JOC *Note*

An Efficient Route to Pentasubstituted Acylferrocenes

Jakob Norinder, Hanna K. Cotton, and
Jan-E. Bäckvall*,[†]

*Department of Organic Chemistry, Arrhenius Laboratory,
Stockholm University, SE-106 91 Stockholm, Sweden*

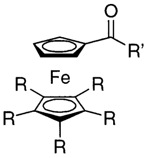
jeb@organ.su.se

Received August 30, 2002

Abstract: A number of pentasubstituted acylferrocenes were selectively prepared from ferrous chloride, sodium acylcyclopentadienides, and the corresponding pentasubstituted lithium cyclopentadienides in good yields. The selectivity is governed by the different steric and electronic properties of the acylcyclopentadienides vs the pentasubstituted cyclopentadienides.

Ferrocene compounds have gained much interest over the last two decades.[1] Acylferrocenes are important key intermediates in the synthesis of chiral ferrocene ligands such as N,S, P,S, P,N, and P,P ligands.[1b,c,2] We have recently employed chiral ferrocenyl N,S ligands in the enantioselective copper(I)-catalyzed alkylation of allylic acetates.[2] In our ongoing project developing more efficient ferrocene ligands it was of interest to study the effect of ferrocenes with one pentasubstituted ring. Pentasubstituted ferrocenes are generally prepared from the reaction of a pentasubstituted cyclopentadienyl anion and another cyclopentadienyl anion with an iron source.[3−5] Recently, pentaaryl-substituted ferrocenes were also obtained by perarylation of the unsubstituted cyclopentadienyl ring using palladium-catalyzed cross-coupling reactions.[6]

For the synthesis of pentasubstituted acylferrocenes, two strategies were considered: (i) the ferrocene sandwich structure can be obtained from the pentasubstituted cyclopentadiene and the unsubstituted cyclopentadiene, followed by acylation of the unsubstituted cyclopentadienyl ring or (ii) the ferrocene sandwich structure can be formed from the pentasubstituted cyclopentadiene and an acylcyclopentadiene.



1a R = Me, R' = Me
1b R = Me, R' = Et
1c R = Et, R' = Me
1d R = Et, R' = Et
1e R = Ph, R' = Me
1f R = Ph, R' = Et

FIGURE 1. Pentasubstituted acylferrocenes, prepared from sodium acylcyclopentadienide, pentasubstituted lithium cyclopentadienide, and $FeCl_2$.

Examples of pentasubstituted acylferrocenes obtained by both strategies can be found in the literature. The former approach for the synthesis of acetyl-pentamethylferrocene (**1a**) is exemplified by Friedel−Crafts acylation of pentamethylferrocene in 30% yield[7] and by acylation of pentaphenylferrocene with *ortho*-chlorobenzoyl chloride in a high yield.[8] With the less active acetyl chloride, no Friedel−Crafts acylation took place on pentaphenylferrocene, propably due to the electron-withdrawing effect of the phenyl substituents, causing pentaphenylferrocene to be less susceptible toward electrophilic aromatic substitution, compared to ferrocene and pentamethylferrocene.[9] Furthermore, the pentasubstituted ferrocenes have to be synthesized prior to the Friedel−Crafts acylation, often in low yields.[3,10]

The second approach mentioned above is more attractive and exemplified by the preparation of compound **1a** by consecutive addition of lithium pentamethylcyclopentadienide (**2a**) and lithium acetylcyclopentadienide to $Fe(acac)_2$.[4a] A yield of 39% was obtained using 2 equiv of both $Fe(acac)_2$ and **2a**. However, the reactions involving $Fe(acac)_2$ are difficult to reproduce because they are sensitive toward ligand exchange and oxidation, giving decamethyldihydrofulvalene as a byproduct.[4a] Another method employing iron pentacarbonyl as an iron source yielded compound **1a** in four steps.[11]

The need for a more efficient method for the synthesis of pentasubstituted acylferrocenes is apparent. In this publication, we report a simple and robust method for obtaining compounds **1a**−**f** (Figure 1) in good yields by reacting sodium acylcyclopentadienide (**3a** or **3b**) and the pentasubstituted lithium cyclopentadienides **2a**, **2b**, or **2c** with $FeCl_2$.

In our synthesis of pentasubstituted acylferrocenes from two different cyclopentadienyl anions, we chose to use $FeCl_2$ since it is more stable than $Fe(acac)_2$. High quality $FeCl_2$ was purchased as beads. Prior to use, the beads were suspended in refluxing THF. The sodium salt

---

[†] Fax: +46 8 154908.

(1) (a) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995. (b) Kagan, H. B.; Riant, O. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press, Inc.: Greenwich, CT, 1997; Vol. 2, pp 189−235. (c) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (d) Togni, A. *Angew. Chem.* **1996**, *108*, 1581; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475.

(2) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923.

(3) (a) Cunningham, K. L.; McMillin, D. R. *Polyhedron* **1996**, *15*, 1673. (b) Lee, S.-G.; Lee, H.-K.; Lee, S. S.; Chung, Y. K. *Organometallics* **1997**, *16*, 304. (c) Bunel, E. E.; Valle, L.; Manriquez, J. M. *Organometallics* **1985**, *4*, 1680.

(4) (a) Bildstein, B.; Hradsky, A.; Kopacka, H.; Malleier, R.; Ongania, K.-H. *J. Organomet. Chem.* **1997**, *540*, 127. (b) Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Togni, A.; Albinati, A.; Müller, B. *Organometallics* **1994**, *13*, 4481.

(5) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

(6) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

(7) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.

(8) Jones, G.; Butler, D. C. D.; Richards, C. J. *Tetrahedron Lett.* **2000**, *41*, 9351.

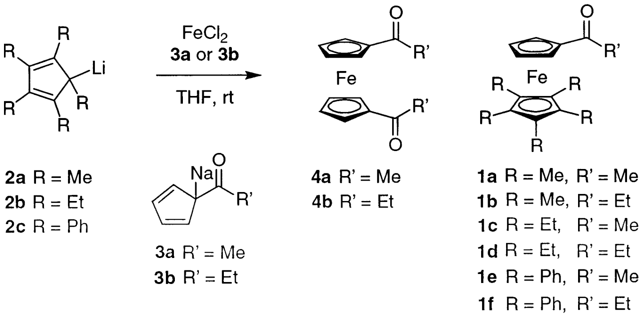
(9) We could not obtain the desired product by employing the reaction conditions for Friedel−Crafts acylation according to: Slocum, D. W.; Duraj, S.; Matusz, M.; Cmarik, J. L.; Simpson, K. M.; Owen, D. A. *Met.-Containing Polym. Syst.* **1985**, 59.

(10) (a) Field, L. D.; Ho, K. M.; Lindall, C. M.; Masters, A. F.; Webb, A. G. *Aust. J. Chem.* **1990**, *43*, 281. (b) McVey, S.; Pauson, P. L. *J. Chem. Soc.* **1965**, *87*, 4312. (c) Field, L. D.; Hambley, T. W.; Lindall, C. M.; Masters, A. F. *Polyhedron* **1989**, *8*, 2425. (d) Aroney, M. J.; Buys, I. E.; Dennis, G. D.; Field, L. D.; Hambley, T. W.; Lay, P. A.; Masters, A. F. *Polyhedron* **1993**, *12*, 2051.

(11) Herberich, G. E.; Gaffke, A.; Eckenrath, H. J. *Organometallics* **1998**, *17*, 5931.

10.1021/jo026373v CCC: $22.00

SCHEME 1



3a was obtained according to a literature procedure in which sodium cyclopentadienide is allowed to react with ethyl acetate in THF.[12] The corresponding sodium salt **3b** was prepared by the same procedure using methyl propionate. Since the reaction mixture contained 1 equiv of alcohol, the solvents were removed and the residue was washed with pentane. The desired compounds were obtained in high yields. The isolated salts **3a** and **3b** both contained varying amounts of THF. In the case of **3b**, residual methyl propionate could not be removed. Nevertheless, this did not seem to affect the outcome of the reactions.

Lithium salts **2a**−**c** were obtained by treatment of the pentasubstituted cyclopentadienes with *n*-BuLi. For practical reasons, we chose to work with the isolated lithium salts **2a** and **2b**. However, caution has to be taken, as they are highly reactive and prone to ignite in air. Compound **2c** could not be stored and was used immediately after preparation according to a published procedure.[5]

The pentasubstituted acylferrocenes **1a**−**f** were readily prepared by mixing sodium acylcyclopentadienide **3a** or **3b** with the appropriate pentasubstituted lithium cyclopentadienide **2a**, **2b**, or **2c** and FeCl$_2$ at room temperature (Scheme 1). After the reaction was complete, the product mixture was filtered through either silica or alumina and purified by column chromatography to give the desired products **1a**−**f** in good yields.

When equimolar amounts of sodium acylcyclopentadienide and pentasubstituted lithium cyclopentadienide are added simultaneously to FeCl$_2$, a mixture of ferrocenes is expected. If the cyclopentadienides were equally reactive, a statistical distribution (1:2:1) of **4**, **1**, and the symmetric decasubstituted ferrocene would be obtained.

The preparation of **1a**, by simultaneous addition of equimolar amounts of the starting materials resulted in a considerably higher selectivity than that from a statistical distribution. The product **1a** was obtained in 57% yield and with a selectivity of 95% (entry 1, Table 1). In this reaction, and in all following reactions, the decasubstituted ferrocenes were never detected. Using 1.3 equiv of lithium pentamethylcyclopentadienide increased the yield of **1a** to 69% (entry 2, Table 1). Compounds **1b**−**d** were similarly prepared in good yields and with a selectivity of >95% employing the same conditions (entry 3−5, Table 1). By using 1.1 equiv of **2a**, **1a** was successfully prepared on a larger scale (15 mmol) yielding 3.6 g (83%). The higher yield on a larger scale may be explained by the moisture-sensitive nature of the starting materials (entry 9, Table 1).

TABLE 1. Preparation of Pentasubstituted Acylferrocenes

entry	product	equiv of **2**	selectivity (%)[a]	isolated yields of **1** (%)
1[b]	**1a**	1.0	95	57
2[b]	**1a**	1.3	>95	69
3[b]	**1b**	1.5	>95[c]	67
4[b]	**1c**	1.3	>95	76
5[b]	**1d**	1.3	>95[c]	58
6[b]	**1e**	1.3	83	53
7[d]	**1e**	1.3	89	66
8[d]	**1f**	1.3	91	64
9[e]	**1a**	1.1	>95[c]	83

[a] Determined from ^{1}H NMR spectra of the crude products. Selectivity is defined as **1**/(**1** + **4**). [b] Prepared on a 0.5−1.8 mmol scale by simultaneous addition of a suspension of **2** and **3** in THF (approximately 6 mL/mmol of cyclopentadienides **2** and **3**) to a suspension of FeCl$_2$ in THF (10 mL/mmol of FeCl$_2$) at room temperature. The reaction mixture was stirred overnight. [c] No bisacylferrocene (**4**) could be detected. [d] Prepared on a 0.5 mmol scale by consecutive addition of **2** and **3** to FeCl$_2$. Reactions were performed at room temperature overnight. [e] Prepared on a 15 mmol scale.

In the preparation of the pentaphenyl acylferrocenes by simultaneous addition, the formation of compound **1e** proceeded with 83% selectivity and gave a yield of 53% (entry 6, Table 1). The outcome of the reaction was improved by consecutive addition of the starting materials, allowing FeCl$_2$ and lithium pentaphenylcyclopentadienide to react for 2 h before sodium acetylcyclopentadienide was added, increasing the yield to 66%. Furthermore, the formation of bisacetylferrocene (**4a**) was decreased and now the selectivity for **1e** was 89% (entry 7, Table 1). Compound **1f** was also prepared by consecutive addition to give the product in 64% yield and with 91% selectivity (entry 8, Table 1).

We believe that the high selectivity for formation of nonsymmetrical ferrocenes **1** is due to both steric and electronic properties of the acylcyclopentadienides and the pentasubstituted cyclopentadienides. Since pentamethylcyclopentadienide and pentaethylcyclopentadienide are good Lewis bases, they readily react with FeCl$_2$. Acylcyclopentadienides, on the other hand, are lesser Lewis bases and, hence, react more slowly with FeCl$_2$. Attack by the second cyclopentadienyl ring is more difficult from a steric point of view, hindering the pentasubstituted lithium cyclopentadienide from being introduced and giving the sodium acylcyclopentadienide time to react. This can explain why direct addition of all three components is possible in the preparation of **1a**−**d**.

The electron-withdrawing ability of the phenyl groups makes lithium pentaphenylcyclopentadienide (**2c**) a weaker Lewis base. Thus, the difference in Lewis basisity of the two cyclopentadienyl rings is not as pronounced in the reaction leading to **1e** and **1f** compared to the reaction leading to **1a**−**d** and indeed more bisacylferrocene (**4**) is obtained in the former case. Pentamethylcyclopentadienyl iron complexes have previously been isolated,[13] and the fact that yield and selectivity are increased by consecutive addition implies that a pen-

---

(12) Hart, W. P.; Macomber, D. W.; Rausch, M. D. *J. Am. Chem. Soc.* **1980**, *102*, 1196.

taphenylcyclopentadienyl iron complex is formed prior to the addition of the acylcyclopentadienide.

In conclusion, we have developed a practical and useful method for the preparation of pentasubstituted acylferrocenes, which is of synthetic interest due to its simplicity and reliability. The present method gives better yields and consists of fewer steps than previously published procedures.

Experimental Section

General. ^{1}H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were recorded using residual $CHCl_3$ (7.26 and 77.16 ppm, respectively) or HDO (4.79 ppm in ^{1}H) as internal standards. High-resolution mass spectra were recorded on a MALDI-TOF apparatus. All experiments were performed by standard Schlenk techniques under an argon atmosphere. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. THF and toluene were freshly distilled from sodium benzophenone ketyl radical prior to use. Pentane was distilled from calcium hydride prior to use. Anhydrous $FeCl_2$ (99.99%) was purchased commercially. Lithium pentamethylcyclopentadienide (**2a**),[14] lithium pentaethylcyclopentadienide (**2b**),[15] and pentaphenylcyclopentadiene[16] were prepared according to known procedures.

Sodium Acetylcyclopentadienide (3a). Following a literature procedure,[12] a mixture of sodium cyclopentadienide (6.0 mL, of a 2.0 M solution in THF, 12 mmol), THF (6 mL), and ethyl acetate (1.32 g, 15 mmol) was refluxed for 2 h. After the mixture was cooled, the solvent and volatile byproducts were removed in vacuo. The crude product obtained was washed with pentane to give 1.79 g as a brown solid. The product was quenched by D_2O, and ^{1}H NMR (D_2O) indicated a mixture of pure **3a** and 0.78 equiv of THF, which corresponds to an assay of 70% (w/w) of **3a** in 80% yield. ^{1}H NMR spectra were in accordance with published data.

Sodium Propanoylcyclopentadienide (3b). Using the same procedure as that for **3a** gave 2.83 g (95%) of a dark brown solid. ^{1}H NMR (D_2O) showed a molar ratio of 1:0.61:0.12 of **3b**, THF, and methyl propionate, which corresponds to an assay of 73% (w/w) of **3b**. ^{1}H NMR (400 MHz, D_2O): δ 6.78−6.56 (m, 2 H), 6.25−6.08 (m, 2 H), 2.66 (q, $J = 7.7$ Hz, 2 H), 1.19 (t, $J = 7.7$ Hz, 3 H).

General Procedure for the Preparation of Acyl-pentaalkylferrocenes 1a−d. A suspension of $FeCl_2$ was prepared by refluxing $FeCl_2$ beads in THF for a minimum of 5 h. The suspension was cooled to room temperature. A suspension of acylcyclopentadienide **3a** or **3b** and pentaalkylcyclopentadienide **2a** or **2b** in THF was transferred via a cannula to the suspension of $FeCl_2$. The reaction mixture was stirred at room temperature for a minimum of 12 h. Thereafter, the solvents were removed in vacuo and the product mixture was filtered through a short column of basic alumina, using ether as a solvent. The crude product was purified by column chromatography, using 9:1 *n*-pentane/ether as an eluent.

Acetyl-pentamethylferrocene 1a. Following the general procedure, a suspension of **2a** (334 mg, 2.35 mmol) and **3a** (337 mg of 70% (w/w), 1.81 mmol) in THF (25 mL) was added to a suspension of $FeCl_2$ (229 mg, 1.81 mmol) in THF (18 mL). The reaction mixture was stirred for 15 h followed by workup, which afforded 374 mg (69%) of **1a** as red crystals. Analytical data were in accordance with those from the literature.[4a]

Propanoyl-pentamethylferrocene 1b. Following the general procedure, a suspension of **2a** (220 mg, 1.55 mmol) and **3b** (205 mg of 73% (w/w), 1.04 mmol) in THF (15 mL) was added to a suspension of $FeCl_2$ (127 mg, 1.00 mmol) in THF (10 mL). The reaction mixture was stirred for 18 h followed by workup, which afforded 210 mg (67%) of **1b** as red crystals, mp 87−88 °C.

Acetyl-pentaethylferrocene 1c. Following the general procedure, a suspension of **2b** (325 mg, 1.53 mmol) and **3a** (215 mg of 72% (w/w), 1.20 mmol) in THF (18 mL) was added to a suspension of $FeCl_2$ (153 mg, 1.20 mmol) in THF (10 mL). The reaction mixture was stirred for 18 h followed by workup, which afforded 334 mg (76%) of **1c** as red crystals, mp 137−138 °C.

Propanoyl-pentaethylferrocene 1d. Following the general procedure, a suspension of **2b** (142 mg, 0.669 mmol) and **3b** (104 mg of 73% (w/w), 0.526 mmol) in THF (13 mL) was added to a suspension of $FeCl_2$ (65.3 mg, 0.515 mmol) in THF (5 mL). The reaction mixture was stirred for 18 h followed by workup, which afforded 114 mg (58%) of **1d** as red crystals, mp 91−92 °C.

Acetyl-pentaphenylferrocene 1e. A suspension of $FeCl_2$ was prepared by refluxing $FeCl_2$ beads (63.4 mg, 0.50 mmol) in THF (3.5 mL) for a minimum of 5 h. The suspension was cooled to room temperature. Lithium pentaphenylcyclopentadienide (**2c**), prepared according to Fu[5] [pentaphenylcyclopentadiene (0.29 g, 0.65 mmol) and *n*-BuLi (0.44 mL of a 1.6 M solution in hexane, 0.70 mmol) in toluene (10 mL) at 100 °C], was dissolved in THF (4 mL). The solution was added dropwise via a cannula to the suspension of $FeCl_2$. After 2 h, a suspension of **3a** (87.9 mg, 74% (w/w), 0.5 mmol) in THF (3 mL) was added via a cannula. The reaction mixture was stirred for 18 h and then filtered through silica. The silica was washed with ethyl acetate. The filtrate was recovered, and the solvents were removed in vacuo. Column chromatography in dichloromethane (100%) afforded 202 mg (66%) of **1e** as red crystals, mp 295−297 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15−7.03 (m, 25H), 4.83 (app t, $J = 1.8$ Hz, 2H), 4.48 (app t, $J = 1.8$ Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 134.9, 132.3, 127.3, 126.7, 88.3, 84.3, 79.1, 75.4, 29.5. IR: 3056 (w), 1669 (s), 1601 (m), 1502 (s), 1444 (m), 1276 (s), 909 (m), 740 (s), 700 (s) cm^{-1}. HRMS (*m*/*z*) calcd for $C_{42}H_{33}FeO$ ($M^+ + H$), 609.1880; found, 609.1822.

Propanoyl-pentaphenylferrocene 1f. The reaction was performed according to the method described for **1e**. The sodium acylcyclopentadienide used in this case was **3b** (109 mg, 73% (w/w), 0.55 mmol). Column chromatography in toluene (100%) afforded 199 mg (64%) of **1f** as red crystals, mp 274−275 °C.

Acknowledgment. Financial support from the Swedish Research Council is gratefully acknowledged. We thank Dr. Martina Lahmann for technical assistance.

Supporting Information Available: Product characterization data for **1b−d** and **1f**, ^{1}H and ^{13}C NMR spectra of compounds **1b−f**, and the ^{1}H NMR spectrum of compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026373V

---

[13] Jonas, K.; Klusmann, P.; Goddard, R. *Z. Naturforsch.* **1995**, *50b*, 394.

[14] Beachley, O. T., Jr.; Blom, R.; Churchill, M. R.; Faegri, K., Jr.; Fettinger, J. C.; Pazik, J. C.; Victoriano, L. *Organometallics* **1989**, *8*, 346.

[15] Chi, K.-M.; Calabrese, J. C.; Reiff, W. M.; Miller, J. S. *Organometallics* **1991**, *10*, 688.

[16] Dyumaev, V. K.; Davydov, D. V.; Beletskaya, I. P. *Russian Chem. Bull.* **1993**, *42*, 571.