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ASYMMETRIC TRANSAMINATION FROM AMINO ACIDS (II)
ASYMMETRIC SYNTHESIS OF AMINES BY CHEMICAL TRANSAMINATION OF OPTICALLY ACTIVE AMINO ACIDS TO KETONES

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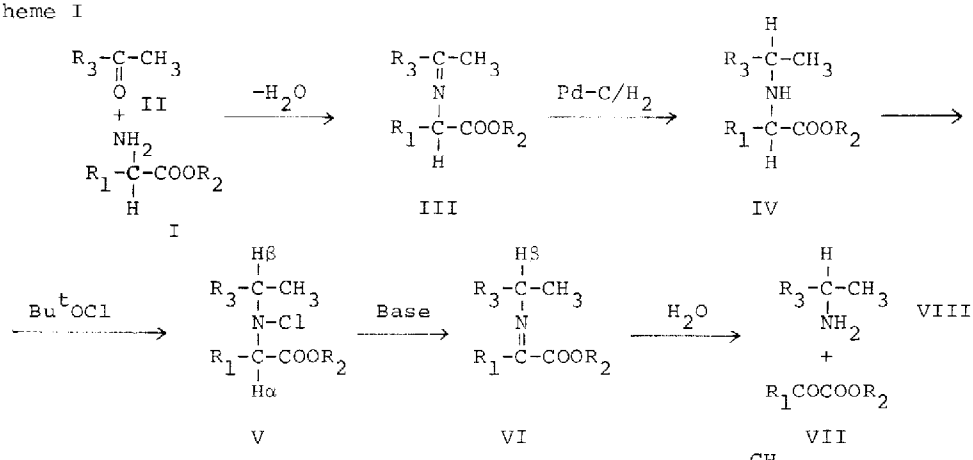
In an extension of a previous paper,[1] in which the asymmetric synthesis of a new amino acid by transamination of the amino group from an optically active amino acid to α-keto acid has been reported, we now report the asymmetric synthesis of amine by a similar transamination from optically active amino acid to ketone instead of to α-keto acid.

The Schiff Bases(III) were prepared from the reaction of optically active amino acid esters(I) with ketones(II) in refluxing benzene using a Dean-Stark apparatus. The amino acid esters(I) used were the methyl ester of L-valine, ethyl esters of L-alanine, L-valine, L-phenylalanine, L-aspartic acid, and L-glutamic acid and t-butyl esters of L-alanine and L-valine. The ketones(II) used were acetophenone and phenylacetone.

Schiff bases(III) were reduced by catalytic hydrogenation with 5% Pd on charcoal in C_2H_5OH to give the N-alkylated amino acid esters(IV) as a diastereomeric mixture. Treatment of IV with t-butyl hypochlorite and sodium ethoxide and the subsequent hydrolysis of the newly formed Schiff bases(VI) with 5% sulfuric acid gave optically active amines(VIII). In some cases, VPC analysis of the intermediate IV, showed two well separated peaks which correspond to each diastereoisomer. Therefore, optical yields were calculated from the ratio of the peak areas of this VPC data.

Results of asymmetric synthesis by catalytic hydrogenation are shown in Tables I and II. When L-amino acid esters are used as chiral reagents, the

Scheme I

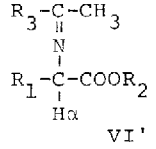


R_1: a) $C_6H_5CH_2$-, b) $C_2H_5OCOCH_2$- c) $C_2H_5OCOCH_2CH_2$- d) $(CH_3)_2CH$- e) CH_3-

R_2: CH_3, C_2H_5-, Bu^t-, R_3: C_6H_5-, $C_6H_5CH_2$-

absolute configurations of the amines obtained always belong to the S-series. The steric effect by the side chain of the amino acid esters is not clear, but sterically larger ester groups of amino acids give better optical yields (runs 1,2 and 3,4 in Table I, and runs 2,3,4 in Table II). Optical yields calculated from the VPC analysis of IV agree very closely with the experimental value. This means that no epimerization and racemization occur in the whole process.

The process of this reaction is slightly different from the previous one.[1] Formation of VI, instead of VI', from V with a base is due to the fact that Hα in V is more acidic than is Hβ because Hα is located at the α position of the ester group. Treatment of V with a base gives exclusively VI. This transamination reaction is built up by the migration of the double bond from III to VI. This migration pattern is more similar to biological transamination scheme than is the previous pattern.[1]



VI'

A typical procedure is as follows. A solution of L-alanine ethyl ester(I) (2.14 g, 18.3 mmoles) and phenylacetone II(2.44g, 18.3 mmoles) in benzene(60 ml) were refluxed for 48 hr using a Dean-Stark apparatus to give the Schiff base(III) (R_1=CH_3, R_2=C_2H_5, R_3=$C_6H_5CH_2$). The solvent was evaporated and the residual oil

Table I Asymmetric Synthesis of 2-Amino-3-phenyl propane(VIII, $R_3=C_6H_5CH_2$)

Run	Chiral Reagents Used	Product			
	L-Amino Acid Esters	2-Amino-3-phenylpropane(VIII, $R_3=C_6H_5CH_2$)			
		Chemical yield(%) a)	Optical yield(%) b)	Confign.	Optical yield based on VPC Analysis of IV(%)
1	Ala-OC_2H_5	37	66(63)	S	
2	Ala-OBu^t 2)	37	85(89)	S	
3	Val-OC_2H_5	56	50(53)	S	48
4	Val-OBu^t 3)	63	87(83)	S	81
5	Phe-OC_2H_5	25	21(23)	S	
6	Asp(-OC_2H_5)-OC_2H_5	40	49(53)	S	
7	Glu(-OC_2H_5)-OC_2H_5	17	63(65)	S	

a) Based on II, determined by VPC using naphthalene as the internal standard.

b) Optically pure (S)-VIII($R_3=C_6H_5CH_2$), $[\alpha]_D^{15}$+34.5°(c=10.62, C_2H_5OH). Numbers in parentheses are optical yields based on the benzoate. Optically pure (S)-benzoate: $[\alpha]_D^{15}$+72°(c=1.14, CH_3OH)(W. Leithe, Ber. 65, 660(1932)).

was dissolved in alcohol(50 ml). An alcoholic solution (50 ml) of III was catalytically hydrogenated with 5% Pd on charcoal (1.0 g) at a 60Kg/cm^2 pressure of H_2 at room temperature for 16 hr. After filtering the catalyst, the alcohol was removed. The crude product was purified chromatographically with silica gel(200 g) and ether-n-hexane(2:3) as the eluting solvent to give a diastereomeric mixture of the N-alkylated amino acid ester(IV)(2.56 g, 59% based on II).

A solution of t-butyl hypochlorite(0.98 g, 9 mmole) in dry ether(5 ml) was added to a dry ether solution (10 ml) of purified IV(2.0 g, 8.5 mmole) under cooling, then an alcoholic solution of sodium ethoxide prepared from Na(0.275 g, 0.012 atom) and absolute alcohol(10 ml) were added. The reaction was continued for one hour at 40°C(bath temperature). After evaporation of the solvent, 5% H_2SO_4 was added to the residue and the whole was kept at room temperature for 2 hr. The reaction mixture was worked up as usual to give 2-amino-3-phenyl

Table II Asymmetric Synthesis of α-Phenethylamine (VIII, $R_3=C_6H_5$)

Run	Chiral Reagents Used: L-Amino Acid Esters	Product: α-Phenethylamine (VIII, $R_3=C_6H_5$) Chemical yield(%) a)	Optical yield(%) b,c)	Confign.	Optical yield based on VPC analysis of IV(%)
1	Ala-OC_2H_5	20	69(71)	S	68
2	Val-OCH_3	12	30(36)	S	31
3	Val-OC_2H_5	14	50(59)	S	56
4	Val-OBu^t 3)	10	—(85)	S	88
5	Phe-OC_2H_5	13	50(55)	S	48
6	$\begin{matrix}OC_2H_5\\ \vert\\ \text{Asp-}OC_2H_5\end{matrix}$	8	—(45)	S	51

a) based on II, determined by VPC using durene as the internal standard. b) Optically pure (R)-VIII($R_3=C_6H_5$) : $[\alpha]_D^{20}$+31°(c=2.0844, C_2H_5OH)(K. Parck, J. Prak. Chem., [2], 86, 284(1912). c) Numbers in parentheses are optical yields based on the benzoate. Optically pure (S)-benzoate : $[\alpha]_D^{20}$-52.5°(c=0.7947, C_6H_6)(W. J. Pope and J. Read, J. Chem. Soc., 103, 444(1913)).

propane(VIII, $R_3=C_6H_5CH_2$, 0.72 g, 37% based on II), bp 83-86°(15 mmHg), $[\alpha]_D^{15}$+22.7°(C_2H_5OH)(Optical yield 66%).

The N-Benzoyl derivative of VIII($R_3=C_6H_5CH_2$) was obtained by the usual method. The product was purified by silica gel column chromatography with ether-n-hexane(1:1) as the eluting solvent, (yield 86%), $[\alpha]_D^{25}$+45.1°(CH_3OH) (Optical yield 63%).

The application of this reaction to the synthesis of various optically active amines will be reported in the near future.

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