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Inorganic Chemistry Communications 8 (2005) 429–432
INORGANIC CHEMISTRY COMMUNICATIONS
www.elsevier.com/locate/inoche

The synthesis and structural characterization of novel *N-meta*-ferrocenyl benzoyl amino acid esters

David Savage [a], Nicola Neary [a], Gwen Malone [a], Steven R. Alley [b], John F. Gallagher [b], Peter T.M. Kenny [a,b,*]

[a] *School of Chemical Sciences, Dublin City University, Dublin 9, Ireland*
[b] *National Institute for Cellular Biotechnology, Dublin City University, Dublin 9, Ireland*

Received 7 April 2004; accepted 31 January 2005
Available online 14 March 2005

Abstract

A series of *N-meta*-ferrocenyl benzoyl amino acid esters **3**–**10** have been prepared by coupling *meta*-ferrocenyl benzoic acid **2** to the amino acid esters using the conventional 1,3-dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBt) protocol. The amino acids employed in the synthesis were glycine, L-alanine, L-leucine, L-phenylalanine, β-alanine, 4-aminobutyric acid, 2-aminobutyric acid and 2-aminoisobutyric acid. The compounds were fully characterized by a range of NMR spectroscopic techniques and mass spectrometry (MALDI-MS, ESI-MS).

Keywords: Ferrocene; Bioorganometallic chemistry; MALDI; Amino acid esters

The organometallic compound ferrocene is a promising candidate for incorporation in novel materials due to its stability, spectroscopic properties, electrochemical properties and ease of use. As a direct consequence of these factors, research in the area of ferrocenyl derivatives has seen a dramatic increase in attention over the past decade, primarily for the ultimate goals of achieving novel sensor compounds, peptide mimetic models and unnatural drugs [1–10]. The incorporation of a ferrocene group onto proteins has shown the mediation of electron transfer between electrodes and the protein redox site [3,5]. The synthesis and structural characterization of novel *N*-ferrocenoyl and *N*-ferrocenyl amino acid and peptide derivatives has been reported [11–28]. The aim of this research is to incorporate three key moieties in the synthesis of unusual biological materials, 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. In this communication, we report the synthesis and structural characterization of a series of novel *N-meta*-ferrocenyl benzoyl amino acid ester derivatives. We recently reported the synthesis and structural characterization of a series of *N-para*-ferrocenyl benzoyl amino acid ester derivatives [28] and the *N-ortho*-ferrocenyl benzoyl amino acid derivatives will be reported in due course.

The *meta*-ferrocenyl benzoic acid **2** was prepared using conventional diazonium salt chemistry. Treatment of ethyl-3-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 *meta*-substituted ferrocenyl ethyl benzoate **1**. The ester group was cleanly cleaved by treatment with 10% sodium hydroxide to yield *meta*-ferrocenyl benzoic acid **2**. The ^{1}H NMR spectrum showed signals for the aromatic ring protons at δ 8.03 (s), δ 7.8 (d), δ 7.77 (d) and δ 7.43 (t), integrating for one proton each, characteristic of a *meta*-disubstituted aromatic ring. The

* Corresponding author. Tel.: +353 1 7005 689; fax: +353 1 7005 503.
E-mail address: peter.kenny@dcu.ie (P.T.M. Kenny).

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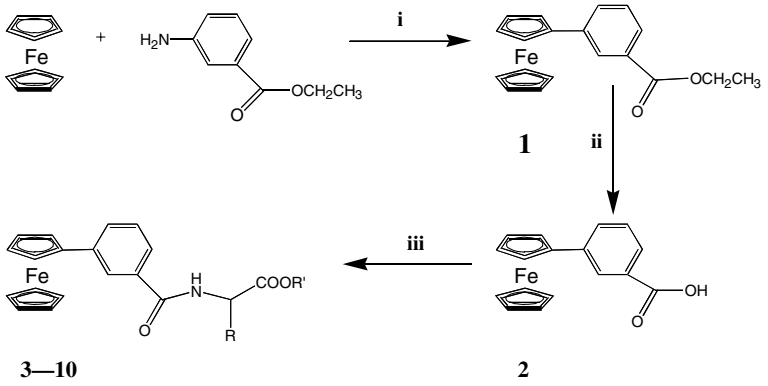
doi:10.1016/j.inoche.2005.01.031

carboxylic acid proton was present at δ 13.2. The ferrocenyl *ortho* and *meta* protons on the (η^5-C_5H_4) ring were observed at δ 4.84 and δ 4.39, respectively, and an intense singlet was present at δ 4.03 for the (η^5-C_5H_5) ring. The condensation of *meta*-ferrocenyl benzoic acid with the free N-terminal amino acid methyl esters of glycine, L-alanine, L-leucine, L-phenylalanine, and the free N-terminal amino acid ethyl esters of β-alanine, 4-aminobutyric acid, 2-aminobutyric acid and 2-aminoisobutyric acid under basic conditions in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) yielded *N-meta*-ferrocenyl benzoyl amino acid esters **3**–**10**, as yellow/orange colored crystals (Scheme 1). The yields obtained ranged between 55% and 68% and all gave analytical and spectroscopic data in accordance with the proposed structure [29]. The *N-meta*-ferrocenyl benzoyl derivatives were characterized by a combination of ^{1}H NMR, ^{13}C NMR, DEPT-135 and ^{1}H–^{13}C COSY (HMQC) spectroscopy, matrix assisted laser desorption ionization mass spectrometry (MALDI) and electrospray ionization mass spectrometry (ESI).

All the proton and carbon chemical shifts for compounds **3**–**10** 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**–**10** showed peaks in the ferrocene region characteristic of a mono substituted ferrocene moiety [11,12,28]. The protons in the *ortho* position of the (η^5-C_5H_4) ring appear in the region δ 4.63–4.96, whereas the protons in the *meta* position occur in the range δ 4.28–4.48. The (η^5-C_5H_5) ring appears in the region δ 3.97–4.04. The protons of the *meta*-disubstituted benzoyl group appear as a triplet, doublet, doublet and singlet in the region δ 7.2–8.00. For example, in the case of the β-alanine derivative **7**, the aromatic protons are present as a triplet, two doublets and a singlet at δ 7.39, δ 7.64, δ 7.71 and δ 7.89, respectively. 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 4.39 and 4.85, respectively. The N*H* proton appears as a triplet at δ 8.62 and a quartet at δ 3.51 corresponds to the –NHCH_2CH$_2$CO– protons. The triplet at δ 2.61 is due to the second methylene group adjacent to the carbonyl group.

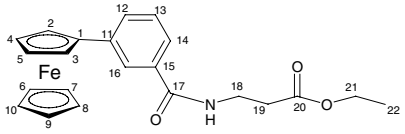
The ^{13}C NMR spectra of compounds **3**–**10** show signals in the region δ 66.7–84.6 indicative of a monosubstituted ferrocene subunit. The *ipso* carbon of the (η^5-C_5H_4) ring appears in a very narrow range of δ 84.3–84.6. This signal is absent in the DEPT 135 spectra. The carbon atoms of the aromatic ring are non-equivalent and therefore six signals are visible in the region δ 124.2–140.7. The methylene carbon atoms of derivatives **3**, **5**, **6**, **7**, **8**, **9** and **10** were identified by DEPT-135. A complete assignment of the ^{1}H and ^{13}C NMR spectra of compound **7** is presented in Table 1.

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 [30–32]. As the compounds were not amenable to electron ionization studies, MADLI was employed in the analysis of compounds **3**, **5**, **7**, **8**, **9**, and **10**, whereas compounds **4** and **6** were analyzed by electrospray ionization mass spectrometry (ESI-MS). MALDI confirmed the correct relative molecular mass for all the compounds and examination of the mass spectra revealed the presence of intense radical-cations, with cation adducts due to sodium and potassium adducts 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. It has been reported that the molecular radical cation of ferrocene and not the protonated molecular ion is generated during MALDI analysis [33]. Fragment ions were not observed or were of very low intensity in



Scheme 1. Synthesis of the *N-meta*-ferrocenyl benzoyl amino acid esters **3**–**10**; Gly(OMe) **3**, Ala(OMe) **4**, Leu(OMe) **5**, Phe(OMe) **6**, β-Ala(OEt) **7**, 4-Aba(OEt) **8**, 2-Aba(OEt) **9**, Aib(OEt) **10**: (i) $NaNO_2$, HCl, 5 °C; (ii) NaOH/MeOH, H_2O; (iii) DCC, HOBt, Et_3N, amino acid ester.

Table 1
^{1}H and ^{13}C spectroscopic data for **7**



Site	^{1}H NMR	^{13}C NMR	HMQC
1		84.6	
2, **3**	4.85		67.1
4, **5**	4.39		69.7
6 to 10	4.03		70.1
11		134.9	
12	7.64		129.5
13	7.39		128.9
14	7.71		124.3
15		140.6	
16	7.89		125.2
17		167.8	
18	3.51		35.7
19	2.61		34.3
20		173.4	
21	4.08		61.3
22	1.19		14.6

the MALDI spectra. This is in contrast to the analysis of the related *para*-ferrocenyl benzoyl amino acid derivatives by FABMS where important fragment ions were observed [28]. The ESI mass spectra displayed $[M + H]^+$ species and intense adducts due to sodium and potassium were present 22 and 38 Da higher than the protonated molecular ion species. A fragment ion was observed at *m*/*z* 261 due to the ferrocenylphenyl subunit at the N-terminal.

In conclusion, the novel *N*-*meta*-ferrocenyl benzoyl amino acid esters **3**–**10** were prepared in good yields using organic peptide synthetic protocols. The compounds were characterized by NMR spectroscopic techniques and by mass spectrometry.

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). We also thank John Kelly of Bruker Daltonics, UK for the MALDI mass spectra.

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[29] Synthesis of compound **7**. β-Alanine ethyl ester hydrochloride (0.3 g, 2.0 mmol) and triethylamine (0.5 ml) were added to a solution of *meta*-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 gave **7** as orange needles, (0.44 g, 68%). m.p.104–106 °C. Mass spectrum: Found: $[M]^+$ 405.104, $C_{22}H_{23}N_1O_3Fe$ requires: 405.103. IR ν_{max}(KBr): 3629, 2933, 1740, 1625, 1548, 1455, 1261, 1186 cm^{-1}. UV–vis λ_{max} MeCN: 324 (ε 1580), 448 (ε 410) nm. ^{1}H NMR (400 MHz) δ (DMSO): 8.62 (1H, t, J = 6.4 Hz, –CON*H*–), 7.89 (1H, s, ArH), 7.71 (1H, d, J = 7.6 Hz, ArH), 7.64 (1H, d, J = 7.6 Hz, ArH), 7.39 (1H, t, J = 7.6 Hz, ArH), 4.85 {2H, t, J = 1.2 Hz, *ortho* on (η^5-C_5H_4)}, 4.39 {2H, t, J = 1.2 Hz, *meta* on (η^5-C_5H_4)}, 4.08 (2H, q, J = 7.2 Hz, –OCH_2CH$_3$), 4.03 {5H, s, (η^5-C_5H_5)}, 3.51 (2H, q, J = 6 Hz, –NHCH_2CH$_2$–), 2.61 (2H, t, J = 7.2 Hz, –NHCH$_2$CH_2–), 1.19 (3H, t, J = 7.2 Hz, –OCH$_2$CH_3).

^{13}C NMR (100 MHz) δ ($CDCl_3$): 173.4, 167.8, 140.6, 134.9, 129.5, 128.9, 125.2, 124.3, 84.6, 70.1, 69.7, 67.1, 61.3 (−ve DEPT), 35.7 (−ve DEPT), 34.3 (−ve DEPT), 14.6.

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