Facile Production of D-Histidine by Asymmetric Transformation of L-Histidine

Tadashi SHIRAIWA,* Kazuyuki SHINJO, Yoko MASUI, Atsushi OHTA, Hisashi NATSUYAMA, Hideya MIYAZAKI, and Hidemoto KUROKAWA
Faculty of Engineering, Kansai University, Yamate-cho, Suita, Osaka 564
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Synopsis. An asymmetric transformation from L-histidine [L-His] to D-His was achieved by using salicylaldehyde as a catalyst for epimerization, and (2*R*, 3*R*)-tartaric acid as a resolving agent, in acetic acid. Treatment of the obtained salt with triethylamine in methanol gave D-His with 100% optical purity in 95% yield based on the starting L-His.

Both D- and L-amino acids are useful as chiral reagents in asymmetric syntheses. L-Amino acids are obtained as natural products, whereas D-amino acids are difficult to obtain in large quantities. Although an optical resolution of synthetic DL-amino acid gives both D- and L-amino acids, DL-histidine [abbreviated as DL-His] has not been synthesized on an industrial scale because there is no efficient procedure for preparation of its imidazole ring. L-His, therefore, is inexpensive but D-His is significantly costly. The optical resolution of DL-His by using (2*R*, 3*R*)-tartaric acid [(*R*)-TA], as a resolving agent, gives a salt of D-His with (*R*)-TA as a less soluble diastereomeric salt.[1] In addition, an optically active amino acid is racemized easily by using aldehydes as a catalyst in a carboxylic acid.[2,3] We therefore attempted an efficient production of D-His by the asymmetric transformation of L-His.

Experimental

Materials. L-His ($[\alpha]_D^{20}$+12.2° (*c* 3.00, 6 mol dm^{-3} HCl)) and (*R*)-TA ($[\alpha]_D^{20}$+13.2° (*c* 2.00, water)) were purchased from Kokusan Chemical Works, Ltd. and Wako Pure Chemicals Ind., respectively.

Asymmetric Transformation. A mixture of 3.10 g (20.0 mmol) of L-His, 3.00 g (20.0 mmol) of fine powdery (*R*)-TA, and 2.00 or 10.0 mmol of salicylaldehyde or butanal in 20 cm^3 of acetic acid was stirred for 0.5—7 h at 80 or 90 °C, and subsequently for 0. 5 h in an ice bath. The salt formed (5.7—6.1 g) was collected by filtration, washed thoroughly with diethyl ether, and dried.[4] The D-His·(*R*)-TA salt thus obtained was of 100% optical purity: $[\alpha]_D^{20}$+13.3° (*c* 2.00, water). Found: C, 39.32; H, 4.98; N, 13.52%. Calcd for $C_{10}H_{15}N_3O_8$: C, 39.35; H, 4.95; N, 13.77%. After suspending the obtained salt in 70 cm^3 of methanol, followed by adding 2 molar equivalents of triethylamine for the salt, the mixture was stirred for 1 h in an ice bath. Insoluble D-His was collected by filtration, washed with methanol, and dried. The optical purity of the obtained D-His was estimated on the basis of the specific rotation ($[\alpha]_D$+12.43° (6 mol dm^{-3} HCl))[5] of L-His. The D-His obtained was of 100% optical purity. Found: C, 46.11; H, 5.84; N, 27.13%. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08%; $[\alpha]_D^{20}$−12.5° (*c* 3.00, 6 mol dm^{-3} HCl). The degrees of crystallization of D- and L-His ($DC_{(D)}$ and $DC_{(L)}$/%) were calculated from the formulae

$$DC_{(L)}/\% = (1/2)\,[\text{Yield}/\% \times (100 - \text{Optical purity}/\%)]/100, \quad (1)$$

$$DC_{(D)}/\% = \text{Yield}/\% - DC_{(L)}/\%, \quad (2)$$

where the yield was calculated on the basis of 20.0 mmol (3.10 g) of His and, when L-His was obtained, the subscripts D and L in Eqs. 1 and 2 were exchanged with each other.

Rate Constant for Racemization. L-His (40.0 mmol) was dissolved in 50 cm^3 of formic acid, acetic acid, or propanoic acid at 40, 70, or 90 °C. After adding 4.00 mmol of salicylaldehyde or butanal, the solution was stirred at each temperature. A 5-cm^3 aliquot of the solution was pipetted out at appropriate time intervals, cooled rapidly, and diluted to 10 cm^3 with water. The optical rotation of the solution was measured at 589 nm with a Union Giken PM-101 digital polarimeter equipped with a quartz cell of 5.00 cm path length. The rate constant for racemization (k_R/s^{-1}) was calculated by the least-squares method from

$$\ln \alpha_0/\alpha_t = k_R \cdot t, \quad (3)$$

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time. The half-life period ($t_{1/2}$/s) was calculated by using the k_R value from Eq. 3.

Results and Discussion

Racemization of L-Histidine. Racemization of L-His was regarded as a first-order reaction because a linear relationship was found between ln α_0/α_t and time t. The rate constant (k_R/s^{-1}) and half-life period ($t_{1/2}$/s) are summarized in Table 1.

The racemization of L-His was accelerated by using salicylaldehyde as a catalyst rather than butanal. We reported that, in racemization of L-proline [L-Pro] and (*R*)-2-piperidinecarboxylic acid [(*R*)-Pia], the rate of racemization by use of butanal increased with a decrease in acidities of the carboxylic acids used as solvents.[6] An alternative result has been reported that the rates of racemization of optically active amino acids may be largest in acetic acid.[2] As seen in Table 1, the rate of racemization of L-His is largest in acetic acid and the tendency differs from those of L-Pro and (*R*)-Pia.[6] In the racemization of L-His, after forming the Schiff base by reaction of L-His with an aldehyde, the racemization seems to proceed by protonation on its nitrogen atom by the carboxylic acid, followed by α-proton abstraction

Table 1. Kinetic Data for Racemization of L-Histidine[a]

Aldehyde	Carboxylic acid	Temperature	k_R[b]	$t_{1/2}$[c]
		°C	10^{-4} s^{-1}	10^3 s
SA[d]	AcA[e]	40	3.42	2.03
Butanal	FrA[f]	90	0.114	60.8
	AcA[e]	70	3.06	2.27
		90	34.2	0.203
	PrA[g]	90	10.4	0.666

a) Conditions: L-His 40.0 mmol; aldehyde 4.00 mmol; carboxylic acid 50 cm^3. b) k_R: Rate constant for racemizaion. c) $t_{1/2}$: Half-life period. d) Salicylaldehyde. e) Acetic acid. f) Formic acid. g) Propanoic acid.

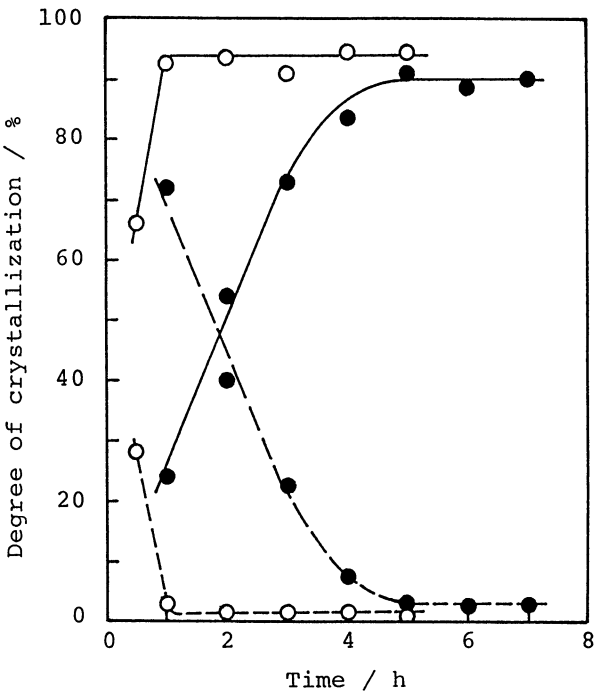

Fig. 1. Comparison of asymmetric transformation by use of salicylaldehyde and butanal as catalyst for epimerization.
Conditions: L-His 20.0 mmol; (*R*)-TA 20.0 mmol; aldehyde 10.0 mmol; acetic acid 20 cm^3; temperature 90 °C. Aldehyde: ○ Salicylaldehyde; ● butanal.
Degree of crystallization: —— $DC_{(D)}$; — — $DC_{(L)}$.

by its carboxylate anion.[2,3] On the other hand, the racemization of L-Pro or (*R*)-Pia proceeds by formation of the Schiff base with concomitant protonation by the carboxylic acid, followed by α-proton abstraction by the resulted carboxylate anion.[2] Since the formation of the Schiff bases seems to be extremely rapid, the rates of racemization of L-Pro and (*R*)-Pia are determined by the process of α-proton abstraction, as described in our previous paper,[6] and that of L-His by both processes of protonation and α-proton abstraction. An order of protonation at 90 °C is estimated from the acidity constant[7] at 90 °C to be formic acid > acetic acid > propanoic acid and that of proton abstraction to be formate anion < acetate anion < propanoate anion. The rate of racemization of L-His, therefore, is estimated to be most rapid in acetic acid, as summarized in Table 1.

Asymmetric Transformation from L-Histidine to D-Histidine. The asymmetric transformation from L-His to D-His was tried by using half molar equivalent of salicylaldehyde or butanal for L-His in acetic acid (Fig. 1); D-His with 15% optical purity was obtained by using 0.1 molar equivalent of butanal at 5 h. Figure 1 suggests that the rate of epimerization of the L-His·(*R*)-TA salt by use of salicylaldehyde as the catalyst is larger than that by butanal, as predicted from the racemization of L-His. The asymmetric transformation was also successfully achieved by using 0.1 molar equivalent of salicylaldehyde for L-His in acetic acid (Table 2). The asymmetric transformation gave efficiently D-His with 100% optical purity in 95% yield, based on the starting L-His, by reacting for 6—7 h at 80 °C and for 3—4 h at 90 °C, respectively.

Table 2. Asymmetric Transformation from L-Histidine to D-Histidine[a]

Temperature	Stirring time	Yield of salt	D-Histidine	
			Yield[c]	Optical purity
°C	h	g [%[b]]	%	%
80	0.5	6.05 [99.2]	93.2[d]	55.0
	1	6.03 [98.9]	92.9[d]	27.0
	2	6.03 [98.9]	92.3	87.3
	3	6.07 [99.5]	96.5	90.1
	4	6.07 [99.5]	97.5	94.1
	5	6.05 [99.2]	95.4	95.7
	6	6.03 [98.9]	95.1	100
	7	6.05 [99.2]	96.6	100
90	1	6.01 [98.5]	95.4	92.5
	2	6.04 [99.0]	95.8	95.7
	3	6.06 [99.3]	95.4	100
	4	6.05 [99.2]	94.6	100

a) Conditions: L-His 20.0 mmol; (*R*)-TA 20.0 mmol; salicylaldehyde 2.00 mmol; acetic acid 20 cm^3. b) The yield was calculated on the basis of 20.0 mmol (6.10 g) of the salt of His with (*R*)-TA. c) The yield was calculated on the basis of the starting L-His (20.0 mmol, 3.10 g). d) Partially racemized L-His.

References

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4) Since the absolute value of a difference in the specific rotation between the D-His·(*R*)-TA and L-His·(*R*)-TA salts is extremely small, an estimation of the optical purity of the obtained salt from their specific rotations may result in a large error; lit,[1] of the D-His·(*R*)-TA salt, $[\alpha]_D$+13.3° (*c* 3.69, water); lit,[1] of the L-His·(*R*)-TA salt, $[\alpha]_D$+16.4° (*c* 5.47, water). The optical purity of the obtained salt, therefore, was not estimated from their specific rotations.
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