ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA THE CATALYTIC REDUCTION OF SUBSTITUTED ACYLAMINOACRYLIC ACID AZLACTONE DERIVATIVES.

25. REDUCTIVE AMINOLYSIS OF 2-PHENYL- AND 2-METHYL-Δ^2-OXAZOLIN-5-ONES UPON TREATMENT WITH A CHIRAL $PdCl_2$–R-PHENYLGLYCINE METHYL ESTER CATALYTIC SYSTEM

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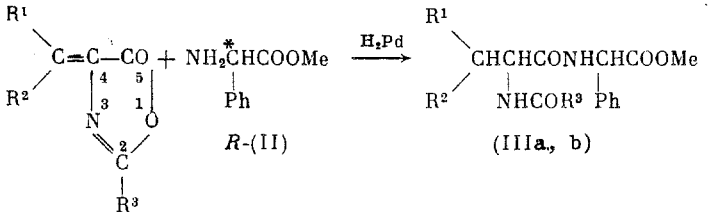
We have studied the reaction of Δ^2-oxazolin-5-ones with R-phenylglycine methyl ester in the presence of $PdCl_2$; the reaction gives phenylalanine or valine dipeptide derivatives with the RS-configuration. The presence of triethylamine during the reductive aminolysis of oxazolinones in dimethoxyethane solvent significantly increases the stereoselectivity of the reaction process. The stepwise mechanism of the reaction has also been explored.

The use of S-α-phenylethylamine, one of the most readily available chiral agents, in the catalytic reductive aminolysis (RA) of 4-arylidene-Δ^2-oxazolin-5-ones has led to the preparation of aromatic amino acid amide derivatives in high yield [1]. In the case of 4-alkylidene-Δ^2-oxazolin-5-ones, on the other hand, RA in the presence of S-phenylethylamine occurred with substantially poorer stereoselectivity: the SS-diastereomer excess was less than 25%. Our search for new chiral agents for the RA of Δ^2-oxazolin-5-ones for the synthesis of both aromatic and aliphatic amino acids has led us to consider the application of R-phenylglycine methyl ester (PhyOMe) (II) as the nucleophile in the above-mentioned catalytic system; (II) is readily available from R-phenylglycine, a commercial product which is used in the synthesis of antibiotics. Studies of this type of catalytic system are also of interest with regard to the asymmetric synthesis of dipeptides via RA reactions of Δ^2-oxazolin-5-ones.

DISCUSSION OF RESULTS

The RA reaction of (I) with R-PhyOMe (II) was carried out at 20°C and 1.2-1.3 atm H_2 in dimethoxyethane (DME) or t-BuOH according to the equation summarized in Scheme 1 and gave the optically active dipeptides (III).

Scheme 1



(I a,b) (II) (IIIa, b)

$R^1 = H$, $R^2 = Ph$, $R^3 = Me$ (a); $R^1 = R^2 = Me$, $R^3 = Ph$ (b).

The catalytic system (CS) was prepared in situ by reduction of $PdCl_2$ with hydrogen in the presence of (II) (CS-1). The reaction products were analyzed by PMR spectroscopy. The ratio of SR- and RR-dipeptide diastereomers (III) was determined based on the integrated intensity ratio of the signals corresponding to the methoxy protons. Signal assignments were made based on enantiomeric GLC analysis of phenylalanine or valine [2], which were

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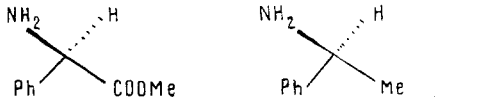
TABLE 1. Reductive Aminolysis of Δ^2-Oxazolin-5-ones (I) [1 mmole (I), 1.5 mmoles R-(II), 0.2 mmole Et_3N, 0.2 mmole $PdCl_2$, 5 ml solvent]

Compound	Solvent	Amine	DE SR-(III), %	$k \cdot 10^2$, min^{-1}	DE SS-amide for CS-2, % [1]
(Ia)	DME	–	6	2,3	40
	t-BuOH	–	22	1,0	50
	DME	Et_3N	47	2,0	
	t-BuOH	Et_3N	19	2,7	
	i-PrOH	Et_3N	21	1,8	
(Ib)	DME	–	24	1,2	5
	t-BuOH	–	22	1,2	25
	DME	Et_3N	45	1,0	
	t-BuOH	Et_3N	18	2,7	

obtained after acidic methanolysis [3] or hydrolysis of (III). In the PMR spectra of (III) the signals for the OCH_3 group protons which were more upfield corresponded to the SR-isomer of (III). The diastereomer ratio for (III) could also be determined based on the signals for the acetyl [in the case of (IIIa)] or isopropyl (IIIb) group protons. The reaction rates were measured based on the amount of hydrogen consumption, and can be described in terms of first-order equations with respect to (I).

It should be noted that R-(II) corresponds to the same configuration series as S-α-phenylethylamine (Scheme 2), which participates in the RA of (I) to give predominantly the S-configuration at the new α-site [1].

Scheme 2



R-(II) *S*-α-phenylethylamine

If the stereochemical pathway of this reaction were retained (with these two nucleophiles) we would expect SR-dipeptides (III) to be formed. In fact, RA of (I) upon treatment with CS-1 led to the formation of the SR-isomers of (III) (Table 1). The properties of CS-1 differed, however, from those of the previously studied system [$PdCl_2$–S-phenylethylamine] (CS-2). Thus, the stereoselectivity for the RA of (Ia) in DME was significantly lower than the stereoselectivity for (Ib) [the diastereomer excess (DE) was 6 and 24%, respectively]. Furthermore, in the case of CS-2, an inverse pattern was observed, namely, the asymmetric effect for the reaction upon exchange of a methyl group in the 2-position by a phenyl group for all (I) studied decreased sharply, regardless of the nature of the substituent attached to C^4 [1]. In the case of CS-1, the enantioselectivity for the RA of (Ia) improved substantially in the transition from DME to t-BuOH (6 and 22%, respectively), but the RA of (Ib) was not affected (24 and 22%, respectively). Conversely, in the case of CS-2 substitution of DME by t-BuOH for the RA of (Ia) did not lead to as great an increase in stereoselectivity as for the RA of (Ib).

In the case of CS-1 a significant increase in reaction stereoselectivity was observed for both oxazolinones (Ia) and (Ib) upon RA in DME in the presence of Et_3N: the DE for Sr-(IIIa) was 47%, De (IIIb) 45%. In t-BuOH as solvent, however, Et_3N addition had no effect on reaction stereoselectivity. RA of (Ia) in i-PrOH in the presence of Et_3N gave a DE for SR-(IIIa) of 21%.

In order to examine the possibility that these reactions occur via the intermediate formation of dehydrodipeptides $R^1C{=}C(R^2)(NHCOR^3){-}CONH\overset{*}{C}HCOOMe$ (IVa, b) (the a and b designations are given in Scheme 1), as is the case for the RA of 2-trifluoromethyloxazolin-5-ones with amino acid esters [4], we investigated the diastereoselectivity for the reduction of (IV). Hydrogenation of (IVa) in the presence of $PdCl_2$ and without any extraneous nucleophile proceeded to a high degree of conversion and gave dipeptides (IIIa) with a large diastereoselective effect: DE RR-(IIIa) was 19% (Table 2). Upon reduction of (IVa) in the presence of

TABLE 2. Diastereoselective Hydrogenation of N-Acetyldehydrophenylalanyl-R-phenylglycine (IVa) [1 mmole (IVa), 1.5 mmoles amine, 0.2 mmole $PdCl_2$, 15 ml DME]

Amine	DE RR-(IIIa), %	$k \cdot 10^2$, min^{-1}
–	19	0,5
R-(II)	6	3,8
Et_3N	4	2,3

TABLE 3. Two-Step Synthesis of Dipeptides (III)

$$(I) \xrightarrow[Et_3N]{H_2,\ Pd} (V) \xrightarrow[(Et_3N)]{R\text{-(II)}} (III)$$

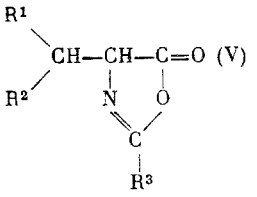
[1 mmole (I), 1.5 mmoles (II), 0.2 mmole $PdCl_2$, 1.5 mmoles Et_3N, 15 ml solvent]

Compound	Solvent	Amine for aminolysis	DE SR-(III), %	Compound	Solvent	Amine for aminolysis	DE SR-(III), %
(Ia)	DME	–	34	(Ib)	DME	–	40
	t-BuOH	–	24		*t*-BuOH	–	20
	DME	Et_3N	44		DME	Et_3N	40
	t-BuOH	Et_3N	36		*t*-BuOH	Et_3N	18

CS-1 the DE for RR-(IIIa) was reduced to 6%. The presence of Et_3N additive also decreased the asymmetric effect for the hydrogenation of (IVa) [DE RR-(IIIa) 4%]. Reduction of (IVb) did not take place under these reaction conditions.

The preparation of (III) with different configurations for the RA of (Ia) and the diastereoselective hydrogenation of (IVa) precludes the possibility that RA of (I) occurs via the intermediate formation of dehydrodipeptides (IV).

Another possible pathway for RA involves initial hydrogenation of the C=C bond and subsequent aminolysis of the saturated oxazolinone (V)



The RA of (I) in t-BuOH containing the CS-2 proceeds according to this mechanism [1].

In order to verify the feasibility of the intermediate formation of (V), we examined the two-step process, namely, reduction of (I) to (V) followed by aminolysis of (V) with R-(II). Reduction of (I) in the absence of base takes place only with great difficulty, so the hydrogenation of (I) was studied in the presence of Et_3N. The second step, aminolysis of (V) via reaction with R-(II), was studied both in the presence and absence of Et_3N. The result of this two-step process was the preparation of (III) having predominantly the SR-configuration (Table 3). The observed stereoselectivity was the same for the one- (Table 1) and two-step reaction processes (Table 3) when t-BuOH was used as the solvent and when the reactions in DME included Et_3N. These results lead us to conclude that under our experimental conditions (t-BuOH or DME + Et_3N) we cannot exclude the possibility that RA occurs via the intermediate formation of (V). In fact, during the RA of (Ia) in DME with Et_3N additive the presence of (Va) was detected by IR spectroscopy among the reaction products after incomplete hydrogenation.

The large differences observed during RA and the two-step process when DME is used as the solvent [DE for SR-(IIIa) 6 and 34%, DE for SR-(IIIb) 24 and 40%, respectively] suggest that RA of (I) under these conditions occurs within the inner sphere of the catalytic

complex without diffusion of the intermediate products into the bulk solution. In the presence of Et_3N additive, on the other hand, the reaction mechanism changes and RA apparently takes place via a two-step process.

The large stereoselectivity obtained upon RA of (I) in DME in the presence of CS-1 and Et_3N additive has enabled us to isolate pure SR-(IIIa) and SR-(IIIb) after recrystallization. The asymmetric induction properties of this newly studied system CS-1 for the preparation of phenylalanine peptides are fully consistent with the properties of CS-2. However, the previously studied system CS-2 has several advantages for the preparation of free optically pure phenylalanine, since hydrolysis of the amide leads to an easily separable mixture of phenylalanine and phenylethylamine. In the case of the asymmetric synthesis of valine derivatives, however, CS-1 is more efficient than CS-2 for the RA of (Ib). A distinguishing feature of CS-1 is its high stereoselectivity for the RA of 2-phenyloxazolin-5-ones.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WP-250 spectrometer (δ, ppm). Enantiomeric GLC analyses were carried out on a Biokhrom-1 chromatograph equipped with an FID and a glass capillary column (15 m × 0.25 mm) filled with N-docosanoyl-L-valine tert-butylamide chiral phase [2], with a (nitrogen) carrier gas flow rate of 1 ml/min and an injector temperature of 170°C. Phe and Val, obtained via hydrolysis of peptides (III), were analyzed in the form of their N-trifluoroacetylated isopropyl ester derivatives at a column temperature of 145°C, or GLC analyses were performed immediately on AcPheOMe and BzValOMe, obtained directly via acidic methanolysis [3], using the same chiral phase and column temperatures of 170 and 150°C, respectively. Optical rotations were determined on an A1-EPO photoelectronic polarimeter; IR spectra were measured on a Specord M-80 spectrophotometer. The sample of $PdCl_2$ was pure grade, 2-methyl-4-benzylidene-Δ^2-oxazolin-5-one (Ia), mp 150°C; 2-phenyl-4-isopropylidene-Δ^2-oxazolin-5-one (Ib) was prepared according to [5], mp 97-99°C (from absolute alcohol).

R-Phenylglycine Methyl Ester Hydrochloride (II). Prepared according to [6] in 69% yield, mp 202-206°C (alcohol). $[\alpha]_D^{20}$ −139.6° (C 2.14, MeOH). PMR spectrum (CD_3OD): 3.74 s (OCH_3), 5.18 s (CH), 7.44 m (C_6H_5).

Reductive Aminolysis of (I) [4]. A solution of 17 mg $PdCl_2$ in 3 ml solvent was reduced by hydrogen in the presence of 0.75 mmoles R-(II) hydrochloride and 0.75 mmoles triethylamine (for conversion of the nucleophile to its free base form)* for 15 min. The reactor was then charged with 0.5 mmole (I) in 4 ml solvent and the rate of hydrogen consumption was measured. After reaction completion the catalyst was removed by centrifugation and the solution was passed through a Dowex 50 W × 4 column, then evaporated, and the diastereomer ratio in the residue analyzed by PMR and GLC. Yield of (III), 70%.

Two-Step Process. A solution of 0.5 mmole (I) was hydrogenated in 7 ml DME in the presence of 0.75 mmole Et_3N and 17 mg $PDCl_2$ for 5 h. The catalyst was removed by centrifugation and the solution evaporated with mild heating. To the resulting saturated oxazolinone (V) was added 7 ml solvent, 0.75 mmole R-(II) hydrochloride, and 0.75 mmole (or 1.5 mmoles Et_3N), and the mixture allowed to stand 12 h. The reaction mixture was worked up on the Dowex 50 W × 4 column, evaporated, and analyzed.

Hydrogenation of N-Acetyldehydrophenylalanylphenylglycine Methyl Ester R-(IVa). A solution of 17 mg $PdCl_2$ in 3 ml solvent was reduced with hydrogen for 15 min and 0.5 mmole (IVa) was then added. Catalyst reduction was also carried out in the presence of 0.75 mmole R-(II) (CS-1) and 0.75 mmole Et_3N. The reactor was then charged with 0.5 mmole (IVa) and the rate of hydrogen absorption measured.

N-Acetylphenylalanylphenylglycine Methyl Ester (IIIa). PMR spectrum ($CDCl_3$): 1.87 s [CH_3CO in RR-(IIIa), 1.99 s [CH_3CO in SR-(IIIa)], 3.03 m (CH_2Ph), 3.66 s [OCH_3 in SR-(IIIa)], 3.69 s [OCH_3] in RR-(IIIa)], 4.9 m (CH), 5.5 m (CH), 7.2 m (C_6H_5). After recrystallization from ethyl acetate:hexane (2:1) pure SR-(IIIa) was obtained, mp 190-191°C, $[\alpha]_\lambda^{20}$ (λ, nm) (C 0.95, C_2H_5OH): −337° (365), −219° (420).

*When the RA was carried out in the presence of Et_3N 1.5 mmoles of the latter were added, R-(II)·HCl:triethylamine = 1:2.

N-Benzoylvalylphenylglycine Methyl Ester (IIIb). PMR spectrum ($CDCl_3$): 0.84 d, 0.87 d [CH_3CH in SR-(IIIb)], 1.04 d, 1.07 d [CH_3CH in RR-(IIIb)], 2.15 m (CH), 3.64 s [OCH_3 in SR-(IIIb)], 3.72 s [OCH_3 in RR-(IIIb)], 4.77 m (CH), 5.55 m (CH), 7.5 m (C_6H_5). After recrystallization from a mixture of ethyl acetate:hexane (2:1) pure SR-(IIIb) was obtained, mp 153-154°C, $[\alpha]_\lambda^{20}$ (λ, nm) (C 1.23, C_2H_5OH): −227.6° (365), −151.2° (420).

Methanolysis of (IIIa) [3]. Peptide (IIIa) (73 mg) was dissolved in 3 ml absolute MeOH and a stream of HCl was passed through the solution for 10 min. The mixture was heated at 90°C in a Teflon ampul for 90 min, then evaporated, DME added, and the mixture passed through a Dowex 50 W × 4 column. After evaporation of the eluate AcPheOMe was obtained in 53% yield. Enantiomeric excess was determined by GLC on a chiral phase at 170°C.

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ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA THE CATALYTIC REDUCTION OF SUBSTITUTED ACYLAMINOACRYLIC ACID AZLACTONES.

26. AMINOLYSIS OF 2-METHYL-4-BENZYLOXAZOLIN-5-ONE UPON REACTION WITH S-PHENYLALANINE DERIVATIVES

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The kinetics of aminolysis and racemization of 2-methyl-4-benzyloxazolin-5-one upon reaction with S-phenylalanine methyl ester have been studied in dimethoxyethane solvent. The rates of aminolysis and racemization are comparable. Addition of an achiral component, namely Et_3N, to the reaction mixture, however, dramatically increases the rate of racemization. The presence of Et_3N also increases the ratio of rate constants for the formation of RS- and SS-diastereomers, which determines the reaction stereoselectivity.

The reductive aminolysis (RA) reaction of 2-methyl-4-benzylideneoxazolin-5-one (I) upon treatment with $PdCl_2$–S-phenylalanine derivative (dimethylamide or ester) catalytic system (CS) leads to the predominant formation of RS-dipeptide derivatives. The reaction stereoselectivity upon treatment with these types of CS increases substantially upon addition of an achiral component, namely Et_3N, in sharp contrast to the behavior of the $PdCl_2$–S-α-phenylethylamine (PEA) CS [1]. The reductive aminolysis of (I) can occur via two pathways (Scheme 1).

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