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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY NONENZYMATIC TRANSAMINATION. VERSATILITY OF THE REACTION AND ENANTIOMERIC EXCESSES OF THE PRODUCTS

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Diverse α-keto acids were transformed into the corresponding α-amino acids with enantiomeric excesses ranging from 60 to 96% by the reaction with chiral pyridoxamine analog, (R)- or (S)-15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (4), and Zn^{2+} in the molar ratio of 2:1, in methanol. The use of the S enantiomer of 4 gave (R)-α-amino acids, and vice versa.

In a series of studies pursuing a system mimicking vitamin B_6-dependent enzymes capable of enantio-face differentiation,[2-5] we have reported the synthesis of several chiral pyridoxamine analogs. They were: the S enantiomer of 15-aminomethyl-14-hydroxy-2,8-dithia[9](2,5)pyridinophane (3),[3,4] the R and S enantiomers of 15-aminomethyl-14-hydroxy-5,5-dimethyl-2,8-dithia[9](2,5)pyridinophane (4).[4] Stereoselective transamination between (S)-3 and phenylpyruvic acid in the presence of Zn^{2+} (the molar ratio Zn^{2+}/(S)-3 was 1.3/1) was performed.[3] This nonenzymatic transamination gave phenylalanine in fairly good yield but in rather low enantiomeric excesses ranging from 6 to 26%, with the sign of the optical rotation dependent on the solvent used. Nevertheless, such stereoselective transamination systems seemed still worthwhile because most of the vitamin B_6 analog fully retaining the original chirality can be recovered in the aldehyde form and recycled.[3]

Here we wish to describe the extended application of the above system to the asymmetric synthesis of α-amino acids in general, including an important finding that the reduction of the molar ratio Zn^{2+}/chiral pyridoxamine analog to 0.5/1 remarkably increases the enantiomeric excess of the products. The preferred solvent is methanol.

The mixture of a sodium salt of the α-keto acid (1), chiral pyridoxamine analog (4 or 3) and $Zn(ClO_4)_2 \cdot 6H_2O$ in molar ratio of 2:1:1 or 2:1:0.5 in an appropriate solvent was stirred for 24 hours at room temperature and the resulting chelated aldimine intermediate[6] was decomposed by addition of 1 M hydrochloric acid. Amino acid (2) was isolated from the mixture by ion exchange chromatography as has been described before.[3] The results are tabulated in Table 1. The pyridoxal type of chiral vitamin B_6 analog (6 or 5) was recovered in 75-85% in all cases.

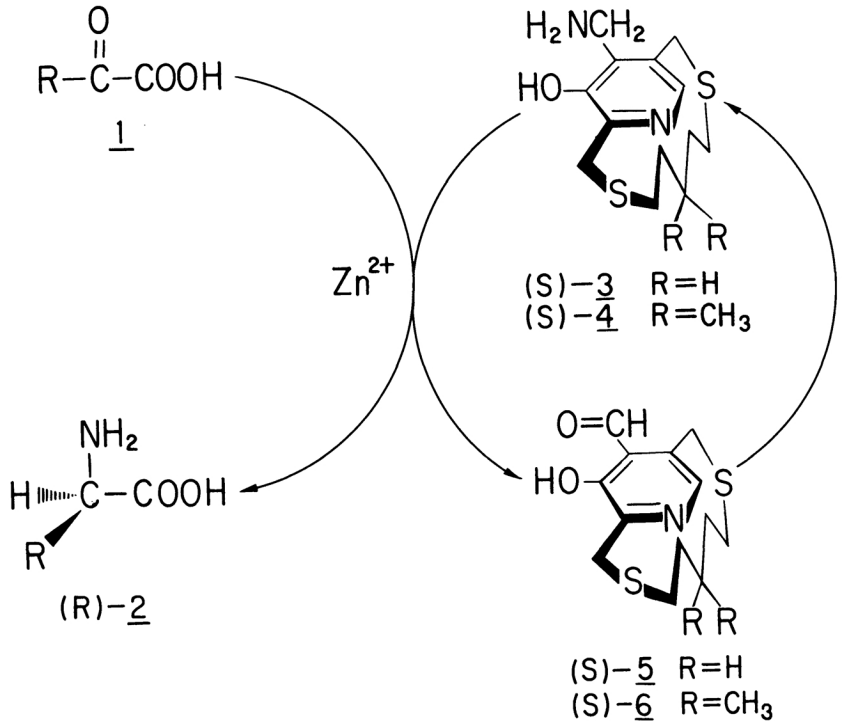
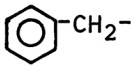
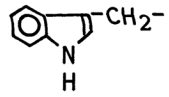


Figure 1. Transamination reaction between pyridoxamine analogs of S configuration and α-keto carboxylic acids.

It is apparent from comparing the entries 2, 3, and 10 with 7, 8, and 12 respectively, that higher enantiomeric excesses of amino acids are obtained by using 4 than by using 3; i.e., the branched "ansa-chain"[7] in the molecule of 4 functions more effectively for the stereoselective reaction than the linear one in 3. As the reaction medium, the protic solvents (entries 1, 2, and 7) seem to be superior to the aprotic ones (entries 3 and 8): the use of protic solvent generally gave better yields and equal or higher enantiomeric excesses. Methanol was the best solvent among those examined here. In all cases but one (entry 16)[8], the employment of the S enantiomer of pyridoxamine analog (4 or 3) gave the R enantiomer[9] of the amino acid (2) in excess and vice versa. This is typically exemplified in a couple of experiments for leucine (entries 4 and 5). The most striking results in Table 1 are that reduction of the molar ratio of Zn^{2+} enhances enantiomeric excesses of the products; reducing the molar ratio of Zn^{2+} vs. 4 from 1/1 to 0.5/1 resulted in a remarkable increase of the enantiomeric excess without much influencing the chemical yields[10] (compare entries 1, 9, 13, and 15 with 4, 11, 14, and 17 respectively). Thus the employment of a combination of chiral 4, one half equimolar Zn^{2+} and methanol in addition to the keto acids gave the products with enantiomeric excesses ranging from 60 to 96%. No irregularity concerning the interdependence of absolute configurations between 4 employed and the products was found under these conditions. The chemical yields of the amino acids were not optimized

Table 1. Transamination reactions between chiral pyridoxamine analog (4 or 3) and RCOCOOH (1)[a)]

entry	R	Py[b)]	solvent[c)]	Zn^{2+}/4 (or 3)	product: chemical yield[d)] (%)	product: e.e.[e)] (%)	product: major enantiomer	product: name
1		4, S	MeOH	1/1	65	73	R	leucine
2		4, R	BuOH	1/1	66	71	S	leucine
3		4, R	MeCN	1/1	33	64	S	leucine
4	CH_3	4, S	MeOH	0.5/1	66	95	R	leucine
5	CH_3 $\diagdown$ CH-CH_2- / CH_3 $\diagup$	4, R	MeOH	0.5/1	68	96	S	leucine
6		3, S	MeOH	0.5/1	65	77	R	leucine
7		3, S	BuOH	1/1	61	43	R	leucine
8		3, S	MeCN	1/1	51	43	R	leucine
9		4, S	MeOH	1/1	75	52	R	valine
10	CH_3 $\diagdown$	4, S	BuOH	1/1	72	44	R	valine
11	CH- / CH_3 $\diagup$	4, R	MeOH	0.5/1	57	79	S	valine
12		3, S	BuOH	1/1	64	31	R	valine
13		4, R	MeOH	1/1	75	47	S	alanine
14	CH_3-	4, R	MeOH	0.5/1	72	69	S	alanine
15		4, S	MeOH	1/1	75	23	R	phenylalanine
16		4, S	BuOH	1/1	61	12	S	phenylalanine
17		4, R	MeOH	0.5/1	60	61	S	phenylalanine
18		4, S	MeOH	0.5/1	62	60	R	tryptophan

a) The compounds 1 (0.6 mmol), 4 or 3 (0.3 mmol), and $Zn(ClO_4)_2 \cdot 6H_2O$ (0.3 mmol or 0.15 mmol) were dissolved in one of the solvents (150 ml). b) Pyridoxamine analog, enantiomer. c) Methanol (MeOH), 1-butanol (BuOH), and acetonitrile (MeCN) were used. d) Calculated on the basis of the pyridoxamine analog and the isolated amino acids. e) Calculated on the basis of the observed specific rotations of the amino acids obtained and of the corresponding authentic chiral specimen.

because ion exchange chromatography was repeated during their isolation in order to prevent the contamination with the chiral vitamin B_6 analogs.

The stereochemical features observed in this nonenzymatic transamination reaction might be well rationalized by assuming the stereoselective protonation to

the key intermediate constituted by an octahedral zinc chelate, which will be discussed elsewhere.[11)]

We wish to emphasize that this work also constitutes a rare example of a biomimetic reaction with the possibility of practical application.

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7) As 3, 4, 5, and 6 are ansa-compounds, their aliphatic chains bridging between 2 and 5 positions of their pyridine ring are tentatively called "ansa-chains" in this communication.
8) Stereoselective transamination between (S)-3 and phenylpyruvic acid was found to be much influenced by the reaction solvent used (ref. 2). Entry 16 suggests that 1-butanol is not a suitable solvent for the stereoselective transamination, although reducing the quantity of Zn^{2+} to 1/2 resulted in reversing the sign of the optical rotation of the product (R, 10% e.e.).
9) As far as the amino acids in this paper are concerned, R enantiomers correspond to D-amino acids and vice versa.
10) At the same time we observed an appreciable enhancement of the reaction rate.
11) Y. Tachibana, M. Ando, and H. Kuzuhara, Chem. Lett., submitted for publication.

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