Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Organometallic Chemistry 691 (2006) 463–469
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

The synthesis and structural characterization of *N-ortho-ferrocenyl* benzoyl amino acid esters. The X-ray crystal structure of *N*-{*ortho*-(ferrocenyl)benzoyl}-L-phenylalanine ethyl ester

David Savage [a], Gwen Malone [a], Steven R. Alley [b], John F. Gallagher [b], Alok Goel [b], Paula N. Kelly [b], Helge Mueller-Bunz [c], Peter T.M. Kenny [b,*]

[a] *School of Chemical Sciences, Dublin City University, Dublin 9, Ireland*
[b] *National Institute for Cellular Biotechnology, Dublin City University, Dublin 9, Ireland*
[c] *Department of Chemistry, University College Dublin, Belfield, Dublin 4 Ireland*

Received 11 July 2005; received in revised form 30 August 2005; accepted 5 September 2005
Available online 19 October 2005

Abstract

A series of *N-ortho*-ferrocenyl benzoyl amino acid ethyl esters **3**–**9** have been prepared by coupling *ortho*-ferrocenyl benzoic acid **2** to the amino acid ethyl esters of glycine, L-alanine, L-leucine, L-phenylalanine, β-alanine, 4-aminobutyric acid and (±)-2-aminobutyric acid using the conventional 1,3-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole protocol. The compounds were fully characterized by a range of NMR spectroscopic techniques and by mass spectrometry (MALDI-MS, ESI-MS). The X-ray crystal structure of the L-phenylalanine derivative **6** has been determined.

Keywords: Ferrocene; Amino acid esters; Bioorganometallic chemistry; MALDI; X-ray crystal structure

1. Introduction

Research in the area of bioorganometallic chemistry has seen an increase in attention over the past decade. The incorporation of ferrocene in novel materials has been reported primarily due to its stability, spectroscopic properties, electrochemical properties and ease of use [1,2]. As a direct consequence of these factors, research in the area of ferrocenyl derivatives has seen an increase in attention, primarily for the preparation of novel sensor compounds, peptide mimetic models and unnatural drugs [3–9]. The incorporation of a ferrocene group onto proteins has shown the mediation of electron transfer between electrodes and the protein redox site [3,4]. The synthesis and structural characterization of novel *N*-ferrocenoyl and *N*-ferrocenyl amino acid and peptide derivatives has been reported [10–26]. A review on bioorganometallic chemistry of ferrocene has recently been published [27]. We now report the synthesis and structural characterization of a series of *N-ortho*-ferrocenyl benzoyl amino acid esters **3**–**9**. These unusual materials are composed of three key moieties, namely, (i) an electroactive core, (ii) a conjugated linker that can act as a chromophore and (iii) an amino acid derivative that can interact with other molecules via hydrogen bonding. The amino acids employed in the synthesis were glycine, L-alanine, L-leucine, L-phenylalanine, β-alanine, 4-aminobutyric acid and (±)-2-aminobutyric acid. The compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and by MALDI and ESI mass spectrometry. In addition the X-ray crystal structure of the L-phenylalanine derivative **6** is also reported.

We have already reported the synthesis and structural characterization of a series of *N-para* and *N-meta*-ferrocenyl benzoyl amino acid ester derivatives [28–30].

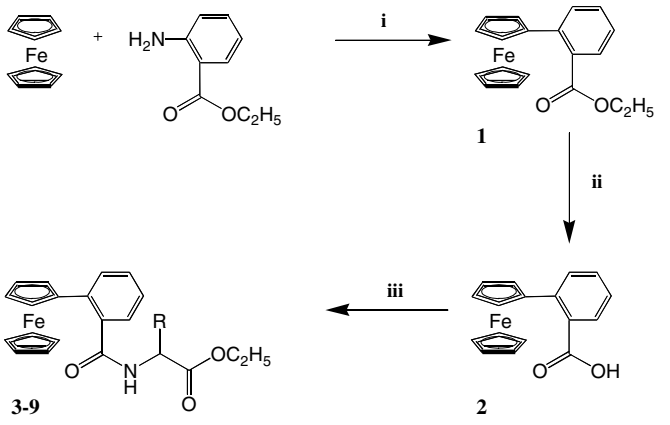
* Corresponding author. Tel.: +353 1 7005689; fax: +353 1 7005503.
E-mail address: peter.kenny@dcu.ie (P.T.M. Kenny).

0022-328X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2005.09.019

2. Results and discussion

2.1. Synthesis

ortho-Ferrocenyl benzoic acid **2** was prepared using conventional diazonium salt chemistry. Treatment of ethyl-2-aminobenzoate with sodium nitrite in the presence of hydrochloric acid yielded the diazonium salt, which was then reacted with ferrocene in situ to yield the *ortho*-substituted ferrocenyl ethyl benzoate **1**. Prior to coupling with the C-protected amino acids, the ester group was cleanly cleaved by treatment with 10% sodium hydroxide to yield *ortho*-ferrocenyl benzoic acid **2**. The ^{1}H NMR spectrum showed signals for the aromatic ring protons at δ 7.83 (d), δ 7.44 (t), δ 7.37 (d) and δ 7.27 (t), integrating for one proton each, characteristic of a *ortho*-disubstituted aromatic ring. The carboxylic acid proton was present at δ 12.8. The ferrocenyl *ortho* and *meta* protons on the (η^5-C_5H_4) ring were observed at δ 4.55 and δ 4.32, respectively, and an intense singlet was present at δ 4.08 for the (η^5-C_5H_5) ring. *ortho*-Ferrocenyl benzoic acid **2** was coupled under basic conditions to the free *N*-terminal amino acid esters of glycine, L-alanine, L-leucine, L-phenylalanine, β-alanine, 4-aminobutyric acid and (±)-2-aminobutyric acid in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) as outlined in Scheme 1. The *N-ortho*-ferrocenyl benzoyl amino acid esters **3–9** were obtained as yellow/orange coloured crystals. The yields obtained ranged between 55% and 68% and all gave analytical and spectroscopic data in accordance with the proposed structures. The compounds are reasonably stable however they can slowly decompose over a period of time. The percentage yields obtained are comparable to those obtained for both the *para* and *meta* analogues [28–30]. The *N-ortho*-ferrocenyl benzoyl derivatives **3–9** were characterized by a combination of ^{1}H NMR, ^{13}C NMR, DEPT-135 and ^{1}H–^{13}C COSY (HMQC) spectroscopy, and by either matrix assisted laser desorption ionization mass spectrometry (MALDI) for compounds **3**, **4**, **7**, **8**, and **9**, or electrospray ionization mass spectrometry (ESI) for compounds **5** and **6**. Crystals of sufficient quality for X-ray diffraction studies were also obtained for compound **6**.



Scheme 1. Synthesis of the *N*-ortho-ferrocenyl benzoyl amino acid esters **3–9**; Gly(OEt) **3**, Ala(OEt) **4**, Leu(OEt) **5**, Phe(OEt) **6**, β-Ala(OEt) **7**, 4-Abat(OEt) **8**, 2-Aba(OEt) **9**. (i) $NaNO_2$, HCl, 5 °C, (ii) NaOH/MeOH, H_2O, (iii) DCC, HOBt, Et_3N, amino acid ester.

2.2. ^{1}H and ^{13}C NMR spectroscopic analysis

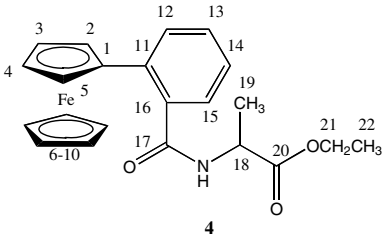
All the proton and carbon chemical shifts for compounds **3–9** were unambiguously assigned by a combination of DEPT-135 and ^{1}H–^{13}C-COSY (HMQC). The ^{1}H and ^{13}C NMR spectra for compounds **3–9** showed peaks in the ferrocene region characteristic of a mono substituted ferrocene moiety [10,28–30]. The protons of the *ortho*-disubstituted benzoyl group appear in the region δ 6.88–7.81. For example, in the case of the L-alanine derivative **4** the (η^5-C_5H_5) ring appears as a singlet in the ^{1}H NMR spectrum at δ 4.03 whereas the *meta* and *ortho* protons on the (η^5-C_5H_4) ring are present at δ 4.27 and 4.63, respectively. The N*H* proton appears as a doublet at δ 8.75 and another doublet at δ 1.31 integrating for three protons corresponds to the side chain methyl group. The aromatic ring protons are present in the region δ 7.21–7.79.

The ^{13}C NMR spectra of compounds **3–9** show signals in the region δ 68.5–85.7 indicative of a monosubstituted ferrocene subunit. The *ipso* carbon of the (η^5-C_5H_4) ring appears in the range of δ 84.5 to 85.7. This signal is absent in the DEPT-135 spectra. The carbon atoms of the phenyl spacer group are non-equivalent and therefore six signals are visible in the region δ 125.8–137.9. The two quaternary carbon atoms of this phenyl group were identified by DEPT-135. In the case of the L-alanine derivative **4** the signals were present at δ 136.8 and 136.2 and were absent in the DEPT-135 spectrum. The four other aromatic peaks appeared at δ 130.4, 129.2, 127.8 and 125.8, respectively. The signal due to the *ipso* carbon of the ferrocenyl group was at δ 84.7 and absent in the DEPT 135 spectrum. Upfield from the ferrocenyl *ipso* carbon signal the (η^5-C_5H_5) ring appears at δ 69.6 whereas the signals due to the *meta* and *ortho* carbons are present at δ 69.6 and 68.6, respectively. The methylene carbon of the ethyl ester group appears at δ 60.9 and displays a negative peak in the DEPT 135 spectrum. The α-carbon is present at δ 48.3. The methyl groups of the alanine side chain and the ethyl ester are present at δ 17.0 and 14.5, respectively. All the methylene carbon atoms of the derivatives **3–9** were also identified by DEPT-135. A complete assignment of the ^{1}H and ^{13}C NMR spectra of compound **4** is presented in Table 1.

2.3. Mass spectrometry

Since the introduction of soft ionization techniques such as matrix assisted laser desorption ionization (MADLI) and electrospray ionization (ESI), a wide range of thermolabile and non-volatile compounds can be subjected to mass spectrometric analysis [31–33]. Compounds **3–9** were not amenable to electron ionization studies, therefore MADLI and ESI were employed in the analysis. Both

Table 1
^{1}H and ^{13}C spectroscopic data for **4**



4

Site	^{1}H NMR	^{13}C NMR	HMQC
1		84.7	
2,5	4.63		68.6
3,4	4.27		69.6
6–10	4.03		69.8
11		136.8[a]	
12	7.11–26		130.4
13	7.11–26		129.2[a]
14	7.41		127.8[b]
15	7.79		125.8
16		136.2[b]	
17		169.8	
18	4.36		48.3
19	1.31		17
20		172.9	
21	4.12		60.9
22	1.22		14.4

[a,b] Signals may be reversed.

MALDI and ESI confirmed the correct relative molecular mass for all the compounds and examination of the mass spectra revealed the presence of intense radical-cations. Cation adducts due to sodium and potassium were also present. The vast majority of analytes subjected to analysis by soft ionization techniques such as MALDI furnish protonated molecular ion species as a result of proton transfer reactions between the analyte and matrix or cation adduction. However, it has been reported that the molecular radical cation of ferrocene and not the protonated molecular ion is generated during analysis by MALDI [34]. More interestingly, in contrast to the related *para* and *meta* derivatives an important fragment ion at m/z $[M-65]^{+\cdot}$ resulting from loss of the unsubstituted (η^5-C_5H_5) ring, was observed in all the mass spectra and this ion is unique for the *ortho* series. The formation of this fragment ion is probably due to steric interactions between the unsubstituted (η^5-C_5H_5) ring and the *ortho* benzoyl substituents. In the case of the glycine derivative **3** the molecular ion was present at m/z 391 and the fragment ion at m/z 326. For the alanine and β-alanine derivatives **4** and **7** this fragment ion was shifted 14 mass units higher to m/z 340 and for the amino butyric acid derivatives **8** and **9** to m/z 354. Compounds **5** and **6** were analyzed by electrospray ionization mass spectrometry (ESI-MS). The ESI mass spectra displayed both radical cation and $[M+H]^{+}$ species and intense adducts due to sodium and potassium were present 22 and 38 Da higher than the protonated molecular ion species.

2.4. X-ray crystallographic studies of **6**

The single crystal X-ray structure of **6** has been determined (Fig. 1) with selected bond lengths and angles listed in Table 2 with crystallographic details given in the footnote. There is an increasing number of metallocene based amino acid/peptide structures on the Cambridge Structural

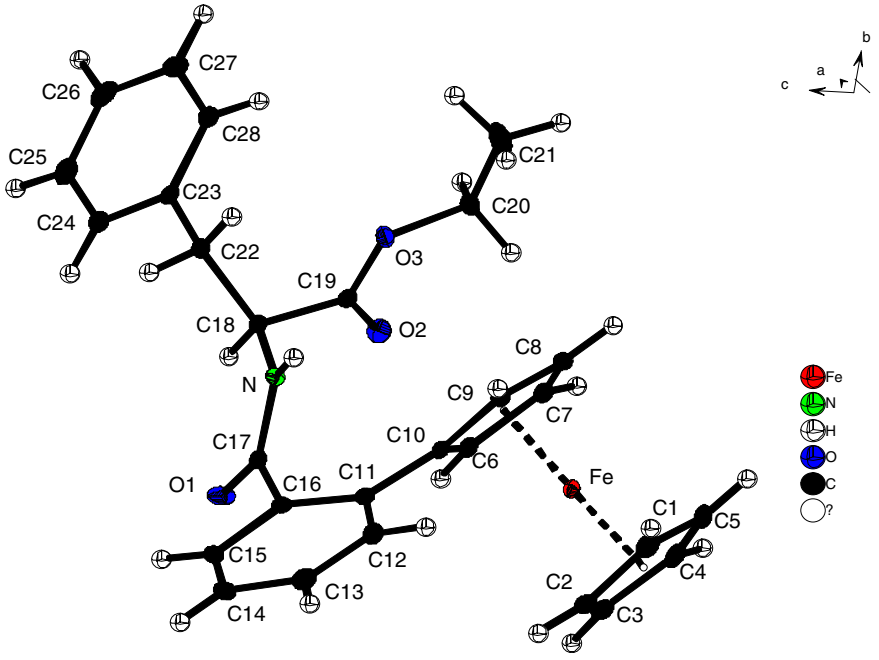


Fig. 1. Molecular drawing using ORTEP: displacement ellipsoids are drawn at the 50% probability level.

Table 2
Selected bond lengths (Å) and angles (°) for **6**

Fe...Cg1	1.647(2)	O(1)–C(17)–N	123.30(15)
Fe...Cg2	1.646(2)	N–C(17)–C(16)	115.11(13)
Cg1...Fe...Cg2	178.24(2)	N–C(18)–C(19)	108.99(11)
N–C(17)	1.347(2)	N–C(18)–C(22)	110.07(12)
N–C(18)	1.454(2)	C(19)–C(18)–C(22)	112.80(12)
O–(1)–C(17)	1.225(2)	O(2)–C(19)–O(3)	125.15(15)
O–(2)–C(19)	1.202(2)	O(2)–C(19)–C(18)	124.32(14)
O–(3)–C(19)	1.332(2)	O(3)–C(19)–C(18)	110.52(12)
O–(3)–C(20)	1.456(2)	C(23)–C(22)–C(18)	114.06(12)
C–(15)–C(16)–C(17)	116.09(14)	C(10)–C(11)–C(16)–C(17)	7.8(2)
C–(11)–C(16)–C(17)	124.07(14)		

Where Cg1 and Cg2 are the centroids of substituted and unsubstituted cyclopentadienyl rings, respectively.

Database (CSD) [35], but compounds incorporating the Fc-C_6H_4- moiety are relatively rare in comparison to the Fc systems, where Fc = (η^5-C_5H_5)Fe(η^5-C_5H_4).

2.4.1. Molecular and crystal structure study of 6

Compound **6** crystallizes with one molecule in the asymmetric unit of space group $P2_12_12_1$ (No. 19). The key geometric parameters are amide C=O 1.225(7) Å, OC–NH 1.347(2) Å, HN–CH 1.454(2) Å and ester C=O/C–O 1.202(2)/1.332(2) Å, respectively, which are similar to the previously reported L-alanine and glycine derivatives [28,29]. Cyclopentadienyl rings (Cp1 and Cp2) are slightly staggered with C1n...Cg1...Cg2...C2n torsion angles ($n = 1$–5) in the 7.80(2)–8.30(2)° range. Centroids Cg1 and Cg2 of the Cp rings are equidistant from the iron core, Fe...Cg1/Cg2 distances are 1.647(2)/1.646(2) with 178.24(2)° Cg1...Fe...Cg2 angle.

There is an intermolecular hydrogen bond N–H...O=C (ester), with H...O 2.28(2) Å, N–H...O 169(2)°, similar to the L-alanine derivative and in contrast to amide...amide intermolecular interactions found in glycine and (±)-2-aminobutyric acid derivatives [29]. There is also a significant intermolecular contact between a methylene hydrogen (H22) and a (Cp1) ring hydrogen (H7), contact distance being 2.26(2) Å. These two interactions generate a one-dimensional chain along the *b*-axis and the packing along the chain comprises alternating 'head to tail' arrangement of identical molecules.

ortho-Ferrocenyl and amide groups of the central phenyl ring are significantly twisted. The angle between the central phenyl and the Cp ring planes is 37.8(2)°, whereas the angle between the phenyl ring and the O=C–N plane is 49.65(2)°. The torsion angle C10–C11–C16–C17 between the two substituents is 7.8°. Although conjugating groups are usually planer to the phenyl ring and provide extended conjugation, steric effects force these groups out of plane in the solid state.

3. Conclusions

The *N-ortho*-ferrocenyl benzoyl amino acid esters **3**–**9** were prepared by coupling *ortho*-ferrocenyl benzoic acid with the amino acid esters using conventional organic peptide synthetic protocols. The compounds were fully characterized by a range of NMR spectroscopic techniques and by mass spectrometry. The mass spectra of compounds **3**–**9** show a diagnostic fragment ion at m/z $[M-65]^{+\cdot}$ which is absent in the mass spectra of the corresponding *para* and *meta* analogues. In addition the X-ray crystal structure of compound **6** has been determined.

4. Experimental

4.1. General procedures

All chemicals were purchased from Sigma/Aldrich and used as received. Commercial grade reagents were used without further purification, however, solvents were purified prior to use. Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 405 FT-IR spectrometer and UV–Vis spectra on a Hewlett–Packard 8452A diode array UV–Vis spectrophotometer. NMR spectra were obtained on a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (ppm) are relative to TMS and all coupling constants (J) are in Hertz. Matrix assisted laser desorption ionization mass spectra were obtained on a Bruker Ultraflex TOF/TOF mass spectrometer employing a nitrogen laser at 337 nm. Electrospray ionization mass spectra were performed on either a Bruker Esquire ion trap mass spectrometer or a Micromass Q-ToF Ultima quadrupole time of flight mass spectrometer.

Crystal data were collected at 113(2) K using a Brüker SMART APEX CCD area detector diffractometer. A full sphere of the reciprocal space was scanned by ϕ–ω scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS [36]. The structures were solved by direct methods using SHELXS-97 [37] and refined by full matrix least-squares on F^2 for all data using SHELXL-97 [38]. All hydrogen atoms were located in the difference fourier map and allowed to refine freely with isotropic temperature factors. Anisotropic temperature factors were used for all non-hydrogen atoms.

4.2. General procedure for the synthesis of the starting materials 1 and 2

4.2.1. ortho-Ferrocenyl ethyl benzoate 1

Concentrated hydrochloric acid (6 ml) was added with intermittent cooling to a solution of ethyl-2-aminobenzoate (3 g, 18.2 mmol) in 15 ml of water. A solution of sodium nitrite (1.4 g, 20.3 mmol) in 15 ml of water was then added slowly to this mixture with stirring keeping the temperature below 5 °C furnishing a pale yellow solution. The resulting diazo salt was added to a solution of ferrocene (3.8 g, 20.4 mmol) in diethyl ether (90 ml) and allowed to react for 12 h. The reactant mixture was then washed with water; the ether layer was dried over $MgSO_4$ and the solvent was

removed in vacuo to yield the crude product. The crude product was purified using column chromatography {eluant 2:3 petroleum ether (40–60 °C): diethyl ether}.

^{1}H NMR (400 MHz) δ (DMSO): 7.88 (1H, d, $J = 8$ Hz, ArH), 7.50 (1H, t, $J = 8$ Hz, ArH), 7.39 (1H, d, $J = 8$ Hz, ArH), 7.30 (1H, t, $J = 8$ Hz, ArH), 4.46 {2H, s, *ortho* on (η^5-C_5H_4)}, 4.33 {2H, s, *meta* on (η^5-C_5H_4)}, 4.14 (2H, q, $J = 7.2$ Hz, –OCH_2CH$_3$), 4.09 {5H, s, (η^5-C_5H_5)}, 1.13 (3H, t, $J = 7.2$ Hz, –OCH$_2$CH_3).

^{13}C NMR (100 MHz) δ (DMSO): 170.3, 138.7, 132.6, 131.7, 130.5, 128.8, 126.3, 86.6, 70.1, 69.7, 68.8, 61.5 (-ve DEPT), 14.2.

4.2.2. ortho-Ferrocenyl benzoic acid ***2***

Sodium hydroxide (0.3 g, 7.5 mmol) was added to *ortho*-ferrocenyl ethyl benzoate **1** (2.4 g, 7.2 mmol) in a 1:1 mixture of water/methanol and was refluxed for 3 h. Concentrated HCl was added until pH 2 was reached. The solution was allowed to cool and the product was isolated by filtration.

m.p. 124–126 °C.

IR ν_{max} (KBr): 1693, 1607, 1402, 1227 cm^{-1}.

UV–Vis λ_{max} CH_2Cl_2: 356 (ε 1310), 450 (ε 430) nm.

^{1}H NMR (400 MHz) δ (DMSO): 12.8 (1H, s, –COO*H*), 7.83 (1H, d, $J = 8$ Hz, ArH), 7.44 (1H, t, $J = 8$ Hz, ArH), 7.37 (1H, d, $J = 8$ Hz, ArH), 7.27 (1H, t, $J = 8$ Hz, ArH), 4.55 {2H, s, *ortho* on (η^5-C_5H_4)}, 4.32 {2H, t, *meta* on (η^5-C_5H_4)}, 4.08 {5H, s, (η^5-C_5H_5)}.

^{13}C NMR (100 MHz) δ (DMSO): 171.2, 137.0, 133.4, 131.1, 129.9, 127.8, 126.1, 85.4, 69.9, 69.2, 68.6.

4.3. General procedure for the synthesis of N-{ortho-(ferrocenyl)benzoyl} amino acid esters ***3–9***

4.3.1. N-{ortho-(ferrocenyl)benzoyl} glycine ethyl ester ***3***

Glycine ethyl ester hydrochloride (0.3 g, 2.2 mmol) and triethylamine (0.5 ml) were added to a solution of *ortho*-ferrocenyl benzoic acid (0.5 g, 1.6 mmol), 1-hydroxybenzotriazole (0.3 g, 2.2 mmol) and 1,3-dicyclohexylcarbodiimide (0.45 g, 2.2 mmol) in CH_2Cl_2 (50 ml) at 0 °C. After 30 min the solution was raised to room temperature and allowed to proceed for 48 h. The precipitated *N*,*N*′-dicyclohexylurea was removed by filtration and the filtrate was washed with water, 10% potassium hydrogen carbonate, 5% citric acid and dried over $MgSO_4$. Recrystallization from petroleum ether (40–60 °C): ethyl acetate furnished *N*-{*ortho*-(ferrocenyl)benzoyl} glycine ethyl ester **3** as orange needles (0.38 g, 62%).

m.p. 99–101 °C, $E'^0 = 109$ mV.

Analysis: found: C, 64.35; H, 5.47; N, 3.80.

$C_{21}H_{21}N_1O_3Fe$ requires: C, 64.47; H, 5.41; N, 3.58.

Mass spectrum: found: $[M]^{+\cdot}$ 391.089.

$C_{21}H_{21}N_1O_3Fe$ requires: 391.087.

IR ν_{max} (KBr): 3298, 1740, 1643, 1529 cm^{-1}.

UV–Vis λ_{max} CH_2Cl_2: 340 (ε 1060), 446 (ε 340) nm.

^{1}H NMR (400 MHz) δ (DMSO): 8.76 (1H, d, $J = 5.6$ Hz –CON*H*–), 7.81 (1H, d, $J = 8$ Hz, ArH), 7.43 (1H, t, $J = 8$ Hz, ArH), 7.20–7.28 (2H, m, ArH), 4.68 {2H, t, $J = 2$ Hz, *ortho* on (η^5-C_5H_4)}, 4.28 {2H, t, $J = 2$ Hz, *meta* on (η^5-C_5H_4)}, 4.16 (2H, q, $J = 7.2$ Hz, –OCH_2CH$_3$), 4.05 {5H, s, (η^5-C_5H_5)}, 3.92 (2H, d, $J = 6.4$ Hz, –NHCH_2CO–), 1.24 (3H, t, $J = 7.2$ Hz, –OCH$_2$CH_3).

^{13}C NMR (100 MHz) δ (DMSO): 170.6, 170.2, 136.8, 136.0, 130.4, 129.3, 127.8, 125.8, 84.5, 69.8, 69.1, 68.6, 60.9 (-ve DEPT), 41.4 (-ve DEPT), 14.4.

4.3.2. N-{ortho-(Ferrocenyl)benzoyl}-L-alanine ethyl ester ***4***

L-Alanine ethyl ester hydrochloride (0.3 g, 2.0 mmol) was used. Recrystallization from petroleum ether (40–60 °C): ethyl acetate furnished the title compound as a yellow solid (0.39 g, 60%).

m.p. 54–56 °C, $E'^0 = 111$ mV, $[\alpha]_D^{25} = +9°$ ($c = 2$, CH_2Cl_2).

Analysis: found: C, 65.24; H, 6.00; N, 3.43.

$C_{22}H_{23}N_1O_3Fe$ requires: C, 65.20; H, 5.72; N, 3.46.

Mass spectrum: found: $[M]^{+\cdot}$ 405.104.

$C_{22}H_{23}N_1O_3Fe$ requires: 405.103.

IR ν_{max} (KBr) :3323, 1757, 1635, 1530, 1459 cm^{-1}.

UV–Vis λ_{max} MeCN: 330 (ε 1130), 450 (ε 290) nm.

^{1}H NMR (400 MHz) δ (DMSO): 8.75 (1H, d, $J = 6.8$ Hz, –CON*H*–), 7.79 (1H, d, $J = 8$ Hz, ArH), 7.41 (1H, t, $J = 8$ Hz, ArH), 7.21–7.26 (2H, m, ArH), 4.63 (2H, d, $J = 1.6$ Hz, *ortho* on (η^5-C_5H_4)), 4.36 {1H, t, $J = 8$ Hz, –C*H*(CH_3)}, 4.27 {2H, d, $J = 1.6$ Hz, *meta* on (η^5-C_5H_4)}, 4.12 (2H, q, $J = 6.4$ Hz, –OCH_2CH$_3$), 4.03 {5H, s, (η^5-C_5H_5)}, 1.31 {3H, d, $J = 7.2$ Hz, –CH(CH_3)}, 1.22 (3H, t, $J = 6.4$ Hz, –OCH$_2$CH_3).

^{13}C NMR (100 MHz) δ (DMSO): 172.9, 169.8, 136.8, 136.2, 130.4, 129.2, 127.8, 125.8, 84.7, 69.8, 69.6, 68.7, 68.6, 68.5, 60.9 (-ve DEPT), 48.3, 17.0, 14.4.

4.3.3. N-{ortho-(Ferrocenyl)benzoyl}-L-leucine ethyl ester ***5***

L-Leucine ethyl ester hydrochloride (0.3 g, 1.5 mmol) was used. Recrystallization from petroleum ether (40–60 °C): ethyl acetate yielded the title compound as an orange solid (0.46 g, 64%).

m.p. 88–90 °C, $E'^0 = 106$ mV, $[\alpha]_D^{20} = +3°$ ($c = 1.2$, CH_2Cl_2).

Analysis: found: C, 67.16; H, 6.64; N, 3.21.

$C_{25}H_{29}N_1O_3Fe$ requires: C, 67.12; H, 6.53; N, 3.13.

Mass spectrum: found: $[M]^{+\cdot}$ 447.2.

$C_{25}H_{29}N_1O_3Fe$ requires: 447.15.

IR ν_{max} (KBr): 3324, 3266, 1744, 1644 cm^{-1}.

UV–Vis λ_{max} CH_2Cl_2: 334 (ε 1140), 448 (ε 260) nm.

^{1}H NMR (400 MHz) δ (DMSO): 8.69 (1H, d, $J = 7.6$ Hz, –CON*H*–), 7.81 (1H, d, $J = 8$ Hz, ArH), 7.41 (1H, t, $J = 8$ Hz, ArH), 7.26 (1H, t, $J = 8$ Hz, ArH), 7.16 (1H, d, $J = 8$ Hz, ArH), 4.60 {2H, s, *ortho* on (η^5-C_5H_4)}, 4.30–4.36 [1H, m, –C*H*{$CH_2CH(CH_3)_2$}], 4.28 {1H, s, *meta* on (η^5-C_5H_4)}, 4.12 {1H, s, *meta* on (η^5-C_5H_4)}, 4.11 (2H, q, $J = 6.4$ Hz, –OCH_2CH$_3$), 4.05 {5H, s, (η^5-C_5H_5)}, 1.57–1.81 [3H, m, –{CH_2C*H*(CH_3)$_2$}], 1.22 (3H, t, $J = 6.4$ Hz, –OCH$_2$CH_3), 0.87 [6H, d, $J = 6.4$ Hz, –CH{$CH_2CH(CH_3)_2$}].

^{13}C NMR (100 MHz) δ (DMSO): 172.8, 170.3, 136.6, 136.3, 130.5, 129.1, 127.7, 125.8, 84.7, 69.8, 69.6, 68.5, 68.4, 60.9 (-ve DEPT), 51.0, 39.5 (-ve DEPT), 24.6, 23.3, 21.4, 14.4.

4.3.4. N-{ortho-(ferrocenyl)benzoyl}-L-phenylalanine ethyl ester **6**

L-Phenylalanine ethyl ester hydrochloride (0.3 g, 1.3 mmol) was used. Recrystallization from petroleum ether (40–60 °C): ethyl acetate yielded the title compound as red needles. The crystals were of sufficient quality for an X-ray diffraction study. (0.43 g, 68%).

m.p. 110–112 °C, $E'^0 = 95$ mV, $[\alpha]_D^{20} = -6°$ ($c = 2$, CH_2Cl_2).

Analysis: found: C, 69.67; H, 5.63; N, 2.96.

$C_{28}H_{27}N_1O_3Fe$ requires: C, 69.86; H, 5.65; N, 2.91.

Mass spectrum: found: $[M]^{+\cdot}$ 481.1345.

$C_{28}H_{27}N_1O_3Fe$ requires: 481.1340.

IR ν_{max} (KBr): 2929, 1728, 1656, 1531 cm^{-1}.

UV–Vis λ_{max} CH_2Cl_2: 336 (ε 5750), 448 (ε 1440) nm.

^{1}H NMR (400 MHz) δ (DMSO): 8.75 (1H, d, $J = 8$ Hz, –CON*H*–), 7.66 (1H, d, $J = 7.2$ Hz, ArH), 7.20–7.31 (6H, m, ArH), 7.16 (1H, t, $J = 7.2$ Hz, ArH), 6.88 (1H, d, $J = 7.2$ Hz, ArH), 4.54–4.60 {1H, m, –C*H*(CH_2Ph)}, 4.49 {1H, s, *ortho* on (η^5-C_5H_4)}, 4.03–4.10 {5H, m, *meta* on (η^5-C_5H_4), *ortho* on (η^5-C_5H_4) and –OC*H*$_2$CH$_3$}, 3.76 {5H, s, (η^5-C_5H_5)}, 2.83–2.89 {2H, m, –CH(C*H*$_2$Ph)}, 0.99 (3H, t, $J = 7.2$ Hz, –OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz) δ (DMSO): 171.9, 169.9, 137.9, 136.8, 136.1, 130.4, 129.5, 129.1, 128.6, 127.5, 126.9, 125.7, 84.4, 69.8, 69.0, 68.7, 68.5, 61.1 (-ve DEPT), 54.0, 31.1 (-ve DEPT), 14.4.

4.3.5. N-{ortho-(ferrocenyl)-benzoyl}-β-alanine ethyl ester **7**

β-Alanine ethyl ester hydrochloride (0.3 g, 2.0 mmol) was used. Recrystallization from petroleum ether (40–60 °C): ethyl acetate yielded the title compound as an orange solid (0.39 g, 59%). $E'^0 = 107$ mV.

Analysis: found: C, 64.95; H, 5.96; N, 3.53.

$C_{22}H_{23}N_1O_3Fe$ requires: C, 65.20; H, 5.72; N, 3.46.

Mass spectrum: found: $[M]^{+\cdot}$ 405.104.

$C_{22}H_{23}N_1O_3Fe$ requires: 405.103.

IR ν_{max} (KBr): 2932, 1735, 1670, 1520 cm^{-1}.

UV–Vis λ_{max} MeCN: 319 (ε 1590), 446 (ε 350) nm.

^{1}H NMR (400 MHz) δ ($CDCl_3$): 7.68 (1H, d, $J = 7.6$ Hz, ArH), 7.29–7.33 (2H, m, ArH), 7.14–7.18 (1H, m, ArH), 5.80 (1H, t, $J = 5.6$ Hz, –CON*H*–), 4.42 {2H, t, $J = 1.6$ Hz, *ortho* on (η^5-C_5H_4)}, 4.18 {2H, t, $J = 1.6$ Hz, *meta* on (η^5-C_5H_4)}, 3.94–4.04 {7H, m, –OC*H*$_2$CH$_3$, (η^5-C_5H_5)}, 3.43 (2H, q, $J = 6.4$ Hz, –NHC*H*$_2$CH$_2$–), 2.37 (2H, t, $J = 6.4$ Hz, –NHCH$_2$C*H*$_2$–), 1.13 (3H, t, $J = 7.2$ Hz, –OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz) δ ($CDCl_3$): 172.6, 170.7, 136.5, 136.4, 131.2, 129.6, 128.1, 126.6, 85.7, 70.2, 69.7, 68.9, 61.0 (-ve DEPT), 35.3 (-ve DEPT), 34.0 (-ve DEPT), 14.6.

4.3.6. N-{ortho-(ferrocenyl)-benzoyl}-4-amino butyric acid ethyl ester **8**

4-Amino butyric acid ethyl ester hydrochloride (0.3 g, 1.8 mmol) was used. Recrystallization from diethyl ether yielded the title compound as a brown solid (0.42 g, 62%).

m.p. 62–63 °C, $E'^0 = 108$ mV.

Mass spectrum: found: $[M]^{+\cdot}$ 419.108.

$C_{23}H_{25}N_1O_3Fe$ requires: 419.118.

IR ν_{max} (KBr): 3389, 3086, 2925, 1752, 1647, 1542, 1406, 1196 cm^{-1}.

UV–Vis λ_{max} MeCN: 325 (ε 1640), 445 (ε 280) nm.

^{1}H NMR (400 MHz) δ ($CDCl_3$): 7.78 (1H, d, $J = 7.6$ Hz, ArH), 7.38–7.41 (2H, m, ArH), 7.25–7.28 (1H, m, ArH), 5.51 (1H, br.s, –CON*H*–), 4.53 {2H, s, *ortho* on (η^5-C_5H_4)}, 4.29 {2H, s, *meta* on (η^5-C_5H_4)}, 4.06–4.10 {7H, m, –OC*H*$_2$CH$_3$, (η^5-C_5H_5)}, 3.28 (2H, q, $J = 6.4$ Hz, –NHC*H*$_2$CH$_2$CH$_2$–), 2.20 (2H, t, $J = 7.2$ Hz, –NHCH$_2$CH$_2$C*H*$_2$–), 1.70–174 (2H, m, –NHCH$_2$C*H*$_2$-CH$_2$–), 1.24 (3H, t, $J = 7.6$ Hz, –OCH$_2$C*H*$_3$).

^{13}C NMR (100 MHz) δ ($CDCl_3$): 173.6, 170.9, 136.5, 136.3, 131.2, 129.7, 128.2, 126.7, 85.7, 70.2, 69.8, 69.0, 60.9 (-ve DEPT), 39.6 (-ve DEPT), 32.0 (-ve DEPT), 24.6 (-ve DEPT), 14.6.

4.3.7. N-{ortho-(ferrocenyl)-benzoyl} (±)-2-amino butyric acid ethyl ester **9**

(±)-2-Amino butyric acid ethyl ester hydrochloride (0.3 g, 1.8 mmol) was used. Recrystallization from diethyl ether furnished the title compound as orange needles (0.37 g, 55%).

m.p. 67–69 °C, $E'^0 = 111$ mV.

Mass spectrum: found: $[M]^{+\cdot}$ 419.107.

$C_{23}H_{25}N_1O_3Fe$ requires: 419.118.

IR ν_{max} (KBr): 3260, 2980, 1742, 1636, 1541, 1196, 1153 cm^{-1}.

UV–Vis λ_{max} MeCN: 323 (ε 1590), 444 (ε 360) nm.

^{1}H NMR (400 MHz) δ ($CDCl_3$): 7.72 (1H, d, $J = 8$ Hz, ArH), 7.31–7.35 (2H, m, ArH), 7.19 (1H, d, $J = 8$ Hz, ArH), 5.86 (1H, d, $J = 7.6$ Hz, –CON*H*–), 4.46–4.55 {3H, m, *ortho* on (η^5-C_5H_4), –C*H*(CH_2CH_3)], 4.19 {2H, s, *meta* on (η^5-C_5H_4)}, 4.07 (2H, q, $J = 7.2$ Hz, –OC*H*$_2$CH$_3$), 3.96 {5H, s, (η^5-C_5H_5)}, 1.68–1.73 {1H, m, –CH(C*H*$_2$CH$_3$)}, 1.59–1.64 {1H, m, –CH(C*H*$_2$CH$_3$)}, 1.17 (3H, t, $J = 7.2$ Hz, –OCH$_2$C*H*$_3$), 0.69 {3H, t, $J = 7.2$ Hz, –CH(CH$_2$C*H*$_3$)}.

^{13}C NMR (100 MHz) δ ($CDCl_3$): 172.2, 170.3, 136.8, 136.1, 131.4, 129.8, 128.2, 126.6, 85.7, 70.2, 70.1, 69.6, 69.0, 69.0, 61.7 (-ve DEPT), 54.0, 25.8 (-ve DEPT), 14.6, 9.8.

4.4. Crystallographic footnotes for **6**

Crystallographic data **6**: chemical formula $C_{28}H_{27}NO_3Fe$, red needles, molecular weight 481.36 g mol^{-1}, crystal size = $0.90 \times 0.70 \times 0.60$ mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), unit cell dimensions $a = 10.625(3)$ Å ($\alpha = 90°$), $b = 10.737(3)$ Å ($\beta = 90°$), $c = 19.966(5)$ Å ($\gamma = 90°$), $V = 2277.9(9)$ Å^3, $Z = 4$, density = 1.404 g cm^{-3},

$\mu = 0.693\ \text{mm}^{-1}$, 39116 reflections collected in the range 2.04–28.29°, 5429 independent reflections, 406 parameters, R factor = 0.028, $wR_2 = 0.067$.

5. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 275972 for **6**. Copies of the data can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

D.S. thanks the Irish American Partnership and Dublin City University for the funding of a studentship award 1999–2002. This research was partly supported by the National Institute for Cellular Biotechnology under the Programme for Research in Third Level Institutions (PRTLI, round 3, 2001–2006).

References

[1] G. Jaouen (Ed.)J. Organomet. Chem. 589 (1999) 1–126 (special issue on Bioorganometallic chemistry).
[2] R.D. Adams (Ed.)J. Organomet. Chem. 637–639 (2001) 1–875 (special issue on Ferrocene chemistry).
[3] M. Kira, T. Matsubara, H. Shinohara, M. Sisido, Chem. Lett. (1997) 89.
[4] A. Nomoto, T. Moriuchi, S. Yamazaki, A. Ogawa, T. Hirao, J. Chem. Soc., Chem. Commun. (1998) 1963.
[5] H. Fink, N.J. Long, A.J. Martin, G. Opromolla, A.J.P. White, D.J. Williams, P. Zanello, Organometallics 16 (1997) 2646.
[6] H. Plenio, C. Aberle, Organometallics 16 (1997) 5950.
[7] T.J. Peckham, A.J. Lough, I. Manners, Organometallics 18 (1999) 1030.
[8] T. Itoh, S. Shirakami, N. Ishida, Y. Yamashita, T. Yoshida, H.-S. Kim, Y. Wataya, Bioorg. Med. Chem. Lett. 10 (2000) 1657.
[9] T. Moriuchi, A. Nomoto, K. Yoshida, T. Hirao, Organometallics 20 (2001) 1008.
[10] H.-B. Kraatz, J. Lusztyk, G.D. Enright, Inorg. Chem. 36 (1997) 2400.
[11] P. Saweczko, H.-B. Kraatz, Coord. Chem. Rev. 192 (1999) 185.
[12] J.F. Gallagher, P.T.M. Kenny, M.J. Sheehy, Inorg. Chem. Commun. 2 (1999) 200.
[13] J.F. Gallagher, P.T.M. Kenny, M.J. Sheehy, Inorg. Chem. Commun. 2 (1999) 327.
[14] H.-B. Kraatz, D.M. Leek, A. Houmam, G.D. Enright, J. Lusztyk, D.D.M. Wayner, J. Organomet. Chem. 589 (1999) 38.
[15] T. Moriuchi, A. Nomoto, K. Yoshida, T. Hirao, J. Organomet. Chem. 589 (1999) 50.
[16] O. Brosch, T. Weyhermuller, N. Metzler-Nolte, Eur. J. Inorg. Chem. 2 (2000) 323.
[17] A. Hess, J. Sehnert, T. Weyhermuller, N. Metzler-Nolte, Inorg. Chem. 39 (2000) 5437.
[18] Y.M. Xu, H.-B. Kraatz, Tetrahedron Lett. 42 (2001) 2601.
[19] T. Moriuchi, K. Yoshida, T. Hirao, Organometallics 20 (2001) 3101.
[20] T. Moriuchi, K. Yoshida, T. Hirao, J. Organomet. Chem. 637 (2001) 75.
[21] A. Wieckowska, R. Bilewicz, A. Misicka, M. Pietraszkiewicz, K. Bajdor, L. Piela, Chem. Phys. Lett. 350 (2001) 447.
[22] H.-B. Kraatz, Y.M. Xu, P. Saweczko, J. Organomet. Chem. 637 (2001) 335.
[23] T. Moriuchi, A. Nomoto, K. Yoshida, A. Ogawa, T. Hirao, J. Am. Chem. Soc. 123 (2001) 68.
[24] S. Maricic, U. Berg, T. Frejd, Tetrahedron 58 (2002) 3085.
[25] S. Maricic, T. Frejd, J. Org. Chem. 67 (2002) 7600.
[26] D.R. van Staveren, T. Weyhermuller, N. Metzler-Nolte, J. Chem. Soc., Dalton Trans. (2003) 210.
[27] D.R. van Staveren, N. Metzler-Nolte, Chem. Rev. 104 (2004) 5931.
[28] D. Savage, J.F. Gallagher, Y. Ida, P.T.M. Kenny, Inorg. Chem. Commun. 5 (2002) 1034.
[29] D. Savage, G. Malone, J.F. Gallagher, Y. Ida, P.T.M. Kenny, J. Organomet. Chem. 690 (2005) 383.
[30] D. Savage, N. Neary, G. Malone, S.R. Alley, J.F. Gallagher, P.T.M. Kenny, Inorg. Chem. Commun. 8 (2005) 429.
[31] M. Karas, D. Bachmann, U. Bahr, F. Hillenkamp, Int. J. Mass Spectrom. Ion Processes 78 (1987) 53.
[32] K. Tanaka, H. Waki, Y. Ido, S. Akita, Y. Yoshida, T. Yoshida, Rapid Commun. Mass Spectrom. 2 (1988) 151.
[33] J.B. Fenn, J. Am. Soc. Mass Spectrom. 4 (1993) 524.
[34] T. Donovan McCarley, R.L. McCarley, P.A. Limbach, Anal.Chem. 70 (1998) 4376.
[35] F.H. Allen, O. Kennard, Chem. Des. Automat. News 8 (1993) 131.
[36] G.M. Sheldrick, SADABS, Brüker AXS Inc., Madison, WI, 2000.
[37] G.M. Sheldrick, SHELXS-97, University of Göttingen, 1997.
[38] G.M. Sheldrick, SHELXL-97-2, University of Göttingen, 1997.