Organic Chemistry

Asymmetric synthesis of β-*N*-substituted α,β-diamino acids *via* a chiral complex of Ni^{II} with a dehydroalanine derivative

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Asymmetric synthesis of β-*N*-substituted (*S*)-α,β-diamino acids was accomplished by Michael addition of amines to the Ni^{II} complex of the Schiff base derived from (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone (BPB) and dehydroalamine. Diastereoselectivity of the reaction is kinetically and thermodynamically controlled. The chiral auxiliary reagent, BPB, can be recovered and reused.

Key words: dehydroalanine, amines, Michael addition, β-*N*-substituted α,β-diamino acids, (S)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone, asymmetric synthesis.

β-Hetero-substituted amino acids have been found in nature[1,2] and have been used in recent years for the synthesis of medical preparations.[3,4]

β-*N*-Substituted α,β-diamino acids are of interest not only as compounds possibly possessing biological activities but also as promising precursors in the preparation of new chiral ligands for the catalytic asymmetric synthesis of cyanohydrins.[5]

Asymmetric synthesis of β-hetero-substituted amino acids involving Michael addition of nucleophiles to the dehydroalanine residue of a Ni(II) complex (**1**) containing an (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone (BPB) chiral moiety has been described previously.[3,4]

In the present study, this approach is used to prepare optically active β-*N*-substituted α,β-diamino acids.

Results and Discussion

The Michael addition of amines **2a—e** to the C=C bond in complex **1** (Scheme 1) was carried out at 22 °C. The course of the reaction was monitored by TLC on SiO_2. Complex **1** completely reacted over a period of 2—3 h to give diastereomeric complexes **3a—e** and **4a—e**. Diastereomers **3** have the (*S*)-configuration of the α-carbon atom in the amino-acid fragment, while diastereomers **4** are characterized by the (*R*)-configuration of this atom, as shown based on the optical rotatory dispersion (ORD) data by analogy with previous studies.[6,7]

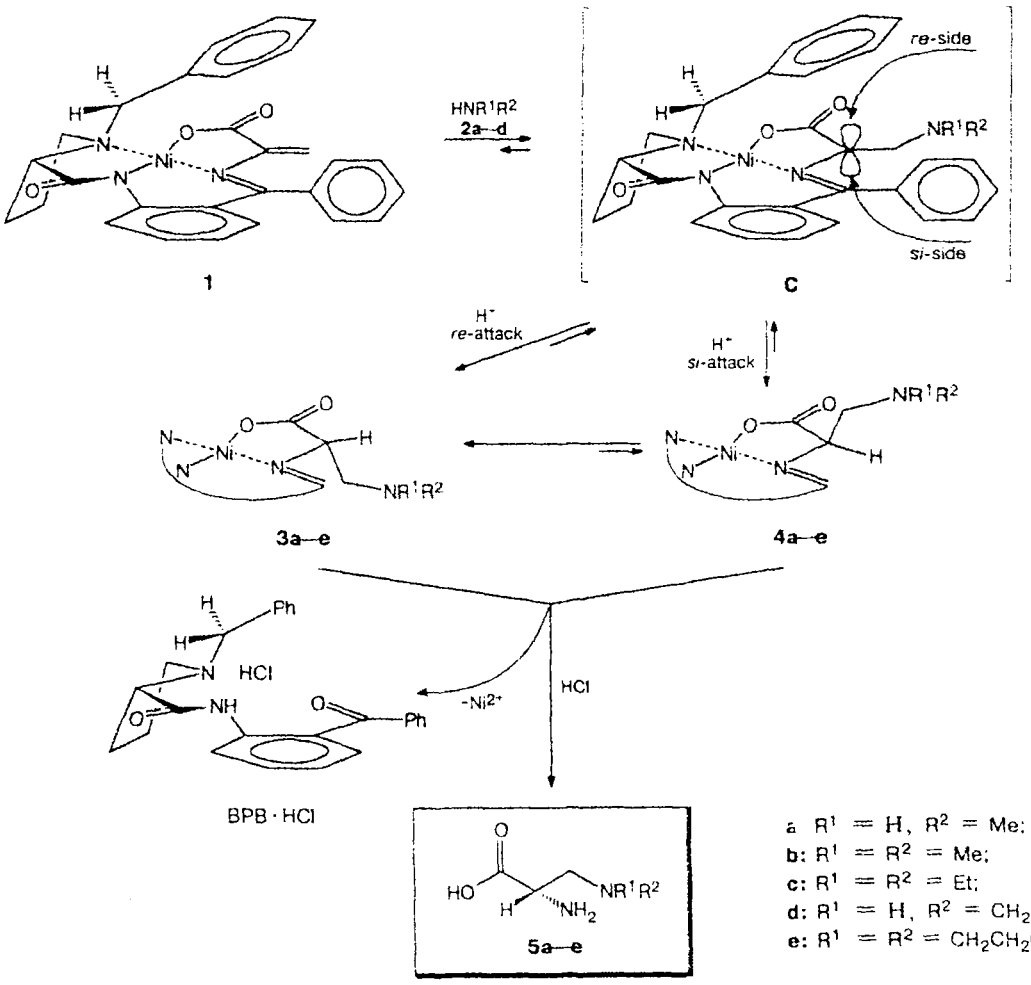
The diastereomeric composition of the products was determined by ^1H NMR spectroscopy or estimated using TLC. After 0.5—1 h, the ratio of diastereomers **3** to **4** was approximately 3 : 1, and after prolonged storage (2—4 days), it became as high as ≥9 : 1 (Table 1).

The kinetic diastereoselectivity of the reaction of complex **1** with amines **2** is determined by the step of protonation of the intermediate carbanion **C** (Scheme 1). The ratio between the rates of protonation of carbanion **C** from the *si*-side and from the *re*-side is relatively small and is close to the ratio of the corresponding rates of deuteration of carbanions with a similar structure.[8] Since the steps of protonation and/or addition are re-

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 504—507, March, 1997.

1066-5285/97/4603-0483 $18.00

Scheme 1



versible, a thermodynamic equilibrium between diastereomers **3** and **4** is established in which diastereomers **3** with the (*S*)-configuration of the α-amino-acid fragment predominate, as was also the case with similar complexes with simple alkyl groups.[8]

Diastereomerically pure complexes **3c,e** were isolated by crystallization of diastereomeric mixtures. We were not able to isolate complexes **3a,b,d** in a pure state. During isolation by preparative chromatography on SiO_2, adducts decompose and the initial complex **1** is recovered. Therefore, in the latter cases, nonseparated mixtures of diastereomeric complexes, formed after the equilibrium was established, were used for the isolation of amino acids (Scheme 1).

Table 1. Ratio of diastereomers **3** to **4** under the thermodynamic control conditions

Amine	3/4 ratio
2a	94 : 6
2b	95 : 5
2c	96 : 4
2d	90 : 10
2e	97 : 3

The complexes were decomposed by excess HCl in aqueous methanol, and the amino acids were isolated using the KU-2×8 cation exchanger.[9] In the case of amino acid **5b**, a column-free isolation procedure was developed (see Experimental). Chiral BPB is recovered almost quantitatively and can be reused.

Amino acids **5a–e** were isolated in optically active forms. It should be noted that the alternative Seebach asymmetric synthesis gives only a racemic product in the case of amino acid **5a**.[10]

Apparently, amino acids **5** are generally unstable compounds. Although in this work we did not study their properties in detail, the following data attest that some of them are unstable both free and as hydrochlorides. Free amino acid **5b** turns dark and acquires an unpleasant smell on storage, and its recrystallization from hot ethanol is accompanied by a substantial loss of

the product. The dihydrochloride of amino acid **5b** is stable during storage; however, we were not able to isolate it in an optically pure state. Moreover, the optical purity of the dihydrochloride of amino acid **5b**, isolated from a 95 : 5 (according to ^{1}H NMR) mixture of complexes **3b** + **4b**, was only ~70% (according to the data of enantiomeric GLC analysis). In addition, it was shown by ^{1}H NMR monitoring that at ~20 °C, the monohydrochloride of amino acid **5e** in D_2O slowly decomposes.

Experimental

Reagents of the "chemically pure" grade were used. Acetonitrile was distilled over P_2O_5. TLC was carried out on SiO_2 plates (Merck, 60 F254 or Silufol UV-254). For column chromatography, SiO_2 40/100 (Chemapol) was used. ^{1}H NMR spectra were recorded using Bruker instruments (200 and 400 MHz) with internal standards (HMDS for solutions in $CDCl_3$ and HCOOH in D_2O). Optical rotation angles were measured on a Perkin—Elmer M241 polarimeters, and ORD spectra were recorded on Jasco-ORD/UV-5 spectropolarimeter. The melting points are given without corrections. The enantiomeric GLC analysis of amino acids **5b,c** was carried out for their *N*-trifluoroacetyl-*O*-*n*-propyl-derivatives in a column with a Chirasil-Val type stationary phase.[9]

Complex 1 was prepared by a procedure described previously.[6]

***(S)*-2-Amino-3-(methylamino)propionic acid (5a).** A mixture of complex **1** (5 g, 9.8 mmol), K_2CO_3 (2.79 g, 20 mmol), and $MeNH_2 \cdot HCl$ (1.35 g, 20 mmol) in 12 mL of MeCN was stirred for 48—52 h at 22 °C. The course of the reaction was monitored by TLC on SiO_2 (using $CHCl_3$—Me_2CO, 3 : 1, as the eluent). Then the mixture was filtered, and the filtrate was concentrated to dryness. The residue was transferred into 30 mL of $CHCl_3$, and the solution was washed with H_2O (3×20 mL) and concentrated to dryness. The residue was dried *in vacuo* to give 4.56 g (86%) of a mixture of complexes **3a** and **4a** in a ratio of 94 : 6 (according to ^{1}H NMR). Found (%): C, 64.26; H, 5.48; N, 10.49. $C_{29}H_{30}N_4NiO_3$. Calculated (%): C, 64.36; H, 5.58; N, 10.35.

A solution of the mixture of complexes **3a** and **4a** (4.4 g, 8.1 mmol) in 20 mL of MeOH was added with stirring to 15 mL of 6 *N* aqueous HCl heated to 45—50 °C. The mixture was stirred for 30 min until the red color of the complex disappeared, and the solvent was evaporated to dryness. The residue was diluted with 40 mL of H_2O, and concentrated aqueous NH_3 was added until the pH was brought to 5. Then the chiral reagent BPB was extracted with $CHCl_3$ (3×20 mL) (yield 98%). Amino acid **5a** was isolated from the aqueous layer using the KU-2×8 cation exchanger[9] and recrystallized from a 6 *N* HCl—H_2O—EtOH mixture to give 0.98 g (78%) of **5a** · HCl. M.p. 182—184 °C. Found (%): C, 30.96; H, 7.30; N, 17.50. $C_4H_{10}N_2O_2 \cdot HCl$. Calculated (%): C, 31.07; H, 7.18; N, 18.12. ^{1}H NMR (200 MHz, D_2O), δ: 2.76 (s, 3 H, Me); 3.39 (dd, 1 H, β-H_a, J = 12.4 and 5.9 Hz); 3.46 (dd, 1 H, β-H_b, J = 12.4 and 7.8 Hz); 4.03 (dd, 1 H, α-H, J = 5.9 and 7.8 Hz). $[\alpha]_D^{25}$ +20.7 (*c* 0.8; 6 *N* HCl).

***(S)*-2-Amino-3-(dimethylamino)propionic acid (5b).** A mixture consisting of complex **1** (20 g, 39 mmol), a 4.3 *N* solution of Me_2NH (16 mL, 69 mmol) in Pr^{i}OH, and 40 mL of Pr^{i}OH was stirred at intervals until a homogeneous solution formed, and allowed to stand for 48 h at 22 °C. Then the solution was slowly poured in 50 mL of 6 *N* HCl and stirred for 30—40 min. The precipitate formed was filtered off, washed with H_2O, and dried in air to give 13.5 g (82%) of BPB · HCl. The aqueous solution was concentrated, and the precipitate of BPB · HCl was filtered off. An additional 2.5 g (15.2%) BPB · HCl was thus isolated. Water (2 mL) was added to the dark green syrup-like residue, and the mixture was dissolved in boiling ethanol. The solution was cooled and allowed to stand for 12 h at −5 °C. The crystalline precipitate thus obtained was filtered off, washed with ethanol, and once again crystallized from hot aqueous ethanol to give 4.8 g (54.9%) of compound **5b** · 2 HCl · H_2O. Found (%): C, 27.03; H, 7.29; N, 12.3; Cl, 31.42. $C_5H_{12}N_2O_2 \cdot 2\,HCl \cdot H_2O$. Calculated (%): C, 26.91; H, 7.23; N, 12.56; Cl, 31.78. ^{1}H NMR (200 MHz, D_2O), δ: 2.90 (s, 6 H, Me); 3.41 (dd, 1 H, β-H_a, J = 13.7 and 4.8 Hz); 3.65 (dd, 1 H, β-H_b, J = 13.7 and 9.7 Hz); 4.35 (dd, 1 H, α-H, J = 9.7 and 4.8 Hz). $[\alpha]_D^{25}$ +16.5 (*c* 1.5; 6 *N* HCl). According to the enantiomeric GLC analysis, the optical purity of the product was 67%.

***(S)*-2-Amino-3-(diethylamino)propionic acid (5c).** A mixture of complex **1** (5 g, 9.8 mmol), Et_2NH (4 mL, 38 mmol), and 12 mL of MeCN was stirred for 48 h at 22 °C. Then the mixture was worked up as in the experiment with $MeNH_2$ to give 4.9 g (85%) of a mixture of complexes **3c** and **4c**; it was recrystallized from Me_2CO to give 4.5 g (78%) of diastereomerically pure complex **3c**. Found (%): C, 65.53; H, 6.48; N, 9.39. $C_{32}H_{36}N_4NiO_3$. Calculated (%): C, 65.58; H, 6.23; N, 9.6. $[\alpha]_D^{25}$ +2786 (*c* 0.004; MeOH).

Product **5c** · 2 HCl · H_2O (1.75 g, 88%) was prepared from complex **3c** (4.5 g, 7.7 mmol) as described for compound **5a**. M.p. 125—127 °C. Found (%): C, 33.80; H, 8.20; N, 11.22. $C_7H_{16}N_2O_2 \cdot 2\,HCl \cdot H_2O$. Calculated (%): C, 33.47; H, 8.02; N, 11.15. ^{1}H NMR (200 MHz, D_2O), δ: 1.27 (t, 6 H, Me, J = 7.3 Hz); 3.32 (q, 4 H, NC$\underline{H}_2$Me, J = 7.3 Hz); 3.48 (dd, 1 H, β-H_a, J = 13.9 and 4.9 Hz); 3.71 (dd, 1 H, β-H_b, J = 13.9 and 8.9 Hz); 4.43 (dd, 1 H, α-H, J = 4.9 and 8.9 Hz). $[\alpha]_D^{25}$ +9.7 (*c* 1; 6 *N* HCl). According to the enantiomeric GLC analysis, the optical purity of the product was 85%.

***(S)*-2-Amino-3-(2-hydroxyethylamino)propionic acid (5d).** A mixture of complex **1** (5 g, 9.8 mmol), ethanolamine (2.8 mL, 48 mmol), and 12 mL of MeCN was stirred for 96 h at 22 °C. Then the mixture was worked up as in the previous experiment to give 4.9 g (85%) of a 9 : 1 mixture of complexes **3d** and **4d** (according to the ^{1}H NMR data).

Product **5d** · HCl · H_2O 0.94 g (74%) was obtained from a mixture of complexes **3d** and **4d** (4.6 g, 8 mmol) by a procedure similar to that described above, m.p. 123—125 °C. Found (%): C, 29.95; H, 7.50; N, 13.72. $C_5H_{12}N_2O_3 \cdot HCl \cdot H_2O$. Calculated (%): C, 29.62; H, 7.40; N, 13.82. ^{1}H NMR (400 MHz, D_2O), δ: 3.21—3.35 (m, 2 H, NC$\underline{H}_2$); 3.49 (dd, 1 H, β-H_a, J = 12.8 and 8.7 Hz); 3.53 (dd, 1 H, β-H_b, J = 12.8 and 6.1 Hz); 3.77—3.89 (m, 2 H, CH_2OH); 4.04 (dd, 1 H, α-H, J = 8.7 and 6.1 Hz). $[\alpha]_D^{25}$ +15.1 (*c* 1; 6 *N* HCl).

***(S)*-2-Amino-3-[bis(2-hydroxyethyl)amino]propionic acid (5e).** A mixture of complex **1** (5 g, 9.8 mmol), diethanolamine (2.8 mL, 29 mmol), and 12 mL of MeCN was stirred for 96 h at 22 °C and worked up as in the previous procedure. The mixture of diastereomeric complexes **3e** and **4e** thus obtained was recrystallized from Me_2CO to give 4.8 g (80%) of complex **3e**. Found (%): C, 62.39; H, 6.05; N, 8.94. $C_{32}H_{36}N_4NiO_5$. Calculated (%): C, 62.45; H, 5.90; N, 9.10.

Product **5e** · HCl (1.4 g, 84%) was obtained from complex **3e** (4.5 g, 7.3 mmol) by a procedure similar to that described above, m.p. 145—147 °C. Found (%): C, 36.55; H, 7.39; N, 12.25. $C_7H_{16}N_2O_4 \cdot HCl$. Calculated (%): C, 36.76; H, 7.49; N, 12.27. ^{1}H NMR (400 MHz, D_2O), δ: 3.39—3.48 (m, 2 H, NC$\underline{H}_2$); 3.52—3.60 (m, 2 H, NC$\underline{H}_2$CH_2O); 3.67

(dd, 1 H, β-H_a, J = 12.8 and 5.6 Hz); 3.72 (dd, 1 H, β-H_b, J = 12.8 and 10.5 Hz); 3.86—3.98 (m, 4 H, CH_2OH); 4.18 (dd, 1 H, α-H, J = 10.5 and 5.6 Hz). $[\alpha]_D^{25}$ +27.2 (*c* 0.9; 6 *N* HCl).

This work was carried out with the financial support of the Russian Foundation for Basic Research (Project No. 96-03-33424).

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Received October 30, 1996