Asymmetric Synthesis of Alanine by Catalytic Hydrogenation of Chiral N^{α}-Acetyldehydroalaninamides

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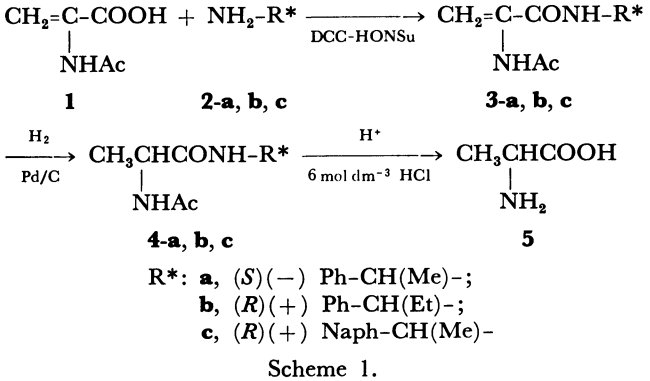
Synopsis. Asymmetric hydrogenation of chiral N^{α}-acetyldehydroalaninamides was studied. The asymmetric yield of the resulting alanine was in the range 0—24%. The effects of reaction temperature, solvent polarity and asymmetric moieties on the asymmetric yields were examined.

Several studies[1-7] have been performed on asymmetric reduction of α,β-dehydroamino acid derivatives yielding amino acids. Among these studies, heterogeneous hydrogenations of optically active linear derivatives of dehydroamino acids were reported,[1,2] and the steric course of the asymmetric hydrogenation was explained by the application of the Prelog rule.[8] However, no detailed studies on the effects of temperature and solvent polarity on asymmetric hydrogenation have been reported. In the present study, asymmetric catalytic hydrogenation of chiral N^{α}-acetyldehydroalaninamides was carried out and the temperature dependence on the asymmetric hydrogenation was studied using various solvents.

The chiral N^{α}-acetyldehydroalaninamides used were N^{α}-acetyl-*N*-[(*S*)-methylbenzyl]dehydroalaninamide (**3-a**), *N*-[(*R*)-α-ethylbenzyl]amide (**3-b**), and *N*-[(*R*)-1-(1-naphthyl)ethyl]amide (**3-c**). The compounds **3-a**, **b**, and **c** were prepared by the coupling of *N*-acetyldehydroalanine (**1**) and the corresponding chiral amines (**2-a**, **b**, and **c**) with dicyclohexylcarbodiimide in the presence



Scheme 1.

of *N*-hydroxysuccinimide. The hydrogenation reactions were carried out at 1 atm of hydrogen by using palladium on charcoal suspended in several solvents (methanol, ethanol, 2-propanol, and ethyl acetate). The reaction temperature was in the range of −50 °C to 50 °C. After the hydrogenation, the resulting N^{α}-acetylalaninamides (**4-a**, **b**, and **c**) were hydrolyzed to form alanine. The chemical yield of alanine was in the range of 78—98% as determined by an amino acid analyzer. The asymmetric yield of alanine was determined by gas chromatographic analysis employing a chiral stationary phase (Chirasil-Val[9]).

The results are summarized in Figs. 1, 2, and 3. In the reaction of compound **3-a**, a clear temperature effect on the asymmetric yield was observed. With the decrease in solvent polarity, the asymmetric yield of (*R*)-alanine increased at lower temperature. The effect observed could not be explained by the application of the Prelog rule,[8] which was employed in the previous reports.[1,2] Since a similar temperature effect was observed in the reaction of compound **3-b**, the same reaction mechanism would prevail in the hydrogenation of these two compounds.

In the reaction of compound **3-c**, the temperature effect was not so large. With the decrease in solvent polarity, the asymmetric yield of (*R*)-alanine increased except in the reaction using ethyl acetate as the solvent. This result was definitely different from the results

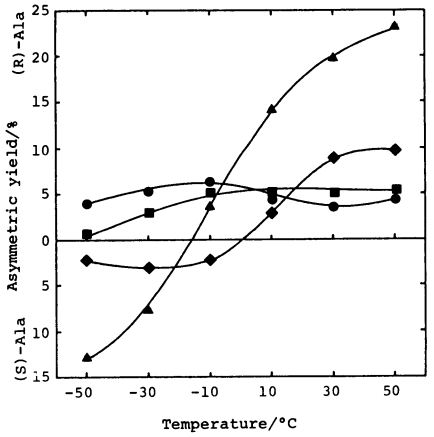


Fig. 1. Temperature effect in asymmetric hydrogenation of compound **3-a**. ●: In methanol, ■: in ethanol, ◆: in 2-propanol, ▲: in ethyl acetate.

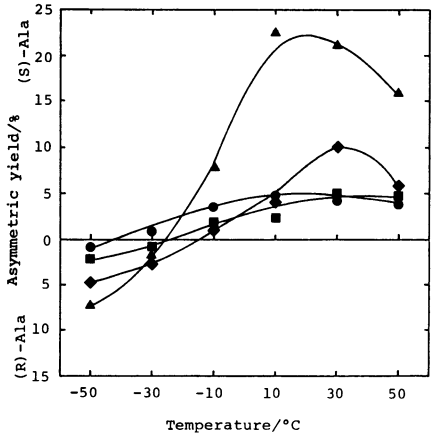


Fig. 2. Temperature effect in asymmetric hydrogenation of compound **3-b**. ●: In methanol, ■: in ethanol, ◆: in 2-propanol, ▲: in ethyl acetate.

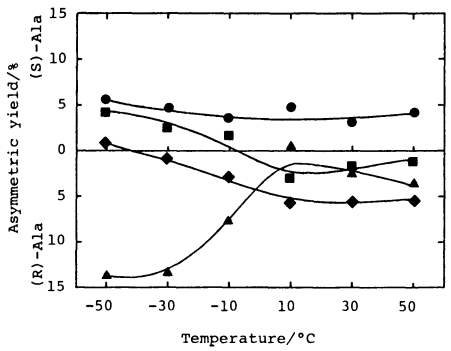


Fig. 3. Temperature effect in asymmetric hydrogenation of compound **3-c**. ●: In methanol, ■: in ethanol, ◆: in 2-propanol, ▲: in ethyl acetate.

obtained in the reactions of compounds **3-a** and **b**. Therefore, mechanisms prevailed in the reaction of compound **3-c** could be distinct from those of compounds **3-a** and **b**.

The results obtained could indicate the participation of several reaction mechanisms in the asymmetric synthesis. The mechanisms in these reactions could be changed by the reaction temperature, solvent polarity and asymmetric moieties.

Experimental

All the melting points were uncorrected. Optical rotations were measured with a JASCO DIP-181 Digital Polarimeter. The gas chromatographic analysis were carried out with a Hitachi 163 gas chromatograph and the peaks on the chromatogram were integrated with a Hitachi 834-30 chromatoprocessor. Amino acid analysis were carried out with a Yanagimoto LC-5S instrument.

N$^{\alpha}$-Acetyl-N-[(S)-methylbenzyl]dehydroalaninamide (3-a). *N*-Acetyldehydroalanine[10] (**1**) (3.25 g, 25 mmol) was dissolved in ethyl acetate (60 ml) together with (*S*)-methylbenzylamine (**2-a**) (3.00 g, 25 mmol), *N*-hydroxysuccinimide (2.9 g, 25 mmol) and dicyclohexylcarbodiimide (6.18 g, 25 mmol) at −15 °C. Stirring was continued at −15 °C for 1 h and at room temperatue for 10 h. The solution was filtered and the filtrate was washed with 10% aqueous citric acid, saturated aqueous sodium hydrogencarbonate and brine and dried over magnesium sulfate, and was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (silica-gel column, 4 mm i.d.×350 mm). From the eluate with benzene–ethyl acetate (3:1), white solid was obtained, yield, 1.48 g (26.3%). It was recrystallyzed from methanol for elemental analysis, mp 119—121 °C, $[\alpha]_D^{15}$ −21.2° (*c* 0.523, methanol), Found: C, 67.19; H, 7.05; N, 11.97%. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.79; N, 12.06%.

Other *N$^{\alpha}$*-acetyldehydroalaninamides (**3-b** and **c**) were prepared in a similar way. The physical properties were as follows: **3-b**; mp 135—137 °C, $[\alpha]_D^{15}$ +20.2 (*c* 0.523, methanol), Found: C, 68.02; H, 7.57; N, 11.18%. Calcd for $C_{14}H_{18}N_2O_2$; C, 68.27; H, 7.37; N, 11.37%. **3-c**; mp 111—113 °C, $[\alpha]_D^{15}$ −61.8 (*c* 0.964, methanol), Found: C, 72.30; H, 6.59; N, 9.82%. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92%.

Alanine (5). The compound **3-a** (23 mg, 0.1 mmol) was dissolved in 5 ml of methanol and hydrogenated with 5% palladium on charcoal (100 mg) for 24 h at 30 °C under hydrogen (1 atm). After the reaction was over, the catalyst was removed by filtration, and the filtrate was evaporated to dryness. The resulting *N$^{\alpha}$*-acetylalaninamide (**4-a**) was hydrolyzed with 6 mol dm^{-3} HCl at 110 °C in a sealed tube with refluxing in a toluene bath for 10 h. A part of the solution was diluted appropriately and analyzed with an amino acid analyzer to determine the chemical yield of alanine (96.3%). A part of the resulting alanine was converted to *N*-(trifluoroacetyl)alanine isopropyl ester in the usual mammer and then subjected to gas chromatographic analysis employing a chiral stationary phase (Chirasil-Val[9]). The peaks due to (*R*)- and (*S*)-alanine on the chromatogram were in baseline separation.

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