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ASYMMETRIC CATALYTIC SYNTHESIS OF LYSINE BY HYDROGENATION OF α-NITROCAPROLACTAM

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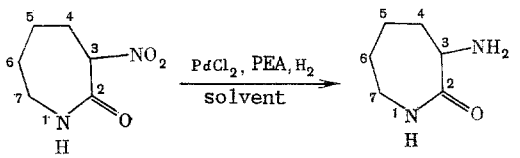
One of the methods for synthesizing lysine from caprolactam is catalytic hydrogenation of α-nitrocaprolactam (I). The enantioselective hydrogenation of (I) was first achieved using the chiral metal-complex catalyst $Ru_2Cl_4(-)\text{-DIOP}]_3$ [1]. Reaction carried out at 75°C and 30 atm H_2 for 70 h gave (+)-α-aminocaprolactam (II) hydrochloride with $[\alpha]_D$ +10.3° (enantiomeric excess (EE) 39%), hydrolysis of which gave S-lysine·2HCl with mp 187-188°C (yield and optical rotation not indicated).

It was established in [2] that the enantioselective hydrogenation of (I) can be carried out on a palladium catalyst in the presence of S-α-phenylethylamine (PEA). In the present work this reaction is studied in detail.

DISCUSSION OF RESULTS

The hydrogenation of (I) was studied at atmospheric pressure in the presence of a chiral Pd complex obtained *in situ* by reduction of $PdCl_2$ with hydrogen in the presence of PEA. The rate of reaction was determined from the absorption of H_2. As a result of hydrogenation there was a quantitative yield of (II), which was isolated as its hydrochloride. The optical yield of the reaction was determined as the enantiomeric excess (EE, %) by comparison of the $[\alpha]_D$ of the product obtained with that of optically pure S-(II)·HCl [3].



(I) S-(II)

It should be noted that hydrogenation of (I) on heterogeneous catalysts (Pd black, 1% Pd/SiO_2, and Raney Ni) in EtOH containing PEA proceeds only at high pressure (100 atm) and gives an optically inactive product (II). On Raney Ni catalysts modified by RR-(+)-tartaric acid and S-lysine, hydrogenation of (I) does not occur even at 100 atm and 50°C.

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TABLE 1. Hydrogenation of (I) on a Chiral Pd Catalyst Obtained in the Presence of PEA at 20°C and 1 atm

Batch no.	Quantity of $PdCl_2$, mmoles	Conc. of components, moles/liter		Solvent	$\tau_{1/2}$, min	(II), $[\alpha]_D^{20}$, deg (C 2—3; 1 *N* HCl)	EE *, %
		(I)	PEA				
1	0,18	0,07	0,10	EtOH	46	−1,28 **	–
2	0,36	0,07	0,04	»	39	−1,95 **	–
3	Pd(0)	0,025	–	DME	–	−0,64	2,6
4	0,18	0,07	0,04	»	240	−1,03	4,2
5	»	0,05	0,05	»	180	−1,47	6,0
6	»	0,05	0,07	»	145	−2,70	10,9
7	3,60	0,1	1,5	»	25	−2,0	8,2
8	7,20	0,04	1,2	»	12	−3,2	13,1
9	0,36	0,1	***	–	80	−3,0	12,0

*EE—enantiomeric excess of S-(II)·HCl; optically pure S-(II)·HCl has $[\alpha]_D^{20}$ −24.5° (C 3.2; 1 N HCl) [3].
**Specific notation given for λ 350 nm in H_2O.
***Without solvent in PEA; $\tau_{1/2}$—time for half conversion.

TABLE 2. Hydrogenation of (I) in Different Solvents ($PdCl_2$ 0.36 mmoles, PEA 1 mmole, (I) 2 mmoles, solvent 20 ml, 20°C)

Solvent	$\tau_{1/2}$, min	EE S-(II), %	Solvent	$\tau_{1/2}$, min	EE of S-(II), percent
EtOH	20	1	Dioxane	170	3
t-BuOH	80	2	DME	240	4,2 *
C_6H_6	140	1,5	THF	150	4,8

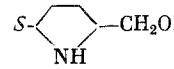
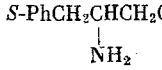
*Hydrogenation of (I) carried out at 20, 35, and 50°C; EE of S-(II) unchanged.

Hydrogenation of (I) also does not occur in the presence of the homogeneous chiral catalyst Rh(PheNOP) [4] in benzene—EtOH medium.

Thus, out of all the catalysts used only the Pd complex with PEA is capable of enantioselective hydrogenation of (I). As can be seen from Table 1, hydrogenation of (I) in the presence of this catalyst leads to the formation of the (−)-enantiomer of (II)·HCl, which, according to [3], corresponds to the S configuration of the α-center in (II), and this is borne out when S-(+)-lysine·2HCl is obtained after hydrolysis of the reaction product (II). Thus, the results obtained by us differ from the information in [1], where for S-(II)·HCl a positive value of [α] is reported.

Hydrogenation of (I) proceeds at a higher rate of EtOH in comparison with the aprotic solvent, dimethoxyethane (DME) (see Table 1). In the latter an increase in the rate of hydrogenation also occurs when the concentration of PEA in the reaction medium is increased. In the presence of a zero-valent complex of Pd with PEA (No. 3) as described in [5], the rate of hydrogenation is extremely low. Only introduction of 1.5 mmoles of free PEA base into the medium permits the reaction to go to completion. Use of a Pd complex with a molar ratio Pd:PEA = 1:3 (No. 4) but obtained *in situ* leads to a considerable increase in rate, which is comparable with the rates obtained when the quantity of PEA is increased by a factor of 2 and 3 (No. 5 and 6 respectively). With a substantial increase in the quantity of $PdCL_2$ and PEA for a constant concentration of substrate (No. 7 and 8), the rate of hydrogenation increases markedly. The stereoselectivity of the reaction depends on both the solvent and the concentration of PEA. In EtOH the optical yield is considerably less than in DME. In the latter the EE of S-(II) first increases with an increase in concentration of PEA, reaching a maximum value of 11% at a molar ratio Pd:PEA = 0.18:1.5 (No. 6), and with a further increase in concentration of PEA it is virtually unchanged. Hydrogenation in PEA without a solvent (No. 9) gives similar results. The data obtained suggest the formation of a catalytically active Pd complex, probably containing PEA and solvent as ligands and capable of enantioselective hydrogenation of (I).

TABLE 3. Hydrogenation of (I) on Pd Complexes in the Presence of Chiral Amines ((I) 2 mmoles, ligand 1 mmole, $PdCl_2$ 0.36 mmoles, solvent 20 ml)

Ligand	Solvent	T., °C	Time for half conversion $\tau_{1/2}$, h
S-PhCH(Me)N(Me)$_2$ [6]	DME	20	12
S-PhCH(Me)NHCH(Me)$_2$ [7]	THF	20	6 *
S-AlaOMe **	DME	20	5
S-PheOMe **	»	70	4,5
S-ValOMe **	»	20	10
S-  —CH_2OH [8]	THF	20	6,5
S-$PhCH_2CHCH_2OH$ [8] 	»	20	1 ***

*S-(II) with EE 2% obtained.
**Ligands introduced into reaction mixture in the form of free bases.
***R-(II) with EE 7.2% obtained.

In this connection it was of interest to investigate the effect of ligand structure, type of solvent, and temperature of reaction on the enantioselectivity of hydrogenation of (I). Comparison of a number of solvents in the hydrogenation of (I) showed (Table 2) that there is a higher degree of selectivity when solvents of ether type (THF, DME, dioxane) are used, and a lower degree occurs when EtOH, t-BuOH, and benzene are used. In DMF hydrogenation of (I) does not occur. Changing the temperature of hydrogenation of (I) in DME in the region 20-50°C does not affect the optical yield.

The possible enantioselective hydrogenation of (I) when treated with Pd complexes obtained *in situ* in the presence of different chiral amines was also investigated (Table 3). It was found that hydrogenation of (I) in the presence of secondary and tertiary amines either did not occur or proceeded at a negligible rate. An enantioselective effect is obtained only when S-N-isopropyl-α-phenylethylamine is used as a ligand. In the presence of amino acid esters the rate of reaction is also low and an inactive product is formed in all cases. With prolinol hydrogenation takes place slowly and without enantioselectivity, while with phenylalaninol it proceeds rapidly to give (II) with an R configuration (EE 7.2%). Bases containing amide groups and also alkaloids (anabasine and aphylline) give Pd complexes which cannot reduce the nitro group in (I).

The cause of the enantioselective effect when (I) is hydrogenated is possibly the formation of a pro-chiral intermediate of (I) with the Pd complex, during the reduction of which there is removal of the α-proton and stereoselective addition of it subsequently. The mobility of the α-proton of (I) in a basic medium is supported by the PMR spectrum of (I) in CD_3OD in the presence of NaOD, in which the signal at 5.7 ppm (C^3H) disappears as a result of the exchange of H for D.

EXPERIMENTAL

PMR spectra were recorded on a Bruker (250 MHz) spectrometer, IR spectra were run on UR-20 and Specord spectrophotometers; optical rotation was recorded on a Spectropol-1 spectropolarimeter. The following were used: $PdCl_2$ (pure); S-α-phenylethylamine with $[\alpha]_D^{20}$ −40.4° (without solvent); S-N-isopropyl-α-phenylethylamine with $[\alpha]_D^{20}$ −60° (C 1.7; EtOH); S-phenylalaninol with $[\alpha]_D^{20}$ −37° (C 2.4; EtOH).

α-Nitrocaprolactam. This was obtained according to [1], mp 163-164°C (EtOH). IR spectrum (KBr disk, ν, cm^{-1}); 1680 (C=O), 1570, 1340 (NO_2), 3250 (NH). PMR spectrum (CD_3OD, δ, ppm): 1.25-2.31 m (6H, $C^{4,5,6}H_2$), 3.15 t (2H, C^7H_2), 5.70 d. d (1H, C^3H).

Hydrogenation of (I) on Pd Complexes. This was carried out according to [9]. 2 mmoles of (I) in 20 ml of DME was hydrogenated in the presence of Pd complex obtained from 3 mmoles of $PdCl_2$ and 3 mmoles of PEA with reduction by H_2. On completion of the reaction 20 ml of MeOH was introduced into the mixture in order to decompose the complex and Pd was separated. The filtrate was evaporated under vacuum and the residue was dissolved in water, supplemented

with 0.5 ml of 10% NaOH, and extracted with ether. The aqueous layer was acidified to pH 5 and evaporated to dryness. The residue was dried, abs. EtOH was added to it, NaCl was filtered off, and the filtrate was evaporated. 0.3-0.32 g (90-94%) of S-α-aminocaprolactam·HCl (II) was obtained. IR spectrum (KBr disk, ν, cm^{-1}): 2850-3100 (NH_2), 1680 (C=O), 1490-1600 (δNH_2). PMR spectrum (CD_3OD, δ, ppm): 1.30-2.09 m (6H, $C^{4,5,6}H_2$), 3.16 t (2H, C^7H_2), 4.15 d. d (1H, C^3H). $[\alpha]_D^{20}$ −2.7° (C 2; 1 N HCl), EE 10.9%.

Hydrolysis of S-(II)·HCl. This was carried out according to [3]. S-Lysine·2HCl with $[\alpha]_D^{20}$ +1.7° (C 4; 6 N HCl) was obtained. Previously determined optically pure S-lysine·2HCl had $[\alpha]_D^{20}$ +15.8° (C 3-6; 6 N HCl).

CONCLUSIONS

The enantioselective hydrogenation of α-nitrocaprolactam (I) is effected on a chiral Pd complex, obtained *in situ* in the presence of S-α-phenylethylamine, to give S-α-aminocaprolactam (II), hydrolysis of which gives S-lysine. The optical yield varies from 1 to 13% according to the solvent and concentration of chiral ligand. On a Pd complex with S-N-isopropyl-α-phenylethylamine, enantioselective hydrogenation of (I) gives an excess of the S-enantiomer of (II) (2%). On a Pd complex with S-phenylalaninol, hydrogenation of (I) leads to the R configuration of (II) with EE 7.2%.

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