Asymmetric Transformation of Alanine *via* Optically Labile Imidazolines

Saizo SHIBATA,* Hajime MATSUSHITA, Kunio KATO, Masao NOGUCHI, Masahiko SABURI,** and Sadao YOSHIKAWA**

Central Research Institute, The Japan Tobacco and Salt Public Corporation, 6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227

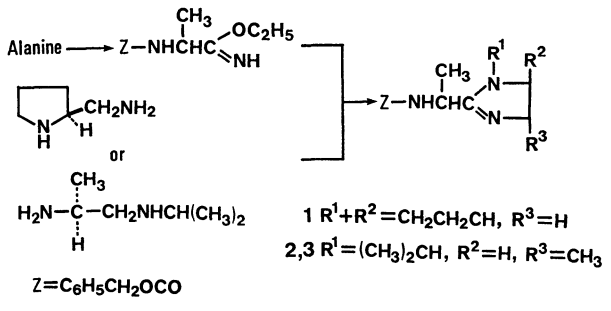
***Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113*

(Received February 14, 1979)

Hydrolysis of an imidazoline derived from (*S*)-alanine and (*S*)-2-(aminomethyl)pyrrolidine afforded (*R*)-alanine in the optical yield of 93.8% (e.e.). The asymmetric transformation was explained on the basis of preferential crystallization of one epimer followed by epimerization of the other epimer in a solution. It was found that the epimerization was catalyzed by amines. (2*S*)-*N*-isopropyl-2-aminopropylamine was also examined as a diamine component of imidazolines.

In an ideal and complete optical resolution, a racemic compound would be separated into 50% of each enantiomer. On the other hand, an asymmetric transformation is a unique method to obtain optically active compounds because it is possible to convert a racemic compound into one of the isomerides in 100% yield. Optically labile compounds are suitable for the asymmetric transformation and it has been reported by many workers.[1] On the other hand, optically stable compounds are not suitable for the transformation, and conversion of the compounds into the optically labile intermediates is indispensable. From this point of view, amino acids, aldehydes, and ketones have been studied in our laboratories.[2]

We also studied on the asymmetric transformation of carboxylic acids. It was reported by Yonetani *et al.* that imidazoline derivatives of amino acids are racemized easily.[3] The asymmetric transformation of α-substituted carboxylic acids might be possible using the optical lability of the derivatives in an asymmetrical circumstance. The *N*-protected alanine was used as a model of the carboxylic acid. (*S*)-2-(Aminomethyl)-pyrrolidine and (2*S*)-*N*-isopropyl-2-aminopropylamine were used as chiral diamine components to prepare the imidazoline derivatives.



Experimental

Optical activities were determined with a JASCO Digital Automatic Polarimeter Model DIP 4. Nuclear magnetic resonance spectra were obtained with a JNM-PS-100 Spectrometer with tetramethylsilane as an internal standard. Accurate mass determinations were carried out on a Hitachi RMU-7 instrument operated at 70 eV.

(S)-(+)-2-(Aminomethyl)pyrrolidine. This compound was prepared as reported previously:[4] bp 72.5—74 °C/2933 Pa; (lit, bp 65 °C/1466 Pa).

(2S)-(+)-N-Isopropyl-2-aminopropylamine. (*S*)-Alanine (60 g, 0.67 mol) was converted to (*S*)-*N*-phthaloylalanyl chloride by the method described by Job and Bruice:[5] bp 149—154 °C/400 Pa; yield 125.7 g (79%). Isopropylamine (34.3 g, 0.58 mol) and sodium hydrogencarbonate (53.6 g, 0.64 mol) were dissolved in 426 ml of water and the solution was cooled in an ice bath to 10 °C. To this solution, a solution of (*S*)-*N*-phthaloylalanyl chloride (125.7 g, 0.53 mol) in dioxane (193 ml) was added dropwise with vigorous stirring. After the addition had been completed, the white precipitates thus formed were collected by filtration and washed with water. Recrystallization of the crude product from methanol gave *N*-isopropylamide of (*S*)-*N*-phthaloylalanine (55.1 g, 0.21 mol). Removal of the phthaloyl group from *N*-isopropylamine of (*S*)-*N*-phthaloylalanine (55.1 g, 0.21 mol) by equimolar hydrazine hydrate gave (*S*)-*N*-isopropylalaninamide (*ca.* 0.2 mol). (*S*)-*N*-Isopropylalaninamide (*ca.* 0.2 mol) was reduced by lithium aluminium hydride in tetrahydrofuran (reflux 15 h). After the usual treatment, (2*S*)-*N*-isopropyl-2-aminopropylamine was obtained by fractional distillation: bp 144—146 °C (13.5 g, 0.116 mol, 17.3% yield based on (*S*)-alanine); $[\alpha]_D^{20}$ +22.2° (neat); MS *m/e* 116.1296 (M^+, $C_6H_{16}N_2$; calcd 116.1313); IR (Nujol) 1370 and 1380 cm^{-1}($CH(CH_3)_2$);NMR ($CDCl_3$) δ=1.07 (N-C-CH_3, *d*) and 1.07 ppm (N-C-$(CH_3)_2$, *d*).

(−)-Ethyl (S)-2-(Benzyloxycarbonylamino)propioimidate. Preparation of this compound was previously reported:[6] mp 72.5—74 °C; $[\alpha]_D^{25}$ −1.3° (*c* 12.65, 99.5% ethanol); (lit, mp 71.5—73.0 °C; $[\alpha]_D^{24}$ −1.4° (*c* 12.65, anhydrous ethanol)).

(+)-Ethyl (R)-2-(Benzyloxycarbonylamino)propioimidate. This compound was prepared from (*R*)-alanine by the same method described for the preparation of (−)-ethyl (*S*)-2-(benzyloxycarbonylamino)propioimidate:[6] mp 72.5—74 °C; $[\alpha]_D^{23}$+1.3° (*c* 12.65, 99.5% ethanol); MS *m/e* 250.1306 (M^+, $C_{13}H_{18}N_2O_3$; calcd 250.1316); IR (Nujol) 1645 (C=N) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ=7.27 (phenyl, s), 5.08 (phenyl-CH_2-O, s), 1.35 (N-C-CH_3, d) and 1.29 ppm (O-C-CH_3, t).

Preparation of Imidazolines. Imidazoline derivatives of alanines were prepared by the coupling method described by Hirotsu *et al.*[6]

Imidazoline Derivative (1): The reaction of (*S*)-2-(aminomethyl)pyrrolidine and the (*S*)- or the (*R*)-imidate mentioned above gave the imidazoline derivative (**1**). Preparation from the (*S*)-imidate: Yield 86%; mp 86—87.5 °C; $[\alpha]_D^{23}$ −94.1° (*c* 1.0, methanol); MS *m/e* 287.1634 (M^+, $C_{16}H_{21}N_3O_2$, calcd 287.1633); IR (Nujol) 1620 (C=N) and 1710 cm^{-1} (C=O);

Table 1. Configuration and optical purity of alanine residues of imidazoline derivatives

Diamine component	Config. of starting alanine	Imidazoline	Alanine obtained after hydrolysis[a]		
			Config.	e.e. (%)	Yield (%)
(*S*)-2-(Aminomethyl)pyrrolidine	*S*	**1**	*R*	93.8	89.2[b]
	R	**1**	*R*	93.2	90.1
(2*S*)-*N*-Isopropyl-2-aminopropylamine	*S*	**2**	*S*	91.9	5.6
	R	**3**	*R*	91.8	4.3

a) Configuration, optical purity, and yield were determined according to the DNP-method after hydrolysis of imidazoline derivatives.[3] b) Based on imidazoline.

NMR ($CDCl_3$) $\delta=1.40$ (N=C–C–CH_3, d) and 5.05 ppm (phenyl-CH_2–O, s). Preparation from the (*R*)-imidate: Yield 75%; mp 86—87.5 °C; $[\alpha]_D^{23}$ −94.9° (*c* 1.0, methanol); MS *m/e* 287.1643 (M^+, $C_{16}H_{21}N_3O_2$, calcd 287.1633); IR (Nujol) 1620 (C=N) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) $\delta=1.40$ (N=C–C–CH_3, d) and 5.05 ppm (phenyl–CH_2–O, s).

Imidazoline Derivative (2): This compound was prepared from (2*S*)-*N*-isopropyl-2-aminopropylamine and the (*S*)-imidate: Yield 57%; mp 71.5—73 °C; $[\alpha]_D^{23}$ −57.9° (*c* 1.0 methanol); MS *m/e* 303.1930 (M^+, $C_{17}H_{25}N_3O_2$, calcd 303.1945); IR (Nujol) 1610 (C=N) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) $\delta=1.38$ (N=C–C–CH_3, d) and 5.03 ppm (phenyl–CH_2–O, s).

Imidazoline Derivative (3): This compound was prepared from (2*S*)-*N*-isopropyl-2-aminopropylamine and the (*R*)-imidate: Yield 64%; mp 120—122.5 °C; $[\alpha]_D^{23}$ −36.2° (*c* 1.0, methanol); MS *m/e* 303.1955 (M^+, $C_{17}H_{25}N_3O_2$, calcd 303.1945); IR (Nujol) 1600 (C=N) and 1695 cm^{-1} (C=O); NMR ($CDCl_3$) $\delta=1.37$ (N=C–C–CH_3, d) and 5.08 ppm (phenyl–CH_2–O, s).

Determination of the Optical Purity and the Configuration of the Alanine after the Asymmetric Transformation. The configuration and the optical purity of the alanine residues of the imidazoline derivatives were determined as DNP-alanine (DNP; 2,4-dinitrophenyl) prepared after hydrolysis of the derivatives according to the method described by Yonetani *et al.*[3] (hydrolysis conditions: 6 M HCl, 110 °C, 20 h). The specific optical rotation of the prepared DNP-alanine was observed at 546 nm and the concentration of the solution was calculated from the extinction coefficient at 360 nm; authentic DNP-(*S*)-alanine: $[\alpha]_{546}^{32}$ +221° (*c* 0.22, 1% $NaHCO_3$); $\lambda_{max}^{1\%\ NaHCO_3}$ 360 nm ($\varepsilon=1.72\times10^4$).

Results and Discussion

Imidazoline derivatives prepared from (*S*)-2-(aminomethyl)pyrrolidine and the imidates derived from (*S*)-alanine and (*R*)-alanine have the same crystal habit (platelets) and melting point, and showed identical spectral data. The hydrolysis of these imidazoline derivatives gave (*R*)-alanine (Table 1). These facts indicate that the bond between α-carbon and hydrogen is labile enough to epimerize in the course of the preparation. (Hereafter the imidazoline was called **1**).

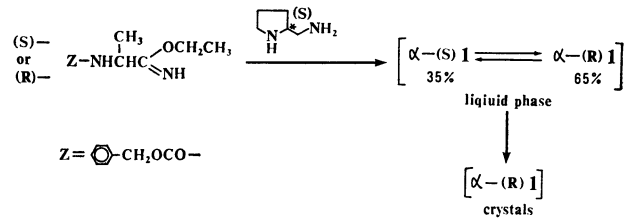
High optical yield (93.8 or 93.2%) of alanine obtained in the case of **1** was considered to be due to a combination of epimerization and resolution by preferential crystallization of one diastereomer. In order to clarify the resolution process, optical purity of alanine residue of **1** in the reaction mixture was examined. Two batches of a reaction mixture of **1** were examined. After removal of the solvent from the reaction mixture under reduced pressure, the oily residue was directly hydrolyzed in one

Table 2. Configuration and optical purity of alanine obtained by the hydrolysis of the reaction mixture of **1** before and after crystallization

	Alanine obtained after hydrolysis[a]		
	Config.	e.e. (%)	Yield (%)
Oily mixture	*R*	35.1	84.1[b]
Crystallized crude mixture	*R*	63.5	87.0

a) Configuration, optical purity, and yield were determined according to the DNP-method after hydrolysis of imidazoline.[3] b) Based on imidate

experiment. In another experiment, the oily residue was allowed to stand at room temperature for 12 h. The crystallized crude mixture was then subjected to hydrolysis without any purification, and the configuration and the optical yields of the resultant alanine were determined. The results are shown in Table 2. The optical yield (35.1%) of the alanine obtained from the oily mixture was the same as that obtained from the hydrolyzate of the imidazoline derivatives after the mutarotation in methanol (*vide infra*). Since no purification was performed in both cases, the difference between the oily mixture and the crystallized mixture is attributable to the epimerization promoted by the preferential crystallization of one diastereomer out of the liquid phase in which a rapid equilibration is maintained.



It is required for this mechanism that the rate of epimerization is fast enough. The rates of epimerization of **1** in several solvents (methanol, ethanol, benzene, and dichloromethane) were observed (Fig. 1). It was fast in methanol or ethanol but the epimerization was not detected in the aprotic solvents. A mixture of dichloromethane and ethanol (equimolar quantities with **1**) was examined as a solvent because, in the course of coupling reaction of ethyl (*S*)- or (*R*)-2-(benzyloxycarbonylamino)propioimidate with (*S*)-2-(aminomethyl)pyrrolidine in dichloromethane, ethanol in amounts equimolar to **1** is to be produced. No epimerization

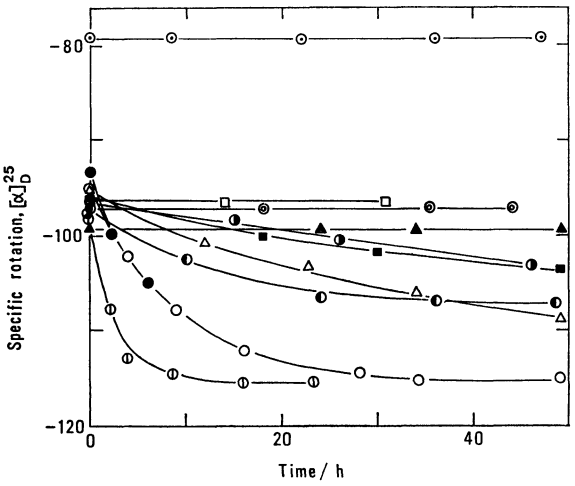


Fig. 1. Mutarotation of **1**.
○: Methanol, △: ethanol, ⊙: benzene, ▲: dichloromethane, □: ethanol (1 molar equivalent) in dichloromethane, ◎: ethanol (5 molar equivalents) and triethylamine (0.5 molar equivalents) in dichloromethane, ●: the reaction mixture of **1**, ◑: pyrrolidine (5.7 molar equivalents) in dichloromethane, ◐: propylamine (5.7 molar equivalents) in dichloromethane, ◑: *N*-methylpyrrolidine (5.7 molar equivalents) in dichloromethane, ■: quinuclidine (5.7 molar equivalents) in dichloromethane.

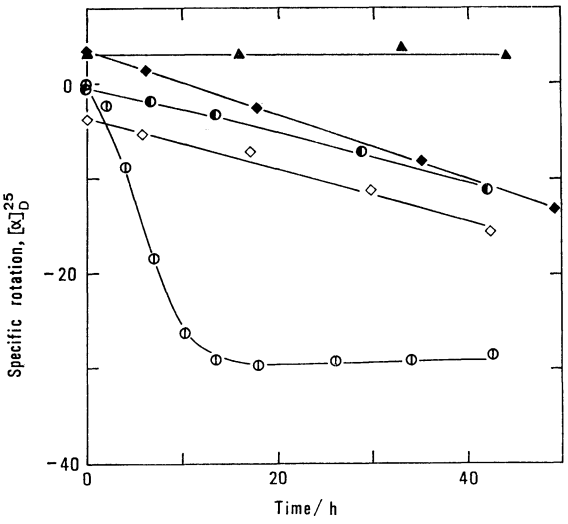


Fig. 2. Mutarotation of **2**.
◐: Propylamine (5.7 molar equivalents) in dichloromethane, ◆: dipropylamine (5.7 molar equivalents) in dichloromethane, ◇: *N*-isopropylethylenediamine (5.7 molar equivalents) in dichloromethane, ◑: pyrrolidine (5.7 molar equivalents) in dichloromethane, ▲: dichloro methane.

could be observed under such circumstance. An increase in the content of ethanol and an addition of some triethylamine in dichloromethane was also examined. As shown in the figure, no epimerization was observed. On the other hand, when the crystalline imidazoline **1** was dissolved in the crude reaction mixture of imidazoline, which contains an excess amount of (*S*)-2-(aminomethyl)pyrrolidine, an appreciable epimerization was observed. The rate was as fast as that in methanol. This suggested that (*S*)-2-(aminomethyl)pyrrolidine catalyzes this epimerization. Accordingly, the rate of epimerization in a dichloromethane solution containing (*S*)-2-(aminomethyl)pyrrolidine was studied, and it is observed that the rate was fairly fast. There are a pyrrolidine ring moiety and a primary amine group in (*S*)-2-(aminomethyl)-pyrrolidine. In order to reveal the effect of the nature of amines on the ability of acceleration of the rate, the rates in dichloromethane solutions each containing propylamine, pyrrolidine, *N*-methylpyrrolidine and quinuclidine are examined. The acceleration of the rate of epimerization was found to be in the order of pyrrolidine (cyclic secondary amine)>propylamine (acyclic primary amine)>*N*-methylpyrrolidine and quinuclidine (tertiary amine). The small effect of tertiary amine on the acceleration of the rate suggests that this catalytic action of amines does not depend only on the basicity of amines.

Imidazoline derivatives **2** and **3** were prepared from (2*S*)-*N*-isopropyl-2-aminopropylamine and the imidates derived from (*S*)-alanine and (*R*)-alanine respectively. The imidazoline derivative **2** was isolated as longitudinal crystals by recrystallization from petroleum ether and **3** was isolated as fine needles by recrystallization from acetone–petroleum ether. The physical data of these imidazoline derivatives were apparently different. Hydrolysis of **2** and **3** gave the starting alanines, (*S*) and (*R*) respectively, both with high optical purity (Table 1). It is considered that the epimerizations of both diastereomers **2** and **3** are rather slow. Epimerization of **2** was examined and the results are shown in Fig. 2. The results indicate that the rate of epimerization promoted by primary or acyclic secondary amine was far slower than pyrrolidine. Since the rate of crystallization of **2** or **3** seemed to be similar to that of **1**, the failure of asymmetric transformation in the case of **2** or **3** may be attributed to the slow epimerization. This fact suggests that the efficient catalytic action of (*S*)-2-(aminomethyl)pyrrolidine was attributed to the pyrrolidine moiety and does not due to the chelate effect of the diamine.

It is explicable that the alanine was obtained in low yield by the hydrolysis of **2** and **3**. The existence of an isopropyl group on nitrogen atom in diamine moiety is common to these imidazolines. The difficulty of the hydrolysis is explained on the basis of the steric hindrance of this isopropyl group. Similar description was given in the case of hydrolysis of proteins containing valine or isoleucine residue.[7]

It was revealed that the epimerization of the imidazoline derivatives were efficiently catalyzed by pyrrolidine. The asymmetric transformation of **2** was attempted using pyrrolidine. The imidazoline **2** (53 mg) was dissolved in the dichloromethane solution containing pyrrolidine (5.7 molar equivalent). After 24 h the solvent was removed under reduced pressure. Because the excess pyrrolidine prevented the crystallization, the residue was dissolved in dichloromethane and washed with water to remove the pyrrolidine. The dichloro-

methane layer was dried and evaporated under reduced pressure, and the residue was recrystallized from acetone–petroleum ether to give 23 mg of crystals in the form of fine needles. The melting point (111—115°) and IR spectrum of the crystals were almost identical with those of **3**. It showed that the asymmetric transformation from **2** to **3** occured by the catalytic action of pyrrolidine. The low yield of **3** based on **2** was considered the removal of the pyrrolidine interrupted the epimerization during crystallization.

References

1) M. M. Harris, "Progress in Stereochemistry," ed by W. Klyne and P. B. D. Mare, Buntterworths Scientific Publications, London (1958), Vol. 2, p. 157.

2) M. Saburi and S. Yoshikawa, *Kagakusosetsu*, **13**, 109 (1976); H. Matsushita, Y. Tsujino, M. Noguchi, and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **49**, 3629 (1976); H. Matsushita, Y. Tsujino, M. Noguchi, M. Saburi, and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **51**, 862 (1978).

3) K. Yonetani, Y. Hirotsu, and T. Shiba, *Bull. Chem. Soc. Jpn.*, **48**, 3302 (1975).

4) S. Schnell and P. Karrer, *Helv. Chim. Acta*, **38**, 2036 (1955).

5) R. C. Job and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 809 (1974).

6) Y. Hirotsu, T. Shiba, and T. Kaneko, *Bull. Chem. Soc. Jpn.*, **40**, 2945 (1967).

7) R. Takahashi, "Seikagaku Jikkenkoza," Tokyokagakudojin, Tokyo (1976), Vol. 1, II, p. 30.