Heterogeneous Asymmetric Hydrogenation of a Chiral Tripeptide containing Dehydroalanine and α,β-Dehydrobutyrine Residues

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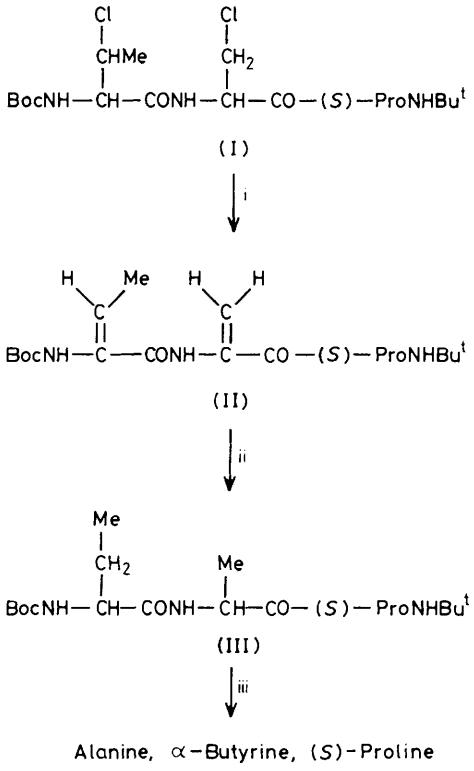
The heterogeneous asymmetric hydrogenation of a linear tripeptide containing dehydroalanine and α,β-dehydrobutyrine has been carried out, giving asymmetric yields of alanine and butyrine of 94 and 54%, respectively.

Several studies on the heterogeneous asymmetric hydrogenation of α,β-dehydroamino acid derivatives have been performed.[1,2] In a previous study, heterogeneous catalytic hydrogenation of chiral tripeptides containing dehydroalanine residues was carried out and (*R*)-alanine was obtained in relatively high asymmetric yields (43—93%).[2] We now report the heterogeneous asymmetric hydrogenation of the linear tripeptide (II) containing two dehydroamino acid residues,

† Deceased.



Scheme 1. i, DBU; ii, H_2, catalyst; iii, H_2O, H^+.

dehydroalanine and α,β-dehydrobutyrine (α-aminocrotonic acid).

The catalytic hydrogenation reaction actually involves 1,4- and 1,7-asymmetric induction. Compound (II)‡ was prepared from the corresponding β-chlorotripeptide (I) by β-elimination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1). The ratio of the (*E*)- and (*Z*)-forms of the α,β-dehydrobutyrine residue in compound (II) was hydrogenated by using several catalysts, such as Raney-Ni (W-1 type), 5% palladium on charcoal, 5% palladium hydroxide on charcoal, and platinium oxide (PtO_2), in tetrahydrofuran (THF) as a solvent under a hydrogen atmosphere. The resulting tripeptide (III) was hydrolysed with 6 M HCl for 8 h at 110 °C in a sealed tube under reduced pressure. The chemical yield of alanine and butyrine (α-aminobutyric acid) was in the range 79—97% and 51—98%, respectively, as determined by an amino acid analyser. In order to determine the asymmetric yield, the alanine and butyrine in the hydrolysate were converted into the corresponding *N*-(trifluoroacetyl)amino acid isopropyl esters in the usual manner and then subjected to gas chromatographic analysis employing a chiral stationary phase (Chirasil-Val[4]). The peaks due to (*R*)- and (*S*)-alanine and to (*R*)- and (*S*)-butyrine were in the baseline separation.

Table 1. Heterogeneous catalytic hydrogenation of compound (II).[a]

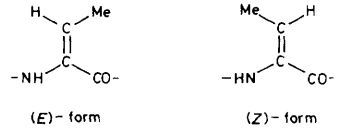
		Alanine			Butyrine[b]		
Catalyst	Temp. /°C	% Yield	% A.Y.[c]	Config.[d]	% Yield	% A.Y.[c]	Config.[d]
Raney-Ni	−30	92	94	(*R*)	73	54	(*S*)
(W-1 type)	−10	93	88	(*R*)	90	54	(*S*)
	10	89	86	(*R*)	87	50	(*S*)
	30	83	77	(*R*)	87	45	(*S*)
	50	80	76	(*R*)	85	41	(*S*)
Pd/C	−30	97	91	(*R*)	84	22	(*S*)
(5%)	−10	93	87	(*R*)	91	36	(*S*)
	10	94	72	(*R*)	89	26	(*S*)
	30	79	72	(*R*)	86	28	(*S*)
	30[e]	82	70	(*R*)	84	24	(*S*)
	50	85	73	(*R*)	82	24	(*S*)
$Pd(OH)_2/C$	−30	95	82	(*R*)	98	25	(*S*)
(5%)	−10	97	88	(*R*)	93	23	(*S*)
	10	93	67	(*R*)	90	25	(*S*)
	30	80	65	(*R*)	68	23	(*S*)
	50	88	57	(*R*)	77	25	(*S*)
PtO_2	−30	91	89	(*R*)	31	6	(*R*)
	−10	93	90	(*R*)	34	3	(*S*)
	10	93	79	(*R*)	87	16	(*S*)
	30	80	56	(*R*)	93	12	(*S*)
	50	86	59	(*R*)	77	12	(*S*)

[a] Hydrogenation was carried out with 0.1 mmol of compound (II), 20 mg of a catalyst in 3 ml of tetrahydrofuran as a solvent under a hydrogen atmosphere. The ratio of the (*E*)-:(*Z*)-forms of the α,β-dehydrobutyrine residue in compound (I) was 8:2, except for e. [b] α-Aminobutyric acid. [c] Asymmetric yield: A.Y. = {[(*R*)-(*S*)]/[(*R*) + (*S*)]} × 100. [d] Configuration of the newly-formed amino acid residue. [e] The ratio of the (*E*)-:(*Z*)-forms of the α,β-dehydrobutyrine residue in compound (II) was 4:6.

The results obtained are summarized in Table 1. The configurations of the resulting alanine and butyrine formed were (*R*) and (*S*), respectively. The asymmetric yields of (*R*)-alanine increased depending on the decrease of reaction temperature and reached 94% at −30 °C. No clear effect of catalyst on the asymmetric yield of (*R*)-alanine was observed. On the other hand, the asymmetric yield of (*S*)-butyrine obtained was influenced by the catalyst used. The asymmetric yield of (*S*)-butyrine obtained reached 54% at −30 °C using Raney-Ni. However, when PtO_2 was used as a catalyst, the asymmetric yield of butyrine was only 5—0%.

The results indicate that Raney-Ni is the most effective catalyst to cause 1,7 and 1,4-asymmetric inductions under the conditions used. The presence of (*S*)-proline t-butylamide in the substrate could be an important factor leading to effective asymmetric induction by heterogeneous hydrogenation. This may be explained by the adsorption of substrate onto the catalyst; the adsorbed substrate formed by the interaction of carbonyl oxygen and the catalyst would then be hydrogenated to yield (*R*)-alanine and (*S*)-butyrine when (*S*)-proline t-butylamide is used as the chiral moiety. This reaction is the first

‡ ^{1}H N.m.r. ($CDCl_3$): δ 1.33 (s, 9H), 1.45 (s, 9H), 1.94 (d, 0.5H), 2.18 (b, 4H), 2.41 (d, 2.5H), 3.68 (b, 2H), 4.47 (b, 1H), 5.08 (s, 1H), 5.86 (s, 1H), 6.46 (b, 0.9H), 7.18 (b, 1H), 8.20 (b, 1H), 8.92 (b, 1H). All analytical data of compound (II) agree with theoretical values. The α,β-dehydrobutyrine residues are present in compound (II) as two geometric isomers, (*E*) and (*Z*), in a ratio of 8:2 (by ^{1}H n.m.r. spectroscopy).



example to our knowledge of 1,7-asymmetric induction in the heterogeneous catalytic hydrogenation of a linear dehydrotripeptide, which may be applied to the synthesis of chiral amino acids and peptides.

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