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ASYMMETRIC TRANSAMINATION FROM AMINO ACIDS (I)
ASYMMETRIC SYNTHESIS OF AMINO ACID BY CHEMICAL TRANSAMINATION FROM OPTICALLY ACTIVE AMINO ACIDS TO α-KETO ACID

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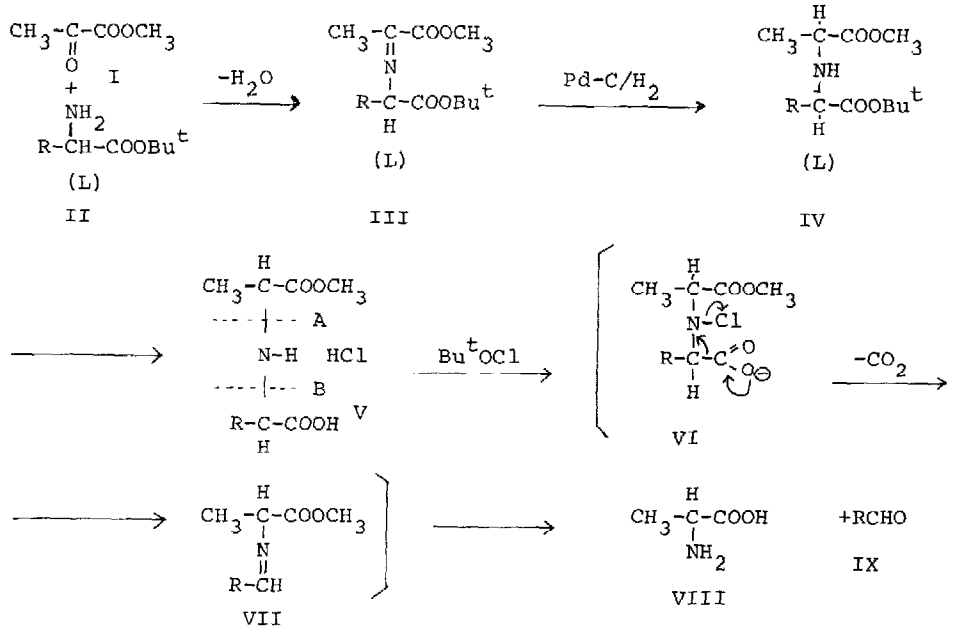
Transamination reactions from α-amino acids to α-keto acids are known to occur in living bodies. These biological transaminations are those in which an amino group is transferred from an α-amino acid to an α-keto acid by the enzyme and pyridoxal phosphate.

A number of attempts using non-enzymatic methods have been made to duplicate the conversion of an α-keto acid to the corresponding α-amino acid.[1] Detailed studies on the syntheses of optically active amino acids from the α-keto acids using optically active benzylamine derivatives have been reported by Harada et al.[2]

We here report the asymmetric synthesis of a new amino acid by direct chemical transamination from optically active amino acids to α-keto esters as shown in scheme I.

The reaction of methyl pyruvate(I) with L-amino acid t-butyl ester(II) gave the Schiff base(III). The intermediate III was not isolated, but immediately hydrogenated with 10% Pd on charcoal to give amino acid methyl t-butyl ester(IV). A new chiral center is formed in IV by 1,3 asymmetric induction, and a diastereoisomeric mixture is produced. The optical yield of this asymmetric synthesis depends on the ratio of these two diastereoisomers. Without separating the diastereoisomers, IV was treated with HCl to give V, leaving the methyl ester intact. Oxidative decarboxylation of V with t-butyl hypochlorite in an alkaline solution and subsequent acid hydrolysis gave L-alanine (VIII) and aldehyde (IX) by regio-specific fission of the C-N bond (B) in two C-N bonds (A and B) in V.

Scheme I



R: a) $(CH_3)_2CH-$, b) $C_6H_5CH_2-$, c) $(CH_3)_2CHCH_2-$, d) Bu^tOCOCH_2-, e) $Bu^tOCOCH_2CH_2-$

Various L-amino acids were used as the chiral reagent for this reaction, the results of which are shown in Table I.

The reduction, III ⟶ IV, was examined in several solvents, CH_3OH, C_2H_5OH, $AcOC_2H_5$, THF and n-hexane. Optical yields of L-alanine were always in the range of 65%-76%.

Several oxidizing agents for V were examined but most were fruitless. Such hypochlorous acid derivatives as t-butyl hypochlorite and NaClO, as well as NBS, and NCS in an aqueous alkaline medium gave good results.(Table II).

The reaction mechanism of this oxidation is not clear, but it is supposed that this reaction might proceed through V ⟶ VI ⟶ VII ⟶ VIII + IX by N-halodecarboxylation.[3)]

The following is a typical procedure. A solution of methyl pyruvate(I) (561 mg, 5.5 mmoles) and L-phenylalanine t-butyl ester(IIb)(1.11 g, 5.0 mmoles) in anhyd. THF(25 ml) was stirred at 0°C for 3 hr with molecular sieves 5A producing the Schiff base(IIIb) which, after filtration of the molecular sieves,

Table I Asymmetric Synthesis of L-alanine[a)]

Chiral L-Amino Acid t-Butyl Ester(L-II) used	L-Alanine obtained	
	Chemical yield(%)[b)]	Optical yield(%)[c)]
L-Val-OBu^t(IIa)	37	71
L-Phe-OBu^t(IIb)	58	70
L-Leu-OBu^t(IIc)	43	62
L-Asp(OBu^t)-OBu^t(IId)	35	57
L-glu(OBu^t)-OBu^t(IIe)	41	53

a) Optimum reaction conditions were not investigated. b) Based on II, and determined with an amino acid analyzer c) Calculated from the $[\alpha]_D$ value of the optically pure N-2,4-dinitrophenyl derivative of L-alanine $[\alpha]_D^{25}$+143.9° (N-NaOH)

Table II Oxidizing Agents and Product Yields

Oxidizing Agents	Chemical Yield of L-Alanine(%)[a,b)]
t-BuOCl	75
NBS	47
NCS	65
NaClO[c)]	58

a) Vb(1.0 eq), K_2CO_3(1.5 eq) and the oxidizing reagent(1.1 eq) were in aqueous solution b) By amino acid analysis c) Without K_2CO_3

underwent catalytic hydrogenation with 10% Pd on charcoal(300 mg) in THF(35 ml) under an initial pressure of 30Kg/cm^2 at room temperature. After filtration of the catalyst, THF was removed at reduced pressure and the residue was purified by SiO_2 column chromatography(solvent system: petroleum ether-ether 3:1) to give a pale yellow oil(IVb)(1.18 g, 77% based on IIb) as a diastereoisomeric mixture. Removal of the t-butyl group of IVb(921 mg, 3 mmoles) was performed by treating with HCl gas in anhyd. dioxane(20 ml). After evaporation of the dioxane, the residue(Vb) was dissolved in H_2O(20 ml) containing K_2CO_3(621 mg,

4.5 mmoles). Under ice-cooling, t-butyl hypochlorite (358 mg, 3.3 mmoles) was added to this solution with protection from light. Stirring was continued for 4.5 hr. The pH of the reaction mixture was ajusted to 1.0 with 10% HCl. The whole was extracted with ether (30 ml×2) to remove organic impurities. The aqueous layer was refluxed for 2 hr. Part of the aqueous layer was placed in an amino acid analyzer and gave a chemical yield of alanine(75%).

To calculate the optical yield, the pH of the aqueous solution containing alanine was ajusted to about 7.0 with 10% NaOH, and the alanine in the solution was converted to crude DNP-alanine(450 mg) in the conventional manner.[4] The resulting DNP derivative was purified by the subsequent use of preparative TLC (SiO_2 treated with 0.25M NaH_2PO_4, solvent system: $CHCl_3$-$(C_2H_5)_2O$ 12:1) and a Celite column treated with pH 6.6 phosphate-citrate buffer to give DNP-L-alanine mp 173-176°(decomp), $[\alpha]_D^{25}$+100.8°(c=0.25, N-NaOH)(optical yield 70%), whose IR and NMR spectra are identical with the authentic sample.[5]

When L-amino acid t-butyl esters are used as the chiral reagent in this asymmetric transamination toward pyruvic ester, L-alanine is always synthesized in a considerably high optical yield. This chemical transamination reaction is of interest in connection with biochemical transamination.

References

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