BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (4), 1227—1228 (1979)

Asymmetric Synthesis of Alanine by Hydrogenolytic Asymmetric Transamination between (*R*)-2-Amino-2-phenylethanol and Ethyl Pyruvate[1)]

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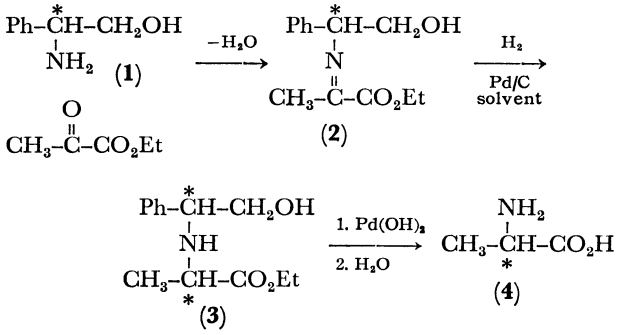
(Received August 4, 1978)

Synopsis. Hydrogenolytic asymmetric transamination between (*R*)-2-amino-2-phenylethanol and ethyl pyruvate was studied. The optical purity of the resulting alanine was in the range 10—62 %. The effect of solvents and the asymmetric moieties in the syntheses were explained by the chelation hypothesis based on the substrate-catalyst complex.

In the previous study from this laboratory, hydrogenolytic asymmetric transaminations between optically active α-alkylbenzylamines, (*R*)-phenylglycine, or alkyl (*R*)-phenylglycinate and ethyl pyruvate were studied.[2-5)] The effect of the asymmetric moieties and the solvents used in the asymmetric syntheses was explained by the chelation hypothesis.[2-5)]

In the present study, in order to extend the application of the chelation hypothesis, the asymmetric transamination between optically active amino alcohol (**1**) and ethyl pyruvate was carried out. (*R*)-2-Amino-2-phenylethanol (**1**) was prepared from ethyl (*R*)-phenylglycinate by reduction with lithium aluminium hydride. Alcohol **1** and ethyl pyruvate were dissolved in benzene to form the Schiff base (**2**), which was hydrogenated by the use of palladium on charcoal in various solvents and then hydrogenolyzed with palladium hydroxide on charcoal and the reaction product was hydrolyzed to form alanine. The resulting alanine was purified by the use of a Dowex 50 column; The yield was in the range 46—73%. A part of alanine was converted into DNP-alanine with 2,4-dinitrofluorobenzene and the resulting DNP-alanine was purified by celite column chromatography. The optical purity of DNP-alanine was in the range 10—62%. The results are summarized in Table 1.

In all these kinds of reactions, the configuration of the resulting alanine was (*S*). When a polar solvent was used, the optical purity was lower and when a less polar solvent was used, the optical purity of alanine increased steadily (Fig. 1, R=CH_2OH). The results could be explained by assuming the substrate-catalyst complex as in the previous studies (Fig. 2).[2-5)] In a less polar solvent, the substrate-catalyst complex (**2a**) could be formed prior to hydrogenation. However, in a polar solvent, the amount of **2a** would decrease and the non-chelated structure **2b** would increase because of the



Scheme 1.

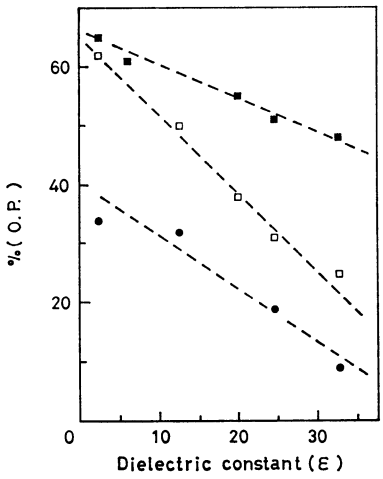


Fig. 1. Optical purities of alanine by hydrogenolytic transamination by using various solvents. ■: R=CH_3,[4)] □: R=CH_2OH, ●: R=$COOCH_3$.[5)]

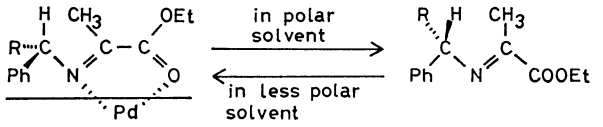


Fig. 2. Conformations of substrate in polar and in less polar solvents.

TABLE 1. OPTICALLY ACTIVE ALANINE SYNTHESIZED BY HYDROGENOLYTIC ASYMMETRIC TRANSAMINATION

Solvent	Yield of Ala[a)]	$[\alpha]_D^{25}$ of DNP-Ala (*c*, 1 M NaOH)	O.P.[b)] (%)	Config. of Ala
PhH	56	+89.6 (1.00)	62	S
t-BuOH	46	+71.3 (1.04)	50	S
i-PrOH	54	+54.8 (0.86)	38	S
EtOH	56	+45.1 (1.38)	31	S
MeOH	73	+36.2 (1.03)	25	S
MeOH-H_2O (2: 1 v/v)	67[c)]	+21.8 (1.06)	15	S
H_2O	53[c)]	+15.0 (0.84)	10	S
Hexane	56[c)]	+55.4 (1.14)	39	S

a) Calculation based on ethyl pyruvate. b) Optical purity (O.P.) was difined as ($[\alpha]_D$ obsed/$[\alpha]_D$ in literature) × 100. DNP-(*S*)(+)-alanine, $[\alpha]_D^{25}$ +143.9 °C (1 M NaOH). c) The reaction mixtures were not homogeneous solutions.

stronger solvation of the substrate. In both structures **2a** and **2b**, the substrate would be adsorbed at the less bulky side of the molecules and then the hydrogenation would take place. In the case of **2a**, the adsorption would involve the rotation of the C–N bond. From the structures **2a** and **2b**, (*S*)- and (*R*)-alanine, respectively, were expected to form. The relationship between the R group (Fig. 2) of the asymmetric center and the optical activity was compared with the results obtained from the previous studies using (*S*)-α-methylbenzylamine[4] or methyl (*R*)-phenylglycinate[5] (Fig. 1). As the R group of **2a** becomes small, the difference in bulkiness between phenyl and the R groups increases, the optical purity of the resulting alanine would become higher. When the R group becomes larger, the optical activity would decrease. It was found in the present reactions (R= CH_2OH) that the optical purities were lower than those of the reactions using (*S*)-α-methylbenzylamine (R= CH_3)[4] and were higher than those of the reactions using methyl (*R*)-phenylglycinate (R=$COOCH_3$).[5] This suggests that the hydroxymethyl group would be in the bulkiness between methyl and carboxy methyl groups. These results indicate that the chelation hypothesis could also be applied to the hydrogenolytic transamination between alcohol (**1**) and ethyl pyruvate.

Experimental

The NMR spectra were obtained by using a Hitachi H-60 instrument, and the IR spectra were measured with a Hitachi 215 type grating infrared spectrophotometer. The specific rotations were measured with a JASCO DIP-181 type digital polarimeter using a 50 mm cell.

(R)-2-Amino-2-phenylethanol (1). A mixture of (*R*)-phenylglycine ($[\alpha]_D^{25}$ −163° [*c*=1.13, 5 M HCl])[6] (20 g, 0.133 mol) and absolute ethanol (300 ml) was treated with thionyl chloride at temperatures from −5 to −10 °C for 1 h. The temperature was allowed to rise to 40 °C at which it was kept for 4 h. The resulting mixture was evaporated to dryness. The residual white solid was dissolved in a small amount of water and the solution was made alkaline by adding 3 M NaOH and 50% potassium carbonate with stirring at −10 °C. The separated ethyl (*R*)-phenylglycinate was extracted with ether twice. The ether layer was dried with sodium sulfate in a refrigerator overnight and the ester was distilled under reduced pressure 98—99 °C/2 Torr, yield 18.5 g (77%) $[\alpha]_D^{25}$ −125° (*c*=1.42, EtOH).[7] δ ($CDCl_3$): 1.15 (3H, t, *J*= 6.6 Hz), 1.90 (2H, s), 4.10 (2H, q, *J*=6.6 Hz), 4.50 (1H, s), 7.25 (1H, s). Ethyl-(*R*)-phenylglycinate (14.2 g, 0.08 mol) was dissolved in 100 ml of dry ether and the solution was added dropwise to a mixture of lithium aluminium hydride (9.0 g, 0.24 mol) and 300 ml of dry ether under vigorous stirring. After being stirred for 2 h, the mixture was cooled to −10 °C and a small amount of water was added with stirring. The aluminium hydroxide precipitated was removed by filtration and the precipitate was washed thoroughly with ether three times. The combined ether solution was evaporated to dryness, and the residual oil crystallized by washing with hexane. The slightly yellow crystals (**1**) (yield 9.57 g, 87%) were recrystallized from benzene to yield colorless needles. Mp 75—76 °C, $[\alpha]_D^{25}$ −27.3° (*c*=1.08, methanol).[8] Found: C, 70.17; H, 8.09; N, 10.04 %. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21%. IR(KBr): 3310, 3250, 2900, 2820, 1600, 1490, and 1450 cm^{-1}; δ($CDCl_3$): 2.70 (3H, br, s, NH_2 and OH), 3.3—4.2 (3H, ABC multiplet), 7.2 (5H, s).

Alanine (4). The aminoalcohol **1** (1.0 g, 7.3 mmol) and ethyl pyruvate (0.847 g, 7.3 mmol) were dissolved in 20 ml of dry benzene. The mixture was stirred at room temperature for 4 h with anhydrous sodium sulfate. After separation of sodium sulfate by filtration, the filtrate was evaporated to dryness. The residual light yellow oil (**2**) was dissolved in 20 ml of dry benzene and hydrogenated with 5% palladium on charcoal (1.5 g) for 24 h at 1 atm. After the reaction was over, the catalyst was removed by filtration and washed with 3 M hydrochloric acid. The combined solution was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and the pH was adjusted to about 4.5 with the use of sodium hydrogen carbonate. Palladium hydroxide on charcoal (1.0 g) was added to the solution and hydrogenolysis was carried out for 24 h. After the reaction was completed, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The resulting ethyl alaninate was hydrolyzed with 3 M hydrochloric acid under reflux for 4 h. After evaporation of hydrochloric acid under reduced pressure, 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 M aqueous ammonia and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 4% sodium hydrogencarbonate and washed with ethyl acetate three times to remove a small amount of **1**. The aqueous solution was acidified with 3 M hydrochloric acid and evaporated to dryness and the residue was extracted with absolute ethanol. The alcoholic solution was evaporated to dryness *in vacuo* and free alanine was obtained by using a Dowex 50 column. The yield of the resulting alanine[9] was 0.366 g (56 %). The alanine was converted into DNP 2,4-dinitrophenylalanine in the usual way,[2] and the resulting DNP derivative was purified by the use of a celite column treated with pH 6.8 phosphate buffer. The specific rotation of the DNP-(*S*)-alanine was: $[\alpha]_D^{25}$ +89.6° (*c*=1.00, 1 M NaOH); optical purity 62%.

References

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6) (*R*)-α-phenylglycine, $[\alpha]_D^{25}$ −168° (5 M HCl) in Ref. 3.

7) Ethyl (*R*)-phenylglycinate hydrochloride, $[\alpha]_D^{25}$ −119° (*c*=1.45, ethanol), Ref. 5, $[\alpha]_D^{25}$ −115° (ethanol).

8) M. B. Watson and G. W. Youngson, *J. Chem. Soc.*, **1954**, 2145. (I) Mp 75—76 °C, $[\alpha]_D^{25}$ −25.5° (methanol): R. Lukes *et al.*, *Collect. Czech. Chem. Commun.*, **23**, 1367 (1958). (I) $[\alpha]_D^{25}$ −24.5° (methanol).

9) Alanine was confirmed by using an amino acid analyzer and also by the use of thin layer chromatography as the DNP derivative.