ASYMMETRIC SYNTHESIS OF ASPARTIC AND α-METHYLASPARTIC ACIDS VIA Ni(II) COMPLEXES WITH SCHIFF BASES OF GLYCINE AND ALANINE AND CHIRAL CARBONYL-CONTAINING REAGENTS

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We propose a method for the synthesis of aspartic and α-methylaspartic acids by alkylation with ethyl bromoacetate of the α-carbon atom of the amino acid moiety in Ni(II) complexes of Schiff bases of glycine with (S)-2-[(N-benzylprolyl)amino]benzophenone and alanine with (S)-2-[(N-benzylprolyl)amino]-benzaldehyde, respectively. Attempts to synthesize α-methylaspartic acid by oxidative cleavage of the C=C bond to a COOH group in the complex of the Schiff base of α-allylalanine with (S)-2-[(N-benzylprolyl)amino]benzophenone were unsuccessful.

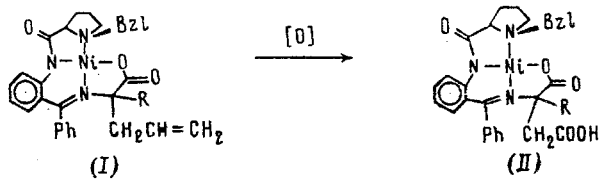
In recent times very much interest has been centered on the investigation of biochemical properties of amino acids of unusual structure, especially α-methyl substituted analogs of naturally occurring amino acids [1]. In the field of asymmetric synthesis of these amino acids the groups of Schöllkopf and Seebach [2-4] have been very successful.

We have developed general methods for the asymmetric synthesis of α-amino acids by using chiral regenerable reagents: (S)-2-[(N-benzylprolyl)amino]benzophenone (BBP) and (S)-2-[(N-benzylprolyl)amino]benzaldehyde (BBA) [5,6]. Alkylations with alkyl halides of Ni(II) complexes of Schiff bases of glycine and alanine with BBP and BBA give the possibility of synthesizing α-amino acids and their α-methyl substituted analogs in high asymmetric yields. In contrast to methods in [2-4], in this case it is not required to use such strong bases as BuLi or $(i\text{-}Pr)_2NLi$ and very pure solvents. The purpose of this work is to develop methods for the asymmetric synthesis of aspartic and α-methylaspartic acids, the simplest functionally substituted amino acids.

RESULTS AND DISCUSSION

Two general strategies may be selected for the asymmetric synthesis of aspartic and α-methylaspartic acids: 1) oxidation of the allyl group (Scheme 1) in the readily available complexes (I) of allylalanine or allylglycine (R = Me and H, respectively), and 2) alkylation of the glycine or alanine moiety in complexes (IIIa-c) with halide-containing derivatives of acetic acid (Scheme 2).

Scheme 1



(I) (II)

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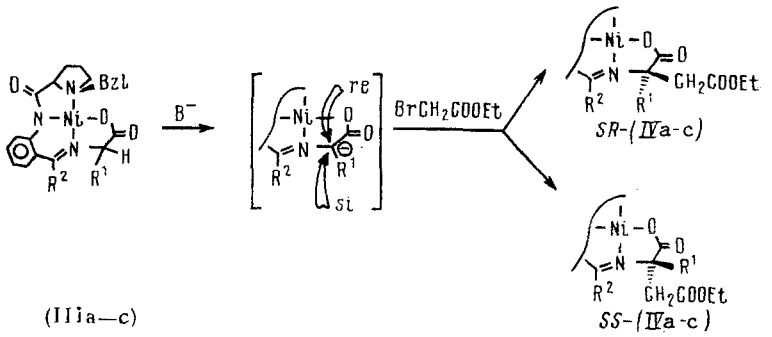
Scheme 2



(IIIa—c)

R^1 = H, R^2 = Ph(IIIa); R^1 = Me, R^2 = Ph (IIIb), H (IIIc).

Oxidation of the Allyl Group in Complex (I) (R = Me). For substrates that are insoluble in water, phase-transfer oxidation in the presence of quaternary ammonium salts in the system benzene—aqueous $KMnO_4$ solution [7] has been proposed.

The applicability of that method for the oxidation of an allyl group to a carboxylic acid was studied with the example of complex (I) (R = Me), which is easily prepared by alkylation of (IIIb) with allyl bromide [6].

In addition to a small amount of starting complex (about 10%), under phase-transfer conditions of oxidation four more novel complexes are formed. Only one of these four complexes contained a fragment of α-methylaspartic acid, which was confirmed by electrophoresis and by mass spectral investigations of the isolated amino acid. In the case of oxidation under these conditions, the contents of complex (II) (R = Me) does not exceed 20%. Changing the order of addition of the reagents leads to complete conversion of (I) (R = Me); however, the composition of the final mixture of complexes does not change significantly. Using a large excess of $KMnO_4$ in the latter case leads exclusively to complex (II) (R = Me), but at the same time its yield does not exceed 20%. Thus, under these conditions oxidation of the allyl group in complexes cannot be used as a preparative method for the synthesis of aspartic acid.

Synthesis of Aspartic and α-Methylaspartic Acids by Alkylation of Complexes (IIIa-c). Reaction of (IIIa) with $BrCH_2COOEt$ under mild conditions (K_2CO_3, MeCN in the presence of the phase-transfer catalyst cetyltrimethylammonium bromide (CTABr) at reflux temperature) leads in 4 h to complete conversion of (IIIa) and formation of diastereomeric complexes (IVa) in a chemical yield of 90.5% and a ratio of isomers SS:SR ≈ 90:10. Decomposition of the mixture of complexes with a water—alcohol solution of HCl with subsequent hydrolysis of the ester group gives (S)-Asp with an optical purity of 81% (determined by GLC [8]).

Diastereomeric complexes (SR)-(IVa) and SS-(IVa) can be well separated over SiO_2 with the system $CHCl_3$—Me_2CO (7:1). The structures of these complexes were confirmed by elemental analyses and PMR spectra. The absolute configurations of (SS)-(IVa) and (SR)-(IVa) were assigned on the basis of comparing the vicinal contributions of the amino acid moiety on the ORD curve of the complexes. It is known [9] that for all complexes the (SS)-configuration is characterized by a positive Cotton effect in the region 350-450 nm and the (SR)-configuration by a negative Cotton effect, which is also found in the case of diastereomers of (IVa). Decomposition of (SS)-(IVa) and (SR)-(IVa) yields (S)-Asp and (R)-Asp with optical purities of 99% and 95%, respectively.

The pure diastereomers of (IVa) were epimerized with Na_2CO_3 on refluxing in MeCN in the presence of CTABr to equilibrium mixtures with (SS):(SR) ratios of 9.5:1 and 8.2:1 when starting from (SS)-(IVa) and (SR)-(IVa), respectively. The diastereomeric composition of the complexes after epimerization was determined by data of the enantiomeric composition of isolated samples of Asp. The optical purity of (S)-Asp, isolated after epimerization of pure (SS)-(IVa) and (SR)-(IVa), was 81% and 78%, respectively. Comparison of these values with the optical purity of (S)-Asp that was isolated immediately after decomposition of the reaction mixture obtained by alkylation of (IIIa) with $BrCH_2COOEt$ showed that the diastereoselectivity of that reaction is determined by thermodynamic differences of the diastereomers.

Complex (IIIb), in contrast to complex (IIIa), does not react with $BrCH_2COOEt$ under these conditions. Treatments of (IIIb) with alkylating agents that are halogen derivatives of acetic acid: $ClCH_2COONa$, $ClCH_2CONH_2$, and $BrCH_2COOEt$, or their analog $ClCH_2CN$, and on using a rather wide range of bases and solvents (t-BuONa in t-BuOH, NaOH in MeCN, NaOH in DMF, K_2CO_3 in MeCN in the presence of CTABr) were unsuccessful. Checking was carried out by TLC on SiO_2 (chloroform–acetone, 7:1). Only in the case of reaction of (IIIb) with $ClCH_2CONH_2$ (NaOH in MeCN or in DMF) the formation of minor amounts of a novel complex was detected while the reaction mixture smelled strongly of ammonia. When $ClCH_2CN$ was used, under all the conditions a strong blackening of the reaction mixture without formation of new products was observed.

Failures in the alkylation of (IIIb) we relate largely to the great steric hindrance around the reaction center, which leads to considerable lowering of the rate of alkylation at a relatively high rate of decomposition of the alkylating agents.

We assumed that when the chiral inductor BBA is used instead of BBP the negative contribution to the steric factor might be lowered significantly.

Indeed, alkylation of complex (IIIc) with $BrCH_2COOEt$ proceeds under mild conditions (K_2CO_3 in refluxing MeCN) and gives after 6 h a mixture of diastereomeric complexes (IVc) in quantitative yield and an (SS)-(IVc):(SR)-(IVc) ratio of 63:37. Assignment of the absolute configurations of the amino acid fragments in the diastereomeric complexes was done according to the vicinal contribution of the amino acids in the optical rotatory dispersion (ORD) spectra of the complexes. One complex having a positive contribution in the region 350-420 nm and a negative one in the region 420-550 nm was assigned the (SS)-configuration, and the other complex having opposite Cotton effects in these regions of the spectrum was assigned the (SR)-configuration. The structures of the complexes were confirmed by PMR spectroscopy, UV spectra, and elemental analyses.

Diastereomeric complexes (IVc) were separated by chromatography over SiO_2 with the system i-PrOH–CH_2Cl_2 (1:30). The diastereomeric complexes can also be separated by crystallization from acetone after first hydrolyzing the ester group in (IVc) to the carboxyl group with a 1.5-fold excess of KOH in H_2O–MeOH (4:5). Isolation of (S)- and (R)-α-methylaspartic acids from the pure diastereomeric complexes was carried out by standard method [6]; the optical purity of the amino acids was 98 and 100%, respectively. The optical purity of isolated α-methylaspartic acid was determined by comparing the angle of rotation with published data [3].

Thus, the synthesis of α-methylaspartic acid in complexes of such a type can only be carried out successfully when the ligand BBA is used. Regretfully, up to now the synthesis of that ligand has not been developed well enough: the method is time-consuming and the yield of the ligand is not higher than 30% (in contrast to ligand BBP, the synthesis of which is developed very well and of which the yield, when prepared by method [10], is 95%). Ligand BBA cannot only be used for the synthesis of α-methylaspartic acid, but also for a whole series of other α-methyl substituted amino acids (among them also strongly sterically hindered amino acids of which the synthesis cannot be realized when ligand BBP is used [6]). Therefore, for the preparation of such amino acids in preparative amounts it is necessary to develop a convenient method for the synthesis of BBA.

EXPERIMENTAL

In our experiments, we used analytically pure $KMnO_4$ and K_2CO_3 of the firm Reakhim, the phase-transfer catalysts Aliquat 336 and cetyltrimethylammonium bromide (CTABr) of the firm Serva, and glycine and alanine of the firm Reanal. Chemically pure bromoacetic ester of the firm Reakhim was distilled first, $ClCH_2CN$ was prepared from $ClCH_2CONH_2$ (Reakhim) according to [11]. All solvents used in the experiments were purified according to [12]. The enantiomeric purity of aspartic acid was determined by GLC according to [8].

ORD spectra were recorded on a Jasco ORD/UV-5 spectrometer, UV spectra on a Specord M-40 spectrometer, and PMR spectra on a Bruker WP-200 spectrometer (200 MHz). Angles of rotation were measured on a Perkin-Elmer 241 polarimeter.

Preparation of chiral ligands BBA and BBP and the Ni(II) complexes of the Schiff bases of alanine and glycine were basically carried out according to [5] and [6], respectively. Synthesis of complex (I) (R = Me) was carried out according to [6].

Oxidation of the Allyl Group in Complex (I) (R = Me). To a solution of 3.1 g (0.006 mole) of the complex and 0.3 g of Aliquat 336 in a mixture of 30 ml of benzene and 6 ml of AcOH is added with vigorous stirring at 0°C a solution of 3.2 g (0.02 mole) of $KMnO_4$ in 30 ml of water. The mixture is stirred at ~20°C for 6 h. The reaction is monitored by TLC on SiO_2 ($CHCl_3$–Me_2CO, 7:1). The chromatogram contained, in addition to a spot of unreacted starting complex, four other novel complexes (A, B, C, and D in the order of decreasing R_f). The reaction mixture was filtered over a fine glass filter and the residue of MnO_2 was washed on the filter with acetone and chloroform. The filtrate was thoroughly extracted with water, the organic layer was evaporated to dryness, and the residue chromatographed over an SiO_2 column (eluent $CHCl_3$–Me_2CO, 7:1). Elution yielded a mixture of complexes A and B. The zone that contained complexes C and D was cut out and the pure complexes were eluted with alcohol. Complete separation of complexes A and B was carried out by chromatography on Kieselgel (Merck) plates with the system $CHCl_3$–Me_2CO (5:1). The complexes were further purified over a column with Sephadex LH-20 resin with the system benzene–alcohol (3:1). Complex C is poorly soluble in organic solvents and it was purified by washing with alcohol on a porous filter.

Decomposition of complexes A, B, C, and D and isolation of the amino acids was carried out by standard methods [6]. According to data of electrophoresis at neutral pH only one amino acid, isolated from complex B, had a negative charge. Mass spectrum of that amino acid as its tris(trimethylsilyl) derivative (molecular weight 363) at an ionization energy of 70 eV: M^+ not observed, m/z 348 [M^+ – Me], m/z 320 [M^+ – 43], m/z 246 [M^+ – COOTMS], m/z 232 [M^+ – CH_2COOTMS], which corresponds with the structure of α-methylaspartic acid.

Synthesis of Aspartic Acid. A mixture of 1 g (2 mmoles) of (IIIa), 1.4 g (10 mmoles) of K_2CO_3, 1 g (6 mmoles) of $BrCH_2COOEt$, 0.02 g of CTABr, and 5 ml of MeCN is refluxed for 5 h until complete disappearance of starting compound (IIIa) occurs. The reaction was monitored by TLC on SiO_2 with chloroform–acetone, 7:1. After cooling the mixture was diluted with chloroform and poured out in an excess of dilute AcOH. The product was extracted with chloroform, the extract was evaporated to dryness, and the residue was chromatographed over an SiO_2 column (40 × 100)* with the system chloroform–acetone, initially at a ratio of 10:1, then of 7:1. Yield 1.06 g (90.5%) of a mixture of (SR)-(IVa) and (SS)-(IVa). (The optical purity of Asp isolated from that mixture of diastereomers was 81%.) On crystallization of the mixture of diastereomers from benzene (SS)-(IVa) precipitates. From the mother liquor (SR)-(IVa) was isolated by chromatography over SiO_2.

(SS)-(IVa): mp 217-219°C. Found %: C 63.92, H 5.55, N 6.92. $C_{31}H_{31}N_3NiO_5$. Calculated %: C 63.72, H 5.34, N 7.18. UV spectrum [MeOH, λ_{max} (log ε)]: 527 (2.41), 417 (3.54), 333 (3.73). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.18 t (3H, CH_3CH_2O, J = 6.5), 2.07 m (2H, Pro), 2.88 m (1H, Pro), 2.44 and 2.72 (AB part of an ABX system, 2H, CH_2COOEt, J_{AB} = 16, J_{AX} = 7, J_{BX} = 2.6), 3.36-3.83 m (3H, Pro), 3.60 and 4.40 (AB, 2H, CH_2Ph, J_{AB} = 12.4), 4.20 m (1H, Pro), 4.20 q (2H, CH_3CH_2O), 6.52-8.25 m (14H, ArH).

(SR)-(IVa): mp 236-240°C. Found %: C 63.60, H 5.60, N 7.83. $C_{31}H_{31}N_3NiO_5$. Calculated %: C 63.72, H 5.34, N 7.18. UV spectrum [MeOH, λ_{max} (log ε)]: 527 (2.31), 418 (3.52), 332 (3.74). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.19 t (3H, CH_3CH_2O, J = 6.5), 1.89 m (1H, Pro), 2.12 m (1H, Pro), 2.46-2.75 m (2H, CH_2COOEt and 2H, Pro), 3.69 t (1H, Pro), 3.82 and 4.74 (AB, CH_2Ph, J_{AB} = 12.5), 4.04-4.33 m (2H, CH_3CH_2O and 2H, Pro), 6.63-8.57 m (14H, ArH).

Aspartic acid was isolated from the complexes by refluxing them in a solution of HCl in water–alcohol. The mixture was neutralized with soda and BBP was extracted with chloroform. The aqueous layer was evaporated until dry, to the residue was added 6 N HCl, and the mixture was refluxed for 5 h to hydrolyze the ester group. Then the amino acid was isolated on a KRS-12 cation-exchanger [5, 6].

Synthesis of α-Methylaspartic Acid by Alkylation of (IIIc). To a solution of 25.3 g (0.058 mole) of (IIIc) in 50 ml of MeCN were added under a stream of nitrogen 40.0 g of finely pulverized K_2CO_3 and 32.2 ml (0.29 mole) of $BrCH_2COOEt$. The reaction mixture was stirred at reflux temperature for 4 h. After cooling the mixture was poured out in an aqueous AcOH solution and extracted with $CHCl_3$. The organic layer was separated, evaporated, and the residue was chromatographed over an SiO_2 column (90 × 8 cm) by eluting with

*As in Russian original – Editor.

CH_2Cl_2–i-PrOH, 30:1. There was obtained 21 g (69%) of complex (SS)-(IVc) (fraction 1) and 5.6 g (18%) of complex (SR)-(IVc) (fraction 2). In addition to the pure isomers, 3.1 g (11%) of their mixture was obtained. For the separation of the diastereomeric complexes we applied an alternative method consisting of first hydrolyzing the ester group with one and a half excess of KOH in water–methanol (4:3) and subsequent crystallization of the resulting mixture from acetone.

(SS)-(IVc): Found %: C 59.84, H 6.13, N 8.09. $C_{24}H_{26}N_3NiO_5$. Calculated %: C 59.80, H 5.60, N 8.04. UV spectrum [MeOH, λ_{max}, (log ε)]: 505 (2.06 sh), 407 (3.47), 330 (3.66), 278 (3.92 sh), 260 (4.14). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.19 t (3H, CH_3CH_2O), 1.49 s (3H, α-CH_3), 2.05 m (3H, β-, γ-, and δ-Pro), 2.38 m (2H, β-, and γ-Pro), 2.78 and 3.12 (AB, 2H, CH_2COOEt, J_{AB} = 16.5), 3.36 m (1H, α-Pro), 3.51 and 4.32 (AB, 2H, CH_2Ph, J_{AB} = 12.5), 3.81 m (1H, δ-Pro), 4.14 q (2H, CH_3CH_2O), 6.8-8.5 m (9H, ArH), 7.59 s (1H, CH=N).

(SR)-(IVc): Found %: C 58.97, H 5.60, N 8.29. $C_{24}H_{26}N_3NiO_5$. Calculated %: C 59.80, H 5.60, N 8.04. UV spectrum [MeOH, λ_{max}, (log ε)]: 505 (2.07 sh), 407 (3.52), 330 (3.73), 278 (4.01 sh), 260 (4.23). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.24 t (3H, CH_3CH_2O), 1.65 s (3H, α-CH_3), 2.11 m (3H, β-, γ-, and δ-Pro), 2.41 m (2H, β-, and γ-Pro), 2.94 and 3.25 (AB, 2H, CH_2COOEt, J_{AB} = 17), 3.38 m (1H, α-Pro), 3.48 and 4.57 (AB, 2H, CH_2Ph, J_{AB} = 12.5), 3.78 m (1H, δ-Pro), 4.22 q (2H, CH_3CH_2O), 6.8-8.5 m (9H, ArH), 7.57 s (1H, CH=N).

Decomposition of the complexes and isolation of the amino acids was carried out by standard methods [5].

(S)-α-Methylaspartic acid was isolated in a yield of 71%. Found %: C 40.88, H 6.47, N 9.61. $C_5H_9NO_4$. Calculated %: C 40.82, H 6.17, N 9.52. PMR spectrum (D_2O, δ, ppm, J, Hz): 1.46 s (3H, α-CH_3), 2.59 and 2.85 (AB, 2H, CH_2, J_{AB} = 17.3). $[\alpha]_D^{25}$ +49.08° (c 0.44, 2 N HCl). Lit. [3]: $[\alpha]_D^{25}$ +53.3° (c 0.67, H_2O).

(R)-α-Methylaspartic acid was isolated in a yield of 90%. Found %: C 41.62, H 6.43, N 9.08. $C_5H_9NO_4$. Calculated %: C 40.82, H 6.17, N 9.52. PMR spectrum (D_2O, δ, ppm, J, Hz): 1.46 s (3H, α-CH_3), 2.59 and 2.85 (AB, 2H, CH_2, J_{AB} = 17.3). $[\alpha]_D^{25}$ –49.08° (c 0.45, 2 N HCl).

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