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Asymmetric Syntheses of β-Amino Acids by the Reduction of Enamines

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Asymmetric synthesis of β-amino acids (**4**) was achieved by the reduction of chiral enamines (**3**) with 10% palladium hydroxide catalyst on charcoal or with sodium cyanoborohydride in optical purities of 3—28%. The reduction with the former catalyst afforded higher optical purities of **4** than that with the latter reducing agent. These two methods yielded opposite configurations of **4**. The steric courses of the reactions are discussed.

Keywords——asymmetric synthesis; β-amino acid; chiral enamine; six-membered chelate ring; palladium hydroxide on charcoal; sodium cyanoborohydride

Many naturally occurring optically active β-amino acids and peptides having β-amino acid components have been isolated,[2] and some investigations on stereospecific syntheses of optically active β-amino acids have been reported.[3,4] We have recently developed procedures for the asymmetric synthesis of optically active β-amino acids, involving the addition of chiral amines to C=C bonds,[5a] the reaction of chiral Schiff bases with chiral and achiral Reformatsky reagent,[5b] and the cycloaddition of chiral Schiff bases to ketones.[5c]

We now wish to report a new asymmetric synthesis of β-aminobutyric acid (**4a**) and β-amino-β-phenylpropionic acid (**4b**) by the reduction of chiral enamines (**3b**, **c**, **e** and **f**), in which the *R*(+)- or *S*(−)-α-methylbenzylamino group is involved as the chiral component.

The enamines (**3**) were prepared by heating a solution of equivalent amounts of the amines (**1**) and β-keto esters (**2**) in benzene in the presence of *p*-toluenesulfonic acid as a catalyst. The ^{1}H-nuclear magnetic resonance (^{1}H–NMR) and infrared (IR) spectra of the enamines (**3**) indicated the formation of a six-membered ring compound due to hydrogen bonding. This shows that the enamines (**3**) are in the *Z*-form. The enamines (**3**) were reduced by two methods, using 10% palladium hydroxide on charcoal or sodium cyanoborohydride,[6] followed by hydrogenolysis and then hydrolysis to afford the corresponding β-amino acids (**4**) in overall yields of 11—32%. In order to avoid fractionation during purification, the specific rotation of β-aminobutyric acid (**4a**) was measured in the crude state. β-Amino-

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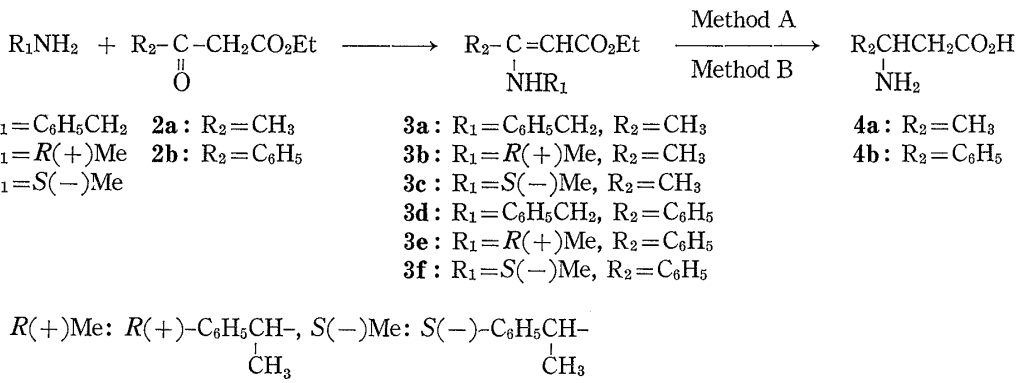

Chart 1

TABLE I. Optically Active β-Amino Acids (**4a** and **b**)

Enamine	Method	β-Amino Acid	Config.	$[\alpha]_D^{20}$ (c, solvent)[a]	Optical purity (%)
3b	A	**4a**	*R*	−2.8°(2.5, H_2O)	7.2
3b	B	**4a**	*S*	+1.0°(7.1, H_2O)	2.6
3c	A	**4a**	*S*	+2.3°(1.6, H_2O)	5.9
3c	B	**4a**	*R*	−1.2°(5.1, H_2O)	3.1
3e	A	**4b**[b]	*R*	+27.8°(2.4, EtOH)	24.4
3e	B	**4b**	*S*	−10.7°(1.8, EtOH)	9.3
3f	A	**4b**	*S*	−31.7°(1.7, EtOH)	27.9
3f	B	**4b**	*R*	+8.5°(3.0, EtOH)	7.4

a) The optical purity is defined as $[\alpha]_D^{obsd.}/[\alpha]_D^{lit.} \times 100$. (*S*)-β-aminobutyric acid, $[\alpha]_D^{19}$ +38.8° (H_2O),[c] (*S*)-β-formamido-β-phenylpropionic acid, $[\alpha]_D^{25}$ −114.5° (EtOH).[7]
b) The specific rotation was measured as the formyl derivative.
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β-phenylpropionic acid (**4b**) was rapidly converted to the formyl derivative,[7] and its specific rotation was also measured without purification. The results are summarized in Table I.

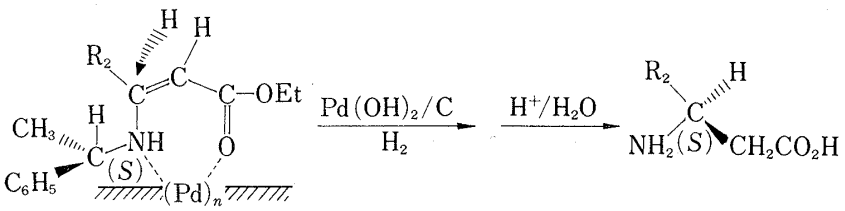
As shown in Table I, the optical purities of **4a** and **4b** were generally a little higher when they were obtained by catalytic hydrogenation rather than by using sodium cyanoborohydride. It is worth noting that the two kinds of reducing agents resulted in different configurations of the β-amino acids. When the optically active enamines (**3b**, **c**, **e** and **f**), which contained *R*(+)- and *S*(−)- amino moieties, were catalytically hydrogenated with 10% palladium hydroxide on charcoal, the resulting β-amino acids (**4a** and **b**) were of (*R*)- and (*S*)-configurations, respectively. On the other hand, the use of sodium cyanoborohydride led to inversion of configuration, compared with the results mentioned above. Namely, *S*- and *R*-4 (**a** and **b**) were formed from *R*- and *S*-enamines, respectively.

The mechanisms and steric courses in these reduction are proposed to be as follows.

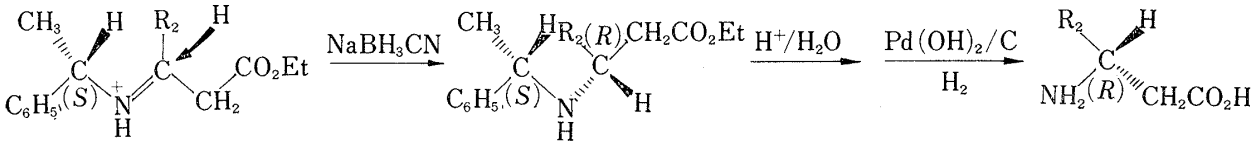
The catalytic reduction of **3** with 10% palladium hydroxide on charcoal is assumed to proceed *via* chelate ring formation as proposed by Harada and Matsumoto.[8] In the intermediate-six membered chelate ring (**5**, *Z*-form), the hydrogen atom is presumed to attack preferentially from the less hindered side to give (*S*)-**4**. On the other hand, the reduction with sodium cyanoborohydride under acidic conditions is presumed to be initiated by protona-

7) F. Bergel and J. Butler, *J. Chem. Soc.*, **1961**, 4047.
8) *a*) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967); *b*) K. Harada and K. Matsumoto, *J. Org. Chem.*, **33**, 4467 (1968); *c*) M. Osawa, A. Hatta, K. Harada, and W. Suetaka, *Bull. Chem. Soc. Jpn.*, **49**, 1512 (1976).

tion to give the protonated quarternary imine (**6**), which would be preferentially attacked by a hydrogen atom from the less hindered side to afford (*R*)-**4**.



5 (Z-form) **4**



6 **4**

Chart 2

TABLE II. β-N-Benzylaminocrotonates (**3a—c**) and -cinnamates (**3d—f**)

	bp or mp (°C/mmHg) (°C)	Yield (%)	$[\alpha]_D^{25}$ (EtOH)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR spectra (δ) in $CDCl_3$
3a	145/3.0	74	——	$C_{13}H_{17}NO_2$	71.20 (71.65	7.82 7.79	6.37 6.47)	1655 (C=O)	9.00—8.55 (broad, 1H, NH), 7.10 (s, 5H, arom), 4.46 (s, 1H, CH), 4.22 (d, 2H, J=6.0 Hz, CH_2), 4.00 (q, 2H, J=7.0 Hz, CH_2), 1.76 (s, 3H, CH_3), 1.15 (t, 3H, J=7.0 Hz, CH_3).
3b	124/1.7	86	−637.8° (c=2.2)	$C_{14}H_{19}NO_2$	72.07 (71.77	8.21 7.94	6.00 5.83)	1660 (C=O)	9.01—8.61 (broad, 1H, NH), 7.13 (s, 5H, arom), 4.59 (q, 1H, J=6.0 Hz, CH), 4.41 (s, 1H, CH), 4.05 (q, 2H, J=7.0 Hz, CH_2), 1.72 (s, 3H, CH_3), 1.48 (d, 3H, J=7.0 Hz, CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_3).
3c	132/2.0	77	+611.8° (c=1.9)	$C_{14}H_{19}NO_2$	72.07 (71.71	8.21 8.13	6.00 5.91)	1660 (C=O)	8.91—8.61 (broad, 1H, NH), 7.12 (s, 5H, arom), 4.58 (q, 1H, J=6.0 Hz, CH), 4.40 (s, 1H, CH), 4.04 (q, 2H, J=7.0 Hz, CH_2), 1.70 (s, 3H, CH_3), 1.46 (d, 3H, J=7.0 Hz, CH_3), 1.22 (t, 3H, J=7.0 Hz, CH_3).
3d	73—74	47	——	$C_{18}H_{19}NO_2$	76.84 (76.78	6.81 6.38	4.98 4.68)	1640 (C=O)	9.07—8.72 (broad, 1H, NH), 7.31 (s, 5H, arom), 7.20 (s, 5H, arom), 4.67 (s, 1H, CH), 4.25 (d, 2H, J=6.0 Hz, CH_2), 4.14 (q, 2H, J=7.0 Hz, CH_2), 1.28 (t, 3H, J=7.0 Hz, CH_3).
3e	93—94	32	+74.2° (c=3.0)	$C_{19}H_{21}NO_2$	77.26 (77.19	7.17 6.96	4.74 4.89)	1670 (C=O)	
3f	93—94	26	−76.2° (c=1.8)						

Experimental

Hydrogenation was carried out using a Skita and Parr catalytic hydrogenation apparatus. Specific rotations were measured with a JASCO DIP-4 polarimeter using a 10 mm cell. IR spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. ^{1}H-NMR spectra were determined with a JEOL C-60H high resolution NMR instrument.

General Procedure for the Synthesis of the Enamines (3)——A mixture of amine (1) (0.1 mol), β-keto ester (2) (0.1 mol), and *p*-toluenesulfonic acid (0.1 g) in benzene (100 ml) was refluxed for 5 hr using a Dean-Stark separator. After removal of the calculated amount of water, the benzene solution was washed with aqueous 1% $NaHCO_3$ (30 ml), then with water (30 ml), and dried over anhydrous Na_2SO_4. The solution was evaporated down *in vacuo*, and the residue was distilled under reduced pressure or recrystallized from EtOH. The enamines (**3e—f**) were used directly for hydrogenation, because of difficulty in their purification by distillation or by crystallization. Their elemental analyses, IR, and ^{1}H-NMR spectral data are listed in Table II.

Examination of the Racemization of Ethyl N-*R*(−)-α-Methylbenzylaminocrotonate (3b)——Compound **3b** (1.16 g, 5 mmol) was refluxed in 6 N HCl (15 ml) for 8 hr. The solution was extracted with ether (10 ml) to remove ethyl acetoacetate (**2a**) and other by-products. The aqueous layer was made alkaline with 10 N NaOH, and then extracted with ether (10 ml). The extract was washed with water (10 ml), and dried over anhydrous Na_2SO_4. After removal of ether, the residue was distilled under reduced pressure to give *R*(+)-α-methylbenzylamine (0.35 g, 58%): bp 78—79°/17 mmHg, $[\alpha]_D^{15}$ +39.6° (*c*=5.8, benzene).

General Procedure for the Synthesis of β-Amino Acids (4)——Method A using 10% Palladium Hydroxide on Charcoal: A solution of enamine (3) (0.01 mol) in EtOH (50 ml) was hydrogenated and hydrogenolyzed over 10% palladium hydroxide on charcoal (1 g) for 12 hr. When the reduction was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was hydrolyzed with 6 N HCl (30 ml) for 10 hr. The hydrolyzate was extracted with ether (20 ml), and the aqueous layer was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and applied to an IR 120 column (H^+ form, 2.2×26.5 cm). The column was eluted with 1.5 N aqueous ammonia and the fractions containing β-amino acid were combined and evaporated to dryness under reduced pressure. The β-amino acids obtained from **3** (**a** and **d**) were recrystallized from water and EtOH. The specific rotations of the optically active β-amino acids obtained from **3** (**b**, **c**, **e** and **f**) were measured in the crude state without purification. **4a** (from **3a**): mp 195—196°. Yield 44%. *Anal.* Calcd. for $C_4H_9NO_2$; C, 46.59; H, 8.80; N, 13.58. Found: C, 46.74; H, 8.61; N, 13.40. **4b** (from **3d**): mp 239°. Yield 23%. *Anal.* Calcd. for $C_9H_{11}NO_2$; C, 65.44; H, 6.71; N, 8.48. Found: C, 65.76; H, 6.79; N, 8.56.

Method B using $NaBH_3CN$: Hydrochloric acid (6 N) was added dropwise to a stirred solution of enamine (3) (0.01 mol), $NaBH_3CN$ (0.7 g, 0.01 mol) and a small amount of bromocresol green indicator in EtOH (30 ml) under cooling with ice and water, until the color changed to yellow; additional HCl was added as necessary in order to maintain the yellow color. After 3 hr, the reaction mixture was evaporated down under reduced pressure. The residue was dissolved in AcOEt (30 ml) and washed with 1% $NaHCO_3$ (20 ml) and water (20 ml), then dried over anhydrous Na_2SO_4. After removal of AcOEt, the residue was hydrolyzed with 6 N HCl followed by hydrogenolysis over 10% palladium hydroxide on charcoal, and worked up by the method described in Method A.