

Solid-state synthesis of chiral ferrocenylaldimines from methyl esters of α -amino acid hydrochlorides in the presence of potassium carbonate

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The solid-state interaction of the three-component mixtures (ferrocenylcarbaldehyde : methyl ester of amino acid hydrochloride : K_2CO_3) afforded new optically active Schiff bases.

Key words: solid-state interaction, ferrocenylcarbaldehyde, methyl esters of amino acid hydrochlorides, Schiff bases.

The previous studies^{1,2} of solid-state reactions of aldehydes with amines and their derivatives established that salts of primary amines react in the presence of K_2CO_3 with aldehydes to form Schiff bases. In this work, we extended this convenient method of modification of the amino group to methyl esters of α -amino acid hydrochlorides. Schiff bases of amino acid esters are traditionally obtained^{3,4} from free amines in solutions. The preparation of imines from amino acid ester hydrochlorides in a solution of CH_2Cl_2 in the presence of Et_3N is described.^{5,6} For solid-state reactions, we used methyl ester hydrochlorides of six α -amino acids: L-alanine (**1a**), L-isoleucine (**1b**), L-tryptophan (**1c**), L-serine (**1d**), L-histidine (**1e**), and L-lysine (**4**) (Scheme 1).

Ferrocenecarbaldehyde (**2**) was chosen as the carbonyl component of the reaction because of both its high reactivity in solid-state reactions with amines² and the possibility to use optically active ferrocenylaldimines in the synthesis, in particular, for the asymmetrical cyclopalladation in the ferrocene series.^{7,8}

The reactions of equimolar mixtures of the starting reagents and K_2CO_3 were carried out by keeping them at room temperature with periodical stirring. The reaction course and conversion were monitored by 1H NMR spectroscopy followed by comparison of the ratio of the intensity of the signal of the aldehyde proton to the sum of integral intensities of the one-proton signals of products in the spectra of samples of the reaction mixtures dissolved in $CDCl_3$. The conversions of **2** during the solid-state reactions are presented in Table 1. As can be seen in Table 1, the reaction rate depends substantially on the nature of the amino acid and the treatment of the reaction mixture. The reactions of **1a–c** and **1e** with **2** with stirring of the reagents for three days result in the formation of the corresponding

products in high yields, whereas salts **1d** and **4** react with ferrocenecarbaldehyde, under the same conditions, very slowly. As we have previously shown, the rate of solid-state reactions of aldehydes with amines increases substantially both with heating of the reaction mixtures¹ and when a more intense mechanical action is used: stirring in a ball mill.⁹ Since heating of amino acid

Scheme 1

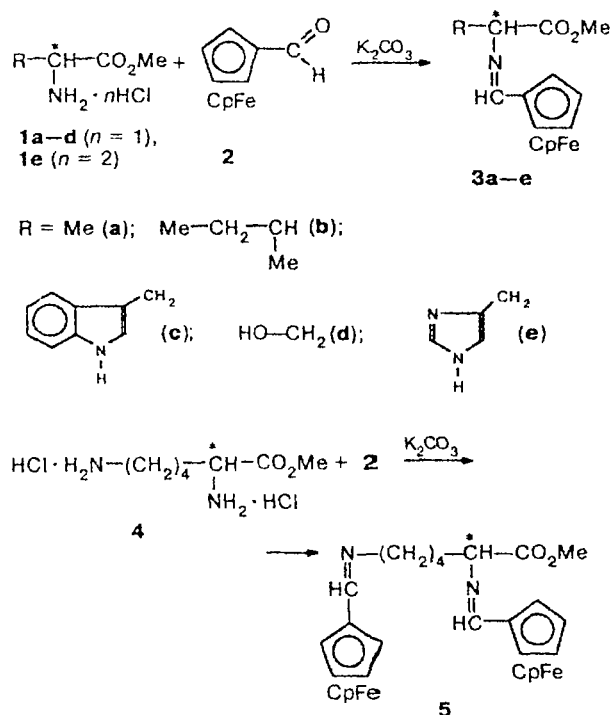


Table 1. Conversion of **2** during the reaction of **1a–e** with **4** under different reaction conditions

Product	Conversion (%)		
	Reaction in flask, 3 days	Reaction in mortar	
		3 days	5 days
3a	80 ^a	—	—
3b	99 ^a	—	—
3c	75 ^a	—	—
3d	5–20 ^b	51 ^b	96 ^c
3e	89 ^c	—	—
5	5 ^a	72 ^a	92 ^a

^a Determined from the ratio of integral intensities of aldimine and aldehyde protons in the ¹H NMR spectra.

^b Determined from the ratio of integral intensities of aldimine and aldehyde protons in the ¹H NMR spectra, cyclic products being neglected.

^c Determined from the ratio of integral intensities of aldimine and H(2) protons of cyclic products and the intensity of the aldehyde protons in the ¹H NMR spectra.

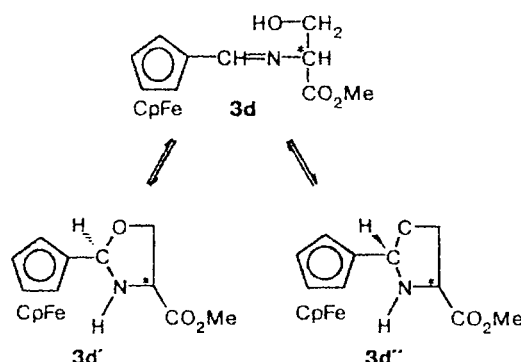
esters can result in the formation of diketopiperazines, to accelerate the reactions of serine and lysine derivatives, we used a more intense action instead of stirring of the reaction mixtures in flasks: periodical grinding with a pestle in a porcelain mortar. In fact, this resulted in considerable acceleration of the interaction and an increase in the yields of products **3d** and **5**. After the end of the reactions, CHCl₃ was added to the reaction mixtures, inorganic salts were filtered off, the solutions were concentrated, and the products were crystallized from appropriate solvents.

The ¹H NMR spectra of the reaction mixtures and final products show that aldimines **3a–c** and **5** are formed, most likely, as one geometric isomer. The reaction of **2** with hydrochloride of lysine methyl ester containing two amino groups results in the formation of bis-adduct **5**. In all stages of the reaction, the intensities of signals of both aldimine protons are equal. This indicates that the introduction of the second imine group into the molecule of intermediate monoaldimine occurs more rapidly than the formation of the latter. The absence of signals of the starting methyl ester of lysine in the spectra in all stages of the reaction of **2** with **4** suggests that the transformation of the amine salt into the free base is the rate-limiting stage of the reaction.

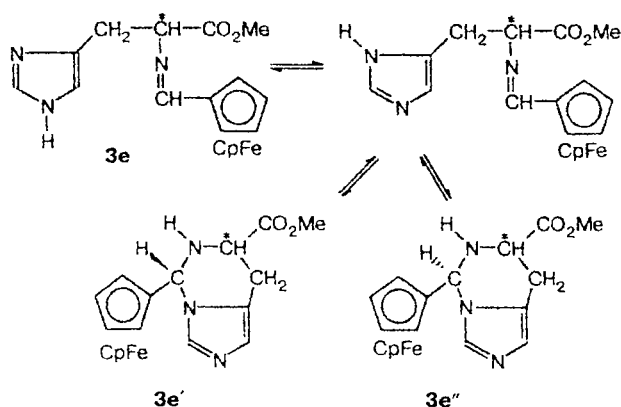
The proton spectra of the products of the solid-state reactions of **2** with **1d** and **1e** exhibit three sets of signals assigned to different protons of the C₅H₅Fe and OMe groups (Table 2). As we have previously shown,² a tautomeric equilibrium between the Schiff bases and diastereomeric oxazolidines is established in solutions of products of the solid-state reactions of ferrocene-carbaldehyde with primary β-hydroxyamines. Evidently, tautomerism is also observed in a solution of L-serine derivative **3d** (Scheme 2), and the ratio of aldimine and diastereomeric oxazolidines in a solution of CDCl₃ at 21 °C is 8 : 2 : 1.

Table 2. Chemical shifts of protons of tautomers of compounds **3d** and **3e**

Proton	3d	3d' and 3d''		3e	3e' and 3e''	
CH=N/H(2)	8.26	5.43	5.10	8.12	5.61	6.08
C ₅ H ₅	4.23	4.20	4.26	4.29	4.15	4.26
CH ₃ O	3.79	3.80	3.83	3.75	3.87	3.78
C ₃ H ₂ N ₂ (imidazole residue)				7.57, 6.89	7.32, 6.80	7.51, 6.81

Scheme 2

It can be assumed that a similar cyclization occurs in a solution of compound **3e** with the mobile hydrogen atom at the nitrogen atom of the imidazole ring. Similar cyclic products have previously been observed in the reaction of histidine with acetaldehyde.¹⁰ The authors suggested the formation of six- and seven-membered cycles due to interaction with different nitrogen atoms of the histidine ring. However, we believe that the formation of compounds with the imidazo[3,4-*c*]pyrimidine structure as two diastereomers at the newly formed chiral center (Scheme 3) is more probable. The ratio of aldimine and two diastereomeric cyclic products in a solution of CDCl₃ at 21 °C is 2.7 : 2 : 1.

Scheme 3

Both products of the solid-state reactions of **2** with **1d** and **1e** have narrow ranges of melting points and intense absorption bands of the C=N bond at 1635 cm^{-1} (for **1d**) and 1655 cm^{-1} (for **1e**) in the IR spectra (KBr). Thus, these compounds in the solid phase are Schiff bases (**3d** and **3e**), and tautomers **3d'**, **3d''** and **3e'**, **3e''**, respectively, are formed only in solutions of these aldimines.

All Schiff bases obtained are stable yellow-orange crystalline compounds, except for compound **3a**, which is stable in the presence of K_2CO_3 ; however, after isolation in the pure state from the reaction mixture, it rapidly decomposed to form unidentified products.

Experimental

^1H NMR spectra were obtained on a Bruker AMX-400 instrument in CDCl_3 . The values of optical rotation were measured on a Perkin–Elmer 141 polarimeter, and mass spectra were obtained on a Kratos-890 mass spectrometer (EI, 70 eV). Ferrocenylaldehyde was synthesized according to the previously published procedure.¹¹

Solid-state reactions of ferrocenylaldehyde 2 with hydrochlorides of amino acid methyl esters 1a–e and 4 (general procedure). Ferrocenylaldehyde (1 mmol) was mixed with the salt of amino acid ester (1 mmol) and anhydrous K_2CO_3 (2 mmol for **1a–e**; 4 mmol for **4**), and the mixture was kept in air in the dark at -20°C with periodical stirring. The reaction course was monitored by periodical recording of ^1H NMR spectra of solutions of samples of the reaction mixture in CDCl_3 . The conversion of **2** was determined by comparison of the ratio of the integral intensity of the signal of the aldehyde proton to the sum of integral intensities of one-proton signals of the reaction products (see Table 1). After the end of the interaction, CHCl_3 was added to the reaction mixture, the precipitate was filtered off, the filtrate was evaporated *in vacuo*, and the residue was crystallized from an appropriate solvent.

N-(Ferrocenylmethylidene)-L-alanine methyl ester (3a). ^1H NMR, δ : 1.49 (d, 3 H, CH_3 , $J = 6.8\text{ Hz}$); 3.76 (s, 3 H, CH_3O); 4.02 (q, 1 H, CHN, $J = 6.8\text{ Hz}$); 4.22 (s, 5 H, C_5H_5); 4.41 (m, 2 H, C_5H_4); 4.66 (m, 1 H, C_5H_4); 4.74 (m, 1 H, C_5H_4); 8.19 (s, 1 H, CH=N). MS, m/z : 299 $[\text{M}]^+$.

N-(Ferrocenylmethylidene)-L-isoleucine methyl ester (3b). Yield 0.310 g (91%), m.p. $66\text{--}68^\circ\text{C}$ (hexane), $\alpha_D^{21} 50.8^\circ$ (c 0.43). ^1H NMR, δ : 0.93 (m, 6 H, 2 CH_3); 1.13 (m, 2 H, CH_2); 2.14 (m, 1 H, CH); 3.59 (d, 1 H, CHN, $J = 8.8\text{ Hz}$); 3.73 (s, 3 H, CH_3O); 4.19 (s, 5 H, C_5H_5); 4.39 (m, 2 H, C_5H_4); 4.67 (m, 1 H, C_5H_4); 4.72 (m, 1 H, C_5H_4); 8.14 (s, 1 H, CH=N). Found (%): C, 63.08; H, 6.95; N, 3.93. $\text{C}_{18}\text{H}_{23}\text{FeNO}_2$. Calculated (%): C, 63.36; H, 6.79; N, 4.11.

N-(Ferrocenylmethylidene)-L-tryptophan methyl ester (3c). Yield 0.269 g (65%), m.p. $117\text{--}119^\circ\text{C}$ (benzene), $\alpha_D^{21} 2.5^\circ$ (c 0.63). ^1H NMR, δ : 3.30 (m, 1 H, CH_2); 3.52 (m, 1 H, CH_2); 3.74 (s, 3 H, CH_3O); 3.95 (s, 5 H, C_5H_5); 4.22 (m, 1 H, CHN); 4.32 (m, 2 H, C_5H_4); 4.56 (m, 1 H, C_5H_4);

4.61 (m, 1 H, C_5H_4); 7.05 (s, 1 H, $\text{C}_8\text{H}_6\text{N}$); 7.18 (m, 2 H, $\text{C}_8\text{H}_6\text{N}$); 7.34 (m, 1 H, $\text{C}_8\text{H}_6\text{N}$); 7.68 (m, 1 H, $\text{C}_8\text{H}_6\text{N}$); 7.89 (s, 1 H, CH=N); 8.01 (br.s, 1 H, $\text{C}_8\text{H}_6\text{N}$). Found (%): C, 66.44; H, 5.41; N, 6.37. $\text{C}_{23}\text{H}_{22}\text{FeN}_2\text{O}_2$. Calculated (%): C, 66.68; H, 5.35; N, 6.76.

N-(Ferrocenylmethylidene)-L-serine methyl ester (3d). Yield 0.266 g (89%), m.p. $152\text{--}153^\circ\text{C}$ (hexane–benzene), $\alpha_D^{21} -289^\circ$ (c 0.17). ^1H NMR, δ : 3.79 (s, 2 H, CH_3O); 3.92–4.08 (m, 3 H, CH and CH_2); 4.23 (s, 5 H, C_5H_5); 4.42 (m, 1 H, C_5H_4); 4.46 (m, 1 H, C_5H_4); 4.64 (m, 1 H, C_5H_4); 4.78 (m, 1 H, C_5H_4); 8.26 (s, 1 H, CH=N). Found (%): C, 57.21; H, 5.56; N, 4.50. $\text{C}_{15}\text{H}_{17}\text{FeNO}_2 \cdot \text{H}_2\text{O}$. Calculated (%): C, 56.80; H, 6.04; N, 4.42.

N-(Ferrocenylmethylidene)-L-histidine methyl ester (3e). Yield 0.292 (80%), m.p. $144.5\text{--}145.5^\circ\text{C}$ (benzene), $\alpha_D^{21} -168.2^\circ$ (c 0.42). Found (%): C, 59.09; H, 5.32; N, 11.20. $\text{C}_{18}\text{H}_{19}\text{N}_3\text{FeO}_2$. Calculated (%): C, 59.20; H, 5.24; N, 11.51.

Bis-N,N-(ferrocenylmethylidene)-L-lysine methyl ester (5). Yield 0.469 g (85%), m.p. $62\text{--}64^\circ\text{C}$ (hexane–benzene), $\alpha_D^{21} -78.6^\circ$ (c 0.45). ^1H NMR, δ : 1.38 (m, 2 H, CH_2); 1.72 (m, 2 H, CH_2); 1.98 (m, 2 H, CH_2); 3.46 (m, 2 H, CH_2); 3.73 (s, 3 H, CH_3O); 3.87 (m, 1 H, CHN); 4.15 (s, 5 H, C_5H_5); 4.20 (s, 5 H, C_5H_5); 4.34 (m, 2 H, C_5H_4); 4.40 (m, 2 H, C_5H_4); 4.60 (m, 2 H, C_5H_4); 4.67 (m, 1 H, C_5H_4); 4.73 (m, 1 H, C_5H_4); 8.11 (s, 1 H, CH=N). Found (%): C, 63.94; H, 6.00; N, 5.09. $\text{C}_{29}\text{H}_{32}\text{Fe}_2\text{N}_2\text{O}_2 \cdot 1/5\text{C}_6\text{H}_{14}$. Calculated (%): C, 63.69; H, 6.16; N, 4.92.

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