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Asymmetric Syntheses of β-Amino Acid and Aspartic Acid by Reformatsky Reaction

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Asymmetric syntheses of β-amino acids and aspartic acid were achieved by the reaction of optically active Schiff bases prepared from aldehydes and optically active amines, *R*(+)- and *S*(−)-α-methylbenzylamines, with Reformatsky reagents in the range of 18—28% optical purities. When the Schiff bases having *R*(+)-amino component were used in the reaction, (*S*)-β-amino acids and (*R*)-aspartic acid were formed. The use of the Schiff bases involving *S*(−)-amino component gave (*R*)-β-amino acids and (*S*)-aspartic acid. The reaction of Schiff bases prepared from aldehydes and benzylamine with optically active Reformatsky reagents having *l*-menthyl ester gave (*S*)-β-amino acids and (*R*)-aspartic acid in the range of 2—5% optical purities. The steric course were also presumed.

Keywords——asymmetric synthesis; β-amino acid; aspartic acid; Reformatsky reaction; optically active Schiff base; six-membered ring transition state

Although there have been reported many studies on asymmetric syntheses of optically active α-amino acids,[2] little has been known relating to the asymmetric synthesis of optically active β-amino acids, with the exception that optically active β-aminobutyric acid was synthesized by the addition of optically active amines to crotonic acid in low optical purities.[3]

We now wish to report an asymmetric synthesis of β-amino acids and aspartic acid by the Reformatsky reaction, which consists in the reaction of Schiff bases with Reformatsky reagents. The Reformatsky reaction with Schiff bases was first investigated by Gilman and Speeter[4] to give the β-lactam and subsequently several similar reaction[5] have been reported.

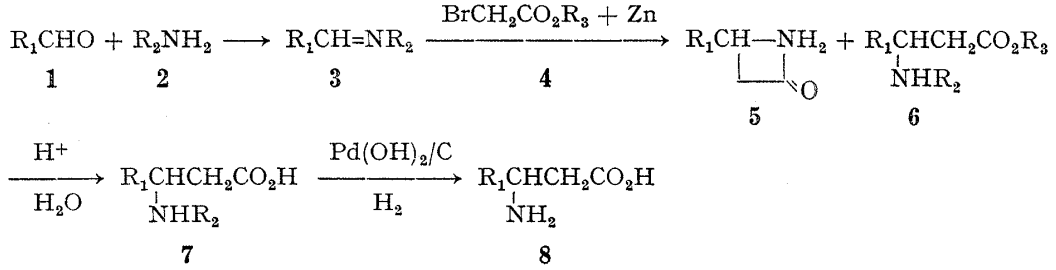


Chart 1

1) Location: *5–1, Oe-hon-machi, Kumamoto, 862, Japan.*
2) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reaction," Prentice-Hall Inc., New Jersey, 1971.
3) A.P. Terentev, R.A. Gracheva, and T.F. Dendeko, *Dokl. Akad. Nauk. SSSR*, **163**, 674 (1965).
4) H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).
5) E. Guingnet, D. Poulain, and M. Tarterat-Adalberou, *Bull. Soc. Chim. Fr.*, **1969**, 514; F. Dordoize, J.L. Moreau, and M. Gaudemar, *CR. Acad. Sci., serie C*, **268**, 2228 (1969); S. Mohan, P.S. Sethi, and A.L. Kapoor, *J. Indian Chem. Soc.*, **48**, 685 (1971); F. Dordoize, J.L. Moreau, and M. Gaudemar, *Bull. Soc. Chim. Fr.*, **1972**, 3841.

The stereochemistry of the β-lactam has also studied in detail.[6] In our present study, the reaction of optically active Schiff bases (**3**), prepared from aldehydes (**1**) and optically active amines (**2**), with a Reformatsky reagent (**4**, R_3=Et) or the reaction of Schiff bases with a optically active Reformatsky reagent (**4**, R_3=*l*-menthyl) was examined. Hydrolysis and hydrogenolysis of the resulting β-lactams (**5**) and β-(alkylamino) propionates (**6**) afforded the optically active β-amino acids (**8a—f**) (Chart 1). When R_1 was the carboxylic acid substituent group, optically active aspartic acids (**8g—i**) were obtained.

The aldehydes (**1**) used as the starting material were acetaldehyde, benzaldehyde, and butyl glyoxalate.[7] Benzylamine, *R*(+)-α-methylbenzylamine, and *S*(−)-α-methylbenzylamine were used as the amines (**2**). The ester moiety of the Reformatsky reagents involved ethyl or *l*-menthyl group. The Schiff bases (**3**) were readily prepared by mixing **1** and **2** in benzene. The Reformatsky reaction was successfully carried out by stirring **3** with **4** (prepared from α-bromoacetate and zinc) in benzene under reflux to give **5** and **6**, followed by hydrolysis by refluxing with 6 N hydrochloric acid. No racemization of optically active **3** during the reaction was observed.[8] The resulting N-benzylamino acids (**7**) were isolated and subsequently hydrogenolyzed over 10% palladium hydroxide on charcoal to remove the benzyl groups. The overall yield of the resulting β-amino acids (**8**) was in the range of 10—42%. In order to avoid the fractionation during purification, the specific rotations of β-aminobutyric acid (**8a—c**) were measured in the crude state without isolation. β-Amino-β-phenylpropionic acid (**8d—f**) was converted to the formyl derivative,[9] and aspartic acid (**8g—i**) was derived to the DNP-aspartic acid.[10] The optical purities of these compounds ranged from 2—28%. The results are summarized in Table.

Table I. Optically Active β-Amino Acids (**8a—f**) and Aspartic Acids (**8g—i**) from Schiff Bases (**3**) and Reformatsky Reagents (**4**)

	8 R_1	**3** R_1	**3** R_2	**4** R_3	$[\alpha]_D^{15}$	Config. of **8**	Optical purity (%)[a]
a	CH_3	CH_3	*R*(+)Me[b]	C_2H_5	+10.0°(*c*=2.9, H_2O)	*S*	26.0
b	CH_3	CH_3	*S*(−)Me[c]	C_2H_5	−11.0°(*c*=2.1, H_2O)	*R*	28.4
c	CH_3	CH_3	$C_6H_5CH_2$	*l*-Menthyl	+2.0°(*c*=5.1, H_2O)	*S*	5.2
d	C_6H_5	C_6H_5	*R*(+)Me	C_2H_5	−20.0°(*c*=2.2, EtOH)	*S*	17.6
e	C_6H_5	C_6H_5	*S*(−)Me	C_2H_5	+21.9°(*c*=2.9, EtOH)	*R*	19.1
f	C_6H_5	C_6H_5	$C_6H_5CH_2$	*l*-Menthyl	−3.7°(*c*=1.3, EtOH)	*S*	3.3
g	HO_2C	HO_2C	*R*(+)Me	C_2H_5	−20.3°(*c*=1.6, 1N NaOH)	*R*	22.0
h	HO_2C	HO_2C	*S*(−)Me	C_2H_5	+16.8°(*c*=2.5, 1N NaOH)	*S*	18.3
i	HO_2C	HO_2C	$C_6H_5CH_2$	*l*-Menthyl	−2.0°(*c*=2.7, 1N NaOH)	*R*	2.2

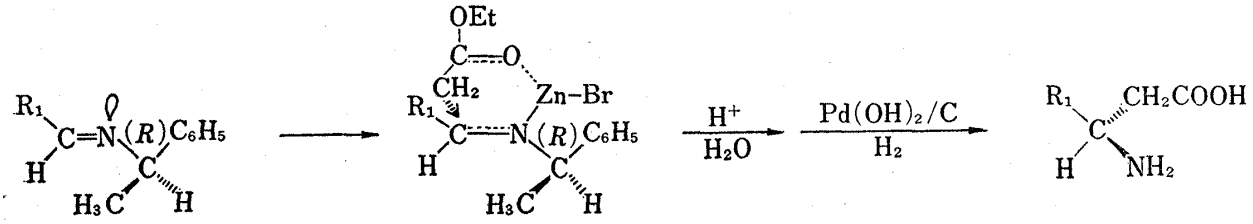
a) The optical purity is defined as $[\alpha]_D^{obsd.}/[\alpha]_D^{lit.} \times 100$.
(*S*)-β-Aminobutyric acid, $[\alpha]_D^{19}$ +38.8° (H_2O),[d] (*S*)-β-Formamido-β-phenylpropionic acid, $[\alpha]_D^{25}$ −114.5° (EtOH),[9] DNP-aspartic acid, $[\alpha]_D^{25}$ +91.9° (1N NaOH).[10]
b) *R*(+)-α-Methylbenzyl.
c) *S*(−)-α-Methylbenzyl.
d) K. Balenovic, D. Cerar, and Z. Fuks, *J. Chem. Soc.*, **1952**, 3316.

When optically active **3**, which was composed of *R*(+)- and *S*(−)-amines, was allowed to react with **4** (R_3=Et), (*S*)- and (*R*)-β-amino acids were respectively formed in the range

6) J.L. Luche and H.B. Kagan, *Bull. Soc. Chim. Fr.*, **1969**, 1680; J.L. Luche and H.B. Kagan, *ibid.*, **1969** 3500; J.L. Luche and H.B. Kagan, *ibid.*, **1971**, 2260.
7) Organic Syntheses, Coll. Vol. 4, 1963, p. 124.
8) M. Furukawa, T. Okawara, and Y. Terawaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 181 (1977).
9) F. Bergel and J. Butler, *J. Chem. Soc.*, **1961**, 4047.
10) J.C. Perrone, *Nature* (London), **167**, 513 (1951); K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

of 18—28% optical purities. On the other hand, when **3** having no chiral moiety were treated with a chiral **4** involving *l*-menthyl ester group, (*S*)-*β*-amino acids were obtained in lower 3—5% optical purities. In the case of aspartic acid, the use of the optically active **3** containing *R*(+)- and *S*(−)-amino component gave (*R*)- and (*S*)-aspartic acids respectively in 18—22% optical purities. When a chiral **4** (R_3=*l*-menthyl) was employed, (*R*)-aspartic acid was formed in a 2.2% optical purity.

The reaction of **3** with **4** is assumed to proceed through the similar mechanism to that[2,12] of the reaction of carbonyl compounds with **4**, and resultingly the steric course will be considered as the following Chart 2.



R_1=CH_3, C_6H_5 (*S*)-*β*-amino acid. R_1=CO_2H (*R*)-aspartic acid

Chart 2

The compound **3** is assumed to be in the stable form (*E*-form) and reacts with **4** through a transition state of six membered ring. In the transition intermediate, the attack of the carbanion takes place in the less hindered side of the carbonium ion to obtain finally **8** after a few steps.

Experimental

Hydrogenations were carried out by Skita and Parr catalytic hydrogenation apparatus. Specific rotations were measured by JASCO DIP 4 Polarimeter using 10 mm cell. IR spectra were recorded with a JASCO IRA-1 Grating Infrared Spectrometer. NMR spectra were determined with a JEDL High Resolution NMR Instrument C-60 H.

***l*-Menthyl *α*-Bromoacetate**——A mixture of α-bromoacetic acid (13.6 g, 0.10 mol), *l*-menthol (17.2 g, 0.11 mol), a small amount of *p*-toluenesulfonic acid, and toluene (60 ml) was refluxed for 4 hr in a flask with a Dean-Stark separator until the caluculated amount of water was separated. The toluene solution was washed with 1% aq. $NaHCO_3$ (30 ml) and then with water (30 ml), and dried over anhydrous Na_2SO_4. After the solvent was removed, the residue was distilled under reduced pressure: yield, 23.1 g (83.5%); bp 115°/4 mmHg; $[\alpha]_D^{15}$ −68.9° (*c*=2.3, EtOH); IR ν_{max}^{film} cm^{-1}: 1740 (C=O); *Anal.* Calcd. for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.64. Found C, 52.28; H, 7.73.

Butyl Glyoxalate (1, R_1=CO_2Bu)——This compound was prepared by the reaction of dibutyl tartrate (10.7 g, 0.04 mol) with lead tetraacetate (21.0 g, 0.047 mol).[7] Yield, 6.8 g (64%); bp 61—72°/18 mmHg (lit. bp 65—79°/20 mmHg).

Schiff Base (3)——A solution of **1** (0.10 mol) in benzene (10 ml) was gradually added with cooling into a solution of **2** (0.10 mol) in benzene (30 ml). The reaction mixture was dried over anhydrous Na_2SO_4 overnight at room temperature. After removal of the solvent, the residue (R_1=C_6H_5) was distilled under reduced pressure.[8] When R_1 group was CH_3 and CO_2Bu, the residue was used directly in the next reaction without purification.

N-Alkylamino Acid (7)——α-Bromoacetate (0.01 mol) was gradually added with stirring into a boiling solution of **3** (0.01 mol) in dry benzene (30 ml) containing zinc powder(1.34 g, 0.02 gr.at.). After the addition was over, the reaction mixture was refluxed for 2 hr, and added with stirring into a concentrated ammonia solution (20 ml). The benzene solution separated was washed with water (20 ml), 3% aq. $NaHSO_3$ (20 ml), and finally water (20 ml) twice, and dried over anhydrous Na_2SO_4. After the solvent was removed by distillation, the residue was refluxed with 6 N HCl (30 ml) for 10 hr. The mixture 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 the solution was applied to a IR 120 column (H^+ form, 2.2×26.5 cm). The

11) M. Mousseron, M. Mousseron, J. Neyrolles, and Y. Beziat, *Bull. Soc. Chim. Fr.*, **1963**, 1483.
12) M. Furukawa, T. Okawara, and Y. Terawaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 1319 (1977).

column was eluted with 1.5 N aq. ammonia and the fractions containing amino acid were combined and evaporated to dryness under reduced pressure. The residue was used in the next hydrogenation. When R_2 was benzyl group, N-benzylamino acid (**7**) was isolated and recrystallized from EtOH. β-(Benzylamino)-butyric acid (**7**, $R_1=CH_3$, $R_2=C_6H_5$): yield, 0.85 g (44%); mp 194°; NMR δ (CF_3CO_2D): 7.38 (s, 5H, arom), 4.41 (d, 2H, $J=3.5$ Hz, CH_2), 3.80 (broad, 1H, CH), 3.03 (d, 2H, $J=7.0$ Hz, CH_2), 1.63 (d, 3H, $J=6.0$ Hz, CH_3). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.47; H, 7.91; N, 7.35. β-(Benzylamino)-β-phenylpropionic acid (**7**, $R_1=C_6H_5$, $R_2=C_6H_5CH_2$): yield, 1.01 g (39%); mp 197—198°; NMR δ (CF_3CO_2D): 7.43 (s, 5H, arom), 7.31 (m, 5H, arom), 4.70 (m, 1H, CH), 4.21 (d, 2H, $J=3.0$ Hz, CH_2), 3.35 (t, 2H, $J=6.0$ Hz, CH_2). *Anal.* Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.43; H, 6.68; N, 5.48.

β-Amino Acid (**8**)——The residue obtained by the procedure described above was dissolved in EtOH and water and hydrogenolyzed over 10% palladium hydroxide on charcoal (0.8 g) for 12 hr. After the reaction was over, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The resulting racemic **8** was isolated and recrystallized from dil. EtOH. (±)-β-Aminobutyric acid (**8**, $R_1=CH_3$): yield, 0.43 g (95%); mp 190—192°. (±)-β-Amino-β-phenylpropionic acid (**8**, $R_1=C_6H_5$): yield, 0.52 g (86%); mp 243—244°. These compounds were identified by comparison with the authentic samples.[12]

The specific rotations of the resulting optically active β-amino acids were measured as the crude product for β-aminobutyric acids (**8a—c**), as the formyl derivatives[10] for β-amino-β-phenylpropionic acid (**8d—f**), and as DNP-aspartic acids for aspartic acids (**8g—i**). The identification of **8i** with aspartic acid was determined by the automatic amino acid analyzer (KLA-5).

4-Oxo-1-benzyl-2-phenylazetidine (**5**, $R_1=C_6H_5$, $R_2=C_6H_5CH_2$) **and Ethyl β-(benzylamino)-β-phenylpropionate** (**6**, $R_1=C_6H_5$, $R_2=C_6H_5CH_2$, $R_3=C_2H_5$)——These compounds were prepared from **3** ($R_1=C_6H_5$, $R_2=C_6H_5CH_2$) (2.0 g, 0.01 mol) and the Reformatsky reagent (**4**, $R_3=C_2H_5$) obtained from ethyl α-bromoacetate (1.67 g, 0.01 mol) and zinc powder (1.34 g, 0.02 gr.at.) by the method described above. The residue was distilled at 154—162°/1.5 mmHg. The distillate was poured into anhydrous ether (5 ml), and recrystallized from EtOH to give the propoinate (0.25 g, 8.8%); mp 178—179°; IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O); NMR δ ($(CD_3)_2SO$): 7.55—7.34 (broad, 10H, 2×arom), 4.50—4.40 (broad, 1H, CH), 3.85 (q, 2H, $J=7.0$ Hz, CH_2), 3.81 (t, 2H, $J=6.0$ Hz, CH_2), 3.25 (s, 2H, CH_2), 0.99 (t, 3H, $J=7.0$ Hz, CH_3). *Anal.* Calcd. for $C_{18}H_{21}NO_2$: N, 4.94. Found: N, 4.92.

The filtrate was evaporated and distilled at 163°/1.5 mmHg to give the azetidine (0.24 g, 10.2%); IR ν_{max}^{film} cm^{-1}: 1760 (C=O); NMR δ ($CDCl_3$): 7.23 (s, 5H, arom), 7.21—7.12 (broad, 5H, arom), 4.36 (q, 1H, $J=3.0$ Hz, CH), 4.25 (q, 2H, $J=15.0$ Hz, CH_2), 3.33 and 2.79 (q, 2H, $J=5.0$ and 3.0 Hz, CH_2).

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