans*-2-benzal-cyclohexanol oxide (84.1%) and *trans*-chalcone oxide (97.9%, crude) from the corresponding epoxy ketones.

### INTRODUCTION

Some time ago the reducing characteristics of zinc borohydride with representative organic compounds containing common functional groups had been explored in this laboratory.<sup>1</sup> And it had been found that a carbonyl group is reduced readily with this reagent, but an epoxy group is inert. Then it occurred to us that zinc borohydride reduction of epoxy ketones might give the corresponding epoxy alcohols, which have been commonly prepared by peracid-epoxy-dation of the corresponding allylic alcohols.<sup>2</sup> In this report we wish to demonstrate an alternative method via the selective reduction of  $\alpha$ ,  $\beta$ -epoxy ketones with excellent yield. The

four epoxy ketones; namely 3, 4-epoxy-4-methyl-2-pentanone, isophorone oxide, *trans*-2-benzal-cyclohexanone oxide, and *trans*-chalcone oxide, were reduced with zinc borohydride to give the corresponding epoxy alcohols in the yields of 79.8, 89.5, 84.1 and 97.9%, respectively.

### EXPERIMENTAL

**General.** All b. p's and m. p's are uncorrected. The infrared spectra were determined either with Beckman IR 8 or IR 33, and the nmr spectra with Varian HA-100. The nmr spectra were recorded in  $\delta$  scale with TMS as an internal standard unless otherwise stated. Tetrahydrofuran was purified by distilling over excess lithium aluminumhydride. The sodium borohydride used

was 95 % gasometrically (Ventron), and used as such without further purification. All glassware was dried thoroughly at 125° in a drying oven and cooled under a stream of dry nitrogen. Thus all reduction experiments were carried out under anhydrous condition. Hypodermic syringes were used to introduce and transfer the solution.

**Preparation of THF solution of Zinc Borohydride<sup>3</sup>.** A mixture of reagent grade (Merck) anhydrous zinc chloride (8.1774 g, 60 mmoles) and 50 ml of THF was stirred in a moisture-free flask (mercury-sealed) until all of the solid disappeared and let stand. To a pre-dried 500 ml flask (mercury-sealed), were added 230 ml of THF and 16.6 % excess over the stoichiometric amount of sodium borohydride (5.58 g, 140 mmoles) with stirring. And the zinc chloride solution, prepared above, was added to the slurry solution of sodium borohydride with a syringe. Stirring was continued for 2 days, then the flask was set aside to settle down the precipitate. An aliquot of the resulting clear supernatant was hydrolyzed with 2 N sulfuric acid-THF mixture and found to be ca. 2 M in hydride, 0.25 M in "Zn(BH<sub>4</sub>)<sub>2</sub>"<sup>3b</sup> and stored as such under positive nitrogen pressure with a connection to a mercury seal. The hydride concentration was practically constant over 30 days at room temperature (15~26 °C)<sup>1</sup>. For all experiments, calculated quantity of the solution was transferred from the supernatant, as needed.

#### Preparation of the Epoxy Ketones

3,4-Epoxy-4-methyl-2-pentanone was prepared by epoxidation of mesityl oxide with hydrogen peroxide.<sup>5</sup> b. p 61~63°/20 mm,  $n_D^{25}$  1.4225 (lit.<sup>5</sup> b. p 61~62°/20 mm,  $n_D^{20}$  1.4238) ir (liq. film) 1721 cm<sup>-1</sup> (C=O), 1240 cm<sup>-1</sup> (C—O—C), 870 cm<sup>-1</sup> (C—O—C).

Isophorone oxide was prepared from isophorone with hydrogen peroxide.<sup>6</sup> b. p 75~76°/6 mm,

$n_D^{23}$  1.4513 (lit.<sup>6</sup> b. p 74~75°/6 mm,  $n_D^{30}$  14513), ir (liq. film) 1710 cm<sup>-1</sup> (C=O), 1250 cm<sup>-1</sup> (C—O—C), nmr (CCl<sub>4</sub>) 0.90 (s, 3), 1.04 (s, 3), 1.40 (s, 3), 2.90 (s, 1).

*trans*-2-Benzalicyclohexanone oxide was prepared from *trans*-2-benzalicyclohexanone.<sup>7</sup> m. p 124~125° (lit.<sup>7</sup> m. p 124~126°). ir (CCl<sub>4</sub>) 1715 cm<sup>-1</sup> (C=O), 1230 cm<sup>-1</sup> (C—O—C), 880 cm<sup>-1</sup> (C—O—C) (lit.<sup>7</sup> 1715 cm<sup>-1</sup> (C=O)), nmr (CS<sub>2</sub>, external TMS) 7.18 (-s, 5), 4.18 (s, 1)

*trans*-Chalcone oxide was synthesized via alkaline epoxydation of *trans*-chalcone.<sup>8</sup> m. p 89.5~90.5° (lit.<sup>8</sup> m. p 89~90°). ir (CCl<sub>4</sub>) 1700 cm<sup>-1</sup> (C=O), 1230 cm<sup>-1</sup> (C—O—C). nmr (CCl<sub>4</sub>) 3.97 (s, 1), 4.01 (s, 1), 7~8 (m, 10).

#### Selective Reduction of Epoxy Ketones with Zinc Borohydride

**Rate Study.** Reduction of *trans*-chalcone oxide is described as a representative. To an oven-dried 100 ml flask with a rubber-capped side arm, equipped with a magnetic stirring bar and a reflux condenser connected to a gas buret, were added 10 ml of 0.25 M zinc borohydride solution (20 mmoles of hydride) and 20 ml of THF. The reduction was started by the dropwise addition of 10 ml of 1 M solution of *trans*-chalcone oxide (10 mmoles, 2.2425 g) with stirring at room temperature. At appropriate time as indicated in Table 1 each 4 ml aliquot of the reaction mixture was removed with a syringe and hydrolyzed with 2 N sulfuric acid-THF mixture. Thus the residual hydride content was measured gasometrically, and the number of moles of hydride consumed per mole of *trans*-chalcone oxide was calculated. The results are summarized in Table 1.

**Product Study.** The following procedure for the reduction of isophorone oxide is a representative. To a 100 ml flask (equipped as in rate study) were added 30 ml of THF and 30 ml of THF solution of 0.25 M zinc borohydride (60 mmoles of hydride). To this 4.63 g (30 mmoles)

of isophorone oxide dissolved in 50 ml of THF was added slowly during 15 min period. After 3 hours stirring, excess hydride was carefully destroyed with 10 ml of saturated sodium sulfate solution. The precipitate was filtered and washed well with 20 ml portions of ether. The combined filtrate was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvents were removed on a rotary evaporator. To the residue 40 ml of anhydrous methanol was added and again evaporated off to expel the boron contaminant as methyl borate. The residue was 4.58 g,  $n_D^{20}$  1.4580. After distillation there was obtained 4.19 g (89.5 %) of *trans*-isophorol oxide was obtained, b. p 97~99°/4 mm,  $n_D^{20}$  1.4630, ir (neat) 3300cm<sup>-1</sup>, 1250cm<sup>-1</sup>, 3610cm<sup>-1</sup> (on dilution, free OH), nmr (CCl<sub>4</sub>) 0.92 (s, 3), 0.97 (s, 3), 1.33 (s, 3), 2.84 (s, 1), 4.05 (doublet of doublet, 1). (For *cis* isomer, lit.<sup>9,21</sup> b. p 46°/0.3 mm  $n_D^{25}$  1.4635, nmr (CDCl<sub>3</sub>) 0.92 (s, 3), 0.94 (s, 3), 1.40 (s, 3), 3.17 (d, 1), 4.10 (m, 1))

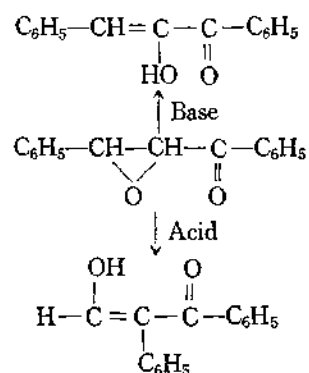
3,4-Epoxy-4-methyl-2-pentanone: Yield 79.8 %, b. p 58~60°/6 mm  $n_D^{28}$  1.4180, ir (liq. film) 3380, 1240, 870 cm<sup>-1</sup> nmr (CCl<sub>4</sub>) 1.2~1.4 (mix. of doublet and singlet, 9) 2.50 (d, 1), 3.48 (m, 1), 3.93 (5, 1) mp. as the tosylate ester (ir. (nujol), 1250, 1180, 1170, 880 cm<sup>-1</sup>) 83~85° (lit.<sup>10</sup> m. p 86°)

*trans*-2-Benzalcylohexanol oxide: Yield 84.1 %, m. p 113~115° (methanol), ir (nujol) 3400, 1220, 880 cm<sup>-1</sup>. nmr (CS<sub>2</sub>; external TMS) 4.18 (s, 1), 7.18 (s, 5)

*trans*-Chalcone oxide: Yield 97.9 % (crude), An attempt to distill the viscous oil resulted in decomposition of the product.  $n_D^{20}$  1.5775 (crude) (lit.<sup>8</sup>  $n_D^{25}$  1.5729 for crude), ir (CCl<sub>4</sub>) 3350, 1230, 880 cm<sup>-1</sup>. nmr (CCl<sub>4</sub>) 3.06 (m, 1) 3.95 (m, 1), 4.66 (m, 1), 7.2 (m, 10)

## RESULTS and DISCUSSION

It is well known that  $\alpha, \beta$ -epoxy ketones undergo facile isomerization in the presence of acids, or bases.<sup>11</sup> For example,



Accordingly mild and neutral reducing agent should be employed for this selective carbonyl reduction of  $\alpha, \beta$ -epoxy ketones. Apparently, sodium borohydride seems to be inadequate since sodium borohydride has been reported to reduce epoxides slowly,<sup>12</sup> and to be sufficiently basic to induce epimerization of  $\alpha$ -substituent of a ketone.<sup>13</sup> Indeed, we found only rare cases of reduction of  $\alpha, \beta$ -epoxy ketones with sodium borohydride.<sup>14</sup> On the other hand zinc borohydride does not reduce the epoxy group,<sup>1</sup> and its neutrality was reported by previous workers.<sup>15</sup> Thus we have found, as shown in *Table 1*, all

Table 1. Reaction of  $\alpha, \beta$ -epoxy ketones with zinc borohydride at room temperature.

Epoxy Ketones	Time, (hr)			
	0.5	1.0	3.0	6.0
3,4-Epoxy-4-methyl-2-pentanone	0.99 <sup>b</sup>	1.00	1.01	1.03
Isophorone oxide	0.96	1.00	1.01	1.01
<i>trans</i> -2-Benzalcylohexanone oxide	0.99	0.99	1.00	1.01
<i>trans</i> -Chalcone oxide	0.97	1.00	1.01	1.01

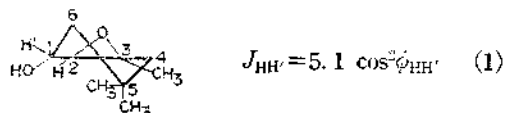
<sup>a</sup> 0.5 M in hydride and 0.25 M in compound.

<sup>b</sup> The number of moles of hydride used for reduction per mole of compound.

four  $\alpha, \beta$ -epoxy ketones were reduced with this reagent within one hour, consuming only one mole of hydride per mole of each compound. This suggests clearly that the reaction is completed when the carbonyl group is reduced to alcohol and the epoxy ring unchanged, and we confirmed this by isolating the products in good yields.

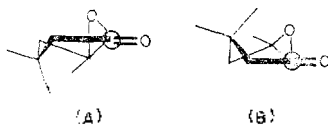
The rapid rate of reduction of  $\alpha, \beta$ -epoxy ketone is impressive (Table 1). All the four  $\alpha, \beta$ -epoxy ketones tested were reduced within 30 min. This is quite a contrast to the slow reductions of the corresponding  $\alpha, \beta$ -unsaturated ketones<sup>16</sup> (mesityl oxide, 24 hr; isophorone, 96 hr; *trans*-2-benzalicyclohexanone, 3 hr; *trans*-chalcone, 48 hr). Presumably the lack of conjugation and the inductive effect of epoxy oxygen of  $\alpha, \beta$ -epoxy ketone are responsible for the fast reductions.<sup>16-18</sup> The lack of conjugation in these epoxy ketones could be seen from the facts that the carbonyl absorption frequency of 3,4-epoxy-4-methyl-2-pentanone ( $1721\text{ cm}^{-1}$ ), isophorone oxide ( $1710\text{ cm}^{-1}$ ), and *trans*-chalcone oxide ( $1700\text{ cm}^{-1}$ ) are higher than those of unsaturated ones, mesityl oxide ( $1685\text{ cm}^{-1}$ ), isophorone ( $1665\text{ cm}^{-1}$ ), *trans*-2-benzalicyclohexanone ( $1658\text{ cm}^{-1}$ ), and *trans*-chalcone ( $1667\text{ cm}^{-1}$ ). As shown in the experimental section, we could obtain the epoxy alcohols in the yields 80~90%. These epoxy alcohols may be prepared by the epoxidation of the corresponding allylic alcohols.<sup>2,9</sup> However, since the allylic alcohols have to be prepared by the selective reduction of  $\alpha, \beta$ -unsaturated ketones, we believe the epoxidation of  $\alpha, \beta$ -unsaturated ketone with hydrogen peroxide and the reduction with zinc borohydride could be a good alternative way to the epoxy-alcohols. Although this study was primarily aimed to demonstrate the selectivity of zinc borohydride in these cases, we found hydride attack was stereo-selective in the case of isophorone oxide. Sodium borohydride has been

reported to yield 80% of *trans*-isophorol oxide and 20% of *cis* isomer without mentioning the overall yield and the physical data of the products.<sup>19</sup> In contrast we isolated only the *trans* alcohol (judged by nmr) in 90% yield. A molecular model of *trans*-isophorol oxide shows that the dihedral angle between the hydrogen at C-1 and the epoxy hydrogen at C-2 would be ca.  $90^\circ$ . Introduction of this value into modified Karplus equation (1)<sup>20</sup> yields that the coupling constant would be 0.



Therefore the epoxy hydrogen is expected to be singlet, and this is what we observed. And splitting pattern of C-1 hydrogen of the *trans* alcohol is a doublet of doublet, whereas that of *cis*-isophorol oxide is splitted further by coupling with the epoxy hydrogen.<sup>21</sup> Also in the ir spectrum of the isolated alcohol we could observe a absorption peak due to "free" O—H ( $3610\text{ cm}^{-1}$ ) on dilution with  $\text{CCl}_4$ , which is expected only for the *trans* alcohol.

The hydride attack from the side of epoxide ring can be rationalized easily as previous workers have pointed out.<sup>18</sup>



Thus, of these two possible conformations, the methyl group at C-5, *cis* to the epoxide ring, should be difficult to be in axial position due to axial methyl-epoxy oxygen interaction (conformer B), therefore conformer (A) should be more stable. Consequently the axial methyl at C-5 of (A), *trans* to the epoxide ring, should

hinder the hydride attack from the backside of the epoxide ring effectively. And the predominant yield of the *trans* alcohol seems to be indicative that zinc borohydride is more bulky than sodium borohydride in its structure.<sup>4</sup>

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