DAEHAN HWAHAK HWOEJEE
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수소화붕소 아연에 의한 케토에스테르의 선택환원

尹 能 民·康 在 孝
서강대학교 이공대학 화학과
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Selective Reduction of Keto Esters with Zinc Borohydride

Nung Min Yoon and **Jahyo Kang**

Department of Chemistry, College of Science and Engineering

Sogang University, Seoul, Korea.

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요 약 대표적 케토에스테르를 수소화붕소아연으로 선택환원하여 해당하는 히드록시에스테르, 또는 락톤을 좋은 수득률로 합성하였다.

ABSTRACT. Selective reduction of carbonyl group with zinc borohydride in the presence of ester functional group was demonstrated with seven representative keto esters. Either hydroxy esters or lactones were obtained in good yields; ethyl 6-hydroxyheptanoate (83.0%), ethyl 2,6-dimethyl-4-hydroxy-2-cyclohexenecarboxylate (82.3%), Ethyl *p*-(*α*-hydroxyethyl)-phenylacetate (78.9%), 4-phenylbutyrolactone (70.2%), and 3-phenylphthalide (92.4%) were obtained from the corresponding keto esters.

INTRODUCTION

Our previous study with zinc borohydride revealed that carbonyl groups are reduced readily but ester groups are inert to this hydride reagent[1,2]. This kind of selectivity can be expected with sodium borohydride, however sodium borohydride has to be used either in alkaline stabilized hydroxylic solvents or in diglyme. In the former solvents the ester groups are hydrolyzed[3a] or transesterified [3b,c], and in the latter the keto groups are reluctant to reduction with sodium borohydride.[4] Thus zinc borohydride, which is reported to be neutral and soluble in common aprotic solvents[1,2], is a promising hydride for selective reduction of keto esters to the corresponding hydroxy esters.

Therefore we have decided to examine the reduction of keto esters with zinc borohydride in order to establish the selectivity of this hydride. Although Gensler *et al.* successfully applied this hydride to the reduction of alkaline sensitive keto lactones[2], we did not include keto lactones in our study, because we observed slow reduction of *γ*-butyrolactone[1] and anticipated that the selective reduction would be difficult

unless the lactone group is sterically hindered to hydride attack.

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 were recorded either with HA-100 or T-60A in δ scale with TMS as an internal standard. Tetrahydrofuran was distilled from excess lithium aluminumhydride. All glassware was dried thoroughly at 125° in an oven and, after set-up, cooled down under a stream of nitrogen. Thus all reductions were carried out under anhydrous condition. Hypodermic syringes were used to transfer the solution.

Preparation of Zinc Borohydride Solution.[5] To a pre-dried 500 m*l* flask(mercury-sealed), were added 230 m*l* of THF and 5.58 g(140 mmoles, 95 %) of sodium borohydride with stirring. To the above slurry solution, was added 8.1774 g (60 mmole) of anhydrous zinc chloride dissolved in 50 m*l* of THF with stirring. After stirring for 2 days 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 "$Zn(BH_4)_2$"[6], and stored as such under positive nitrogen pressure with a connection to a mercury bubbler. The hydride concentration was practically constant over 30 days at room temperature.[1] For all reduction reaction, calculated quantity of the solution was transferred from the supernatant, as needed.

Preparation of Keto Esters

1. Ethyl 6-oxoheptanoate was prepared from the corresponding carboxylic acid as usual manner. Thus *in-situ.* hydroboration of 1-methylcyclohexene(0.5 mole, 48.1 g) in THF with sodium borohydride(0.3 mole, 11.4 g) and dimethyl sulfate(0.3 mole, 37.8 g)[8], followed by alkaline oxidation, gave *trans*-2-methylcyclohexanol in 88% yield(n_D^{16} 1.4618, curde, after evaporation of the solvent). From the crude alcohol, 6-oxoheptanoic acid was prepared by the method of Schaeffer and Snoddy[9] in 41 % yield, followed by esterification. b. p 94~97°/3 mm, n_D^{27} 1.4300 (lit.[10] b. p 107~108°/9 mm, n_D^{25} 1.4305)

2. Ethyl 7-oxododecanoate was prepared from 7-oxododecanoic acid which had been prepared by acylation of 1-morpholinocyclohexene with caproyl chloride, and then alkaline cleavage of the resulting β-diketone.[11] Acid, m. p 55~57° (lit.[11] m. p 56.5~57°). Ester b. p 146~149°/2 mm, n_D^{17} 1.4435, nmr(CCl_4) 0.9~1.6(complex 18), 2.2~2.5(complex, 6), 4.1 (quartet, 2). A portion of this ester was saponified to give 7-oxododecanoic acid(m. p 56~58°), of which ir spectrum was identical with that of authentic one(*vide supra*).

3. Diethyl γ-oxopimelate was prepared from furylacrylic acid. b. p 136~139°/3 mm, n_D^{18} 1.4428(lit.[12] b. p 116~121°/0.3 mm, n_D^{25} 1.4400)

4. Ethyl 2,6-dimethyl-4-oxo-2-cyclohexenecarboxylate was prepared by the method of Horning *et al.*[13], b. p 111~113°/4mm, n_D^{18} 1.4815 (lit.[13] b. p 136~138°/9 mm)

5. Ethyl *p*-acetylphenylacetate was prepared via Friedel-Crafts acetylation of ethyl phenylacetate,[14] m. p 62~63° (lit.[14] m. p 60~62°).

6. Ethyl β-benzoylpropionate was prepared from the corresponding carboxylic acid as usual manner, b p. 139°/3 mm, n_D^{18} 1.5160(lit.[15] b. p 118~120°/2 mm)

7. Methyl *o*-benzoylbenzoate was prepared from *o*-benzoylbenzoic acid. m. p 51~52°(lit.[16] m. p 52°).

Rate Study. Reduction of ethyl *p*-acetylphenylacetate is described as a representative. An oven-dried 100 m*l* flask with a rubber-capped side arm was equipped with a magnetic stirring bar and a reflux condenser connected to a gas

buret, and placed in an ice bath. Then 20 m*l* of 0.25 *M* zinc borohydride solution (40 mmoles of hydride), was introduced into the reaction flask, followed by 10m*l* of THF. To this stirred solution 10 m*l* (10 mmoles) of a 1 *M* solution of ethyl *p*-acetylphenylacetate was added dropwise. Now the resulting reaction mixture was 1 *M* in hydride (0.125 *M* in $Zn(BH_4)_2$ and 0.25 *M* in ethyl *p*-acetylphenylacetate. At appropriate time as indicated in *Table* 1, each 4 m*l* aliquot of the reaction mixture was removed with a syringe and injected into a hydrolyzing mixture containing 2 *N* sulfuric acid and THF. The residual hydride content was measured gasomertrically, and the number of moles of hydride consumed per mole of ethyl *p*-acetylphenylacetate was calculated. Thus ethyl *p*-acetylphenylacetate consumed 0.08(0.5 hr), 0.16(1.0 hr), 0.33(3.0 hr), and 0.57(6.0 hr) moles of hydride per mole of the compound. Since the rate was too slow, the reaction was repeated at room temperature and observed 0.41(0.5 hr), 0.76(1.0 hr), 0.76 (1.0 hr), 0.83(3.0 hr), and 1.07(12.0 hr) moles of hydride uptake per mole of the compound. The results are summarized in *Table* 1.

Reduction of Ethyl 6-Oxoheptanoate (I). The experimental set-up used was essentially same as in rate study. In a reaction flask was placed 50 m*l*(100 mmole of hydride) of 0.25 *M* zinc borohydride solution, followed by addition of 20 m*l* of THF. After thermal equilibriation of the reaction with an ice bath, 8.61 g(50 mmole) of ethyl 6-oxoheptanoate dissolved in 50 m*l* of THF added dropwise with stirring over a period of 15 min. Stirring was continued for 8 hr Excess hydride was carefully hydrolyzed with 10 m*l* of saturated sodium sulfate solution. The precipitate was filtered and washed well with 20 m*l* portions of ether and dried over anhydrous sodium sulfate. The solvents were removed on a rotary evaporator. To the residue was added 40 m*l* of absolute ethanol and again evaporated off to expel the boron contaminant as ethyl borate. The residue(8.35 g, 95.8 %, n_D^{27} 1.4305) was subjected to distillation at reduced pressure to give 7.23 g (83.0 %) of ethyl 6-hydroxyheptanoate, b.p 104~106°/3mm, n_D^{27} 1.4320, ir (liq. film) 3400, 1730cm^{-1}(lit.[10] b.p 103~104°/2mm, n_D^{25} 1.4329)

Reduction of Ethyl 7-Oxododecanoate (II). The procedure is same as described above. To 60 mmoles of hydride, 7.33 g(30 mmoles) of (II) was added. After working up similarly as above 6.52g(88.9%) of the crude hydroxy ester (n_D^{15} 1.4455) was obtained. Distillation at reduced pressure gave 6.03 g(82.3%) of ethyl 7-hydroxydodeconoate b.p 142~143°/2 mm, n_D^{23} 1.4446 with infrared absorption(neat) at 3450cm^{-1} and 1730 cm^{-1}.

Reaction of the pure hydroxy ester with *p*-toluenesulfonyl chloride in pyridine followed by appropriate purification[17] gave a tosylate as colorless liquid. ir(neat) 1180 cm^{-1} and 1190 cm^{-1}. Reduction of the tosylate with excess lithium aluminumhydride afforded 1-dodecanol, b.p 120~122°/5mm, n_D^{28} 1.4420(lit.[18] b.p 143~146°/18 mm). Their spectrum of this alcohol was supperimposable with that of authentic sample.

Reoxidation of the hydroxy ester with chromic acid in aqueous acetic acid yielded the keto ester (II). b.p 155~158°/3 mm, n_D^{20} 1.4420. The ir spectrum was superimposable with that of authentic sample(II) ir(liq. film) 1710, 1730cm^{-1}.

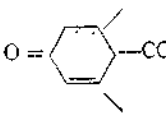
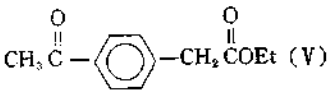
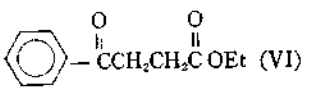
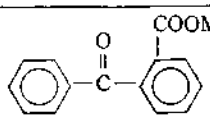
Reduction of Diethyl γ-Oxopimelate (III). The producedure is same as above. To 100 mmoles of hydride, 11.51 g(50 mmole) of (III) was added. After work up as above 11.08 g(95.4%) of crude hydroxy diester was obtained, n_D^{15} 1.4694, ir(ilq. film) 3500, 1735 cm^{-1}. This hydroxy diester underwent lactonization on distillation at reduced pressure as evidenced by the disappearance of O—H peak and a new intense peak at

1780 cm^{-1}(C=O), γ-lactonic). There was obtained 7.27 g(78.1 % based on lactone) of the corresponding lactonic ester as colorless oil. b.p 151~152°/3 mm, n_D^{19} 1.4574(lit.[19] b.p 120~125°/0.1mm, n_D^{20} 1.4539), ir(neat) no O—H, 1735 1780cm^{-1}. nmr(CCl_4) 1.2(t, 3), 1.7~2.7 (complex, 8), 4.1(quartet, 2), 4.4(quintet, 1)

Reduction of Ethyl 2,6-Dimethyl-4-oxo-2-cyclohexenecarboxylate(IV). To a mixture of 80 ml of 0.25 M zinc borohydride solution(160 mmoles of hydride) and 55ml of THF was added 7.85 g(40 mmoles) of the keto ester (IV) dissolved in 25 ml of THF dropwise with stirring. After stirring at room temperature for 6 hr., work-up as described above afforded 7.07 g(89.1 %) of the crude product, n_D^{30} 1.4705. Fractionation at reduced pressure gave 6.57 g(82.3 %) of the corresponding hydroxy ester. b.p 123~125°/mm. n_D^{30} 1.4708. ir(CCl_4) 3380, 3030, 1720, 1620cm^{-1}). nmr(CCl_4) 0.99(d, 3), 1.28(t, 3), 1.66(s, 3) 4.15(quartet, 2), 5.60(m. 1).

Reduction of Ethyl *p*-Acetylphenylacetate (V). A mixture of 60ml of 0.25 M zinc borohydride(120 mmole of hyohide), 15 ml of THF

Table 1. The reactions of zinc borohydride with representative keto esters.

Compound[a]	Temp. (°C)	Hydride used for reduction[b]						
		0.5 hr	1.0 hr	3.0 hr	6.0 hr	12.0 h	24.0 hr	48.0 hr
$CH_3C(=O)CH_2CH_2CH_2CH_2C(=O)OEt$ (I)	0	0.73	1.02	1.03	1.03			
$CH_3(CH_2)_4C(=O)(CH_2)_5C(=O)Et$ (II)	0	0.61	0.95	0.99	0.99	1.03	1.03[d]	
$EtOC(=O)CH_2CH_2C(=O)CH_2CH_2C(=O)OEt$ (III)	0	0.57	0.81		1.22	1.22[c]	1.46[d]	
 (IV)	r.t.	0.62	1.02	1.02	1.10	1.17		
 (V)	0	0.08	0.16	0.33	0.57	0.81[c]		
	r.t.	0.41	0.76	0.83	1.03	1.07		
 (VI)	0	0.08	0.22	0.24	0.26	0.57	1.04[d]	1.30[d]
	r.t.	0.41	0.68	0.99	1.21	1.44		
 (VII)	r.t.	0	0	0	0	0	0	0
	65	0.23	0.46	1.06	1.14			

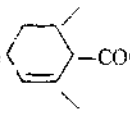
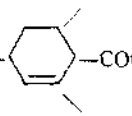
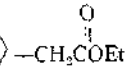
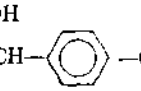
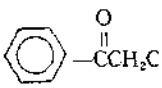
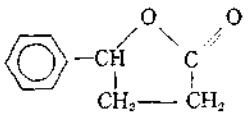
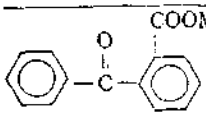
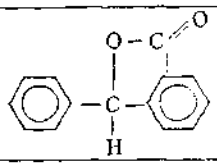
[a] 1M in hydride 2nd 0.25 M in the compound, [b] Number of moles of hydride per mole of the compound
[c] At 10.0hr, [d] Reaction temp. was raised to room temperature after 10hr. reaction at 0°C.

and 6.19 g (30mmoles) of ethyl *p*-acetylphenylacetate dissolved in 25 m*l* of THF was stirred for 6 hrs at room temperature. After the established work-up as above, 5.36 g (85.8%) of the crude hydroxy ester (n_D^{20} 1.5150) was obtained. Distillation afforded 4.93 (78.9%) of pure ethyl *p*-(α-hydroxyethyl) phenylacetate. b.p 151~153°/3mm, n_D^{30} 1.5182. ir (CCl_4) 3400, 1720 cm^{-1} nmr (CCl_4) 1.2 (*t*, 3), 1.3 (*d*, 3), 3.5 (*s*, 2), 4.0 (quartet and a broad singlet, 3), 4.1 (quartet, 1) 7.1 (*s*, 4).

Reduction of Ethyl β-Benzoylpropionate (VI). The same procedure was carried out. To 160 mmoles of hydride 8.25 g (40 mmoles) of the keto ester (VI) was added and stirred for 3 hr at room temperature. Then the mixture was worked up to give 7.57 g (91.8%) of the crude product, n_D^{30} 1.5305. Distillation afforded 5.56 g (based on lactone) of γ-phenyl-γ-butyrolactone. b.p 126~7°/2mm, n_D^{29} 1.5321. ir (CCl_4) no O—H, 1780 cm^{-1}. This colorless liquid was recrystalized in either-petroleum ether (30~60 °C) to give the 4.56g of pure lactone (70.2 %) m.p 34~36° (lit.[9a] 106~13°/0.5mm, m.p 34~36°)

Reduction of Methyl *o*-Benzoyl benzoate (VII). A mixture of 60 m*l* of 0.25 *M* zinc boro-

Table 2. Reduction of keto esters with zinc borohydride[a]

Keto ester	H^-/comp.	Rxn Time (Temp.)	Product	Physical const. Crude (yld)	Purified (yld)
$CH_3C(=O)(CH_2)_4COEt$ (I)	2/1	8 hr (0°)	$CH_3CH(OH)(CH_2)_4COEt$	n_D^{27} 1.4305 (95.8%)	n_D^{25} 1.4320 (83.0%)
$CH_3(CH_2)_4C(=O)(CH_2)_5COEt$ (II)	2/1	8 hr (0°)	$CH_3(CH_2)_4CH(OH)(CH_2)_5COEt$	n_D^{15} 1.4455 (88.9%)	n_D^{25} 1.4446 (82.3%)
$EtOCCH_2CH_2C(=O)CH_2CH_2COEt$ (III)	2/1	8 hr (0°)	$EtOCCH_2CH_2CH(OC(=O)CH_2CH_2)$	n_D^{15} 1.4694 (95.4%)	n_D^{15} 1.4574 (78.1%)
O=  —COOEt (IV)	4/1	6 hr (r.t)	HO—  —COOEt	n_D^{30} 1.4705 (89.1%)	n_D^{25} 1.4708 (82.3%)
$CH_3C(=O)$  $—CH_2COEt$ (V)	4/1	6 hr (r.t)	$CH_3CH(OH)$  $—CH_2COEt$	n_D^{30} 1.5150 (85.8%)	n_D^{25} 1.5182 (76.9%)
 $—CCH_2CH_2COEt$ (VI)	4/1	3 hr (r.t)		n_D^{19} 1.5305 (91.8%)	n_D^{25} 1.5321 (70.2%)
 (VII)	4/1	3 hr (65°C)		m.p 106~12° (96.1%)	m.p 116~8° (92.4%)

yld: yield

[a] Prepared by mixing 140 mmoles of $NaBH_4$ and 60 mmoles of $ZnCl_2$ in THF.

hydride solution (120 mmoles of hydride) and 7.21 g (30 mmoles) of the keto ester (VII) dissolved in 40m*l* of THF was subjected to heating under reflux. Careful hydrolysis of the excess hydride followed by filtration, washing, drying and evaporation of the solvent gave 6.06 g (96.1%) of the crude lactone. m.p 106~112°. Recrystallization from methanol yielded 5.83 g (92.4%) of 3-phenylphthalide as white solid. m.p 116~118° (lit.[21] 116~117°), ir ($CHCl_3$) no O—H, 1760.

RESULTS and DISCUSSION

First we examined the approximate rate and stoichiometry of the reaction of keto esters with zinc borohydride at 0°. The first three aliphatic keto esters were reduced smoothly consuming about one hydride within 6 hr. and apparently reaction did not proceed further at 0°C (see *Table* 1). This clearly suggests that the keto group reduced selectively with the ester group intact. However further reaction at room temperature consumed additional hydride, indicating that the ester group was slowly reduced. In our previous study, all the esters examined, aliphatic or aromatic, showed no sign of reduction even after 24 hr. at room temperature.[1] Presumably the hydride moiety attached to the oxygen, resulted from the reduction of keto group, is attacking the ester function intramolecularly.[22] This intramolecular hydride attack to the ester group, also supported by the fact that the additional hydride uptake of diethyl γ-oxopimelate and ethyl β-benzoylpropionate, both of which have keto group at 4-position, proceeds more rapidly compared to those of other keto esters which have keto group further away.

Aromatic ketones were reduced much more slowly and had to be reduced at elevated temperature. Ethyl *p*-acetylphenylacetate showed a plateau of one hydride consumption at 6~12hr, however, ethyl β-benzoylpropionate did not show such plateau. We believe this caused the lower yield of 4-phenylbutyrolactone.

In order to confirm the products and demonstrate the synthetic utility of this selective reduction, products were isolated at all times. We used neutral condition as possible but did not elaborate to get maximum yields. In *Table* 2, the reaction conditions employed and physical constants of the crude and purified products are summarized. In all cases the refractive indices or melting points were very close between the crude and purified products. The only exception was the product of diethyl γ-oxopimelate, however, we found out that the crude product was hydroxy diester as evidenced by the intense O—H peak in the ir spectrum. Therefore, for practical stand-point of view, elaborate purification steps might be eliminated for any subsequent reactions.

Faced with the reduction of carbonyl group in the presence of ester group, possible metal hydrides to be applied would be either sodium borohydride[23], or alkyl boranes such as disiamylborane.[24] These hydrides are known to reduce carbonyl group readily, but inert or very sluggish for the reduction of ester group under normal conditions. However sodium borohydride has to be used in alkaline stabilized hydroxylic solvents in order to reduce ketone group smoothly,[25] and this alkaline condition could cause complication such as hydrolysis,[3a] racemization[26], etc. On the other hand, disiamylborane is expected to do the job nicely although the applicability of disiamylborane to this kind of selective reduction is yet to be tested. Even if disiamylborane were proved to be good, it may be difficult to apply if the compound has a functional group such as carbon-carbon multiple bond, epoxide, or nitrile.[24]

Conclusion. We have shown that the selective reduction of keto esters to the corresponding hydroxy esters or lactones by zinc borohydride in good yields. We believe this study not only

provides a new synthetic method of hydroxy esters, but also serves to the mechanistic study of the metal hydride reduction.

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5. This is essentially the procedure of Gensler *et al.* (ref. 2) with some modification(ref. 1).
6. Excess amount (16.6%) of sodium borohydride is remaining in the solution as $Na[Zn(BH_4)_3]$ in spite of low solubility(0.1 g/100 g of THF) of sodium borohydride in THF. See ref. 1 and 7.
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