Synthesis and characterisation of novel ferrocenyl thienyl & thiazolyl systems

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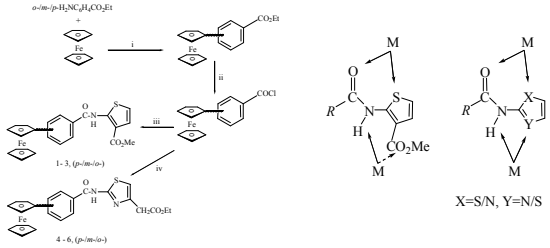
Introduction

Ferrocenyl derivatives are currently under investigation by our group and several series containing both amidothienyl and amidothiazolyl systems have been synthesised and characterised. The incorporation of thienyl/thiazolyl groups into a ferrocenyl- or ferrocenylphenyl system greatly enhances the number of potential donor atoms for coordination with metal fragments *e.g.* Pt^{II}, Pd^{II} with a view to platinum anti-cancer studies and/or interaction with guest molecules through suitable hydrogen bonding interactions.

In nature, thiazole has been found to be vital in certain natural products: examples include the antibiotic bacitracin and the siderophore yersiniabactin. In therapeutic studies the antitumour compound epothilone A and myxothiazole (inhibitor) have been extensively studied.[1]



Schemes 1 and **2**. Synthesis of compounds **1** to **6**: The donor atoms present in **1** to **3**, **4** to **6**.

Synthesis of compounds 1 - 6

The ferrocenylphenylamido thienyl and thiazolyl esters **1-6** have been prepared *via* a Schotten-Baumann reaction of the relevant acid chloride with thienyl or thiazolyl amines. These systems have been characterised by a range of spectroscopic techniques including ^{1}H, ^{13}C (top right), infra-red (solution/KBr), UV-vis, electrochemistry and mass spectrometry.

Yields in a range from 20 – 65% were typically recorded. The structures of **1** - **6** were unambiguously assigned from NMR (Table 2, middle right) and mass spectrometric data.

Structural studies of 1 and 3 - 5

The single crystal X-ray structures of **1** (below) and **3** to **5** have been determined and selected crystallographic and structural details are listed for the *para*-derivatives **1** (below) and **4** (top right). Of interest is the fact that there are no crystal structures currently on the Cambridge Structural Database (version 5.25, April 2004) that contain both a ferrocenyl and thiazole moiety thus highlighting the novel nature of these structural systems.[2,3]

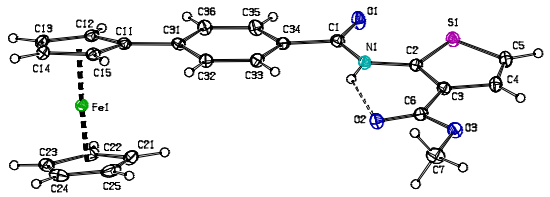


Figure 1 ORTEP diagram of the *para*-ferrocenylphenylamidothienyl ester **1** at the 30% probability level.

1: $C_{23}H_{19}NO_3SFe$, monoclinic, space group $P2_1/n$, a = 10.1428(3), b = 8.0965(2), c = 23.0557(7) Å, β = 95.4912(14)°, V = 1884.67(9) Å^3, Z = 4, T = 150(1) K, density = 1.569 g.cm^{-3} (calc.), $F(000)$ = 920, μ = 0.937 mm^{-1}, 16090 reflections from 2-27.5°, 4313 unique, 3441 > 2σ(I), 268 parameters, R factor = 0.036, wR_2 = 0.088.

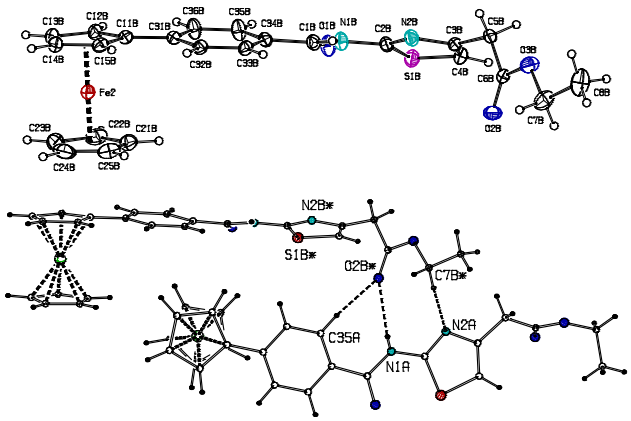


Figure 2 ORTEP diagram of **4** (top) and hydrogen bonding interactions in the crystal structure of **4** (bottom)

Molecular and Crystal structure of 4

Compound **4** crystallises with two molecules in the asymmetric unit in the space group P $\bar{1}$ (No. 2). The A and B molecules aggregate through intermolecular N-H…O=C_{ester} interactions generating a hydrogen bonded chain as (A…B..)$_n$. These are augmented by flanking C-H…O=C and C-H…N interactions as depicted for the A/B$^+$ pair in the diagram (bottom left). Crystallographic details for **4** are summarized below.

4: $C_{24}H_{22}N_2O_3SFe$, triclinic, space group P $\bar{1}$ (No. 2), a = 12.7466(4), b = 12.8752(8), c = 13.5661(7) Å, α = 91.811(3)°, β = 106.096(3)°, γ = 92.735(3)°, V = 2134.35(18) Å^3, Z = 4, T = 150(1) K, density = 1.476 g.cm^{-3} (calc.), $F(000)$ = 984, μ = 0.834 mm^{-1}, 22426 reflections from 2.6-27.5°, 9714 unique, 5617 > 2σ(I), 582 parameters, R factor = 0.050, wR_2 = 0.126. Comparisons of the interactions in **4** and **5** are listed below.

	4A	**4B**	**5**†
N-H…O=C_{ester} (Å)	2.980(4)	2.977(4)	3.055(3)
H…O/N-H…O°	2.35(4) / 164(5)°	2.28(3) / 158(4)°	2.15(3) / 169(3)°
C-H…O=C_{ester} (Å)	3.186(5)	3.394(4)	3.304(3)
H…O/C-H…O°	2.24 / 173°	2.46 / 167°	2.58 / 135°
C-H…$N_{thiazole}$ (Å)	3.642(7)	3.536(5)	3.375(3)
H…N/C-H…N°	2.67 / 168°	2.56 / 169°	2.41 / 166°

Table 1 Comparison of the hydrogen bonding interactions in the *para*- **4** and *meta*- **5** systems: the differences (Å,°) in molecular aggregation is easily discerned. † - repeated across an inversion centre.

NMR spectroscopy

The NMR data confirm the functional groups in the chemical structures in **1** to **6**. Two sets of N-*H* resonances are present with δ 11.97/12.06/10.70 and 10.15/10.32/11.14 (the former due to the intramolecular N-H…O=C_{ester} interaction with the *ortho*-thienyl carboxylate group in **1** to **3**). Other trends *e.g.* the *ortho*-ferrocenyl $H_{12/15}$ signals derive from the twisted C_6 ring from co-planarity with the (η^5-C_5H_4) group. The C=O_{amide} signal for **3** at δ 166.96 is different from **1** and **2** at δ 163.44 and 163.78, respectively, and likewise for **4** to **6** indicating the distortion and change in electronic environment for the amide group with respect to the twisted *ortho*-(ferrocenyl)benzoyl group.

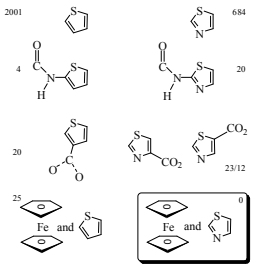
Compound	**^{1}H, N*H***	**^{1}H, $H_{12/15}$ / $H_{13/14}$**	**^{13}C, $C_{C=Oamide/ester}$**
1	11.97	4.89 / 4.56	163.44 / 166.46
2	12.06	4.76 / 4.40	163.78 / 166.40
3	10.70	4.49 / 4.22	166.96 / 165.11
4	10.15	4.74 / 4.43	164.35 / 170.22
5	10.32	4.68 / 4.38	164.79 / 170.17
6	11.14	4.32 / 4.21	167.57 / 169.95

Table 2 Selected ^{1}H and ^{13}C NMR (ppm) data for compounds **1** – **6**

Database analyses

Comparisons of **1** and **3** to **5** with the Cambridge Structural Database (January 2004, release v5.25) reveals several interesting features. Firstly, the thienyl group is a well studied system and 2001 structures are available as C_4S moiety (no restrictions and no H atoms, as in Scheme 3). Other searches are detailed by the fragments depicted in the scheme. However, a search for compounds containing both the ferrocenyl and C_3NS thiazolyl groups yields **0** 'hits'. This is unusual given the widespread application of both systems in organometallic/organic compounds.

In perspective, related CSD searches for the five-membered heteroaromatic rings pyrrole, C_4NH and imidazole, C_3N_2H groups yield 1269 and 1667 structures, respectively, and comparable to thiophene/thiazole in abundance, whereas pyridine as C_5N is present in 34519 structures (*ca.* 10% of the CSD). To date no structures are available on the CSD (Jan. 2004) containing any η^5-C_5 based transition metal metallocenyl (sandwich) type compound with a C_3NS thiazolyl fragment. The vast majority of metallothiazolyl derivatives are therefore in the general area of coordination chemistry.



Fragments used and 'hits' found in the CSD searches

Conclusions and further research

To date we have synthesized several series of organometallic thienyl and thiazolyl derivatives encompassing a range of potential biological and materials applications. Further studies, in combination with high-level *ab initio* calculations are on-going and include formation of metal complexes and incorporation into larger peptide strands.

Acknowledgements

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References

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3 S. Alley, J.F. Gallagher, V.M. Hooper, P.T.M. Kenny and A.J. Lough, *Dalton Trans.*, 2004, *submitted*.