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ASYMMETRIC TRANSAMINATION FROM AMINO ACID (III) ASYMMETRIC SYNTHESIS OF PHENYLGLYCINE BY CHEMICAL TRANSAMINATION FROM OPTICALLY ACTIVE AMINO ACIDS TO BENZALDEHYDE

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D-Phenylglycine, an important constituent of penicillin and cephalosporin antibiotics, was asymmetrically synthesized by hydrocyanation of the Schiff bases prepared from benzaldehyde and L-amino acid t-butyl esters, followed by oxidative decarboxylation. When L-ψ-leucine t-butyl ester was used as a chiral reagent, the optical yield of D-phenylglycine increased to 96.5%.

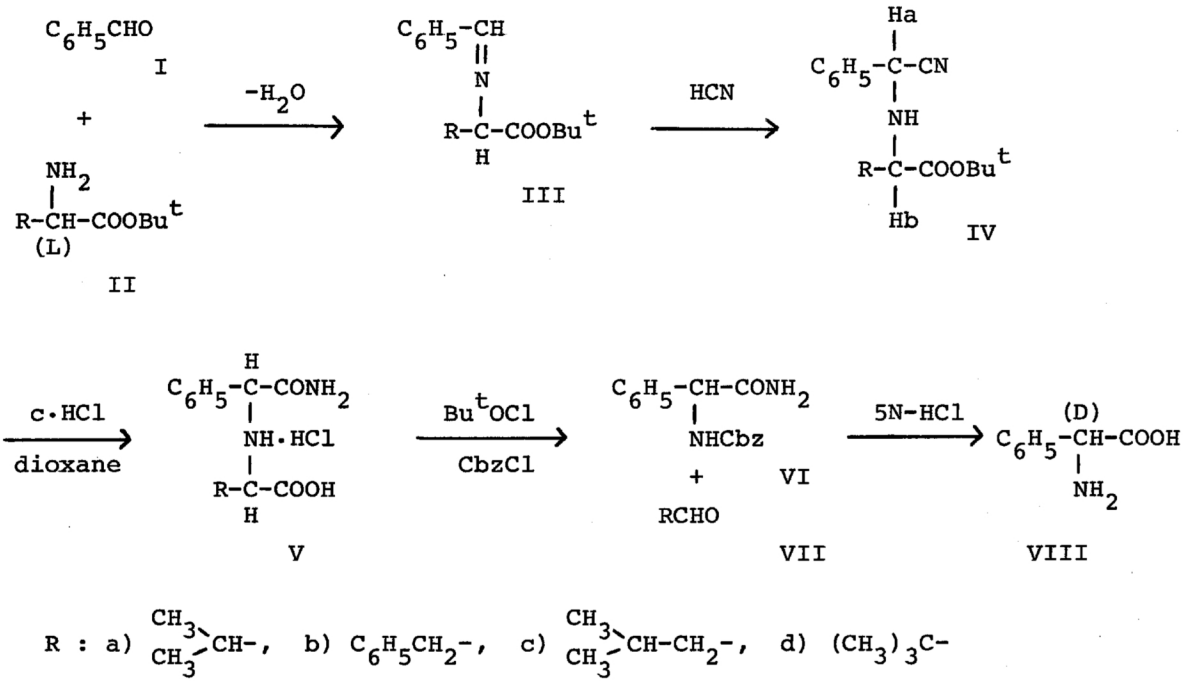
Recently we have reported an asymmetric synthesis of an amino acid by chemical transamination from optically active amino acids to α-keto esters.[1)]

Asymmetric syntheses of α-amino acids have also been studied by the method involving the reaction of hydrogen cyanide, benzoyl cyanide, or trimethylsilyl cyanide with the optically active Schiff bases prepared from several aliphatic aldehydes and optically active benzylic amines, followed by hydrolysis and subsequent hydrogenolysis.[2)]

We wish to report here an asymmetric synthesis of an amino acid via hydrocyanation of the Schiff bases prepared from optically active amino acid t-butyl esters and aldehyde, followed by removal of the t-butyl group and subsequent regiospecific fission of the C-N bond, as developed in the previous paper.[1)]

According to the scheme I, we succeeded in obtaining D-phenylglycine(VIII) from benzaldehyde(I) and optically active L-amino acid t-butyl esters(II). D-phenylglycine is an important material for the synthesis of penicillin and cephalosporin antibiotics.[3)]

Scheme I



R : a) $(CH_3)_2CH-$, b) $C_6H_5CH_2-$, c) $(CH_3)_2CH-CH_2-$, d) $(CH_3)_3C-$

The Schiff base(III) was prepared by the usual method. The hydrocyanation of III with hydrogen cyanide gave the aminonitrile IV, a mixture of diastereoisomers. Without separating the diastereoisomers, IV was treated with dioxane-c·HCl(1:1) to remove the t-butyl group. The hydrolysis of nitrile group to amide easily occurred at the same time to give V by neighboring group participation. Oxidative decarboxylation of V with t-butyl hypochlorite in the presence of carbobenzoxy chloride yielded N-carbobenzoxy-D-phenylglycine amide VI. Hydrolysis of VI gave D-phenylglycine.

The following is a typical procedure. The Schiff base(IIIa) prepared from benzaldehyde(I)(424 mg, 4.0 mmoles) and L-valine t-butyl ester(IIa)(693 mg, 4.0 mmoles) was dissolved in anhyd. methanol(35 ml). The methanolic solution was treated with hydrogen cyanide(0.9 ml, 23 mmoles) at -23°C, and the reaction mixture was stirred for 3 hr at this temperature. Excess reagent and solvent were removed under reduced pressure to give α-aminonitrile(IVa)(1.12 g, 97% yield based on IIa) as a diastereoisomeric mixture. IVa(1.01 g, 3.5 mmoles) in 1:1(v/v) dioxane-c·HCl(25 ml) was kept standing overnight at room temperature. After evaporation of dioxane and hydrochloric acid, the residue (Va) was

Table I Asymmetric Synthesis of VI with Various Amino Acid t-Butyl Esters (IIa∼c)[a)]

Amino acid derivatives used II	Product VI Chem.Y.[b)] (%)	Opt.Y.[c)] (%)	Confn.	IV a∼c NMR(δ)[d)] D-L	L-L	D-L/L-L	Opt.Y.[e)] (%)
L-Val-OBu^t(IIa)	45	63	D	4.62	4.72	81/19	62
L-Phe-OBu^t(IIb)	34	32	D	4.46	4.76	67/33	34
L-Leu-OBu^t(IIc)	39	25	D	4.62	4.69	63/37	26

a) Hydrocyanation of IIIa∼c was carried out in methanol at -23°C.

b) Based on II.

c) Calculated from the $[\alpha]_D$ value of the optically pure D-VI, $[\alpha]_D^{25}$-115.4° (CH_3OH).[6)]

d) Measured at the concentration of IV(50 mg) in $CDCl_3$(0.3 ml), by 100 MHz spectrometer using TMS as an internal standard.

e) Defined as [(D-L)-(L-L)/(D-L)+(L-L)] × 100.

dissolved in H_2O (40 ml) containing $NaHCO_3$(1.03 g, 12.3 mmoles). Under ice-cooling, carbobenzoxy chloride (597 mg, 3.5 mmoles) and t-butyl hypochlorite (380 mg, 3.5 mmoles) was added to this solution under protection from light, and after 4 hr t-butyl hypochlorite (114 mg, 1.05 mmoles) was further added. After an additional 2.5 hr of stirring, the reaction mixture was treated with satd. sodium bisulfite solution (5 ml).

Usual extractive isolation with ethyl acetate(100 ml × 2), followed by the purification with column chromatography on silica gel (solvent: benzene-ethyl acetate 3:1), afforded N-carbobenzoxy-phenylglycine amide(VI)[4)] (461 mg, 45% yield based on IIa), mp 168-170°, $[\alpha]_D^{25}$-73.0°(C=0.920, CH_3OH).

To calculate the optical yield of VI, VI (426 mg, 1.5 mmoles) was hydrolyzed with 5N-HCl(20 ml) under reflux for 6 hr. Isolation using Amberlite IR-120 gave D-phenylglycine(VIII)[4)] (209 mg, 93% yield), $[\alpha]_D^{25}$-99.8°(C=0.871, 2N-HCl) (optical yield 63%).[5)]

In a similar manner, various L-amino acid t-butyl esters(IIa∼c) were used as chiral reagent for this asymmetric synthesis, and the results obtained are

summarized in Table I. In all cases, optically active phenylglycine obtained has the D configuration. When L-valine t-butyl ester was used as chiral reagent, the optical yield of D-phenylglycine was the highest.

It is of practical interest that in nmr spectra of α-amino nitriles(IVa ~ c) two singlet signals referred to D-L and L-L isomeric methine protons(Ha) were observed.[7] The higher singlet signal had larger area in every case. We assigned the higher singlet signal to the methine proton(Ha) of D-L isomer, since D-phenylglycine was preferentially obtained. The optical yields of IVa ~ c determined by nmr agreed well with those of VI as shown in Table I.

The effects of the ester moiety of L-valine esters on this asymmetric hydrocyanation were examined. When ester moieties were methyl and ethyl groups, the optical yield of the resulting α-amino nitriles determined by nmr spectra was 67 and 62%, respectively.[8] These results suggested that the ester moiety of L-valine esters had little effect on the optical yields.

Solvent effects on hydrocyanation of IIIa are summarized in Table II.

Table II Solvent Effects on Asymmetric Hydrocyanation of IIIa

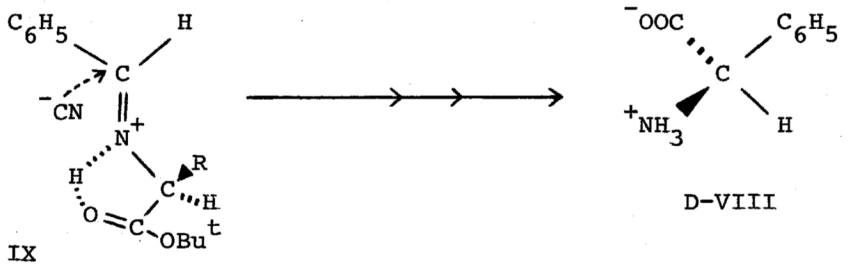
Solvents	n-Hexane	CCl_4	CH_3OH	CH_3CN	DMF
Optical Yield of IVa[a)]	75	70	62	62	44

a) Determined by nmr spectra of IVa obtained.

When non-polar aprotic solvents were used, the optical yields of α-amino nitrile(IVa) increased.

The mechanism of this asymmetric hydrocyanation shown in scheme II would account for the experimental results.

Scheme II



Cyanide ion attacks from the less hindered side of the rigid five membered cyclic conformation formed by intramolecular hydrogen bonding as shown in IX.

According to this mechanism, when R is bulkier than isopropyl group in IIa, the optical yield of phenylglycine would be expected to be much higher. Therefore, hydrocyanation of IIId prepared from benzaldehyde and L-ψ-leucine t-butyl ester(IId)[9] was carried out in n-hexane at -23°C.

In nmr spectra of α-aminonitrile(IVd), singlet methine protons (Ha and Hb) appeared at δ4.58 and 2.86, respectively, while the signals referring to the other isomer were not observed. Subsequent hydrolysis of IVd, followed by oxidative decarboxylation, gave N-carbobenzoxy-D-phenylglycine amide(VI) (mp 169-170°, $[\alpha]_D^{25}$-75.96°(C=0.953, CH_3OH)) whose optical yield was 96.5% after correction for 68% optical purity of IId used.[9]

As ψ-leucine t-butyl ester was found to be a highly effective chiral reagent in the present asymmetric synthesis, investigations are under way on the scope of other types of asymmetric syntheses using chiral ψ-leucine derivatives.

References and Notes

1) S. Yamada and S. Hashimoto, Tetrahedron Lett., 997(1976).

2) a) M. S. Patel and M. Worsley, Canadian J. Chem., 48, 1881(1970).
   b) K. Harada and T. Okawara, J. Org. Chem., 38, 707(1973).
   c) Idem, Bull. Chem. Soc. Japan, 46, 191(1973).
   d) I. Ojima, S. Inaba, and Y. Nagai, Chemistry Lett., 737(1975).

3) M. Gorman and C. W. Ryan, "Cephalosporins and Penicillins", E. H. Flynn, Ed., Academic Press, New York, 1972, p.533.

4) Satisfactory a) analytical and b) spectroscopic data were obtained for this compound.

5) The optical yield was calculated from $[\alpha]_D^{25}$-157.7° (2N-HCl) for optically pure D-(-)-phenylglycine.

6) The calculation based on this transformation of VI to VIII disclosed that optically pure D-VI should have $[\alpha]_D^{25}$-115.4°(CH_3OH).

7) In nmr spectra of IVa, methine proton(Hb) also appeared as two sets of

doublet signals (J=4.8 Hz) at δ3.00 and δ3.16(82:18).

8) Methyl ester of α-aminonitrile : Ha, δ4.68, 4.76; Hb δ3.12, 3.28(83.5:16.5)
Ethyl ester of α-aminonitrile : Ha, δ4.68, 4.76; Hb δ3.10, 3.27(81:19).

9) DL-ψ-leucine was resolved with dibenzoyl-(-)-tartaric acid according to the literature, H. Pracejus and S. Winter, Chem. Ber., 97, 3173(1964). L-ψ-leucine obtained shows $[\alpha]_D^{20}$-6.92(C=4.13, H_2O). Its optical purity was calculated from optically pure L-ψ-leucine, $[\alpha]_D^{20}$-10.15°(H_2O) reported by E. Abderhalden, W. Faust, and E. Haase, Hoppe-Seyler's Z. Physiol. Chem., 228, 187(1934).

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