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Facile Production of (R)-Proline by Asymmetric Transformation of (S)-Proline

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The asymmetric transformation of (S)-proline ((S)-Pro) through formation of the salt with (2S,3S)-tartaric acid achieved in the presence of 0.1 molar equivalent of butanal in butanoic acid at 80 °C to obtain (R)-Pro. The purified salt gave (R)-Pro with 100% optical purity in 85% yield.

Optically active proline (abbreviated as Pro) is useful as a chiral reagent and catalyst in asymmetric syntheses. Although (S)-Pro has been obtained by fermentation or by isolation from protain hydrolysates, (R)-Pro is difficult to obtain from natural products in large quantities. (S)-Pro, therefore, is inexpensive, whereas (R)-Pro significantly costly because it requires synthetic transformations from (R)-glutamic acid.[1] This letter describes an attempt of facile production of (R)-Pro from (S)-Pro. The optical resolution of (RS)-Pro by using (2R,3R)-tartaric acid ((R)-TA) gives its less soluble diastereomeric salt composed of equimolar amounts of (S)-Pro and (R)-TA.[2] The salt of (R)-Pro with (S)-TA, therefore, is less soluble than that of (S)-Pro with (S)-TA. (S)-Pro is racemized in the presence of aldehydes in ethanoic acid.[3] Butanal seems to be favorable for racemization of Pro. The asymmetric transformation of (S)-Pro was tried by using (S)-TA in the presence of butanal. Butanoic acid was used as a solvent because the formed salt was dissolved in ethanoic acid.

A mixture of 0.0200 mol of (S)-Pro and (S)-TA and 0.0020 mol of butanal in 30 cm^3 of butanoic acid was stirred for 1-6 h at 80 °C and successively for 0.5 h in an ice bath. The formed salt of (R)-Pro with (S)-TA was collected by filtration, washed with diethyl ether, and dried. After adding concentrated aqueous ammonia (0.55 cm^3 g^{-1}) to a solution of the salt in 200 cm^3 of methanol, followed by stirring for 0.5 h in an ice bath, the formed diammonium (S)-tartarate was removed by filtration. Drying of the filtrate gave (R)-Pro as the

Table 1. Asymmetric Transformation of (S)-Proline to (R)-Proline

Reaction period	Salt			(R)-Proline	
	Yield	Specific rotation[b]	Optical purity[c]	Yield[d]	Optical purity
h	g [%[a]]	°	%	%	%
1	5.21 [98.3]	-4.91	15.1	97.0	15.1
2	5.15 [97.2]	+18.3	82.8	96.1	84.2
3	5.16 [97.4]	+21.9	93.3	94.8	92.9
3	4.67 [88.1][e]	+24.2	100	85.2	100
4	5.15 [97.2]	+21.9	93.3	93.0	92.5
4	4.62 [87.2][e]	+24.2	100	84.8	100
5	5.16 [97.4]	+22.0	93.6	93.9	93.2
6	5.18 [97.7]	+22.3	94.5	95.2	93.6

a) Yield / % = [Yield x 100 / g] / 5.30; 0.0200 mol of the salt is 5.30 g. b) $[\alpha]_D^{20}$ (c 1.0, water). c) The optical purity was calculated on the specific rotation ($[\alpha]_D^{25}$ -24.2° (c 1, water)) of the salt of (S)-Pro with (R)-TA and that ($[\alpha]_D^{25}$ +44.4° (c 1, water)) of the salt (R)-Pro with (R)-TA; Ref. 2. d) Yield / % = [Yield x 100 / g] / 2.30; 0.0200 mol of Pro is 2.30 g. e) This salt was purified by recrystallization.

residue. (R)-Pro with 93% optical purity was obtained in 93-95% yield by reacting for 3-6 h, as listed in Table 1. To a solution of the salt with 93% optical purity in water (1 cm^3 g^{-1}) was added ethanol (20 cm^3 g^{-1}). After stirring the mixture for 1 h in an ice bath, the purified salt was filtered off, washed with a small amount of diethyl ether, and dried. Treatment of the salt with concentrared aqueous ammonia gave (R)-Pro ($[\alpha]_D^{20}$ +86.2° (c 1.00, water)); lit. of (S)-Pro,[4] $[\alpha]_D^{20}$ -86.2° (c 1, water).

This facile procedure gave (R)-Pro with 100% optical purity in 85% yield based on the (S)-Pro used as the starting material.

References

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