

Boron Trifluoride Etherate as a Catalyst in Acylation of Ferrocene

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Abstract. Ferrocene was acylated in acetic or propionic anhydride, in presence of boron trifluoride etherate giving acetyl ferrocene (**1**) (in quantitative yields) or propionyl ferrocene (**2**) (in high yields). A more general procedure is based on

the reaction between ferrocene and carboxylic anhydrides or acyl halides in presence of ascorbic acid. Acetyl, propionyl, benzoyl, anisoyl and 3-phenyl propionyl ferrocenes (**1–5**) were obtained in moderate to high yields.

Ferrocene and its derivatives [1–3] are interesting building blocks [4, 5, 9] for a plethora of useful compounds, specially chiral catalysts [6, 9] and biological active compounds [10–11].

For synthesis of substituted ferrocenes, acyl ferrocenes are the most important starting materials [9, 16]. They are usually prepared by Friedel–Crafts acylations [13] of the unsubstituted compound.

For preparation of 1,1-diacyl ferrocene, AlCl_3 is the most used catalyst, with a very reactive acylating agent as an acyl halide [14–16] without problems. However, the preparation of monoacyl ferrocenes needs control of the reaction conditions in order to avoid side reactions (di and poly acylation [15] and oxidation of the iron atom [16, 17]).

When AlCl_3 /acyl halide or anhydride was chosen for monoacylation of ferrocene, control of the reaction conditions was carried out by application of ambient or low temperature [4, 14, 18, 19, 24, 25, 32], previous formation of the Perrier complex from the acyl chloride and AlCl_3 [13, 16], addition of metals as Al [15], Mg [16] (to reduce the formed ferricenium cation).

When possible, it is more suitable to use other reagents for synthesis of pure monoacyl ferrocenes: Less reactive catalysts (gaseous boron trifluoride [15, 40], hydrogen fluoride, magnesium halides [20], molybdenum carbonyl [21], polyphosphoric acid [10, 15, 16, 23]) or less reactive acylating agents (anhydrides, mixed anhydrides of trifluoroacetic acid [22]).

In the special case of preparation of acetyl ferrocene, acetic anhydride may be used as solvent in presence of orthophosphoric acid as catalyst ("Graham method") [15, 16, 23, 26–32].

Results and Discussion

For routine preparation of acetyl ferrocene, we used the well known procedure of acetylation of ferrocene catalyzed by orthophosphoric acid [15, 16, 23, 26–32].

The method is good, but has some disadvantages. If a small amount of H_3PO_4 was used, the reaction is very slow, and ferrocene is recovered unchanged or, after prolonged reaction time, 1,1'-diacyl ferrocene is formed [15, 30, 31]. If more H_3PO_4 was added [28, 30] the yields are lower due to complexation of iron. If the reaction was carried out at 100 °C [15], instead of ambient temperature, 1,1-diacyl ferrocene was formed as by-product [28, 31]. In addition, when large excess of sodium bicarbonate was used during work up (or excessive washing of the compound) the yields were also lowered [29].

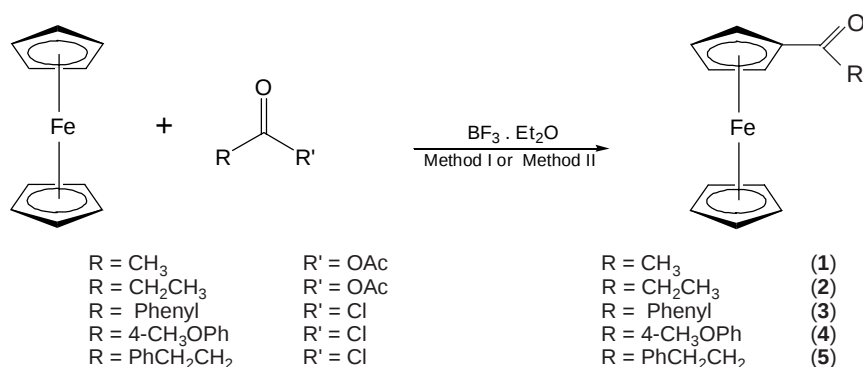
Although propionyl ferrocene was recently prepared by a modified Graham method (catalyzed by polyphosphoric acid [10]), in our hands, the use of orthophosphoric acid as catalyst for reaction between ferrocene and propionic anhydride was unsuccessful, and ferrocene was even recovered unchanged. This suggests that propionic anhydride is less reactive than acetic anhydride.

We were interested to find other Lewis acids which are suitable catalysts for acylation of ferrocene.

Applications of ZnCl_2 and SnCl_4 as catalysts were unsuccessful. Boron tribromide was effective, but less conveniently to handle. Also, the use of acetic acid as co-solvent in the Graham method was unsuccessful. The ferrocene was oxidized and high amounts of ferricenium ion was formed.

We found that both acetyl (almost quantitative yields) or propionyl ferrocene (in high yields) may be prepared by acetylation of the unsubstituted compound in excess of the anhydride as the solvent, catalyzed by boron trifluoride etherate [41] (Method I).

However, in most of cases acyl chlorides are more readily accessible than the corresponding anhydrides. For the use of these acylating agents, we developed another method based on the reaction of ferrocene with equimolar amounts of anhydride or acyl chloride, in presence of ascorbic acid (in order to reduce the formed ferricenium) in dichloromethane at reflux (Scheme 1, Table 1) (Method II). The yields were moderate to high.



Scheme 1 Acylation of ferrocene catalyzed by boron trifluoride etherate

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Experimental

Ferrocene (Aldrich, 97%) was purified by recrystallization from ethanol [2]. If only a small quantity is desired, it may be easily prepared by published methods [1–3, 16, 23–32]. Acetic anhydride (Merck) was stirred with potassium carbonate (to remove acidic impurities), decanted and distilled (if impure anhydride was used, lower yields were obtained). Boron trifluoride etherate (Aldrich, Merck) was used as received. However, when it was dark-coloured, it was purified by distillation [33].

4-Methoxy benzoyl chloride [34] and 3-phenyl propionyl chloride [35] were prepared from the corresponding commercially available (Merck) acids and thionyl chloride. – IR spectra were taken in a Perkin Elmer 1420 spectrophotometer, between KBr plates, using a polystyrene band (1601 cm⁻¹) as reference. – ¹H and ¹³C spectra were taken using Bruker AC 80 (80 MHz) and Bruker DPX 300 (300 MHz) spectrometer, using TMS as internal reference in CDCl₃ as solvent.

A–Acetylation Procedure (Method I) Acetyl Ferrocene and Propionyl Ferrocene

Ferrocene (9.3 g., 50 mmol) was suspended in 35 mL of acetic anhydride or propionic anhydride, and boron trifluoride etherate (7.1g, 6.2 mL, 50 mmol) was added in small portions with stirring at ambient temperature, under N₂ and protected from light. The reaction seems to be completed in five minutes (for propionic anhydride, in 25 minutes), as verified by TLC (if the stirring is continued for more than 4 hours, 1,1'-diacyl ferrocenes were the major products). The mixture was added to ice, neutralized with solid sodium carbonate until it was basic to litmus paper. The product was collected by filtration, washed with water, and dried in air.

The crude products were purified by recrystallization from hexane, but we find that they are sufficient pure for use as stating materials in ferrocene chemistry.

Acetyl ferrocene 1

Obtained in form of orange-red needles, yields were in the range 92–100% (of crude product, several runs).

Propionyl ferrocene 2

Obtained in form of dark orange-red crystals, yield 91% (of crude product). The melting points of the compounds were given in Table 1.

B–Acylation Procedure for Use with Acyl Halides or Anhydrides (Method II)

Ferrocene (50 mmol, 9.3 g) and ascorbic acid (50 mmol, 6.0 g) were suspended in 30 mL of dichloromethane. A solution of the acylating agent (50 mmol in 20 mL of CH₂Cl₂) was added, followed by boron trifluoride etherate (50 mmol, 7.1 g, 6.2 mL), and the mixture was refluxed under N₂ and protected from light. After the reflux time, the mixture was cooled, added to ice, alkalized with sodium carbonate, and the product extracted with ethyl ether. The organic extracts were dried over anhydrous sodium sulfate, evaporated *in vacuo* and the residue (solid or dark oil) recrystallized from hexane. Table 1 summarizes the used acylating agents, the reflux time periods, the products obtained (1–5), the yields and the melting points.

One of the compounds obtained, 3-phenyl propionyl ferrocene (5), is new. A prepared sample was recrystallized three times from hexane.

C ₁₉ H ₁₈ FeO	Calcd.:	C 71.70	H 5.66
(318)	Found:	C 71.43	H 5.54.

C–Spectroscopic Characteristics of the Ferrocene Derivatives

Acetyl Ferrocene 1

¹³C NMR δ/ppm = 202.1 (C=O); 79.3 (C1, subst. Cp ring), 72.3 (C3 and C4), 69.8 (C1 of unsubst. Cp ring), 69.6 (C2 and C5). – ¹H NMR δ/ppm = 4.77 (t, 2H, H2 and H5), 4.50 (t, 2H, H3 and H4), 4.20 (s 5H, unsubst. Cp ring), 2.39 (s, 3H, CH₃) IR ν/cm⁻¹ = 3 118 (CH, arom) 3 098–3 079 (CH, arom), 1 662–1 658 (C=O), 1 415 (C–C arom), 1 360 (CH₃), 1 280 (δ CCOC) 1118 (ν C–CH₃), 1 102 and 1 008 ("ferrocene bands", indicating unsubst. Cp ring)³, 1 022 (CH deformation), 895 (CH deformation, Cp ring). The spectra were in agreement with the structure in [16, 36, 38, 39].

Propionyl ferrocene 2

¹³C NMR δ/ppm = 205.0 (C=O), 78.9 (C1 of Cp ring), 72.0 (C3 and C4), 69.7 (unsubst. Cp carbon), 69.3 (C₂ and C₅), 32.7 (CH₂), 8.5 (CH₃). – ¹H NMR δ/ppm = 4.78 (t, 2H, H2

Table 1 Acylation of ferrocene catalyzed by boron trifluoride etherate (Method II)

Acylating agents	Product obtained (See Scheme1)	Reflux time (hs)	<i>m.p.</i> (°C)	Yield (%)
Acetic anhydride	Acetyl ferrocene 1 ^{a)}	6 ^{a)}	86–87 (lit. 80–84, 85–86, 81–84) [15, 16]	79 ^{a)}
Propionic anhydride	Propionyl ferrocene 2 ^{b)}	4.5 ^{b)}	34–36 (lit. 38–39) [40]	59 ^{b)}
Benzoyl chloride	Benzoyl ferrocene 3	8.5 ^{c)}	105–107 (lit. 107–108) [16]	54
4-Methoxy benzoyl chloride	4-Methoxybenzoyl ferrocene 4 ^{d)}	24 ^{d)}	74–76 (lit. 78–81, 82–83) [14]	32 ^{d)}
3-Phenyl propionyl chloride	(3-Phenyl)propionyl ferrocene 5 ^{e)}	23	79–81 ^{e)}	60

^{a)} 2 hours of reflux, 55%; 3.5 hours of reflux, 75%. ^{b)} The same yield after 6 hours. ^{c)} Low yields after 6 hours.

^{d)} Low yields with 6–8 hours of reflux time. ^{e)} New compound.

and H5), 4.47 (t, 2H, H3 and H4), 4.18 (s, 5H, unsubst. Cp ring), 2.69 (q, 2H, CH₂), 1.17 (t, 3H, CH₃). – IR ν/cm^{-1} = 3090 (CH arom.), 2970 (CH of CH₃), 1665 (C=O), 1450 (C–C, Cp ring), 1350 (CH₃), 1278 (δ CCOC), 1105 and 1000 ("ferrocene bands")³, 880 (CH deformation, Cp ring), 820 (CH deformation, CH₃). The spectra were in agreement with the structure in [10].

Benzoyl ferrocene **3**

¹H NMR δ/ppm = 8.00–7.88 (m, 2H, *orto* Hs, Ph ring), 7.88–7.45 (m, 3H, *m* and *p* Hs, Ph ring), 4.90 (t, 2H, Cp, H2 and H5), 4.57 (t, 2H, Cp, H3 and H4), 4.19 (s, 5H, unsubst. Cp ring). – ¹³C NMR δ/ppm = 199.1 (C=O), 139.8 (C1 of Ph ring), 131.5 (C4 of Ph ring), 128.2 (C3 and C5, Ph ring), 128.0 (C2 and C6, Ph ring), 78.15 (C1 of Cp ring), 72.54 (C3 and C4, Cp ring), 71.51 (C2 and C5, Cp ring), 70.20 (unsubst. Cp ring Cs). – IR ν/cm^{-1} = 3080 (ν CH arom.), 2940–2920 (ν CH, Cp rings), 1622–1595 (ν C=O), 1418–1410 (ν C–C arom of Cp ring), 1288 (δ CCOC), 1103 and 1000 ("ferrocene bands"); 878, 852 and 825 (CH deformation, Ph Cp rings). The spectra were in agreement with the structure in [16, 38, 39].

(4-Methoxy) benzoyl ferrocene **4**

¹³C NMR δ/ppm = 198.0 (C=O), 162.1 (C4 of Ph ring), 131.0 (C1 of Ph ring), 130.0 (C2 and C6, Ph ring), 113.2 (C3 and C5, Ph ring), 78.5 (C1 of Cp), 71.9 (C2 and C5, Cp ring), 71.2 (C3 or C4, Cp ring), 69.0 (unsubst. Cp ring), 54.9 (OCH₃). – ¹H NMR: 3.80 (s, 3H, OCH₃), 4.84 (t, 2H, H2 and H5, Cp ring), 4.50 (t, 2H, H3 and H4, Cp ring), 4.10 (s, 5H, Cp ring), 7.92 (d, 2H, H2 and H6, Ph ring), 7.00 (d, 2H, H3 and H5 Ph ring) (These two doublets is a characteristic pattern for 1,4 disubst. of Ph ring). – IR ν/cm^{-1} = 3060 (CH arom.), 1650 (C=O), 1460–1475 (C–C, Ph and Cp), 1240–1230 (C–O, eter bond) 1104 and 1000 ("ferrocene bands")³, 860 (CH deformation Ph) 840 (CH deformation Cp). The spectra in agreement with structure and lit. [14].

3-(Phenyl propionyl) ferrocene **5**

¹³C NMR: 203.1 (C=O), 141.6 (C1 of Ph ring), 128.6 (C4, Ph ring), 128.4 (C2 and C6, Ph ring), 126.1 (C3 and C5, Ph ring), 78.9 (C1 of Cp ring), 69.9 (unsubst. Cp ring Cs), 69.6 (C2 and C5, Cp ring), 69.2 (C3 and C4, Cp ring). – ¹H NMR: 7.56–7.32 (m, 5H, Ph ring), 4.79–4.78 (t, H2 and H5, Cp ring), 4.50–4.49 (t, 2H, H3 and H4, Cp ring), 4.10 (s, 5H, unsubst. Cp ring), 3.10–2.92 (two t, 4H, CH₂–CH₂). – IR ν/cm^{-1} = 3080 (CH, Cp ring and Ph), 2980 (alkyl CH), 1660 (C=O), 1480–1465 (C–C, Ph and Cp), 1257, 1120 (CH₂–CH₂), (1105 and 1000 ("ferrocene bands")), 850 (CH defor-

mation, Ph and Cp) 791 (CH deformation, alkyl).

For this new compound, we made tentative assignments based on the spectra of related structures such as vinyl ferrocene [36] and some ferrocenyl chalcones [37].

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