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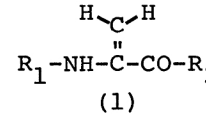
HETEROGENEOUS ASYMMETRIC HYDROGENATION OF CHIRAL DEHYDROTRIPEPTIDES

Michiaki TAKASAKI and Kaoru HARADA*
Department of Chemistry, University of Tsukuba, Niihari, Ibaraki 305

Asymmetric catalytic hydrogenation of chiral tripeptides containing a dehydroalanine residue were carried out using palladium on charcoal as a catalyst. The asymmetric yield of the resulting alanine was in the range of 43 to 93%.

Several studies have been performed on heterogeneous asymmetric hydrogenation of α,β-dehydroamino acid derivatives yielding amino acids. Efficient asymmetric inductions were carried out by catalytic hydrogenations of diketopiperazine derivatives containing a dehydroamino acid residue.[1,2] However, heterogeneous hydrogenations of linear derivatives of dehydroamino acids generally resulted in low or moderate asymmetric yields (av. 0-30%,[3-6] max. 54%[7]). In the present paper, we would like to report a heterogeneous catalytic hydrogenation of tripeptides containing a dehydroalanine and a proline residue by using palladium on charcoal as a catalyst.

The substrates (1) were prepared from the corresponding tripeptides containing a β-chloroalanine residue by the β-elimination reaction using 1,8-diazabicyclo[5,4,0]undecane-7 (DBU).[8] All analytical data of the substrates agreed with the theoretical value. Each substrate (0.1 mmol) was hydrogenated by using 5% palladium on charcoal (20 mg) as a catalyst for 1 or 4 d under hydrogen (1 atm). The resulting tripeptide containing an alanine residue was hydrolyzed with 6 mol dm^{-3} HCl for 8 h at 110 °C in a sealed tube under reduced pressure. The chemical yield was determined with an amino acid analyzer. In order to determine the asymmetric yield, alanine in the hydrolyzate was converted to N-(trifluoroacetyl)alanine isopropyl ester in the usual manner and then subjected to gas chromatographic analysis employing a chiral stationary phase (Chirasil-Val[9]). The peaks due to (R)- and (S)-alanine were in baseline separation.



(1)

	R_1-	-R_2
1-a :	Boc-Gly-	-(S)-Pro-NHBu^t
1-b :	Boc-(S)-Val-	-(S)-Pro-NHBu^t
1-c :	Boc-(R)-Val-	-(S)-Pro-NHBu^t
1-d :	Boc-(S)-Ile-	-(S)-Pro-NHBu^t
1-e :	Boc-(R)-Phe-	-(S)-Pro-NHBu^t
1-f :	Boc-(R)-Pro-	-(S)-Pro-NHBu^t
1-g :	Boc-(R)-Ser-	-(S)-Pro-NHBu^t
1-h :	Boc-(R)-Ser(Bu^t)-	-(S)-Pro-NHBu^t
1-i :	Boc-Gly-	-(S)-Pro-N⌐
1-j :	Boc-(S)-Val-	-(S)-Pro-N⌐

Boc : *t*-Butyloxycarbonyl

Table 1. Chiral alanine obtained by heterogeneous asymmetric hydrogenation of dehydrotripeptides[a)]

Substrate	Reaction temp/°C	Chemical yield/%	Asymmetric yield/%	Config. of Ala
l-a	-30	96	84	R
	+30	88	74	R
l-b	-30	97	87	R
	+30	93	84	R
l-c	-30	97	81	R
l-d	-30	97	90	R
l-e	-30	92	89	R
l-f	-30	96	89	R
l-g	-30	86	82	R
l-h	-30	96	93	R
l-i	-30	92	43	R
l-j	-30	96	74	R
	+30	94	68	R

a) Hydrogenation was carried out with 0.1 mmol of substrate, 20 mg of 5% palladium on charcoal in 3 ml of tetrahydrofuran as a solvent for 1 d (+30 °C) or for 4 d (-30 °C) under hydrogen (1 atm).

The summerized results of the heterogeneous asymmetric hydrogenation of chiral dehydrotripeptides are shown in Table 1. In all reactions, the configuration of the resulting alanine was (R). The chemical yield of alanine was in the range of 86 to 97% and the asymmetric yield in the range of 43 to 93%. Appreciable double asymmetric induction was observed in the reactions of compounds l-h and j. The hydrogenation reactions of substrates containing a proline *t*-butyl amides as the C-terminal amino acid resulted in relatively high asymmetric yields as compared with the results of the substrates containing a proline pyrrolidyl amides.

The results obtained indicate that the contribution of a C-terminal amino acid in the substrates to asymmetric induction was much larger than that of an N-terminal amino acid. The presence of a proline *t*-butyl amide in the substrates could be an important factor in performing an effective asymmetric induction by the heterogeneous hydrogenation. At present, it was considered that the dehydrotripeptides used in this reaction took a rigid structure with the catalyst, and therefore the substrates were hydrogenated to give high asymmetric yields. The detailed study on the mechanism of the asymmetric hydrogenation is now under way.

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