PREPARATION OF 1'- AND 2-SUBSTITUTED FERROCENYLALANINE DERIVATIVES

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Synthesis of N-formyl derivatives of racemic 1,1'-ferrocenedialanine, 1,2-ferrocenedialanine, and 1'-carboxyferrocenylalanine is described. The synthesis started from 1,1'-,1,2-bis(hydroxymethyl)ferrocene, and methyl 1'-(hydroxymethyl)ferrocenecarboxylate, respectively.

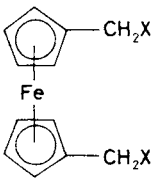
3-Ferrocenylalanine was prepared already previously by the so-called formamidomalonate method, starting from chloromethylferrocene[1] or ferrocenylmethyltrimethylammonium iodide[2,3], or by the so-called azlactone method with ferrocenecarboxaldehyde as the starting compound[1,2,4]. The former method has proven to be more successful and has also been utilized in the synthesis of (η^4-cyclobutadienyliron tricarbonyl)alanine[5]; the azlactone method, on the other hand, was used in the preparation of (η^5-cyclopentadienylmanganese tricarbonyl)alanine[5]. Preparation of the optically active 3-ferrocenylalanine and its peptide derivatives has been described in one of our previous papers[6]. The study of biological activity of 3-ferrocenylalanine[7] and some peptides derived from it[8,9] afforded new information about the drug-receptor interaction and has shown that properties of some peptides are modified by the cylindrical shape of the ferrocene moiety.

The aim of this study has been the preparation of 1'- or 2-substituted derivatives of ferrocenylalanine which might serve as starting compounds for the synthesis of interesting cyclic peptides.

For the preparation of 1'- and 2-substituted ferrocenylalanine derivatives we have chosen the formamidomalonate method (which appeared to be the method of choice also in the case of 3-ferrocenylalanine) because of the higher stability of 1,1'-bis(chloromethyl)ferrocene[10] and high yields of nucleophilic substitution reactions with this derivative[10,11]. The reactivity of methyl 1'-(chloromethyl)ferrocenecarboxylate in nucleophilic substitution reactions has been studied by us previously[12]. The required chloromethylferrocene derivatives were prepared by pyridine-catalyzed reaction of the corresponding hydroxymethyl derivatives with phosphorus trichloride in anhydrous tetrahydrofuran. No reaction was observed in the absence of pyridine The preparation of chloromethylferrocene derivatives appeared to be extremely sensitive to moisture, particularly in the case of 1,1'-bis(chloromethyl)ferrocene: already traces of moisture caused separation of a red viscous phosphorus-containing

compound which on boiling with sodium hydroxide liberated the starting 1,1'-bis(hydroxymethyl)ferrocene. We assume that the compound was a phosphite. In these unsuccessful experiments we also observed the formation of 2-oxa[3]ferrocenophane. Thanks to traces of moisture, the preparation of methyl 1'-(chloromethyl)ferrocenecarboxylate was accompanied with dimethyl 1,1'-oxymethylenediferrocenecarboxylate.

Sodium salt of diethyl formamidomalonate was smoothly alkylated with the starting chloromethyl derivatives of ferrocene *Ia–IIIa* in anhydrous dimethylformamide in the yields of 74% (*Ib*), 60% (*IIb*) and 95% (*IIIb*). Attempts to prepare compound *Ib* from the starting 1,1'-bis(hydroxymethyl)ferrocene and diethyl formamidomalonate with HBF_4 or Ca^{2+}-montmorillonite as catalyst under conditions described for reactions with hydroxymethylferrocene[13,14] were unsuccessful and led in both cases to 2-oxa[3]ferrocenophane. The attempted HBF_4-catalyzed synthesis of *IIIb* from methyl 1'-(hydroxymethyl)ferrocenecarboxylate and diethyl formamidomalonate resulted in isolation of the starting compound.

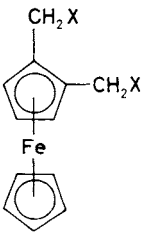


Ia, X = Cl

Ib, X = $C(COOC_2H_5)_2$ / NHCHO

Ic, X = $C(COOH)_2$ / $NHCHO \cdot H_2O$

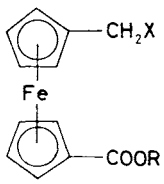
Id, X = CHCOOH / NHCHO



IIa, X = Cl

IIb, X = $C(COOC_2H_5)_2$ / NHCHO

IIc, X = CHCOOH / NHCHO



IIIa, X = Cl ; R = CH_3

IIIb, X = $C(COOC_2H_5)_2$; R = CH_3 / NHCHO

IIIc, X = CHCOOH ; R = H / NHCHO

Alkaline hydrolysis of compounds *Ib–IIIb* proceeded smoothly, however, isolation of the arising acids encountered difficulties. Hydrolysis of the 1,1'-derivative *Ib* afforded, after acidification, the crude acid as a grayish yellow product. Upon crystallization, the product suffered partial decarboxylation as evidenced by elemental analysis of the crystallizate. Compound *Ic* was finally obtained by careful acidification of the hydrolysis product with 10% hydrochloric acid: the substance was precipitated at pH 4, immediately filtered and washed with a small amount of ice-cold water (without crystallization).

The attempted preparation of 1,1'-ferrocenedialanine by heating *Ic* in 6 mol l^{-1} HCl was unsuccessful. Although the decarboxylation and hydrolysis took place,

the product decomposed in the acid medium and, after neutralization, could not be separated from the inorganic salts. Also, attempts to purify the product by chromatography or via the hydrochloride (which, unlike the inorganic salts present, might be soluble in anhydrous ethanol) gave no positive results. Interestingly, in the attempted one-step preparation of 1,1′-ferrocenedialanine by acid hydrolysis of *Ib*, the compound was recovered unchanged from the reaction mixture.

We prepared finally the compound *Id* by a method[15] consisting in alkaline hydrolysis, decarboxylation in a neutral medium and protection of the amino group of 1,1′-ferrocenedialanine by formylation with a mixture of formic acid and acetic anhydride. The obtained formyl derivative *Id* was much less soluble in water and could be chromatographed on silica gel in a water–formic acid mixture (20 : 1) as well as crystallized from aqueous formic acid. The above-mentioned method was also applied for the preparation of compounds *IIb* and *IIIb*, however, in the case of the 1,2-compound the formyl derivative *IIc* was obtained in only very low yield and hydrolyzed during chromatography or crystallization. Compound *IIIb* was obtained in high yield (79%) but decomposed easily on crystallization.

We can conclude that of 1,1′- and 1,2-disubstituted ferrocenedialanine derivatives only 1,1′-ferrocenedialanine and, if a better synthetic access is found, also 1′-carboxyferrocenealanine might find a more general utilization in the synthesis of peptides.

EXPERIMENTAL

^{1}H NMR spectra were measured on a Tesla BS-487A (80 MHz) instrument in deuteriochloroform (98% isotopic purity) with tetramethylsilane as internal standard. Melting points were determined on a Kofler block and are uncorrected. All the syntheses were carried out under nitrogen. The following compounds were prepared according to the given references: 1,1′-bis(hydroxymethyl)ferrocene[10], 1,2-bis(hydroxymethyl)ferrocene[16], methyl 1′-(hydroxymethyl)ferrocenecarboxylate[12], and diethyl formamidomalonate[17].

Tetraethyl 2,2′-Bis(formylamino)-2,2′-(1,1′-ferrocenediyldimethylene)dimalonate (*Ib*)

Freshly distilled phosphorus trichloride (0·32 ml) was added dropwise to a stirred solution of 1,1′-bis(hydroxymethyl)ferrocene (1·0 g; 4·1 mmol) and anhydrous pyridine (0·2 ml) in anhydrous tetrahydrofuran (25 ml). After stirring at room temperature for 3 h, the obtained solution of 1,1′-bis(chloromethyl)ferrocene (*Ia*) was decanted. The remaining phosphorus acid was then washed with anhydrous tetrahydrofuran (15 ml), the tetrahydrofuran solutions were combined and used in the subsequent reaction.

Sodium hydride (0·32 g; 13·4 mmol) was added under stirring to a solution of diethyl formamidomalonate (2·75 g; 13·4 mmol) in anhydrous dimethylformamide (20 ml). After the hydrogen evolution had ceased, the solution of 1,1′-bis(chloromethyl)ferrocene prepared as described above was added. The reaction mixture was stirred at 80°C for 19 h, filtered and the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane (50 ml), the solution was washed with water (20 ml), concentrated to 10 ml and chromatographed on alumina in benzene–ethyl acetate (20 : 1). The main fraction afforded 1·86 g (74%) of *Ib*, m.p. 179—181°C

(dichloromethane–light petroleum). For $C_{28}H_{36}FeN_2O_{10}$ (616·5) calculated: 54·55% C, 5·90% H, 9·06% Fe, 4·54% N; found: 54·61% C, 5·98% H, 9·00% Fe, 4·43% N. ^{1}H NMR spectrum: 1·28 t, 12 H (CH_3); 3·36 s, 4 H, (CH_2); 4·2 m, 16 H, (C_5H_4 + CH_2CH_3); 6·75 s, 2 H, (NH); 8·14 s, 2 H (CHO).

Tetraethyl 2,2′-Bis(formylamino)-2,2′-(1,2-ferrocenediyldimethylene)dimalonate (*IIb*)

The title compound was synthesized as described for compound *Ib* except that the reaction mixture was stirred at room temperature for 24 h. Starting from 1·0 g (4·1 mmol) of 1,2-bis(hydroxymethyl)ferrocene, the reaction gave, after chromatography, 1·52 (59·5%) of *IIb*, m.p. 159–161°C (ethanol–water). For $C_{28}H_{36}FeN_2O_{10}$ (616·5) calculated: 54·55% C, 5·90% H, 9·06% Fe, 4·54% N; found: 54·72% C, 6·94% H, 9·09% Fe, 4·31% N. ^{1}H NMR spectrum: 1·25 t, 12 H (CH_3); 3·54 d, 4 H (CH_2); 4·05 m, 8 H (C_5H_5 + C_5H_3); 4·3 q, 8 H (CH_2—CH_3); 7·06 s, 2 H (NH); 8·18 s, 2 H (CHO).

Diethyl 2-Formylamino-2-(1′-methoxycarbonylferrocenylmethyl)malonate (*IIIb*)

The synthesis was carried out starting from methyl 1′-(hydroxymethyl)ferrocenecarboxylate (2·1 g; 7·7 mmol), diethyl formamidomalonate (2·58 g; 12·7 mmol) and sodium hydride (0·30 g; 12·7 mmol) as described for compound *Ib*. The reaction mixture was stirred at 80°C for 19 h. Chromatographic separation (as described for *Ib*) afforded two fractions. The first fraction contained dimethyl 1,1′-oxydimethylenediferrocenecarboxylate (0·19 g; 4·9%), m.p. 123–125°C (benzene–light petroleum). For $C_{26}H_{26}Fe_2O_5$ (530·2) calculated: 58·89% C, 4·95% H, 21·07% Fe; found: 58·91% C, 4·98% H, 21·05% Fe. ^{1}H NMR spectrum: 3·8 s, 6 H (CH_3); 4·2 m, 12 H (C_5H_4 + CH_2); 4·35 t, 4 H (H_β); 4·75 t, 4 H (H_α). The second fraction afforded 3·35 g (95%) of *IIIb*, m.p. 127–128·5°C (benzene–light petroleum). For $C_{21}H_{25}FeNO_7$ (459·3) calculated: 54·91% C, 5·50% H, 12·16% Fe, 3·05% N; found: 55·11% C, 5·58% H, 12·00% Fe, 3·10% N. ^{1}H NMR spectrum: 1·26 t, 6 H (OCH_2CH_3); 3·37 s, 2 H (Fc—CH_2); 3·84s, 3 H (CH_3O); 4·20 m, 10 H (C_5H_4 + OCH_2CH_3 + H_β); 4·78 t, 2 H (H_α); 6·67 s, 1 H (NH); 8·10 s, 1 H (CHO).

2,2′-Bis(formylamino)-2,2′-(1,1′-ferrocenediyldimethylene)dimalonic Acid (*Ic*)

A solution of *Ib* (1·9 g; 3·1 mmol) in ethanol (19 ml) was added to sodium hydroxide (3·87 g; 96·7 mmol) in water (12 ml). After refluxing for 1·5 h, the ethanol was evaporated under diminished pressure, the residue was cooled and extracted with diethyl ether (2 × 10 ml). The aqueous solution was carefully acidified with 10% hydrochloric acid to pH 4 and the precipitated product was immediately filtered, washed with cold water and dried to give 1·6 g (96%) of dihydrate of *Ic*, melting above 205°C (decomp.). For $C_{20}H_{24}FeN_2O_{12}$ (540·3) calculated: 44·46% C, 4·49% H, 10·34% Fe, 5·19% N; found: 45·15% C, 4·22% H, 10·09% Fe, 5·44% N. Because of low solubility, no NMR spectra could be measured.

N,N′-Diformyl-1,1′-ferrocenedialanine (*Id*)

A solution of *Ib* (1·23 g; 2 mmol) in ethanol (15 ml) was added in one portion to a solution of sodium hydroxide (0·4 g; 10 mmol) in water (10 ml). The mixture was refluxed for 1·5 h, neutralized with 10% hydrochloric acid to pH 7 and again refluxed for 1 h. After evaporation of the solvent in vacuo, the residue was mixed with 98% formic acid (20 ml) and cooled to 10–15°C. Acetic anhydride (7 ml) was added dropwise, the mixture was stirred for 2 h at room temperature, decomposed with water and the separated product was collected on filter, yield 0·55 g (66%) of

Id, m.p. 205°C (decomp.) (aqueous formic acid). For $C_{11}H_{20}FeN_2O_6$ (416·2) calculated: 51·94% C, 4·85% H, 13·42% Fe, 6·73% N; found: 51·30% C, 4·81% H, 13·39% Fe, 6·28% N. Low solubility prevented ^1H NMR measurement.

N-Formyl-1′-carboxyferrocenealanine (*IIIc*)

The title compound was prepared from *IIIb* (0·92 g; 2 mmol) as described for *Id*; yield 0·54 g (79·7%) of *IIIc*, m.p. 177—179·5°C (acetone–ethyl acetate). The compound decomposed on longer heating or standing of its solution. For $C_{15}H_{15}FeNO_5$ (345·2) calculated: 52·19% C, 4·39% H, 16·18% Fe, 4·06% N; found: 52·48% C, 4·33% H, 16·26% Fe, 3·90% N. No NMR spectra were measured because of very low stability in solution (acetone).

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