



Synthesis and characterisation of novel ferrocenyl thienyl & thiazolyl systems

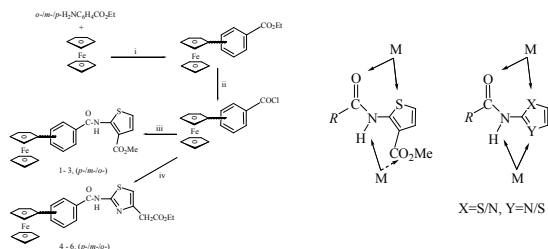
Steven Alley,^{a,b} John F. Gallagher,^{a,b} Vincent M. Hooper,^a Peter T.M. Kenny^{a,b} and Alan J. Lough^c^a School of Chemical Sciences, Dublin City University, Glasnevin, Dublin 9, Ireland^b National Institute for Cellular Biotechnology, Dublin City University, Glasnevin, Dublin 9, Ireland^c Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

National Institute for Cellular Biotechnology

Introduction

Ferrocenyl derivatives are currently under investigation by our group and several series containing both amidothieryl 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 ¹H, ¹³C (top right), infra-red (chlorination/IR), 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}

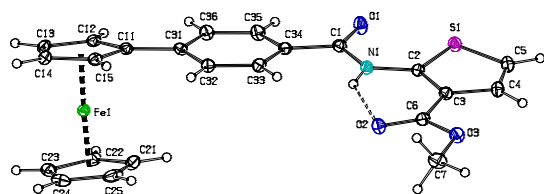


Figure 1 ORTEP diagram of the *para*-ferrocenylphenylamidothienyl ester 1 at the 30% probability level.

1: C₂₂H₁₉NO₃SFe, monoclinic, space group P2₁/n, *a* = 10.1428(3), *b* = 8.0965(2), *c* = 23.0557(7) Å, β = 95.4912(14)°, *V* = 1884.67(9) Å³, *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.

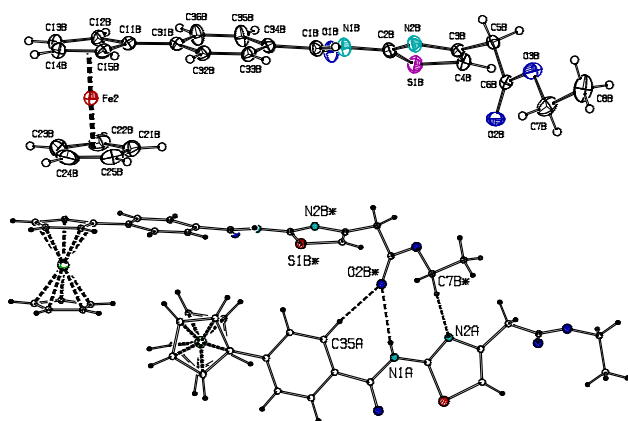


Figure 2 ORTEP diagram of 4 (top) and hydrogen bonding interactions in the crystal structure of 4 (bottom)

References

- R.S. Roy, A.M. Gehring, J.C. Milne, P.J. Belshaw and C.T. Walsh, *Nat. Prod. Rep.* 1999, **16**, 249-263.
- F.H. Allen, *Acta Crystallographica Section B* **58**, 2002, 380-388.
- S. Alley, J.F. Gallagher, V.M. Hooper, P.T.M. Kenny and A.J. Lough, *Dalton Trans.*, 2004, *submitted*.

Molecular and Crystal structure of 4

Compound 4 crystallises with two molecules in the asymmetric unit in the space group P 1̄ (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: C₂₂H₂₂N₂O₃SFe, triclinic, space group P 1̄ (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) Å³, *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 C₆ ring from co-planarity with the (η⁵-C₅H₅) 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.

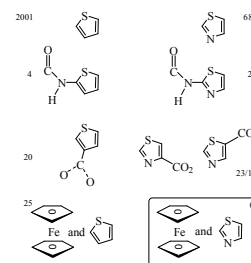
Compound	¹ H, NH	¹ H, H _{12/15} / H _{13/14}	¹³ C, C=Oamide/ester
1	11.97	4.89 / 4.56	163.44 / 166.46
2	12.06	4.76 / 4.40	163.78 / 166.40
3	10.70	4.49 / 4.22	166.96 / 165.11
4	10.15	4.74 / 4.43	164.35 / 170.22
5	10.32	4.68 / 4.38	164.79 / 170.17
6	11.14	4.32 / 4.21	167.57 / 169.95

Table 2 Selected ¹H and ¹³C 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 C₆S 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 C₆NS 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, C₄NH and imidazole, C₃N₂H groups yield 1269 and 1667 structures, respectively, and comparable to thiophene/thiazole in abundance, whereas pyridine as C₅N is present in 34519 structures (*ca.* 10% of the CSD). To date no structures are available on the CSD (Jan. 2004) containing any η⁵-C₅ based transition metal metallocenyl (sandwich) type compound with a C₆NS thiazolyl fragment. The vast majority of metallocenyl 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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