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Ferrocene Compounds. XXIX.* Efficient Syntheses of 1′-Aminoferrocene-1-carboxylic Acid Derivatives

*Lidija Barišić, Vladimir Rapić,** and Veronika Kovač*

Faculty of Food Technology and Biotechnology, University of Zagreb, 10000 Zagreb, Croatia

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The syntheses of 1′-aminoferrocene-1-carboxylic acid (**2a**) and its derivatives are reported. Reaction of 1′-methoxycarbonylferrocene-1-carboxylic acid with ethyl chloroformate / triethylamine / sodium azide gave methyl 1′-azidocarbonylferrocene-1-carboxylate (**4**), which was rearranged in acetic anhydride and hydrolyzed into *N*-acetyl derivative of **2a**. Azide **4** was converted into the corresponding benzyl carbamate **7**, which was hydrolyzed into acid-carbamate **9** and hydrogenated into amino acid **2a**. The crucial intermediate **4** was transformed into *tert*-butyl carbamate **10** and hydrolyzed into *N*-Boc-**2a**.

Key words: ferrocene, 1′-aminoferrocene-1-carboxylic acid, *C*-protected derivatives of, *N*-protected derivatives of.

INTRODUCTION

Organometallic moieties in metallocene derivatives, as well as in the analogues of natural α-amino acids and the derived peptides, selectively influence their physical, chemical, and biological properties.[2]

Distinction can be made between two approaches to the synthesis of such unnatural amino acids. On the one hand, amino acid side chains can be introduced or modified by reaction with a metallocene reagent. Alternatively, the α-amino acid framework can be constructed by an organometallic

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** Author to whom correspondence should be addressed. (E-mail: vrapic@pbf.hr)

reaction. The syntheses of *C*- and *N*-ferrocenyl substituted α-amino acids were performed a long time ago by "classical" methods: Schlögl reported preparation of racemic β-ferrocenylalanine, *N*-benzoyl-β-ferrocenylalanine, 5-ferrocenylmethylhydantoine, *p*-ferrocenylphenylalanine, *N*-ferrocenylglycine, and ferrocenylmethylglycine.[3] Optically active 1,1'-ferrocenylenebisalanine carrying different protecting groups and enzymatically resolved β-ferrocenylalanine were described in recent publications.[4] α-(Ferrocenoyl-methyl)- and α-[(bisferrocenoyl)methyl]glycine derivatives were prepared by S_N-transformations of α-bromoglycine derivatives by the appropriate ferrocene-containing nucleophiles.[2c] The π-electron system of aromatic α-amino acids is the target for the introduction of transition metal complex fragments forming the metallocene moieties: in this way it is possible to synthesize a number of metallocenyl-substituted alanines, tryptophanes, and tyrosines.[5]

The organometallic amino acids described can be incorporated into peptide systems, providing new biomaterials, reversible masked peptides, or efficient redox systems. Racemic or resolved β-ferrocenylalanine and other ferrocene-containing amino acids were used to prepare organometallic derivatives of prolyl-, glycyl-, tyrozyl-, and leucyl-containing peptides.[3,6] An analogue of β-ruthenocenylalanine was used for the carbodiimide synthesis of dipeptides.[7] *N*-Ferrocenylmethyl-α-amino acid derivatives undergo coupling reactions with various amino acids, and after chromatographic purification, the ferrocenylmethyl group can be eliminated with trifluoroacetic acid.[8]

Two special types of metallocene-containing amino acids are homo- **1** and heteroannularly substituted compounds **2** presented in Figure 1.

N,N-Dimethyl derivative of **1** (n = 0, m = 1) was prepared by regioselective lithiation and carboxylation of *N,N*-dimethyl(ferrocenylmethyl)amine.[9]

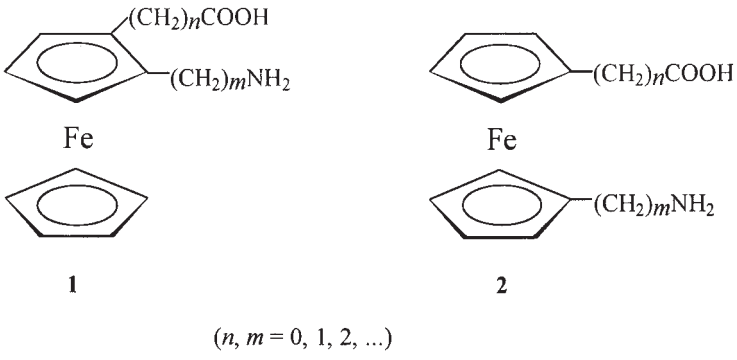
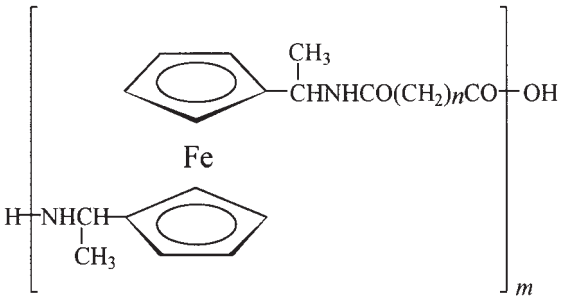


Figure 1. Two special types of metallocene-containing amino acids: homo- (**1**) and heteroannularly substituted compounds (**2**).

Hydrogenation of methyl 2-nitroferrocene-1-carboxylate gave the corresponding amino ester but the attempt to obtain the parent amino acid **1** (*n, m* = 0) by its hydrolysis resulted in decomposition.[10]

RESULTS AND DISCUSSION

During our studies of ferrocene-containing oligoamides **3** (*m* = 4–6, *n* = 0–3), we prepared the corresponding monomers – heteroannularly substituted amino amidoacids **3** (*m* = 1, *n* = 2 and 3) presented in Figure 2 – by reactions of 1,1-(1,1′-ferrocenylene)bis(ethylamine) with either succinic or glutaric anhydride in toluene. The spectral properties and solubility of these compounds indicated their zwitterionic character.[11]



3, *m* = 1–6; *n* = 0–3

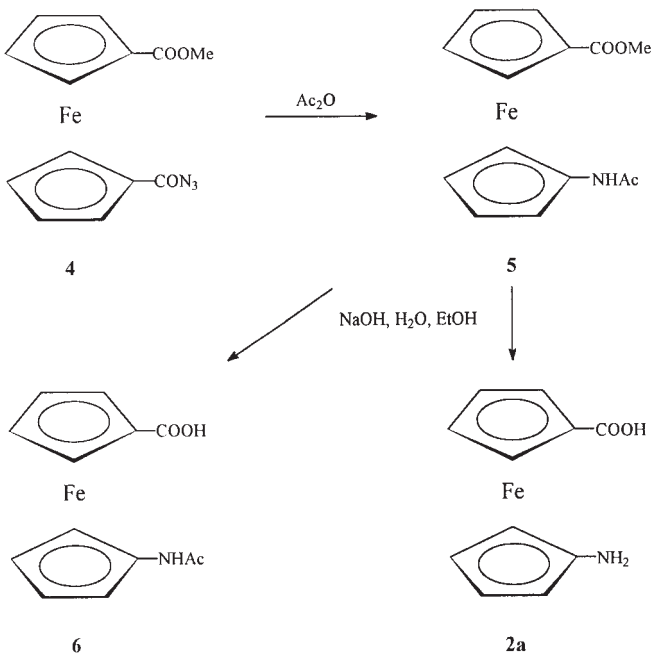
Figure 2. Heteroannularly substituted amino amidoacids **3**.

In continuation of these investigations, we planned to prepare similar amino acids **2** (*n, m* = 0, 1, 2, 3...), having in mind the possibility of their conversion into the corresponding non-natural peptides, as well as a study of their chelates,[12] depending on the length of the aliphatic side chains.

In the meantime, Butler and Quayle reported the synthesis and characterization of first "homologue" of the series **2** (*n* = *m* = 0). They prepared this compound by lithiation of 1′-amino-1-bromoferrocene and quenching with solide carbon dioxide, but its isolation was not fully successful. Treatment of the reaction mixture with methanolic hydrogen chloride resulted in the formation of methyl 1′-aminoferrocene-1-carboxylate contamined with some byproducts.[13]

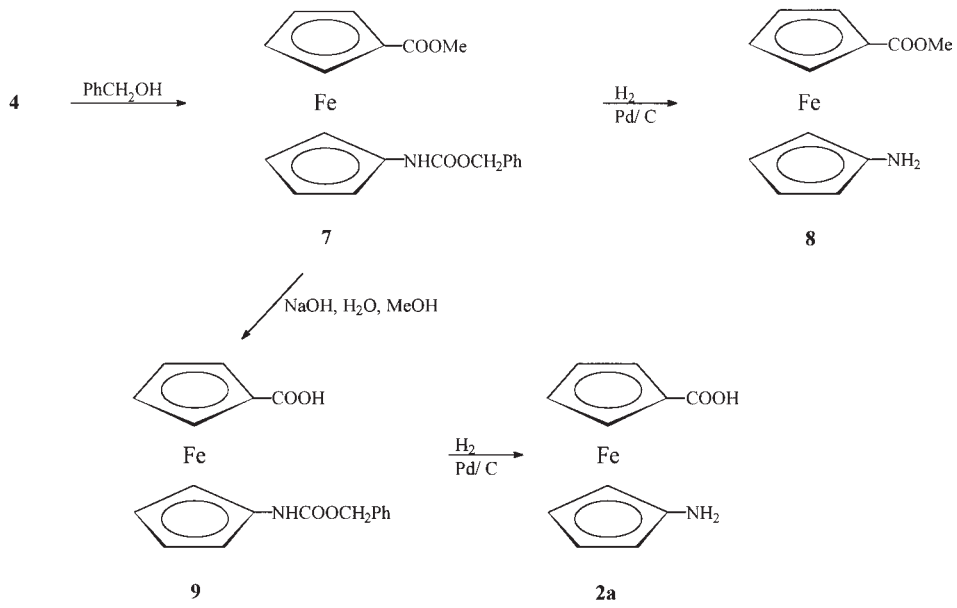
In the first attempt to prepare 1′-aminoferrocene-1-carboxylic acid (**2a**) we started from 1′-methoxycarbonylferrocene-1-carboxylic acid (obtained in

a high overall yield by oxydation of 1,1′-diacetylferrocene[14] into ferrocene-1,1′-dicarboxylic acid, its conversion into the corresponding diester,[15] and its partial hydrolysis[16]). This acid-ester was converted with ethyl chloroformate and triethylamine into mixed anhydride, which gave 73% of methyl 1′-azidocarbonylferrocene-1-carboxylate (**4**) by adding an aqueous solution of sodium azide (under the conditions for ferrocenecarbazide preparation).[17] Azide-ester **4** was rearranged and acylated by heating in acetic anhydride giving methyl 1′-acetamidoferrocene-1-carboxylate (**5**) in 42% yield. Partial hydrolysis of this amide-ester by a double molar quantity of ethanolic-aqueous solution of sodium hydroxide gave 85% of 1′-acetamidoferrocene-1-carboxylic acid (**6**). Attempts to obtain the pure title compound **2a** by refluxing **5** in a large excess of the same reagent were unsuccessful. The reaction mixture was acidified to pH = 5–7, but the amino acid desired did not precipitate. After evaporation to dryness, the obtained residue (contaminated with sodium chloride) could not be extracted by organic solvents (ether, chloroalkanes, alcohols), indicating degradation of compound **2a**. Extractions of aqueous solutions of the raw product (under either acidic or basic conditions) into diethyl ether or dichloromethane were also unsuccessful, indicating the presence of the ionic forms of 1′-aminoferrocene-1-carboxylic acid (**2a**) (Scheme 1).



Scheme 1.

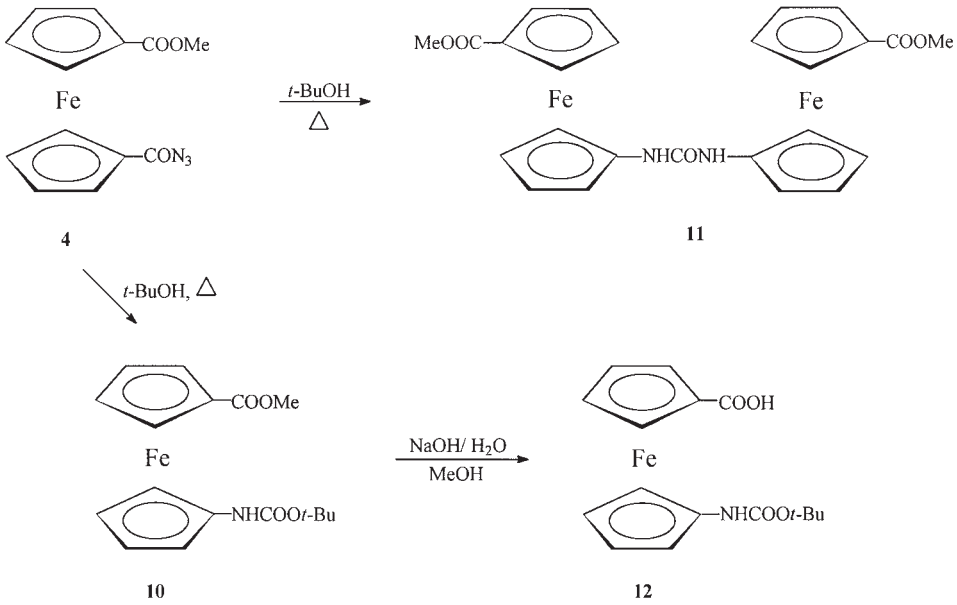
In order to overcome the encountered problems, we have applied a different strategy. By heating azide **4** in benzyl alcohol, 92% of carbamate **7** was obtained, and its hydrogenolysis by H_2 over Pd / C gave 96% of methyl 1′-aminoferrocene-1-carboxylate (**8**), exhibiting the same spectra as the authentic specimen.[13] Hydrolysis of ester-carbamate **7** with a little molar excess of sodium hydroxide in ethanolic-aqueous solution gave 93% of benzyl 1′-carboxy-1-ferrocenecarbamate (**9**). Under circumstances similar to those for conversion **7**→**8**, compound **9** was hydrogenolyzed into 94% of the desired amino acid **2a** in the form of orange crystals. The compound obtained exhibited similar spectra as the authentic specimen,[13] but upon standing its colour changed to a darker hue. The TLC spots and NMR signals broadened and multiplied, indicating its degradation or polymerization into the corresponding peptide (Scheme 2).



Scheme 2.

Another attempt was made to obtain 1′-aminoferrocene-1-carboxylic acid (**2a**) in the form of the stable *N*-Boc-derivative. By heating the crucial intermediate **4** in *tert*-butyl alcohol it was converted into carbamate **10**, followed by a small amount (according to TLC of reaction mixture) of symmetric urea derivative **11**. This byproduct was presumably formed by thermolytical cleavage and dimerization of carbamate **10**. The degree of contamination by this byproduct depends on the reaction conditions: refluxing of the reaction mix-

tures for 3 hours gave 34% of **10** and 16% of **11** and heating at 60° C for 2 hours resulted in 63% of **10** and 10% of **11**. Hydrolysis of carbamate-ester **10** by an equimolar amount of sodium hydroxide in aqueous ethanol gave 90% of *tert*-butyl 1′-carboxy-1-ferrocenecarbamate (**12**).



Scheme 3.

EXPERIMENTAL

Melting points were determined with a Buechi apparatus. The IR spectra were recorded for KBr pellets or CH_2Cl_2 solutions with a Bomem MB 100 mid FT IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian EM 360 or Varian Gemini 300 spectrometer with tetramethylsilane as internal standard. Products were purified by preparative thin layer chromatography on silica gel (Merck, Kieselgel 60 HF_{254}) using dichloromethane / ethyl acetate and dichloromethane / methanol mixtures and/or by recrystallization from (aqueous) ethanol.

Oxidation of 1,1′-diacetylferrocene[14] with bromine in an aqueous-dioxane solution of sodium hyroxide gave 75% of ferrocene-1,1′-dicarboxylic acid,[15] which was converted into 83% of dimethyl ferrocene-1,1′-dicarboxylate. Partial hydrolysis of this diester gave 1′-methoxycarbonylferrocene-1-carboxylic acid in 73% yield.[16]

Spectral assignment of the compounds prepared was achieved by comparison with the recorded spectra of methyl ferrocenecarboxylate and ferrocenecarbazide, as

well as of methyl 1′-aminoferrocene-1-carboxylate and 1′-aminoferrocene-1-carboxylic acid described in Ref. 13.

Methyl ferrocenecarboxylate.[19] – IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 1711 s (C=O, $COOCH_3$); ^1H NMR spectrum ($CDCl_3$) δ/ppm: 3.80 (s, 3 H, $COOCH_3$), 4.20 (s, 5 H, Fc* unsubst. ring), 4.39 (t, 2 H, H-3 H-4, 1.8 Hz, Fc), 4.80 (t, 2 H, H-2 H-5, 1.8 Hz, Fc); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 51.36 ($COOCH_3$), 69.57 (Fc unsubst. ring), 69.93 (C-3 C-4, Fc), 70.09 (C-1, Fc), 71.10 (C-2 C-5, Fc), 171.10 ($COOCH_3$).

Ferrocenecarbazide.[17] – IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 2136 s (N_3), 1683 s (C=O, CON_3); ^1H NMR spectrum ($CDCl_3$) δ/ppm: 4.27 (s, 5 H, Fc unsubst. ring), 4.52 (s, 2 H, H-3′ H-4′, Fc), 4.83 (s, 2 H, H-2′ H-5′, Fc); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 70.10 (Fc unsubst. ring), 70.24 (C-3′ C-4′, Fc), 72.0 (C-1′, Fc) 72.55 (C-2′ C-5′, Fc), 176.23 (CON_3).

*Methyl 1′-Azidocarbonylferrocene-1-carboxylate (**4**)*

1′-Methoxycarbonylferrocene-1-carboxylic acid (1.2 g, 4.2 mmol) was suspended in water (1 ml) and sufficient acetone was added to complete the solution. After cooling to 0 °C, triethylamine (485 mg, 4.8 mmol) in acetone (8 ml) was added. While maintaining the temperature at 0 °C, a solution of ethyl chloroformate (579 mg, 5.3 mmol) in the same solvent (2.2 ml) was added and the mixture was stirred for 30 min. at 0 °C. After that, a solution of sodium azide (417 mg, 6.3 mmol) in water (1.5 ml) was added. The mixture was stirred for 1 hour (0 °C), poured into excess of ice water, and extracted with dichloromethane. The extracts were washed with a 5% aqueous solution of $NaHCO_3$, saturated solution of NaCl, dried over Na_2SO_4 and evaporated *in vacuo* at room temperature to dryness to leave red crystals of **4** (947 mg, 73%). m. p. 101–102 °C.

IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 2138 s (N_3), 1717 s (C=O, $COOCH_3$), 1687 s (C=O, CON_3); ^1H NMR spectrum ($CDCl_3$) δ/ppm: 3.83 (s, 3 H, $COOCH_3$), 4.45 (s, 2 H, H-3 H-4, Fn*), 4.54 (s, 2 H, H-3′ H-4′, Fn), 4.85 (s, 2 H, H-2 H-5, Fn), 4.87 (s, 2 H, H-2′ H-5′, Fn); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 51.59 ($COOCH_3$), 71.55 (C-3 C-4, Fn), 71.81 (C-3′ C-4′, Fn), 72.72 (C-2 C-5, Fn), 73.04 (C-1, Fn), 73.66 (C-2′ C-5′, Fn), 74.07 (C-1′, Fn), 170.29 ($COOCH_3$), 175.90 (CON_3).

Anal. Calcd. for $C_{13}H_{11}N_3O_3Fe$ (M_r = 313.1): C 49.87, H 3.54, 13.42%; found C 49.59, H 3.55, N 13.27%.

*Methyl 1′-Acetamidoferrocene-1-carboxylate (**5**)*

A solution of azide-ester **4** (947 mg, 3 mmol) in acetic anhydride (18 ml) was heated at 80 °C for 8 hours. After cooling, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with a 5% aqueous solution of $NaHCO_3$, saturated solution of NaCl, dried with Na_2SO_4 and evaporated to dryness giving a red oil; TLC-purification with dichloromethane / ethyl acetate (5 : 1) gave orange crystalls (380 mg, 42%). m. p. 108.5–109 °C.

IR spectrum (KBr) ν_{max}/cm^{-1}: 3280 m (N–H), 1713 s (C=O, $COOCH_3$), 1660 s (C=O, $COCH_3$); ^1H NMR spectrum ($CDCl_3$) δ/ppm: 2.09 (s, 3H, $COCH_3$), 3.80 (s, 3H, $COOCH_3$), 4.03 (s, 2 H, H-3′ H-4′, Fn), 4.40 (s, 2H, H-3 H-4, Fn), 4.63 (s, 2 H, H-2′

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* Fc, ferrocenyl; Fn, 1,1′-ferrocenylene.

H-5′, Fn), 4.80 (s, 2 H, H-2 H-5, Fn), 7.40 (bs, 1H, NH); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 23.60 ($COCH_3$), 51.42 ($COOCH_3$), 62.98 (C-3′ C-4′, Fn), 66.04 (C-3 C-4, Fn), 70.86 (C-2′ C-5′, Fn), 72.15 (C-2 C-5, Fn), 71.85 (C-1, Fn), 95.05 (C-1′, Fn), 168.83 ($COCH_3$), 171.69 ($COOCH_3$).

Anal. Calcd. for $C_{14}H_{15}NO_3Fe$ (M_r = 301.1): C 55.84, H 5.02, N 4.65%; found C 60.01, H 5.29, N 4.37%.

*Hydrolysis of Methyl 1′-Acetamidoferrocene-1-carboxylate (**5**)*

Procedure A

A solution of amide-ester 5 (400 mg, 1.5 mmol) in 0.1 M ethanolic solution of NaOH (29 ml, 2.9 mmol) containing four drops of water was refluxed for 4 hours. Thereupon, the reaction mixture (pH ≈ 9) was acidified with 0.1 M HCl / EtOH (6.2 ml, 2.9 mmol) to pH ≈ 3–4 and evaporated to dryness to leave a brown residue; this was dissolved in ethanol and chromatographed on TLC-plates with CH_2Cl_2 / MeOH (9 : 1) giving orange crystals of 1′-acetamidoferrocene-1-carboxylic acid (6) (322 mg, 85%). m. p. > 210 °C.

IR spectrum (KBr) ν_{max}/cm^{-1}: 3100 b (OH, COOH), 3264 m (N–H), 1657 s (C=O, COOH), 1657 s (C=O, $COCH_3$); ^{1}H NMR spectrum ($CDCl_3$) δ/ppm: 1.97 (s, 3H, $COCH_3$), 3.94 (s, 2 H, H-3′ H-4′, Fn), 4.20 (s, 2H, H-3 H-4, Fn), 4.56 (s, 2 H, H-2′ H-5′, Fn), 4.63 (s, 2 H, H-2 H-5, Fn), 9.35 (s, 1H, NH); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 23.53 ($COCH_3$), 62.05 (C-3′ C-4′, Fn), 65.49 (C-3 C-4, Fn), 71.08 (C-2′ C-5′, C-2 C-5, Fn), 67.74 (C-1, Fn), 96.17 (C-1′, Fn), 168.19 ($COCH_3$), 171.34 (*C*OOH).

Anal. Calcd. for $C_{13}H_{13}NO_3Fe$ (M_r = 287.1): C 54.39, H 4.56, N 4.88%; found C 54.53, H 4.31, N 5.05%.

Procedure B

In a similiar way as described under A, an ethanolic-aqueous solution of amide-ester **5** was refluxed with a large molar excess of NaOH for 4 hours. The reaction solution was acidified to pH ≈ 6–7 and evaporated to dryness. The reaction product (contamined with NaCl) could not be extracted with organic solvents (ethers, chloroalkanes, alcohols). Extractions of aqueous solutions of the raw product (under either acidic or basic conditions) into diethyl ether or dichloromethane were also unsuccessful.

*Benzyl 1′-Methoxycarbonyl-1-ferrocenecarbamate (**7**)*

A solution of methyl 1′-azidocarbonylferrocene-1-carboxylate (**4**) (600 mg, 1.9 mmol) in benzyl alcohol (10 ml) was heated in an oil-bath at 100 °C for 30 min. Alcohol was removed *in vacuo* and the residual dark oil was purified by TLC with dichloromethane, giving orange crystals (695 mg, 92%). m.p. 115–116 °C.

IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 3428 m (N–H), 1737 s (C=O, $COOCH_3$), 1712 s (C=O, $COOCH_2Ph$); ^{1}H NMR spectrum ($CDCl_3$) δ/ppm: 3.77 (s, 3H, $COOCH_3$), 4.0 (s, 2 H, H-3′ H-4′, Fn), 4.38 (s, 2H, H-3 H-4, Fn), 4.54 (s, 2 H, H-2′ H-5′, Fn), 4.81 (2H, H-2 H-5, Fn), 5.16 (s, 2H, OCH_2), 6.12 (s, 1H, NH), 7.39 (s, 5H, phenyl); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 51.51 ($COOCH_3$), 62.03 (C-3′ C-4′, Fn), 65.92 (C-3 C-4,

Fn), 66.90 (O*C*H_2), 70.95 (C-2′ C-5′, Fn), 72.04 (C-2 C-5, Fn), 72.32 (C-1, Fn), 96.15 (C-1′, Fn), 128.12 (C-4, phenyl), 128.17 (C-2 C-6, phenyl), 128.46 (C-3 C-5, phenyl), 135.92 (C-1, phenyl), 153.8 (*C*OOCH_2Ph), 171.42 (*C*OOCH_3).

Anal. Calcd. for $C_{20}H_{19}NO_4Fe$ (M_r = 393.2): C 61.09, H 4.87, N 3.56%; found C 61.25, H 5.05, N 3.28%.

*Methyl 1′-Aminoferrocene-1-carboxylate (**8**)*

A solution of carbamate **7** (200 mg, 0.5 mmol) in abs. ethanol was hydrogenolyzed in Paar apparatus in the presence of Pd/ C for 12 hours. The usual work up gave unstable orange oil (126 mg, 96%), which solidified upon standing in refrigerator, exhibiting the same spectra as the authentic specimen.[13]

*Benzyl 1′-Carboxy-1-ferrocenecarbamate (**9**)*

Procedure A

Ester-carbamate 7 (400 mg, 1 mmol) was dissolved in methanol (5 ml) and an aqueous solution (1 ml) of sodium hydroxide (48 mg, 1.2 mmol) was added. After refluxing for 45 min, the reaction mixture was diluted with water and washed with diethyl ether. The aqueous layer was acidified, extracted with dichloromethane, washed with saturated aqueous solution of NaCl, dried with Na_2SO_4 and evaporated to dryness; orange crystals (360 mg, 93%). m.p. 133–134 °C.

IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 3426 m (N–H), 3100 b (OH, COOH), 1704 s (C=O, COOCH_2Ph), 1673 s (C=O, COOH); ^{1}H NMR spectrum ($CDCl_3$) δ/ppm: 3.94 (s, 2 H, H-3′ H-4′, Fn), 4.38 (s, 2H, H-3 H-4, Fn), 4.41 (s, 2 H, H-2′ H-5′, Fn), 4.88 (2H, H-2 H-5, Fn), 5.22 (s, 2H, OCH_2), 7.38 (s, 5H, phenyl), 7.94 (s, 1H, NH); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 61.50 (C-3′ C-4′, Fn), 65.75 (C-3 C-4, Fn), 66.70 (O*C*H_2), 71.53 (C-2′ C-5′, Fn), 72.11 (C-2 C-5, Fn), 72.40 (C-1, Fn), 96.20 (C-1′, Fn), 128.14 (C-4, phenyl), 128.16 (C-2 C-6, phenyl), 128.46 (C-3 C-5, phenyl), 135.95 (C-1, phenyl), 154.01 (*C*OOCH_2Ph), 171.40 (*C*OOCH_3).

Anal. Calcd. for $C_{19}H_{17}NO_4Fe$ (M_r = 379.2): C 60.18, H 4.52, N 3.69%; found C 60.30, H 4.31, N 3.88%.

Procedure B

To avoid the laboriuos and time consuming evaporation of benzyl alcohol, the partially evaporated solution obtained in the procedure describing the synthesis of carbamate **7** was hydrolyzed as described under A. After dissolution in water, the unreacted carbamate **7** and benzyl alcohol were removed by extraction with dichloromethane and, treated in the usual manner, gave 82% of acid-carbamate **9**. The m. p.′s and spectra of samples obtained under A and B were identical.

*1′-Aminoferrocene-1-carboxylic Acid (**2a**)*

Hydrogenolysis of acid-carbamate **9** under the same conditions as described in the procedure describing the synthesis of carboxylate **8** gave an unstable orange product (180 mg, 94%) exhibiting a similar ^{1}H NMR spectrum as the authentic specimen.[13]

tert-*Butyl 1′-Methoxycarbonyl-1-ferrocenecarbamate (**10**)*

Procedure A

A solution of azide-ester **4** (300 mg, 1 mmol) in dry *tert*-butyl alcohol (10 ml) was refluxed for 3 hours and evaporated to dryness. Purification by TLC with dichloromethane and ethyl acetate gave orange crystals of carbamate **10** (117 mg, 34%). m.p. 121.5–122.5 °C followed by *sym*-urea derivative **11** (83 mg, 16%). m.p. 160–160.5 °C.

10. – IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 3433 m (N–H), 1713 s (C=O, $COOCH_3$ and COO*t*-Bu); ^{1}H NMR spectrum ($CDCl_3$) δ/ppm: 1.50 (s, 9H, $C(CH_3)_3$), 3.81 (s, 3H, $COOCH_3$), 3.99 (s, 2 H, H-3′ H-4′, Fn), 4.39 (s, 2H, H-3 H-4, Fn), 4.51 (s, 2 H, H-2′ H-5′, Fn), 4.81 (2H, H-2 H-5, Fn), 5.91 (bs, 1H, NH); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 28.16 C(*C*H$_3$)$_3$, 51.53 (COO*C*H$_3$), 61.88 (C-3′ C-4′, Fn), 65.73 (C-3 C-4, Fn), 70.80 (C-2′ C-5′, Fn), 71.98 (C-2 C-5, Fn), 72.46 (C-1, Fn), 81.98 (*C*(CH$_3$)$_3$), 96.74 (C-1′, Fn), 152.94 (*C*OOC(CH$_3$)$_3$), 171.43 (*C*OOCH$_3$).

Anal. Calcd. for $C_{17}H_{21}NO_4Fe$ (M_r = 359.2): C 56.84, H 5.89, N 3.90%; found C 57.07, H 6.03, N 3.81%.

11. – IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 3420 m (N–H), 1708 s (C=O, $COOCH_3$ and NHCONH); ^{1}H NMR spectrum (DMSO) δ/ppm: 3.66 (s, 3H, $COOCH_3$), 3.97 (s, 2 H, H-3′ H-4′, Fn), 4.42 (s, 2H, H-3 H-4, Fn), 4.58 (s, 2 H, H-2′ H-5′, Fn), 4.70 (2H, H-2 H-5, Fn), 7.70 (bs, 1H, NH); ^{13}C NMR, APT spectrum (DMSO) δ/ppm: 51.25 (COO*C*H$_3$), 60.45 (C-3′ C-4′, Fn), 64.98 (C-3 C-4, Fn), 70.31 (C-2′ C-5′, Fn), 71.50 (C-1, Fn), 72.02 (C-2 C-5, Fn), 99.34 (C-1′, Fn), 152.28 (NH*C*ONH), 170.50 (*C*OOCH$_3$).

Anal. Calcd. for $C_{25}H_{24}N_2O_5Fe_2$ (M_r = 544.2): C 55.18, H 4.45, N 5.15%; found C 55.32, H 4.66, N 5.29%.

Procedure B

The same mixture as described under A was heated at 60 °C for 2 hours. After TLC purification, 72.3 mg (63%) of **10** and 18 mg (10%) of **11** were obtained.

tert-*Butyl 1′-Carboxy-1-ferrocenecarbamate (**12**)*

In a similar way as described in Procedure B for the synthesis of compound **9**, carbamate-ester **10** was hydrolyzed with an equimolar amount of sodium hydroxide in aqueous methanol. After work up, orange crystals of **12** (234 mg, 90%, m. p. 145.5–146 °C) were obtained.

IR spectrum (CH_2Cl_2) ν_{max}/cm^{-1}: 3430 m (N–H), 3000 b (OH, COOH), 1699 s (C=O, COO*t*-Bu), 1677 s (C=O, COOH); ^{1}H NMR spectrum ($CDCl_3$) δ/ppm: 1.66 (s, 9H, $C(CH_3)_3$), 3.99 (s, 2 H, H-3′ H-4′, Fn), 4.42 (s, 2H, H-3 H-4, Fn), 4.60 (s, 2 H, H-2′ H-5′, Fn), 4.96 (s, 2H, H-2 H-5, Fn), 8.67 (bs, 1H, NH); ^{13}C NMR, APT spectrum ($CDCl_3$) δ/ppm: 28.28 C(*C*H$_3$)$_3$, 60.26 (C-3′ C-4′, Fn), 65.23 (C-3 C-4, Fn), 71.19 (C-2′ C-5′, Fn), 71.53 (C-2 C-5, Fn), 73.02 (C-1, Fn), 81.98 (*C*(CH$_3$)$_3$), 98.80 (C-1′, Fn), 155.34 (*C*OOC(CH$_3$)$_3$), 175.54 (*C*OOH).

Anal. Calcd. for $C_{16}H_{19}NO_4Fe$ (M_r = 345.2): C 55.67, H 5.55, N 4.06%; found C 55.91, H 5.31, N 3.81%.

CONCLUSION

Rational and convenient syntheses of heteroannularly substituted 1′-aminoferrocene-1-carboxylic acid (**2a**), as well as its *C*-protected (ester) and *N*-protected stable derivatives and precursors (*N*-acetyl, *N*-Boc, *N*-Cbz), using simple reactions, are described. It was shown that the amino acid obtained has a zwitterionic character. This compound is fairly unstable and upon standing underwent degradation or polymerization into the corresponding peptide.

Our preliminary experiments demonstrated that the procedure presented in Scheme 3 could be applied as a general method for preparation of the amino acids of type 2 (n, m = 1, 2, and 3).[18]

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SAŽETAK

Djelotvorna priprava derivata 1′-aminoferocen-1-karboksilne kiseline

Lidija Barišić, Vladimir Rapić i Veronika Kovač

Opisana je priprava 1′-aminoferocen-1-karboksilne kiseline (**2a**) i njezinih derivata. Reakcijom 1′-metoksi-karbonilferocen-1-karboksilne kiseline s etil-klorformijatom, trietilaminom i natrijevim azidom nastaje 1′-azido-karbonilferocen-1-karboksilat (**4**); međuprodukt dobiven pregradnjom toga spoja u acetanhidridu hidrolizira u *N*-acetilni derivat naslovne aminokiseline. Azid **4** pretvoren je u odgovarajući benzil-karbamat **7** koji je potom hidroliziran u kiselinu-karbamat **9** i hidrogeniran u aminokiselinu **2a**. Ključni međuprodukt **4** preveden je u *tert*-butil-karbamat **10** i hidroliziran u *N*-Boc-**2a**.