[Chem. Pharm. Bull. 27(6)1479—1481(1979)]

UDC 547.284.04 : 541.632.04

Asymmetric Reduction of Various Ketones with the Sodium Salts of α-Amino Acid Borane Complexes

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(Received November 9, 1978)

The sodium salts of amino acid borane complexes (1) produced from equimolar amount of $NaBH_4$ and optically active α-amino acids in tetrahydrofuran at room temperature reduced various ketones to the corresponding optically active alcohols (2—62% optical yield). Sodium prolinate borane complex (2) gave the best results. Asymmetric reduction of (3) with sodium L-prolinate borane complex (2) followed by catalytic hydrogenolysis of benzyl and carbobenzoxy groups gave (4), a cardiotonic agent, in 62% optical yield.

Keywords——asymmetric reduction; prochiral ketone; optical active alcohol; sodium salt of amino acid borone complex; sodium prolinate borane complex; cardiotonic agent

Asymmetric reduction of carbonyl compounds to the corresponding optically active alcohols has been the subject of much recent investigation. Asymmetric reduction with chiral aluminum hydride derivatives has been well studied, but little work has been done with chiral borohydride derivatives,[2] though Grundon *et al.*[2f] recently reported that amino ester borane complexes reduced various ketones in 14.7—22.5% optical yields.

We wish to report here that the chiral sodium salts of α-amino acid borane complexes (1), which can be prepared easily from equimolar amounts of sodium borohydride and optically active α-amino acids at room temperature in tetrahydrofuran, asymmetrically reduced various prochiral ketones to the corresponding optically active alcohols; sodium prolinate borane complexes were found to be the best reagents.

We preliminarily investigated the reduction of acetophenone with the chiral sodium salts of various α-amino acid borane complexes (1) to give optically active 1-phenylethanol (1.8—33% optical yield). The results are summarized in Table I (runs 1—6).

The good results with the prolinate borane complexes shown in Table I (runs 5—6) encouraged us to investigate the asymmetric reduction of various ketones. As can be seen from Table I (runs 7—9), the L-prolinate borane complex (2) reduced various ketones to the corresponding alcohols in reasonably good optical yields (15—50%).

Thus, this convenient asymmetric reduction method with sodium prolinate borane complex was examined for the conversion of the key intermediate[3] (3) to a cardiotonic agent, (−)-4-hydroxy-α-(3,4-dimethoxyphenethylaminomethyl)benzyl alcohol hydrochloride(4),[4] and an excellent yield (62% optical yield) was obtained (Chart 1).

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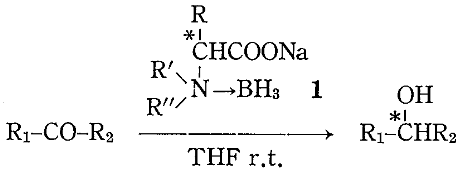
[1] Location: *Kawagishi, Toda-shi, Saitama.*

[2] *a*) J.C. Fiaud and H.B. Kagan, *Bull. Soc. Chim. Fr.*, **36**, 2742 (1969); *b*) M.F. Grundon, W.A. Khan, D.R. Boyd and W.R. Jackson, *J. Chem. Soc.*, (*C*), **1971**, 2557; *c*) R.F. Borch and S.R. Levitan, *J. Org. Chem.*, **37**, 2347 (1972); *d*) J. Balcells, S. Colonna and R. Fornasier, *Synthesis*, **1976**, 266; *e*) J.P. Masse and E.R. Parayer, *Chem. Commun.*, **1976**, 438; *f*) M.F. Grundon, K.G. MeCleery and J.W. Wilson, *Tetrahedron Lett.*, **1976**, 295; *g*) S. Krishnamurthy, F. Vogel and H.C. Brown, *J. Org. Chem.*, **42**, 2534 (1977); *h*) S. Colonna and R. Fornasier, *J. Chem. Soc.*, *Perkin I*, **1978**, 371.

[3] Benzyl (4-benzyloxy)phenacyl-(3,4-dimethoxyphenethyl)carbamate (3); colorless needles, mp 193—198° (dec.), IR $\nu_{\text{max}}^{\text{Nujol}}$: 1675, Mass (MS): *m/e* 405 (M^+), 254, 197, 194 (base); *Anal.* Calcd. for $C_{25}H_{27}NO_4 \cdot HCl$: C, 67.87; H, 6.33; N, 3.17; Cl, 8.14. Found: C, 68.10; H, 6.44; N, 3.15; Cl, 8.77.

[4] $[\alpha]_D^{25}$ −38.0° (c=1 MeOH) for (4); colorless needles, mp 138—139.5° IR $\nu_{\text{max}}^{\text{Nujol}}$: 3520, 3470, 3350, NMR (D_2O) δ: 2.8—3.7 (6H, m), 3.9 (6H, s, $OC\underline{H}_3$), 6.9—7.6 (7H). *Anal.* Calcd. for $C_{18}H_{23}NO_4 \cdot HCl$: C, 61.10; H, 6.96; N, 3 .96. Found: C, 60.69; H, 6.98; N, 3.76.

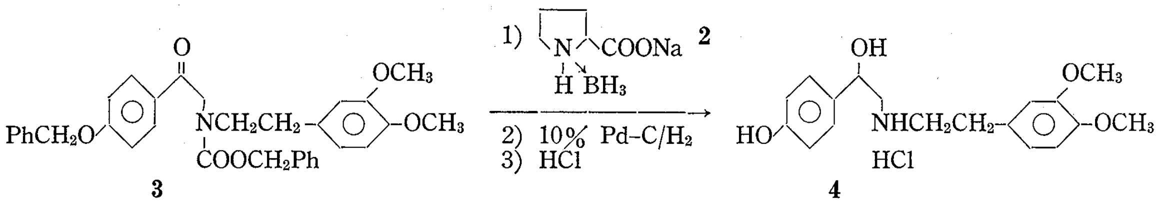
Table I. Reduction of Various Ketones with the Sodium Salts of α-Amino Acid Borane Complexes in THF at Room Temperature



$$R_1\text{-CO-}R_2 \xrightarrow[\text{THF r.t.}]{\mathbf{1}} R_1\text{-}\overset{*}{C}HR_2(OH)$$

Run	Ketone	α-Amino acid	Chemical yield (%)	$[\alpha]_D^{MeOH}$	Optical yield (%)
1	$PhCOCH_3$	D-Valine	75	−0.8	1.8[a]
2	$PhCOCH_3$	D-Leucine	77	−12.3	5.1[a]
3	$PhCOCH_3$	L-Leucine	72	−2.2	4.8[a]
4	$PhCOCH_3$	L-Phenylalanine	76	−10.8	1.8[a]
5	$PhCOCH_3$	L-Proline	92	−14.7	32[a]
6	$PhCOCH_3$	D-Proline	87	+15.1	33[a]
7	$(CH_3)_2CHCH_2COCH_3$	L-Proline	66	+3.6	17[b]
8	$CH_3(CH_2)_4COCH_3$	L-Proline	66	+1.6	15[c]
9	$PhCOCH_2CH_3$	L-Proline	92	−11.2	50[c]

a) $[\alpha]_D$ −35.5° for (−)-1-phenylethanol; L. Horner and D. Degner, *Tetrahedron Lett.*, 1968, 5889.
b) $[\alpha]_D$ −22.4° for (−)-4-methylpentan-2-ol; Dictionary of Organic Compounds, Eyre and Spottiswood, London 1965.
c) $[\alpha]_D$ +11.45° for (+)-heptane-2-ol; Dictionary of Organic Compounds, Eyre and Spottiswood, London 1965.
d) $[\alpha]_D$ −22.5° for (−)-phenyl-1-propanol; Dictionary of Organic Compounds, Eyre and Spottiswood, London 1965.



3

4

Ph=phenyl

Chart 1

The mechanism in these asymmetric reductions is not clear, but we believe that the reaction species are the sodium salts of α-amino acid borane complexes (**1**) for the following reasons.

(a) The infrared spectrum of the reagent prepared by the reaction of L-proline and sodium borohydride was essentially identical with that synthesized from the reaction of sodium L-prolinate and diborane (1,1 eq) (Chart 2).

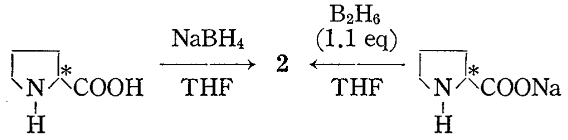


Chart 2

(b) The asymmetric reduction of acetophenone with each reagent gave very similar results.

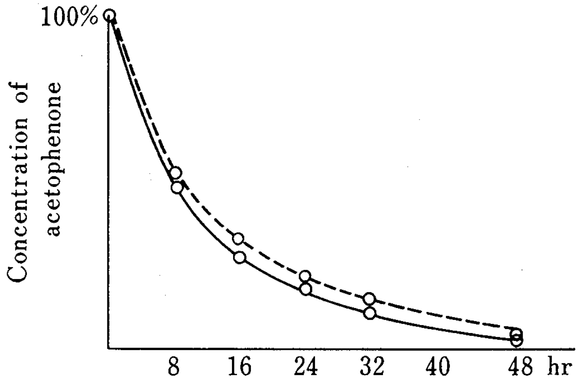


Fig. 1. Rates of Reduction of Acetophenone in THF at Room Temperature

—○—: $NaBH_4$+L-ProOH,
---○---: H-L-ProONa+B_2H_6.

(c) The diminution curves[5] of acetophenone in the asymmetric reductions with the two reagents are almost identical (Fig. 1).

Further studies are now in progress.

Experimental

Melting points and boiling points are uncorrected. The infrared (IR) spectra were taken on Hitachi 215, the HNMR spectra on JEOL JNM-60, and the mass spectra on Hitachi RMU-6M machines. Gas chromatography (GC) was performed on a Shimazu GC-4BPF chromatograph using a PEG 20M glass column.

Optical rotations were measured with JASCO DIP-180. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use. The nature of the product alcohols was confirmed by comparison of IR, nuclear magnetic resonance (NMR), mass spectra (MS) and thin-layer chromatography (TLC) with those of authentic samples.

Representative Asymmetric Reduction of Acetophenone with Sodium L-Prolinate Borane Complex (2)——When a mixture of $NaBH_4$ (0.95 g, 25 mmol) and L-proline (2.9 g, 25 mmol) in THF (50 ml) was stirred for 2 hours at room temperature, an equimolar amount of hydrogen gas was evolved. Acetophenone (3.0 g, 25 mmol) in THF (5 ml) was added to this suspension of sodium L-prolinate borane complex and the mixture was stirred at room temperature for 10 days.[6] The excess reagent was decomposed with water and the resulting mixture was concentrated *in vacuo* and extracted with ethyl acetate. The extract was washed with 10% hydrogen chloride, saturated sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The ethyl acetate solution was evaporated *in vacuo* and the residue was distilled to give optically active 1-phenylethanol, [bp 100° (20 mmHg), 2.8 g, 92% $[\alpha]_D^{MeOH}$ $-14.7°$, (32% optical yield)].

(−)-4-Hydroxy-α-(3,4-dimethoxyphenethylaminomethyl)benzylalcohol Hydrochloride (4)——The ketone (3) (2.7 g) was added to a suspension of (2) prepared from $NaBH_4$ (190 mg) and L-proline (575 mg) in THF (10 ml) and the mixture was stirred at room temperature for 10 days. The excess reagent was decomposed with water and the resulting mixture was concentrated *in vacuo* then extracted with ethyl acetate. The extract was washed with 10% hydrogen chloride, saturated sodium bicarbonate and brine, then dried over anhydrous sodium sulfate. The ethyl acetate solution was evaporated down *in vacuo* and the residue was passed through a short silica gel column (eluted with ether). Removal of the eluate by evaporation gave a viscous oil (2.73 g). IR $\nu_{max}^{Liq.}$: 3450, 1695, 1610. MS *m/e*: 541 (M^+), $[\alpha]_D^{22}$ $+9.0$—$8.9°$ ($c=9.8$ MeOH).

A solution of the resulting oil (680 mg) in methanol (20 ml) was hydrogenated over 10% palladium on a carbon catalyst (250 mg) at room temperature and atmospheric pressure for 2 hours.

The reaction mixture was filtered, treated with dry hydrogen chloride and evaporated down *in vacuo*. The residue was crystallized from methanol-ether to give (4)[4] (355 mg, 80%), mp 130—140°, $[\alpha]_D^{25}$ -24.6—$23.6°$ ($c=1$ MeOH).

Acknowledgement We would like to express our thanks to Emeritus Prof. S. Sugasawa of Tokyo University and Prof. Y. Ban of Hokkaido University for valuable discussions. We are also indebted to Mr. M. Yamazaki and Dr. S. Saito for their encouragement.

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5) GC yields corrected by the use of an internal standard.

6) The reduction of acetophenone with (2) at 40° for 56 hr gave similar results (chem. yield 90%; optical yield 33%).