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Pincer Ligands Based on α-Amino Acids: I. Synthesis of Polydentate Ligands from Pyrrole-2,5-dicarbaldehyde

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Abstract—New chiral pincer ligands having CH=N moieties were synthesized by condensation of 1*H*-pyrrole-2,5-dicarbaldehyde with L-methionine and L-histidine methyl esters. Their reduction under mild conditions ($NaBH_4$, –30°C) gave the corresponding amine ligands in high yields. An improved procedure for the preparation of 1*H*-pyrrole-2,5-dicarbaldehyde was proposed.

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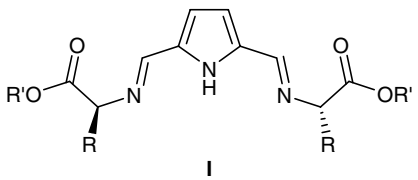
Multidentate ligands having azomethine moieties play an important role in the chemistry of coordination compounds [1]. Metal complexes derived from such ligands are structural analogs of natural metalloenzymes. Ligand environment of metal ions in active centers of many nonheme metalloenzymes is formed from functional groups of amino acids (such as histidine, lysine, cysteine, serine, etc.), and it acts as electron reservoir [2]. In the recent years, modeling of metalloenzyme active sites using di- and polynuclear transition metal complexes has become a rapidly developing field of study at the interface between coordination chemistry and enzymology [3, 4]. Most frequently, expanded porphyrins, macrocyclic Schiff bases, and peptides [4, 5] were used as ligands for such complexes,. Complexes with acyclic pincer Schiff bases have been studied to a considerably lesser extent. Synthetic approaches to such ligands have been developed [6]; however, there are almost no published data on the coordination potential of natural amino acids.

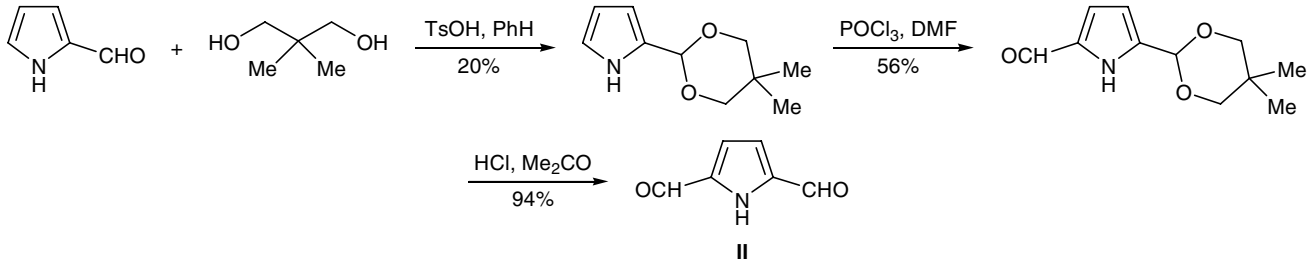


I

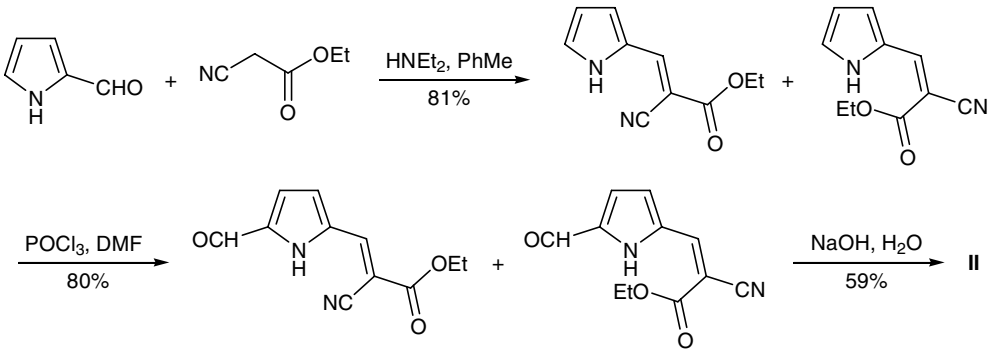
Chiral pincer ligands derived from amino acids and their metal complexes attract undoubted interest as chiral anionic and cationic receptors and sensors capable of recognizing and binding chiral substrates. The present study was aimed at synthesizing previously unknown pincer-like multidentate ligands **I** on the basis of natural amino acids, methionine and histidine.

The main building block for the synthesis of compounds like **I** is 1*H*-pyrrole-2,5-dicarbaldehyde (**II**). The chemistry of pyrrole compounds has been extensively studied [7], and several multistep syntheses of compound **II** from 2-formylpyrrole have been reported. Insofar as direct formylation of 1*H*-pyrrole-2-carbaldehyde at the 5-position cannot be effected with a high yield, the formyl group therein is preliminarily protected via transformation into cyclic acetal (Scheme 1) [8] or condensation with ethyl cyanoacetate (Scheme 2) [9], followed by formylation at C^5 according to Vilsmeier and deprotection [8, 9]. Both these procedures are characterized by poor yields of the target product (11 and 38%, respectively, calculated on the initial 1*H*-pyrrole-2-carbaldehyde); therefore, the use of compound **II** in the chemistry of Schiff bases is strongly limited [10]. We tried to improve the second procedure for the synthesis of diformyl derivative **II** from pyrrole (Scheme 3) by excluding the

Scheme 1.



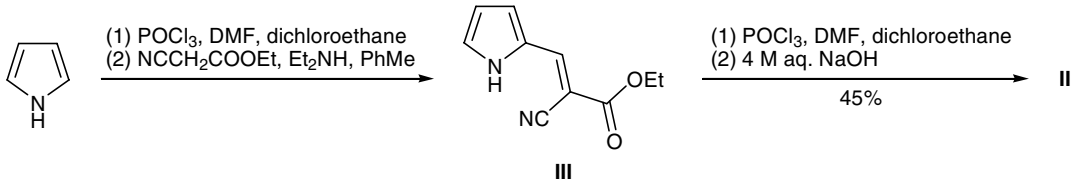
Scheme 2.



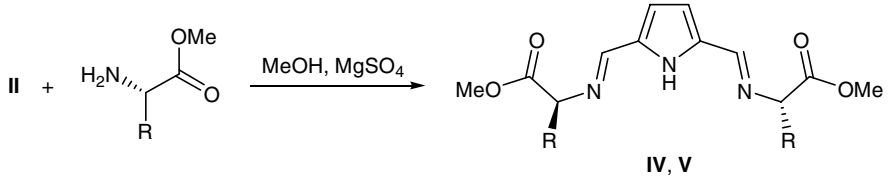
1*H*-pyrrole-2-carbaldehyde isolation step and simplifying the isolation and purification of compounds **III** and **II**. As a result, we succeeded in enhancing the preparative value of the procedure and raising the yield of the target product (each run could give about 50 g of the product in an overall yield of 45%). According to the NMR data, the isolated product is sufficiently pure, and it can be brought into further syntheses without additional purification. As followed from the IR and NMR spectra, no *Z* isomer of ethyl 2-cyano-3-(1*H*-pyrrol-2-yl)acrylate was formed (in contrast to the data of [9]), and the *E* isomer of **III** was the only product.

Dialdehyde **II** smoothly reacted with methionine and histidine methyl esters at a ratio of 1:2 in methanol at room temperature in the presence of magnesium sulfate and 3-Å molecular sieves to give the target pincer-like Schiff bases **IV** and **V** in 70–75% yield (Scheme 4). When the solvent was replaced by ethanol, the condensation was accompanied by transesterification; as a result, Schiff base **VI** was obtained as the only product in the reaction of histidine methyl ester with compound **II** (Scheme 5). The transesterification process is favored by prolonged reaction time (no less than 7 h).

Scheme 3.

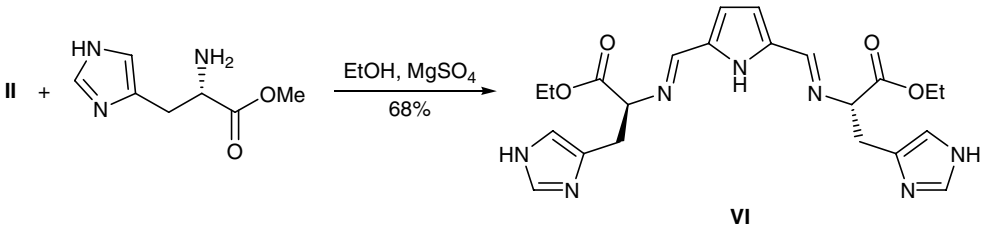


Scheme 4.

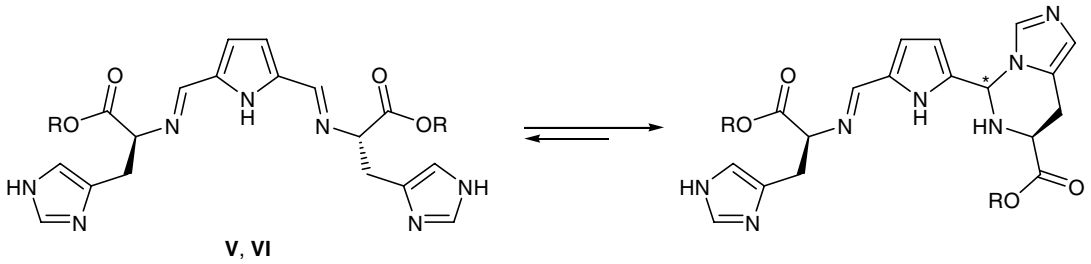


IV, R = $MeSCH_2CH_2$; **V**, R = 1*H*-imidazol-4-ylmethyl.

Scheme 5.



Scheme 6.



Schiff base **IV** is an oily substance, and histidine derivatives **V** and **VI** are low-melting solids; compounds **IV**–**VI** are intensely colored. Their structure was confirmed by the NMR and IR spectra and elemental analyses. The IR spectra of **IV**–**VI** contained absorption bands at 1733, 1736, and 1737 cm^{-1} due to stretching vibrations of the ester carbonyl groups, and azomethine C=N bonds therein gave rise to absorption at 1628, 1629, and 1631 cm^{-1}, respectively.

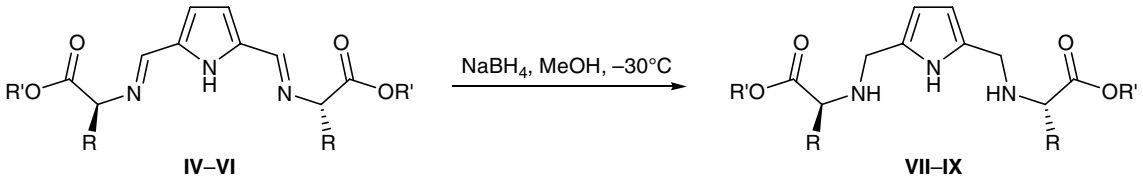
Compounds **V** and **VI** did not undergo intramolecular amination via addition of the imidazole NH group at the C=N bond (Scheme 6), as was observed previously in the synthesis of Schiff bases from histidine and acetaldehyde or ferrocenecarbaldehyde [11]. Schiff bases **IV**–**VI** are readily hydrolyzed even in the presence of traces of moisture. The C=N bond in **IV**–**VI** can be reduced under mild conditions by treatment with sodium tetrahydridoborate at a molar ratio of 1:3 in the corresponding alcohol at –30°C. In such a way we obtained amines **VII**–**IX** in high yields (Scheme 7). Ester **VII** was isolated as an oily substance, while compounds **VIII** and **IX** were low-melting solids. Their structure was confirmed by the NMR and IR spectra and elemental analyses. The IR spectra of **VII**–**IX** lacked absorption near 1630 cm^{-1}, which is typical of C=N bond vibrations in initial Schiff bases **IV**–**VI**, while the position of the ester carbonyl absorption bands did not change to an appreciable extent.

EXPERIMENTAL

The IR spectra were recorded on a Protege-460 spectrophotometer with Fourier transform. The ^1H NMR spectra were measured at 20°C on a Bruker Avance-400 spectrometer. The initial amino acid methyl esters were synthesized according to the procedures described in [12]. Dichloroethane, dimethylformamide, and methanol were distilled over calcium hydride under argon prior to use. The other reagents and solvents were used without additional purification.

Ethyl 2-cyano-3-(1*H*-pyrrol-2-yl)acrylate (III). Dimethylformamide, 56 ml (0.788 mol), was cooled below 5°C, 74 ml (0.788 mol) of $POCl_3$ was added under vigorous stirring, the cooling bath was removed, the flask was filled with argon, 350 ml of dichloroethane was added, and the mixture was cooled to 0°C.

Scheme 7.



IV, **VII**, R = $MeSCH_2CH_2$, R′ = Me; **V**, **VIII**, R = 1*H*-imidazol-4-ylmethyl, R′ = Me; **VI**, **IX**, R = 1*H*-imidazol-4-ylmethyl, R′ = Et.

A solution of 50 ml (0.716 mol) of pyrrole in 350 ml of dichloroethane was added dropwise, the mixture was heated under reflux until vigorous evolution of hydrogen chloride ceased (about 30 min) and cooled to room temperature, a solution of 465 g of $NaOAc \cdot 3H_2O$ in 600 ml of water was added, and the mixture was heated for 15–30 min under reflux. It was then cooled, the organic phase was separated, the aqueous phase was extracted with methylene chloride (400 ml), the extract was combined with the organic phase and washed with water (400 ml), and the solvent was distilled off on a rotary evaporator. The residue was dissolved in 700 ml of toluene, 90 ml (0.843 mol) of ethyl cyanoacetate and 6 ml of diethylamine were added, the mixture was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated (1–2 h) and cooled to –20°C, and the precipitate was filtered off. Yield 95.3 g (70%), light brown crystals, mp 138–140°C (from toluene); published data [9]: mp 135–138°C. IR spectrum (mineral oil), ν, cm^{-1}: 3310 (NH), 2220 (C≡N), 1700 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 t (3H, CH_3), 4.35 q (2H, CH_2), 6.41 m (1H, CH), 6.92 m (1H, CH), 7.22 m (1H, CH), 7.98 s (1H, HC=C), 9.92 s (1H, NH).

1*H*-Pyrrole-2,5-dicarbaldehyde (II). Dimethylformamide, 44 ml (0.551 mol), was cooled below 5°C, 52 ml (0.510 mol) of $POCl_3$ was added under vigorous stirring, the cooling bath was removed, the flask was filled with argon, 300 ml of dichloroethane was added, and the mixture was cooled to 0°C. A suspension of 95.3 g (0.510 mol) of compound **III** in 300 ml of dichloroethane was added, the mixture was heated under reflux until vigorous evolution of hydrogen chloride ceased (0.5–1 h) and cooled to room temperature, a solution of 250 g of $NaOAc \cdot 3H_2O$ in 400 ml of water was added, and the mixture was heated for 15–30 min under reflux. After cooling, the precipitate was filtered off and added to a solution of 200 g of NaOH in 1.6 l of water, and the mixture was heated for 3 h under reflux, cooled, neutralized with 35% sulfuric acid, and filtered. The filtrate was treated with ethyl acetate (8×1 l), and the extracts were combined, dried over Na_2SO_4, and evaporated to dryness. Yield 39.5 g (45%, calculated on the initial pyrrole), brownish powder. An analytically pure sample of compound **II** was obtained by recrystallization of the crude product from water or hexane or by Soxhlet extraction with hexane under argon. mp 120–122°C; published data [9]: mp 120–121°C. IR spectrum (mineral oil), ν, cm^{-1}: 3190 (NH), 1695 (C=O), 1670 (CH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.99 s (2H, CH), 9.76 s (2H, CHO), 10.3 br.s (1H, NH).

(*S*,*S*)-2,5-Bis(1-methoxycarbonyl-3-methylsulfanylpropyliminomethyl)pyrrole (IV). Dialdehyde **II**, 1.23 g (10 mmol), was dissolved in 100 ml of anhydrous methanol, 3.26 g (20 mmol) of freshly distilled methionine methyl ester, 2 g of magnesium sulfate, and 2 g of 3-Å molecular sieves were added, the mixture was stirred for 7 h and filtered, and the solvent was removed from the filtrate under reduced pressure. The residue was extracted with anhydrous diethyl ether, the extract was filtered and evaporated, 100 ml of hexane was added to the residue, and the oily product was separated, washed with hexane, and dried at 40°C under reduced pressure. Yield 3.01 g (75%), brown oily substance. IR spectrum (KBr), ν, cm^{-1}: 1631 (C=N), 1737 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.04 s (6H, SCH_3), 2.1–2.7 m (8H, CH_2), 3.70 s (6H, OCH_3), 4.11 t (2H, CH, J = 6.4 Hz), 6.50 s (2H, CH), 8.06 s (2H, HC=N). Found, %: C 52.41; H 6.75; N 10.03. $C_{18}H_{27}N_3O_4S_2$. Calculated, %: C 52.28; H 6.58; N 10.16.

(*S*,*S*)-2,5-Bis[2-(1*H*-imidazol-4-yl)-1-methoxycarbonylethyliminomethyl]pyrrole (V). Metallic sodium, 0.92 g (40 mmol), was dissolved in 100 ml of anhydrous methanol, 4.84 g (20 mmol) of histidine methyl ester dihydrochloride was added, the mixture was stirred for 1 h, 1.23 g (10 mmol) of dialdehyde **II**, 2 g of magnesium sulfate, and 2 g of 3-Å molecular sieves were added, the mixture was stirred for 7 h and filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with anhydrous acetone, the extract was filtered and concentrated under reduced pressure, 100 ml of diethyl ether was added, and the precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 2.98 g (70%), brown powder, mp 71–73°C. IR spectrum (KBr), ν, cm^{-1}: 1629 (C=N), 1736 (C=O). ^1H NMR spectrum (CD_3OD), δ, ppm: 3.05–3.23 m (4H, CH_2), 3.72 s (6H, OCH_3), 4.18–4.37 m (2H, CH), 6.52 s (2H, CH), 6.77 s (2H, CH), 7.56 s (2H, CH), 7.86 s (2H, HC=N). Found, %: C 56.68; H 5.73; N 22.77. $C_{20}H_{23}N_7O_4$. Calculated, %: C 56.46; H 5.45; N 23.05.

(*S*,*S*)-2,5-Bis[1-ethoxycarbonyl-2-(1*H*-imidazol-4-yl)ethyliminomethyl]pyrrole (VI) was synthesized as described above for compound **V** using 0.92 g (40 mmol) of sodium, 4.84 g (20 mmol) of histidine methyl ester dihydrochloride, 1.23 g (10 mmol) of

dialdehyde **II**, 2 g of magnesium sulfate, 2 g of 3-Å molecular sieves, and 100 ml of anhydrous ethanol. Yield 3.08 g (68%), brown powder, mp 58–60°C. IR spectrum (KBr), ν, cm^{-1}: 1628 (C=N), 1733 (C=O). ^1H NMR spectrum (CD_3OD), δ, ppm: 1.23 t (6H, CH_3, J = 7.1 Hz), 3.00–3.20 m (4H, CH_2), 4.15–4.35 m (2H, CH), 4.17 q (4H, OCH_2, J = 7.0 Hz), 6.52 s (2H, CH), 6.79 s (2H, CH), 7.58 s (2H, CH), 7.87 s (2H, HC=N). Found, %: C 58.35; H 6.12; N 21.43. $C_{22}H_{27}N_7O_4$. Calculated, %: C 58.27; H 6.00; N 21.62.

(*S*,*S*)-2,5-Bis(1-methoxycarbonyl-3-methylsulfanylpropylaminomethyl)pyrrole (VII). A solution of 2.07 g (5 mmol) of Schiff base **IV** in 75 ml of methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and for 1 h at room temperature. A solution of 0.9 g (15 mmol) of acetic acid in 10 ml of methanol was then added, and the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was extracted with diethyl ether, the extract was filtered and concentrated under reduced pressure, 100 ml of hexane was added, and the oily material was separated, washed with hexane, and dried at 45°C under reduced pressure. Yield 1.52 g (73%), light brown oily substance. IR spectrum (KBr), ν, cm^{-1}: 1733 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.60–1.95 m (4H, CH_2), 1.99 s (6H, SCH_3), 2.5 s (4H, CH_2, J = 7.2 Hz), 3.34 t (2H, CH, J = 6.8 Hz), 3.59 d (4H, CH_2N, J = 7.4 Hz), 3.65 s (6H, OCH_3), 5.77 s (2H, CH). Found, %: C 52.02; H 7.63; N 10.27. $C_{18}H_{31}N_3O_4S_2$. Calculated, %: C 51.77; H 7.48; N 10.11.

(*S*,*S*)-2,5-Bis[2-(1*H*-imidazol-4-yl)-1-methoxycarbonylethylaminomethyl]pyrrole (VIII). A solution of 2.13 g (5 mmol) of Schiff base **V** in 75 ml of methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and for 1 h at room temperature. A solution of 0.9 g (15 mmol) of acetic acid in 10 ml of methanol was then added, and the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was extracted with acetone, the extract was filtered and concentrated under reduced pressure, 100 ml of diethyl ether was added, and the precipitate was filtered off, washed with diethyl ether, and dried at 45°C under reduced pressure. Yield 1.50 g (70%), light brown powder, mp 41–43°C. IR spectrum (KBr), ν, cm^{-1}: 1735 (C=O). ^1H NMR spectrum (CD_3OD), δ, ppm: 2.96 d (4H, CH_2, J = 6.5 Hz), 3.64 s (6H, OCH_3), 3.45–3.90 m (6H, CH_2NHCH), 5.85 s (2H, CH), 6.85 s (2H, CH), 7.69 s (2H, CH). Found, %: C 56.16; H 6.55; N 22.65. $C_{20}H_{27}N_7O_4$. Calculated, %: C 55.93; H 6.34; N 22.83.

(*S*,*S*)-2,5-Bis[1-ethoxycarbonyl-2-(1*H*-imidazol-4-yl)ethylaminomethyl]pyrrole (IX) was synthesized as described above for amine **VIII** from 2.27 g (5 mmol) of Schiff base **VI** and 0.57 g (15 mmol) $NaBH_4$ in 75 ml of ethanol. Yield 1.49 g (65%), light brown powder, mp 30–40°C. IR spectrum (KBr), ν, cm^{-1}: 1730 (C=O). ^1H NMR spectrum (CD_3OD), δ, ppm: 2.08 t (6H, CH_3, J = 7.1 Hz), 2.94 d (4H, CH_2, J = 6.6 Hz), 3.45–3.90 m (6H, CH_2NHCH), 4.13 q (4H, OCH_2, J = 7.1 Hz), 5.80 s (2H, CH), 6.67 s (2H, CH), 7.41 s (2H, CH). Found, %: C 57.94; H 6.11; N 21.22. $C_{22}H_{31}N_7O_4$. Calculated, %: C 57.75; H 6.83; N 21.43.

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