Asymmetric Synthesis of Aspartic Acid by Hydrogenation of Optically Active 1,4-Oxazine Derivative[1]

Minoru TAMURA and Kaoru HARADA*

Department of Chemistry, The University of Tsukuba, Niihari-gun, Ibaraki 305

(Received July 25, 1979)

Synopsis. The asymmetric hydrogenation of an optically active heterocyclic compound, (*R*)-3-methoxycarbonylmethylene-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one(**2**), was studied. The compound **2** was hydrogenated with several catalysts, and was converted into optically active aspartic acid. The configuration of the resulting aspartic acid proved to be (*S*), and the optical yield was in the range 12—17%.

Recently we have reported[2] an asymmetric synthesis of alanine by hydrogenolytic transamination by the use of (*R*)-2-amino-2-phenylethanol (**1**) as a chiral reagent. The effects of the asymmetric moieties as well as the solvents on the optical yields were explained by the chelation hypothesis based on the interaction between the substrate and the catalyst.

In the present work, in order to study the effect of the structure of substrate on the optical yield, the optically active heterocyclic compound **2** was prepared from amino alcohol **1** and dimethyl acetylenedicarboxylate, and the asymmetric hydrogenation of **2** was carried out.

Kagan *et al.*[3,4] reported an efficient asymmetric synthesis by hydrogenation of the cyclic compound prepared from (1*S*,2*R*)-2-amino-1,2-diphenylethanol and dimethyl acetylenedicarboxylate. However, since asymmetric hydrogenation of **2** was not described in detail, we would like to report the results of the hydrogenation of **2** with aluminum amalgam, Raney nickel, and other catalysts.

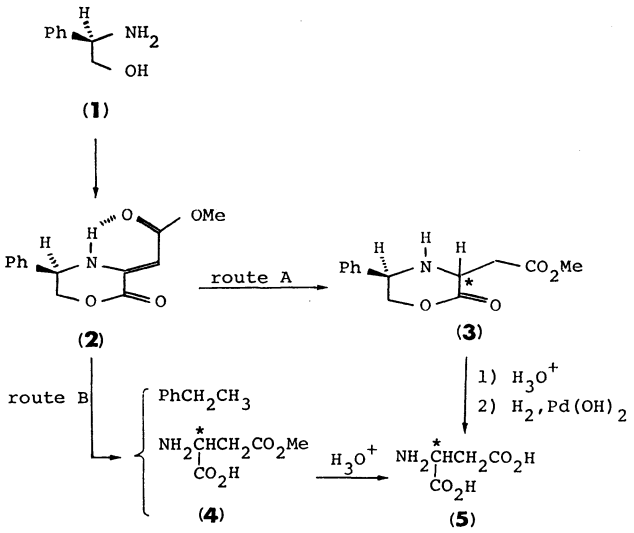
TABLE 1. ASYMMETRIC SYNTHESIS OF ASPARTIC ACID BY HYDROGENATION OF **2**

Temp °C	Catalyst	Time h	Solvent	Route (A or B)	Yield[b]	$[\alpha]_D^{25}$ DNP-Asp[c]	Optical yield[d] (confign.)
5	Al-Hg	6	DME[a]	A	44	+14.1 (0.880)	15 (*S*)
0	Al-Hg	6	DME	A	61	+16.0 (0.702)	17 (*S*)
−20	Al-Hg	7	DME	A	62	+14.7 (1.35)	16 (*S*)
20	Raney Ni	48	EtOH	A	57	+13.0 (0.893)	14 (*S*)
20	Pd	48	MeOH	B	70	+14.7 (0.422)	16 (*S*)
20	Pd on C	48	MeOH	B	42	+14.8 (0.487)	16 (*S*)
20	Pd on C	48	Dioxane	B	48	+10.8 (0.573)	12 (*S*)

a) DME is 1,2-dimethoxyethane. b) The yields of **3** (route A) or **4** (route B). c) The specific rotations were measured in 1 mol dm^{-3} NaOH. d) Optical yield is defined as ($[\alpha]_D$ obsed/$[\alpha]_D$ lit) × 100, DNP-(*S*)-Asp, $[\alpha]_D^{25}$ +91.9° (1 mol dm^{-3} NaOH).

Cyclic compound **2** was prepared through the condensation of optically active amino alcohol **1** and dimethyl acetylenedicarboxylate at room temperature. The IR spectra of **2** indicated the presence of an intramolecular hydrogen bond.[5] In the NMR spectra of **2**, the chemical shift of the NH proton also suggested an intramolecular hydrogen bond.[6] From the results described above, it was concluded that compound **2** is of *Z*-configuration.

Compound **2** was hydrogenated with aluminum amalgam or Raney nickel (Scheme 1; route A). Product **3** was purified by the use of silica gel column chromatography without fractionation. The yield of **3** was



Scheme 1.

44—62%. Hydrolysis and subsequent hydrogenolysis of **3** gave optically active aspartic acid in 74—75% yields from **3**. The optical yields of the aspartic acid were determined as *N*-(2,4-dinitrophenyl)aspartic acid (DNP-Asp).[7] The configuration of aspartic acid was (*S*). The optical yields ranged from 14 to 17%. In the reaction with aluminum amalgam, the reaction temperature was lowered, however, no change of the optical yield was observed.

When palladium black or 5% palladium on charcoal was used as a catalyst, hydrogenation and hydrogenolysis took place simultaneously and β-methyl hydrogen aspartate (**4**) was obtained in 42—70% yields (route B). According to the time-course checked by TLC of the reaction mixture, it seems that hydrogenation takes place prior to hydrogenolysis.

It was found that the reductive cleavage of the benzylic C–N bond and also the homobenzylic C–O bond (Ph–CH_2–CH_2–O)[8] took place in route B. The existence of ethylbenzene in the reaction mixture, which was confirmed by gas-liquid chromatography, would support the hydrogenolytic cleavage of the homobenzylic C–O bond.

Compound **4**, which was obtained by the route B, was hydrolyzed to form optically active aspartic acid. The optical yield of DNP-aspartic acid ranged from 12 to 16%. And the configuration of aspartic acid was (*S*). The results are summerized in Table 1.

The examination of the conformation by the Dreiding model showed that the preferential formation of (*S*)-isomer was caused by the steric effect of the phenyl group on substrate **2**, and that the steric effect would be larger when the phenyl group is pseudo axial than pseudo equatorial. The optical yields obtained by

these reactions suggested that substrate **2** could largely take the conformation in which the phenyl group is pseudo equatorial.

Experimental

The NMR spectra were obtained by using a Hitachi H-60 and R-24 A spectrometers, and the IR spectra were measured with a Hitachi 215 type grating infrared spectrophotometer. The gas chromatography was carried out with a Hitachi 163 type gas chromatograph. The specific rotations were measured with a JASCO DIP-181 type digital polarimeter using a 50 mm cell. The amino acids were analyzed with a Yanagimoto LC-5 S instrument. The mass spectra were obtained by a Hitachi RMU-6 MG type high resolution mass spectrometer.

(R)-3-Methoxycarbonylmethylene-5-phenyl-3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one (2). A solution of (*R*)-2-amino-2-phenyl-ethanol (**1**) ($[\alpha]_D^{25}$ −27.3° [c=1.08, methanol])[2] (0.5 g, 3.65 mmol) in 10 ml of MeOH was added dropwise to a solution of dimethyl acetylenedicarboxylate (0.518 g, 3.65 mmol) in 7 ml of MeOH with stirring for 20 min. After being stirred for additional 2.5 h, the mixture was evaporated and purified by silica gel column chromatography (30×210 mm, E. Merck No. 9385), eluted with benzene–AcOEt (9: 1 v/v) solvent. Compound **2** was obtained as colorless oil (0.791 g; 88%), which crystallized on cooling in a refrigerator. The recrystallization from ether–petroleum ether gave colorless needles. Mp 67—68 °C, $[\alpha]_D^{20}$ −259° (c=0.590, $CHCl_3$). Found: C, 63.11; H, 5.10; N, 5.83%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.29; N, 5.66%. IR($CHCl_3$): 3300 (NH), 3000, 1740 (lactone), 1660 (ester), 1620 (C=C) cm^{-1}. δ($CDCl_3$): 3.65 (3H, s), 4.30—4.85 (3H, ABC m), 5.70 (1H, s, $-\underset{|}{C}=CH$), 7.30 (5H, s), 8.50 (1H, s, NH). The H–D exchange of the proton on NH was very slow (half life $T_{1/2}$: 2 d). Mass: M^+ (247), λ_{max}: 325 nm (ε=8330).

(R)-3-Methoxycarbonylmethyl-5-phenyl-3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one (3) (Route A). An aluminum amalgam prepared from 500 mg of aluminum foil[9] was added to an ice-cooled magnetically stirred solution of **2** (500 mg, 2.02 mmol) in 30 ml of 1,2-dimethoxyethane. The mixture was treated with 4 ml of distilled water, and the stirring was continued for 6 h at 0 °C under nitrogen atmosphere. To the reaction mixture, Celite 545 (0.1 g) was added and filtered under suction, and the residue was washed with 1,2-dimethoxyethane (25 ml) and MeOH (25 ml). After evaporation of the solvent at 0—5 °C, the residue was dissolved in ethyl acetate and was dried (Na_2SO_4). After removal of the solvent at 0—5 °C, the residual oil was purified by silica gel column chromotography mentioned above. The combined fractions were evaporated at 0—5 °C to furnish colorless oli. Yield: 0.307 g (61%). IR (NaCl): 3300 (NH), 2950, 1750 (lactone), 1730 (ester) cm^{-1}. δ($CDCl_3$): 2.71 (1H, s, NH), 2.80—3.10 (2H, 6 peaks, $-C\underline{H}_2-CO_2CH_3$), 3.70 (3H, s), 4.00—4.45 (4H, m), 7.38 (5H, s). Mass: M^+ (249). In the case of Raney nickel, **2** (400 mg, 1.62 mmol) was dissolved in 20 ml of abs EtOH and Raney nickel (W-2 type, 600 mg) was added. Hydrogenation was carried out at room temperature for 48 h (initial pressure of hydrogen was 3 atm).

(S)-Aspartic Acid (Route A). The compound **3** was hydrolyzed with 6 mol dm^{-3} hydrochloric acid (10 ml) under reflux for 5 h. After evaporation, the hydrolyzate was dissolved in a small amount of distilled water and the pH was adjusted to about 4.5 with sodium hydrogen carbonate. Palladium hydroxide on charcoal (0.2 g) was added to the solution and the hydrogenolysis was carried out for 13 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a small amount of water and the solution was applied to a Dowex 50 column (H^+ form). The column was eluted with 3 mol dm^{-3} aqueous ammonia and the eluent was evaporated to dryness. A part of the solution was diluted appropriately and analyzed with an amino acid analyzer (yield: 74%). A part of aspartic acid was converted to DNP-Asp, which was purified by a Celite column (Hyflo-super-cel); $[\alpha]_D^{25}$ +16.0° (c=0.702, 1 mol dm^{-3} NaOH), optical purity 17%. The DNP-aspartic acid was further confirmed by TLC (MeOH: AcOEt=5: 1 v/v).

(S)-β-Methyl Hydrogen Aspartate (4) (Route B). To a solution of **2** (200 mg, 0.810 m mol) in 5 ml of abs. MeOH, palladium black (300 mg) was added, and the mixture was stirred for 48 h under hydrogen (1 atm). The catalyst was removed by filtration and a small part of the filtrate (1 μl) was applied on a gas-liquid chromatography, which showed the presence of ethylbenzene. The residual filtrate was evaporated to dryness and the residue crystallized by addition of a small amount of chloroform. Yield: 83.2 mg (70%); mp 199—200 °C; δ (D_2O): 2.80—3.35 (2H, ABX), 3.77 (3H, s), 4.35 (1H, dd); IR (KBr): 3400 (br), 3000 (br), 2070, 1720, 1650, 1600 cm^{-1}. Found: C, 40.80; H, 6.01; N, 9.22%, Calcd for $C_5H_9NO_4$: C, 40.81; H, 6.16; N, 9.52%.

(S)-Aspartic Acid (Route B). Crude **4** was refluxed with 6 mol dm^{-3} hydrochloric acid (10 ml) for 3 h. After evaporation, the residue was dissolved in a small amount of water and the solution was applied to a Dowex 50 column. The yield of aspartic acid was determined by an amino acid analyzer (91%), and the optical purity of the aspartic acid was determined as DNP-(*S*)-aspartic acid; $[\alpha]_D^{25}$ +14.7° (c 0.422, 1 mol dm^{-3} NaOH), optical purity 16%.

The authors wish to express their thanks to Dr Takenori Kusumi for his valuable discussions. We also would like to thank Dr. Shinya Nomoto for his discussion.

References

1) Sterically Controlled Synthesis of Optically Active Organic Compounds XXX; Part XXIX, Ref. 2.

2) K. Harada and M. Tamura, *Bull. Chem. Soc. Jpn.*, **52**, 1227 (1979).

3) J. P. Vigneron, H. Kagan, and A. Horeau, *Tetrahedron Lett.*, **1968**, 5681.

4) J. P. Vigneron, H. Kagan, and A. Horeau, *Bull. Soc. Chim. Fr.* **1972**, 3836.

5) The wave number of NH (3300 cm^{-1}) was independent of the concentration of the sample in $CHCl_3$.

6) N. F. Chamberlain, "The practice of NMR spectroscopy," Plenum Press, New York (1974), p. 189. The rate of H–D exchange of the NH proton of **2** was very slow.

7) K. Harada and K. Matsumoto, *J. Org. Chem.*, **31**, 2985 (1966).

8) E. W. Garbisch, Jr., *Chem. Commun.*, **1967**, 806.

9) E. J. Corey, R. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2485 (1970).