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An expedient, mild, reductive method for the preparation of alkylferrocenes

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Reductive deoxygenation of acylferrocenes to the corresponding alkylferrocenes proceeded in excellent yields on utilizing a combination of sodium cyanotrihydroborate and boron trifluoride–diethyl ether. This method allows the synthesis of alkylferrocenes with functionalized tethers and is adaptable to large-scale preparations.

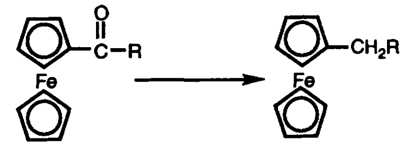
Ferrocenes are a well known class of one-electron donors which exhibit well established reversible redox couples. As such, these systems have been widely utilized in a large number of investigations of electron-transfer phenomena.[1] The mixed-ligand $[Fe(\eta-C_5H_5)(\eta-C_5H_4R)]$ compounds are particularly valuable in this respect since they display a tunable ferrocene–ferrocenium oxidation potential[2] with variation of the substituent on the C_5H_4 ring, thereby offering a unique possibility to influence their electrochemical applications. Furthermore, in recent years modified ferrocenes have been investigated quite intensively for their liquid-crystalline properties.[3] As a consequence, ferrocene derivatives, particularly those possessing functionalized tethers, have emerged as strong candidates for materials and catalysts.[4] Molecular electronic devices, electro-optical materials, multielectron redox catalysts, electrode surface modifiers and construction of dendrimers have been proposed as potential applications[5] for $[Fe(\eta-C_5H_5)(\eta-C_5H_4R)]$ systems.

The most obvious approach for the preparation of alkylferrocenes involves the Friedel–Crafts alkylations of ferrocene. However, these reactions[6] proceed with a low degree of regiocontrol and invariably produce intractable mixtures of mono- and poly-alkylated derivatives in low yields. The Friedel–Crafts acylation reactions,[7] on the other hand, furnish good yields of mono- and di-acylated ferrocenes with a remarkable degree of regioselectivity. Accordingly, a two-step protocol[8] involving regioselective acylation followed by ionic hydrogenation of the acylated ferrocene constitutes the method of choice for the preparation of both simple alkylferrocenes as well as those bearing functionalized pendant arms. The hitherto reported general methods for the deoxygenation of acylferrocenes include catalytic hydrogenolysis,[9] Clemmensen reduction,[10] and reductive deoxygenation employing lithium aluminium hydride[11] in the presence of anhydrous aluminium chloride. However, the presence of other functionalities in the molecule is limited under these reaction conditions. The development of a new mild procedure for the preparation of alkylferrocenes, therefore, remains an important objective.

Results and Discussion

In my laboratory, we are currently developing new applications of boronhydride-based reducing systems[12] in selective transformations. In this context, I chose to explore the use of sodium cyanotrihydroborate in Lewis-acidic media for the reductive deoxygenation of ferrocenyl aldehydes and ketones. The reduction of aryl ketones and aldehydes to the corresponding methylene hydrocarbons has been described with the combination of zinc iodide and $Na[BH_3(CN)]$[13] and, more recently, with boron trifluoride–diethyl ether and $Na[BH_3(CN)]$.[14] However, none of these reagent systems has been employed with ferrocenyl aldehydes and ketones. In a preliminary communication, I have recently reported[15] that a combination of titanium(IV) chloride and $Na[BH_3(CN)]$ deoxygenates acylferrocenes to the corresponding alkylferrocenes. As a sequel to this work, I now report the details of the results accomplished by treating a wide variety of ferrocenyl aldehydes and ketones with $Na[BH_3(CN)]/BF_3{\cdot}OEt_2$ at room temperature, a rapid, high-yielding method for the preparation of alkylferrocenes bearing functionalized tethers (Tables 1 and 2). Compared to titanium(IV) chloride, $BF_3{\cdot}OEt_2$ appears to be the Lewis acid of choice for carrying out this transformation due to rapid conversions and simple work-up.

Table 1 Preparation of monoalkylferrocenes



Reagents and conditions: $BF_3{\bullet}OEt_2$, $Na[BH_3(CN)]$, thf, 25 °C, 1h

Product	R	Yield (%)
1	H	88
2	Me	92
3	Pr^i	92
4	Ph	89
5	$CH_2CH_2CO_2H$	93
6	$CH_2CH_2CO_2Me$	92
7	$(CH_2)_4Cl$	93
8	$(CH_2)_{10}Br$	95

Treatment of acylferrocenes with $BF_3{\cdot}OEt_2$ and $Na[BH_3(CN)]$ in anhydrous tetrahydrofuran (thf) for 1 h led to the formation of the corresponding alkylferrocenes in excellent yields. The results are summarized in Tables 1 and 2. The reactions proceed at room temperature, the procedure is easy to perform and no special handling technique is required. Boron trifluoride–diethyl ether is certainly a more convenient and effective Lewis acid than titanium(IV) chloride[15] for effecting this transformation. The reactions are rapid whereas with titanium(IV) chloride a duration of 8–10 h is needed for complete conversions. Moreover, titanium(IV) chloride forms a precipitate on quenching the reaction with aqueous ammonia, thereby requiring a filtration during work-up.

The scope of the method proved to be quite general for a variety of ferrocenyl aldehydes and ketones. The reaction also proceeds well with α-ferrocenyl carbinols, *e.g.* ferrocenylmethanol and α-ferrocenylethanol were converted into the corresponding alkylferrocenes. This finding suggests that the reductive

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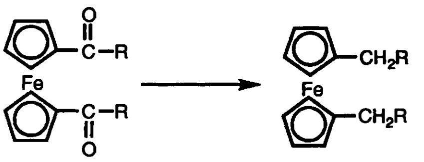
Non-SI unit employed: mmHg ≈ 133 Pa.

Table 2 Preparation of 1,1′-dialkylferrocenes



Reagents and conditions: $BF_3 \cdot OEt_2$, $Na[BH_3(CN)]$, thf, 25 °C, 1h

Product	R	Yield (%)
9	H	90
10	Me	94
11	Ph	92
12	$CH_2CH_2CO_2Me$	90
13	$-CH_2CH_2-$	93

deoxygenation of acylated ferrocenes proceeds through the formation of the corresponding α-ferrocenyl alcohol as the intermediate which is then reduced *via* the facile formation of a remarkably stable α-ferrocenyl alkyl carbocation[16] in the presence of $BF_3 \cdot OEt_2$. The 1,1′-diacylated ferrocenes (Table 2) afforded the corresponding 1,1′-dialkylferrocenes in high yields; the same general procedure was followed except that double the amounts of $BF_3 \cdot OEt_2$ and $Na[BH_3(CN)]$ were used. The ferrocenophane 1,1′-tetramethyleneferrocene **13** was obtained in high yield from the bridged ferrocenyl diketone.[17]

The present method allows synthesis of alkylferrocenes bearing functionalized tethers, *e.g.* 3-carboxypropyl- **5**, 3-methoxycarbonylpropyl- **6**, 5-chloropentyl- **7**, 11-bromoundecyl- **8** and 1,1′-bis(3-methoxycarbonylpropyl)-ferrocene **12** are obtained in excellent yields from the corresponding acylated ferrocenes. Reported attempts[18] to perform Wolff–Kishner or Clemmensen reduction on similar acylferrocenes were unsuccessful. The simplicity of this procedure coupled with the high yields of the pure products and compatibility of this reagent system with a variety of functional groups should make it the method of choice for the preparation of alkylferrocenes particularly for those bearing functionalized pendant chains.

In conclusion, an expedient, high-yielding, method for the reductive deoxygenation of acylferrocenes has been described, suitable for the preparation of alkylferrocenes possessing functionalized pendant arms and adaptable to large-scale preparations.

Experimental

The melting points were measured on a Thomas-Hoover capillary melting point instrument and are uncorrected. Proton NMR spectra were recorded at 60 (EM 360 Varian Associates spectrometer) and 300 MHz (Bruker AM 300 spectrometer) in $CDCl_3$ solutions with $SiMe_4$ as an internal standard, IR spectra on a Perkin-Elmer 298 spectrometer in $CHCl_3$ solutions. Thin-layer chromatography was done on precoated silica gel plates. Tetrahydrofuran was distilled over $LiAlH_4$ prior to use. The commercially available acylferrocenes were used without further purification. The bridged diketone required for the preparation of the ferrocenophane **13** was obtained from commercially available 1,1′-diacetylferrocene following a known procedure.[17] The remaining substrates were prepared[7] by Friedel–Crafts acylations of ferrocene.

General procedure for the preparation of monoalkyl derivatives of ferrocene

Boron trifluoride–diethyl ether (2.84 g, 20 mmol) was added dropwise to a magnetically stirred solution of the acylferrocene (5 mmol) in anhydrous thf (10 cm^3). To the resulting solution was then added sodium cyanotrihydroborate (0.93 g, 15 mmol) portionwise over 10 min and the contents were stirred at room temperature for 1 h. The reaction mixture was then diluted with dichloromethane (30 cm^3), and aqueous ammonia (2 mol dm^{-3}) was added dropwise till the aqueous phase was alkaline (pH 10, indicated by Hydrion pH paper). The organic layer was separated, dried over Na_2SO_4 and concentrated. Flash chromatography of the residue over silica gel using hexanes–diethyl ether (9 : 1) as the eluent afforded the pure alkylferrocenes in 88–96% yields.

For the preparation of the carboxyalkylferrocene **5**, the reaction was quenched by the addition of water instead of aqueous ammonia and the organic phase was washed with water (20 cm^3 × 3).

Methylferrocene 1. M.p. 36 °C (lit.,[9d,10c] 35.5–36.5 °C); $\tilde{\nu}_{max}$/cm^{-1} 3054, 2976, 1416, 1100 and 1057; δ 1.98 (3 H, s), 4.03–4.07 (4 H, m) and 4.09 (5 H, s).

Ethylferrocene 2. B.p. 102–105 °C (4 mmHg) [lit.,[9d] 121–123 °C (10 mmHg)]; $\tilde{\nu}_{max}$/cm^{-1} 3103, 2962, 2933, 2876, 1451, 1430, 1104, 1061, 1040 and 820; δ 1.17 (3 H, t, J 7.5), 2.34 (2 H, q, J 7.5 Hz), 4.03–4.07 (4 H, m) and 4.10 (5 H, s).

2-Methylpropylferrocene 3. B.p. 112–115 °C (0.5 mmHg) [lit.,[19] 118–122 °C (0.5 mmHg)]; $\tilde{\nu}_{max}$/cm^{-1} 3096, 2962, 2947, 2926, 1465, 1104, 1040, 997, 919 and 820; δ 0.84 (6 H, d, J 6.6), 1.57 (1 H, spt, J 6.6), 2.23 (2 H, d, J 6.6 Hz), 4.03 (4 H, s) and 4.08 (5 H, s).

Benzylferrocene 4. M.p. 75–76 °C (lit.,[20] 74.5–75.5 °C); $\tilde{\nu}_{max}$/cm^{-1} 3089, 3061, 3025, 2926, 1600, 1494, 1430, 1104, 1026, 912 and 820; δ 3.68 (2 H, s), 4.06–4.10 (9 H, m) and 7.16–7.3 (5 H, m).

3-Carboxypropylferrocene 5. M.p. 118–119 °C (lit.,[9b] 117–118 °C); $\tilde{\nu}_{max}$/cm^{-1} 3522 (br), 3089, 2947, 2862, 1700, 1409, 1267, 1097, 1040, 1005 and 820; δ 1.90 (2 H, qnt, J 7), 2.43 (4 H, t, J 7 Hz), 4.07 (4 H, br s) and 4.12 (5 H, s).

3-Methoxycarbonylpropylferrocene 6. B.p. 155–158 °C (2 mmHg) [lit.,[21] 168–170 °C (4 mmHg)]; $\tilde{\nu}_{max}$/cm^{-1} 3096, 2954, 2855, 1721, 1437, 1260, 1210, 1175, 1040 and 813; δ 1.84 (2 H, qnt, J 7.5), 2.34 and 2.37 (4 H, 2t, J 7.5 Hz), 3.68 (3 H, s), 4.05 (4 H, br s) and 4.10 (5 H, s).

5-Chloropentylferrocene 7. B.p. 135–140 °C (0.5 mmHg); $\tilde{\nu}_{max}$/cm^{-1} 3096, 2962, 2933, 2855, 1451, 1437, 1267, 1168, 1104, 1033, 997, 884 and 820; δ 1.42–1.55 (4 H, m), 1.73–1.82 (2 H, m), 2.22–2.32 (2 H, m), 3.53 (2 H, t, J 6.6) and 4.1–4.25 (9 H, m) (Found: C, 61.85; H, 6.70. $C_{15}H_{19}ClFe$ requires C, 61.95; H, 6.70%).

11-Bromoundecylferrocene 8. B.p. 145–150 °C (0.5 mmHg); $\tilde{\nu}_{max}$/cm^{-1} 3092, 2958, 2930, 2860, 1450, 1435, 1263, 1162, 1106, 1025, 998, 890 and 825; δ 1.3 (12 H, br s), 1.4–1.55 (4 H, m), 1.85 (2 H, qnt, J 6.8), 2.32 (2 H, t, J 6.8), 3.42 (2 H, t, J 6.8) and 4.03–4.2 (9 H, m) (Found: C, 61.55; H, 5.30. $C_{21}H_{31}BrFe$ requires C, 61.6; H, 5.15%).

General procedure for the preparation of 1,1′-dialkyl derivatives of ferrocene

The same general procedure as described above was followed except that double the amounts of $BF_3 \cdot OEt_2$ and $Na[BH_3(CN)]$ were used.

1,1′-Dimethylferrocene 9. M.p. 40 °C (lit.,[22] 39–40.5 °C); $\tilde{\nu}_{max}$/cm^{-1} 3090, 2976, 2926, 1458, 1040, 1012 and 820; δ 1.97 (6 H, s) and 3.96 (8 H, s).

1,1′-Diethylferrocene 10. B.p. 83–86 °C (0.1 mmHg) [lit.,[11b] 87–89 °C (0.15 mmHg)]; $\tilde{\nu}_{max}$/cm^{-1} 3089, 2977, 2962, 2954, 2924, 1473, 1458, 1267, 1040, 1010, 823 and 763; δ 1.16 (6 H, t, *J* 7.5), 2.35 (4 H, q, *J* 7.5 Hz) and 4.00 (8 H, s).

1,1′-Dibenzylferrocene 11. M.p. 104–105.5 °C (lit.,[9a,20b] 103–105 °C); $\tilde{\nu}_{max}$/cm^{-1} 3082, 3025, 2919, 1600, 1487, 1451, 1033, 919, 877 and 763; δ 3.67 (4 H, s), 4.06 (8 H, s) and 7.12–7.32 (10 H, m).

1,1′-Bis(3-methoxycarbonylpropyl)ferrocene 12. B.p. 182–185 °C (0.1 mmHg) [lit.,[23] 200–210 °C (0.2 mmHg)]; $\tilde{\nu}_{max}$/cm^{-1} 3090, 2954, 1728, 1437, 1246, 1203 and 905; δ 1.80 (4 H, qnt, *J* 7.4), 2.31 and 2.34 (8 H, 2t, *J* 7.4 Hz), 3.66 (6 H, s) and 3.95–4.01 (8 H, m).

1,1′-Tetramethyleneferrocene 13. M.p. 62–63 °C (lit.,[10c] 63–64 °C); $\tilde{\nu}_{max}$/cm^{-1} 3089, 2969, 2926, 2905, 2855, 1473, 1444, 1040, 1019 and 912; δ 1.80–1.90 (4 H, m), 2.38–2.48 (4 H, m) and 3.97–4.1 (8 H, m).

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Received 30*th May* 1996; *Paper* 6/03757G