Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4639-4642, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00955-6

Acylation of Alkyl Ferrocenecarboxylates: An Approach to Unsymmetrical 1,1'-Disubstituted Ferrocene Derivatives and Bridged Metallocene Receptors

Martin C. Grossel,* Darren G. Hamilton† and Tracy A. Vine

* Department of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK

† Current address: University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK

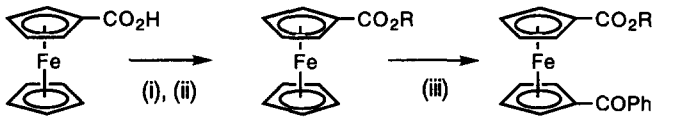
Abstract: Acylation of benzyl ferrocenecarboxylate **3** with benzoyl chloride affords the known ferrocene keto-acid **5** in one step and provides a convenient entry to a variety of unsymmetrical 1,1'-substituted ferrocene derivatives. Similar acylation procedures have been employed to bridge two ferrocene units leading to a series of rigid bis-ferrocene derivatives, which are precursors to more elaborate receptor architectures.

The integration of one or more ferrocene units into a macrocyclic architecture has long been recognised as an attractive way to endow a molecule with secondary functionality.[1] An expanding literature testifies to the very large number and variety of ferrocenyl crowns and cryptands that have been prepared and, because of their relative ease of synthetic access, the overwhelming majority of reported systems involve attachment of a ferrocene moiety to previously known crown ether or cryptand structures.[2] Such derivatives were designed, often successfully, to function as selective cation sensors[3] but more recently, a metallocene derived system capable of both anion and cation detection has been realised.[4]

In contrast to the wealth of metallocene chemistry developed for the synthesis of cation binding and detection systems, there are few descriptions of ferrocene-based host molecules with macrocyclic cavities suitable for the complexation of molecular species. Gokel has reported a series of bis-ferrocene acyclic receptors reminiscent of the "molecular clefts" developed by Rebek. Such structures exploit the ability of the ferrocene unit to act as an atomic ball bearing, allowing conformational flexibility during complexation.[5] Only a small number of macrocyclic metallocene systems have been disclosed, involving various metal centres and bridging units; all these approaches rely on the use of 1,1'-disubstituted metallocene derivatives. We have now re-examined the Friedel-Crafts acylation of ferrocene, a regio-controlled reaction in which an electron-withdrawing group in one ring has the advantageous effect of directing subsequent electrophilic attack to the second (unsubstituted) ring.[6] This degree of control is clearly an important consideration in the synthetic construction of large ferrocene-based architectures, such selectivity being less readily exploited in the lithiation of ferrocene.[7] An additional advantage of the present approach is that 1-ferrocenecarboxylic acid **1**, which is readily available on a multi-gram scale from ferrocene,[8] is used as the starting material.

We initially re-examined the previously reported Friedel-Crafts acylation of methyl ferrocenecarboxylate **2** with benzoyl chloride[9] (**2** is best prepared from methanolysis of ferrocenecarbonyl chloride, a method superior to the literature[10] esterification using

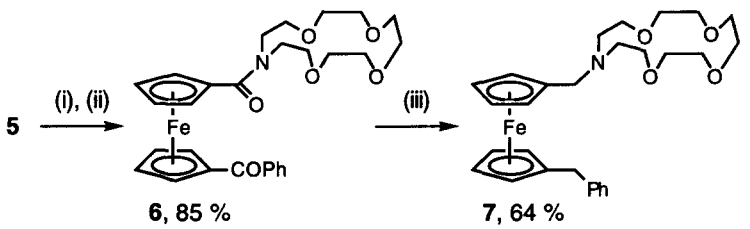
$MeOH/H_2SO_4$). This afforded a good yield of the known[9] keto-ester **4** but alkaline hydrolysis of **4** only gave the parent ester **2**, the product of cleavage at the ferrocene-ketone bond. Such a process has precedent in the cleavage of β-keto esters under strongly basic conditions (Scheme 1).[11]



1 **2** R = Me, 91 % **3** R = CH_2Ph, 94 % **4** R = Me, 62 % **5** R = H, 72 %

Scheme 1. (i) $(COCl)_2$/DCM/DMF/rt; (ii) ROH (**2** R = Me, **3** R = CH_2Ph)/DCM/Pyridine/rt; (iii) PhCOCl/$AlCl_3$/DCM/rt.

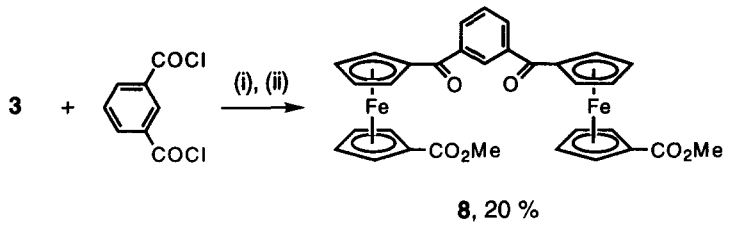
Benzyl ferrocenecarboxylate **3** proved to be a much more amenable substrate. This ester may be obtained in high yield utilising the procedure described for **2**,[12] and subsequent acylation with benzoyl chloride was found to afford the keto-acid **5** directly, avoiding the need for a separate hydrolysis step. Keto-acid **5** could be efficiently converted to keto-amide derivatives such as the novel crown ether **6** by sequential treatment with oxalyl chloride, to form a reactive acid chloride, followed by the addition of aza-15-crown-5.[13] Keto-amide **6** proved to have moderate air sensitivity but could be readily reduced to the air- and light-stable *bis*-methylene-linked aza-crown ether **7** using a $AlCl_3/LiAlH_4$ mixture, a system well known to reduce both aromatic ketones and hindered tertiary amides (Scheme 2).[14]



6, 85 % **7**, 64 %

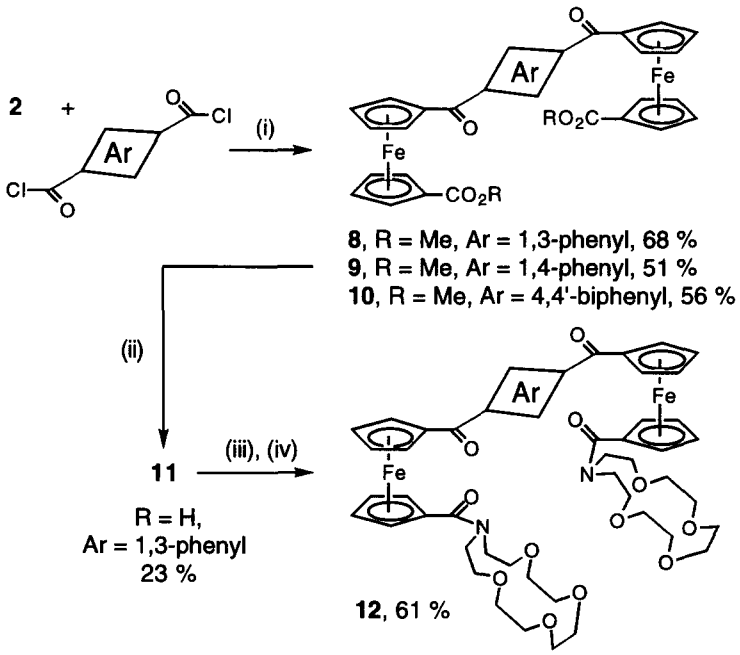
Scheme 2. (i) $(COCl)_2$/DCM/DMF/rt; (ii) Aza-15-crown-5/Pyridine/DCM/rt; (iii)$LiAlH_4/AlCl_3$/THF/reflux.

The simplicity of synthetic access to a variety of heteroannularly substituted ferrocene acids promised by the above procedure prompted an attempt to bridge two ferrocene sub-units via acylation of **3** with isophthaloyl dichloride. Although the acylation procedure was observed to proceed smoothly (TLC) the marked propensity of the benzyl ester functions to hydrolyse during aqueous work-up impeded the isolation of the bridged products since we could find no suitable procedure to effect the direct purification of the highly insoluble mixture of acidic material obtained from the double acylation procedures. However, despite the inherent sensitivity of many ferrocene derivatives to acidic conditions, esterification of the crude acid product mixture allowed isolation of the novel dimethyl ester **8** of the desired bis-ferrocene diacid (Scheme 3).



Scheme 3. (i) $AlCl_3$/DCM/rt; (ii) MeOH/H_2SO_4/reflux

Since **8** should be directly available from the acylation of methyl ferrocenecarboxylate **2** with isophthaloyl dichloride, we next investigated the acylation of **2** with a variety of aromatic diacyl dihalides (Scheme 4). These reactions proceeded smoothly to afford the corresponding bis-ferrocene methyl esters bridged by isophthaloyl **8**, terephthaloyl **9**,[15] and 4,4'-biphenyl **10** spacers in satisfactory yields (50-70 %). In view of the previously encountered problems with the alkaline hydrolysis of keto-ester **4** we examined alternative literature methods of ester cleavage involving attack at the methyl group of the ester function rather than the carbonyl group. Iodotrimethylsilane (Me_3SiI), which is known to perform methyl ester cleavage under mild conditions in aprotic solvents, readily converted the bridged methyl ester **9** into the corresponding diacid **11**, albeit in low yield.[16] Bis-acid **11** could be converted, via its diacyl halide, into the aza-crown derivative **12** employing identical conditions to those used in the synthesis of the model mono-ferrocene derivative **6**.[17]



Scheme 4. (i) $AlCl_3$/DCM/rt; (ii) Me_3SiI/$CHCl_3$/rt; (iii) $(COCl)_2$/DCM/DMF/rt ; (iv) Aza-15-crown-5/Pyridine/DCM/rt.

In summary, the Friedel-Crafts acylation chemistry of ferrocene has been developed to provide a synthetically simple route to heteroannularly substituted ferrocene acids, and their immediate derivatives via acylation of benzyl ferrocenecarboxylate. Additionally, a novel procedure for the construction of "U"-shaped ferrocene based molecular clefts, similar to these described by Gokel, has been developed. Both synthetic pathways benefit from having as their starting point a mono-substituted ferrocene derivative, 1-ferrocenecarboxylic acid, a material which is commercially far cheaper, and more readily synthetically accessible, than the corresponding 1,1'-disubstituted derivative. The synthesis of more complex macrocyclic ferrocene systems using these and related approaches is currently under investigation.

Acknowledgements

We thank the former SERC for funding two research studentships (DGH and TAV).

References and Notes

1. Oepen, G.; Vögtle, F. *Leibigs. Ann. Chem.* **1979**, 1094.
2. For recent advances, see: a) Plenio, H.; Diodone, R. *J. Organomet. Chem.* **1995**, 492, 73. b) Beer, P. D.; Chen, Z.; Drew, M. G. B.; Pilgrim, A. J. *Inorg. Chim. Acta.* **1994**, 225, 137. c) Grossel, M. C.; Goldspink, M. R.; Hriljac, J. A.; Weston, S. C. *Organometallics* **1991**, 10, 851.
3. Beer, P. D. *Chem. Soc. Rev.* **1989**, 18, 409.
4. Beer, P. D.; Chen, Z.; Ogden, M. I. *J. Chem. Soc., Faraday Trans.* **1995**, 91, 295.
5. Medina, J. C.; Li, C.; Bott, S. G.; Atwood, J. L.; Gokel, G. W. *J. Am. Chem. Soc.* **1991**, 113, 366.
6. Rausch, M. D.; Fischer, E. O.; Grubert, H. *J. Am. Chem. Soc.* **1960**, 82, 76.
7. Rausch, M. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, 10, 127.
8. Reeves, P. C. *Org. Synth.* **1978**, 56, 28.
9. Little, W. F.; Eisenthal, R. *J. Am. Chem. Soc.* **1960**, 82, 1577.
10. Benkeser, R. A.; Goggin, D.; Schroll, G. *J. Am. Chem. Soc.* **1954**, 76, 4025.
11. Stetter, H. *Angew. Chem.* **1955**, 67, 769.
12. **3**: m.p. 94-96 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.47-7.38 (5 H, m), 5.28 (2 H, s), 4.84 (2 H, t, J = 2 Hz), 4.41 (2 H, t, J = 2 Hz), 4.11 (5 H, s); FAB MS (m/z) 320 (M^+).
13. **6**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 7 Hz), 7.43-7.34 (3 H, m), 4.84 (2 H, J = 2 Hz), 4.59 (2 H, d, J = 2 Hz), 4.54 (2 H, t, J = 2 Hz), 4.22 (2 H, t, J = 2 Hz), 3.54-3.36 (20 H, broad s); FAB MS (m/z) 535 (M^+).
14. **7**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35-7.18 (5 H, m), 4.11-4.03 (8 H, m), 3.70-3.52 (20 H, m), 2.72 (4 H, s); FAB MS Found 508.4635, $[M+H]^+$ requires 508.4664.
15. **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (4 H, s), 4.95 (4 H, t, J = 2 Hz), 4.85 (4 H, t, J = 2 Hz), 4.75 (4 H, t, J = 2 Hz), 4.40 (4 H, t, J = 2 Hz), 3.72 (6 H, s); FAB MS (m/z) 618 (M^+).
16. **11**: ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.00 (4 H, s), 4.89 (4 H, s), 4.77 (4 H, s), 4.73 (4 H, s), 4.56 (4 H, s).
17. **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (4 H, s), 4.98 (4 H, s), 4.76 (4 H, s), 4.72 (4 H, s), 4.37 (4 H, s), 3.71 (40 H, broad s); FAB MS (m/z) 993 ($[M+H]^+$).

(*Received in UK* 4 *March* 1997; *revised* 14 *May* 1997; *accepted* 15 *May* 1997)