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A novel method to synthesize asymmetrical disubstituted ferrocenes

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Abstract

A convenient new method was developed for the preparation of 1′-substituted-1-bromoferrocenes which are important precursors for the preparation of 1′,1‴-disubstituted-biferrocenes. This method can also be applied to prepare asymmetrical disubstituted ferrocenes, which are potentially useful materials possessing non-linear optical and liquid crystalline properties.

Keywords: Asymmetrical disubstituted ferrocenes; Synthesis; Electron transfer

1. Introduction

The study of intramolecular electron transfer in mixed-valence complex has enabled systematic and creative investigation into the factors that affect rates of electron transfer in solution redox process, solid state materials and biological electron transfer chains [1–5]. In the case of mixed-valence biferrocenium triiodide salts, considerable progress has been made in understanding the effects of the solid-state environment on the rate of electron transfer [6–13]. In a previous paper [14], we have suggested that the difference in the rates of electron transfer in the series of mixed-valence biferrocenium salts is a result of the difference in the tilted angle between the Cp rings. Deviation of the Cp ring from the parallel position were found to correlate quite well with the critical temperature of the electronic delocalization–localization in the mixed-valence biferrocenium salts. However, owing to the methodological limitation in the preparation of 1′-substituted-1-bromoferrocene, i.e. acylation of bromoferrocene in the presence of $AlCl_3$ followed by reduction, none of 1′,1‴-disubstituted biferrocenium triiodide salts containing heterosubstitutents have been prepared. Mostly, the substituents on 1′,1‴ position in mixed-valence biferrocenium salts are simple alkyl groups [6–9], or benzyl derivatives [10,11]. This, to some extent, limits its generality on understanding the fundamental nature of electron transfer rate in mixed-valence biferrocenium compounds. In order to prepare more biferrocenium salts containing various substituents at 1′,1‴ positions and to obtain more evidence to support our previous suggestion [14], we attempted to develop an alternative method to synthesize 1′-substituted-1-bromoferrocene, precursors of 1′,1‴-disubstituted biferrocenes [15]. In Ref. [15] we have reported our preliminary results only briefly. Now we wish to report our results in much more detail.

2. Results and discussion

Reaction of 1,1′-dilithioferrocene [16] with *p*-toluenesulfonyl bromide or polybrominated alkanes according to the literature method successfully gave 1,1′-dibromoferrocene. In our laboratory, the reaction has been scaled up to 250 mmol and the yield was maintained at 60% after work-up and recrystallization. Reaction of 1,1′-dibromoferrocene with one equivalent of butyllithium in drying tetrahydrofuran (THF) led to 1′-lithio-1-bromoferrocene. Although lithioferrocene could be obtained by the reaction of ferrocene with butyllithium [17,18], the disadvantages of this method, however, usually leads to mixtures of mono-metalloferrocenes and dimetalloferrocenes and excess metal alkyl is required. The crude 1′-lithio-1-bromoferrocene without being isolated was in situ treated with various electrophilic reagents, and one of the Cp rings was thus functionalized with various substituents (Scheme 1). We have found that this method not only replaces the traditional Friedel–Crafts reaction for preparing 1′-keto-1-bromoferrocene (**2**) but also successfully produces bromoferrocenes consisting of various functional groups,

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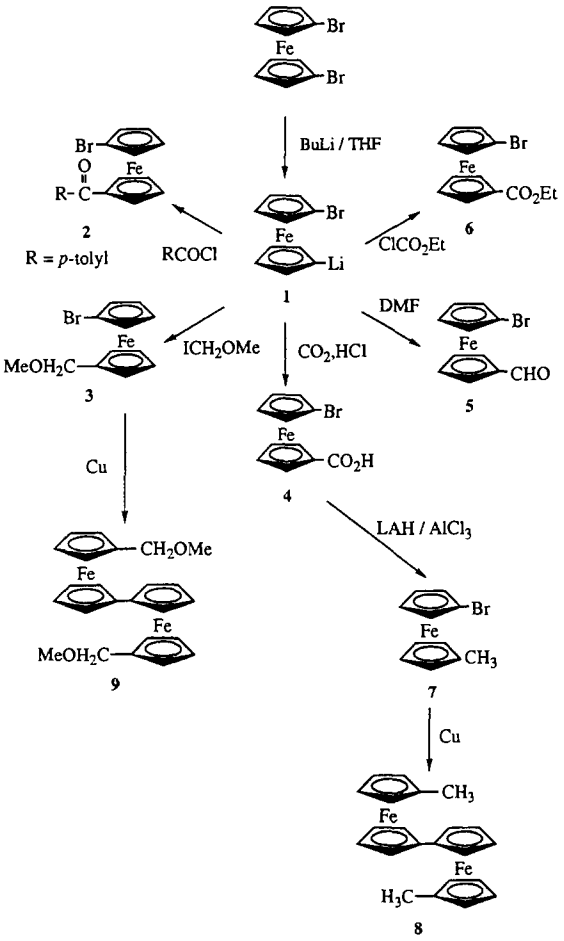
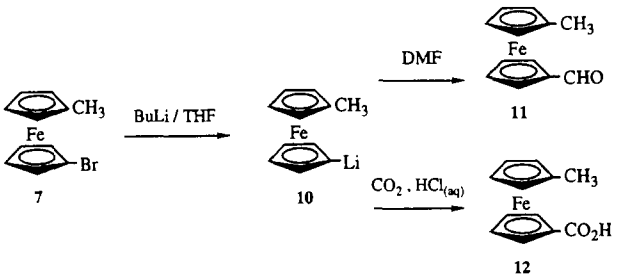
such as alkyl **3**, acid **4**, aldehyde **5** and ester **6** with good yields, which are not easily or possibly obtained by the previous method. It is worthwhile to point out that bromoferrocene is tedious to prepare and cannot be synthesized by the direct bromination of ferrocene. Therefore it has been obtained through the reaction of chloromercuriferrocene with halogen [19,20] and *N*-bromosuccinimide [21] or through the reaction of ferroceneboronic acid with $CuBr_2$ [22,23] and the overall yield from ferrocene to bromoferrocene derivatives is much lower when compared with our method. As the various 1′-substituted 1-bromoferrocenes can be prepared easily, various biferrocene derivatives are obtained efficiently. Biferrocenes **8** and **9** are also synthesized by using the traditional coupling method. These biferrocenes will be oxidized by iodine and the corresponding biferrocenium salts will be studied carefully to elucidate the fundamental nature controlling the electron transfer rate.

In order to study further the possibility of the bromo–metal exchange of the 1′-substituted 1-bromoferrocene, **4** was reduced by lithium aluminum hydride in the presence of aluminum chloride and 1′-methyl-1-bromoferrocene (**7**) was isolated with a good yield.



Scheme 1.



Scheme 2.

Compound **7** was also treated with butyllithium to produce the intermediate **10** which in situ was similarly allowed to react with dimethylformamide (DMF) or CO_2 and then aqueous HCl, and the corresponding aldehyde **11** and acid **12** were obtained with good yields (Scheme 2). This provides an alternative and efficient method for preparing asymmetrically disubstituted ferrocenes which can be potential materials possessing non-linear optical or liquid crystalline properties [24]. Compounds **2**, **5**, **6** and **8** are known. Compounds **3**, **4**, **7**, **9**, **11** and **12** are liquid or low melting point solids and characterized by NMR, mass and high resolution mass spectroscopy (HRMS).

3. Experimental section

3.1. General information

Melting points are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC 200 and MSL 200 spectrometers. The mass spectra were measured on a VG 7-250 GC-MS system at 70 eV. All manipulation involving air-sensitive materials were carried out by using standard Schlenk techniques under nitrogen. Chromatography was performed on neutral alumina (activity II), elution with dichloromethane–hexane. Ether, DMF tetramethylethylenediamine (TMEDA) and THF were dried and freshly distilled before use. Chloroform, dichloromethane and hexane were directly used without further distillation. Butyllithium, dibromotetrafluoroethane and ferrocene were purchased from Aldrich and used directly.

3.2. Preparation of dibromoferrocene

The literature method [15] was modified as follows. Ferrocene (46.5 g, 250 mmol) was placed in a three-necked flask (1000 ml) and then dried under vacuum for 2 h. Dry ether (400 ml), butyllithium (344 ml, 1.6 M in hexane) and TMEDA (83 ml, 550 mmol) were then added under nitrogen while the reaction temperature was kept below 30°C. Ferrocene had gradually dissolved in 2 h and the resulting solution was stirred for another 12 h. The mixture was maintained at −78°C for 1 h and dibromotetrafluoroethane (65.7 ml, 550 mmol)

was slowly added in 30 min. The mixture was stirred at −78°C for 4 h and then stirred at room temperature for 2 h. Water (300 ml) was added and the resulting mixture was extracted with dichloromethane (300 ml). The CH_2Cl_2 layer was dried over sodium sulfate, evaporated at reduced pressure and dissolved in methanol (70 ml). The solution was maintained in a refrigerator overnight. The dibromoferrocene which had precipitated was filtered off, washed with methanol (10 ml × 2) and dried. It amounted to 51.7 g (60.1%), orange needles, (melting point (m.p.), 53–55°C). The compound thus prepared is pure and can be used for further reaction.

3.3. General procedure of 1'-substituted 1-bromoferrocenes

Dibromoferrocene (1.72 g, 5 mmol) was placed in a freshly oven-dried three-necked flask (50 ml) and then dried under vacuum at 2 Torr and 30°C for 4 h. Dried THF (20 ml), followed by butyllithium (3.1 ml; 1.6 M in hexane) was added under nitrogen. The resulting solution was stirred at −25°C for 30 min, during which 1-bromo-1'-lithioferrocene gradually precipitated. Various electrophilic reagents (5 mmol) were then added and the solution was further stirred at −25°C for another 25 mins. Water (20 ml) was added, and the resulting mixture was extracted with ether (25 ml × 2). The combined extracts were dried over sodium sulfate and evaporated at reduced pressure. The residue was chromatographed on a column of alumina (10 × 2 cm). Elution with hexane gave eluates (50 ml) containing some impurities which were discarded. Continued elution with dichloromethane: hexane (1 : 4) gave eluates (150–250 ml) which yielded the desired compound. Recrystallization was from hexane: dichloromethane (5 : 1), if necessary.

1'-*p*-toluoyl-1-bromoferrocene [9b] (**2**) (0.81 g, (42.3%)) was obtained from *p*-toluoyl chloride (0.58 ml, 5 mmol) as purple–yellow plates (m.p., 79–80°C). M^+ at *m/z* 382, 384. ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, Me), 4.12 (t, 2H, Cp), 4.41 (t, 2H, Cp), 4.58 (t, 2H, Cp), 4.94 (t, 2H, Cp), 7.27 (d, 2H, phenyl), 7.84 (d, 2H, phenyl) ppm. HRMS. Found: 381.9656. $C_{18}H_{15}OBrFe$ calc.: 381.9650.

1'-Methoxymethyl-1-bromoferrocene (**3**) (1.06 g (69.0%)) was obtained from methoxy-methyl iodide (0.43 ml, 5 mmol) as reddish oil. M^+ at *m/z* 308, 310. ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H, Me), 4.04 (t, 2H, Cp), 4.10 (s, 2H, CH_2), 4.19 (s, 4H, Cp), 4.34 (t, 2H, Cp) ppm. HRMS. Found: 307.9503. $C_{12}H_{13}OBrFe$ calc.: 307.9499.

1-Bromo-1'-carboxyferrocene (**4**) (1.17 g (75.9%)) was obtained from an excess of CO_2 and then concentrated HCl as purple–yellow plates (m.p., 157–160°C). M^+ at *m/z* 308, 310. ^1H NMR ($CDCl_3$): δ 4.21 (t, 2H, Cp), 4.48–4.51 (m, 4H, Cp), 4.91 (t, 2H, Cp) ppm.

1'-Carbaldehyde-1-bromoferrocene [25] (**5**) (1.06 g (71.7%)) was obtained from DMF (0.40 ml, 5 mmol) as reddish oil. M^+ at *m/z* 292, 294. ^1H NMR ($CDCl_3$): δ 4.21 (t, 2H, Cp), 4.51 (t, 2H, Cp), 4.62 (t, 2H, Cp), 4.82 (t, 2H, Cp), 9.98 (s, 1H, CHO) ppm.

1'-Ethylcarboxylate-1-bromoferrocene [26] (**6**) (1.12 g (66.5%)) was obtained from chloro-ethylcarbonate (0.47 ml, 5 mmol) as reddish oil. M^+ at *m/z* 336, 338. ^1H NMR ($CDCl_3$): δ 3.21 (t, 6H, Me), 4.12 (t, 2H, Cp), 4.28 (q, 2H, CH_2), 4.41 (m, 4H, Cp), 4.82 (t, 2H, Cp) ppm. HRMS. Found: 335.9451. $C_{13}H_{13}O_2BrFe$ calc.: 335.9448.

3.4. Preparation of 7

An excess of aluminum chloride, portion by portion, was added to a mixture of **4** (3.12 g, 10 mmol) in dry ether (200 ml) until the solution became blue. An excess of lithium aluminum hydride was then added in a similar manner until the solution turned yellow. The resulting mixture was heated under reflux for 30 min and then allowed to cooled room temperature. Ice, piece by piece, was added to the mixture until no hydrogen evolved. Water (100 ml) was then added and the resulting mixture was extracted with dichloromethane (200 ml). The combined extracts were dried over sodium sulfate and evaporated at reduced pressure. The residue was chromatographed on a column of alumina (10 × 2 cm). Elution with hexane gave eluates (50 ml) containing some impurities which were discarded. Continued elution with hexane gave eluates (100 ml) which yielded the desired compound as yellow needles (m.p., 29–30°C). M^+ at *m/z* 276, 278. ^1H NMR ($CDCl_3$): δ 1.99 (s, 3H, Me), 4.02 (t, 2H, Cp), 4.04 (t, 2H, Cp), 4.09 (t, 2H, Cp), 4.28 (t, 2H, Cp) ppm. HRMS. Found: 276.9342 (*M*-1). $C_{11}H_{11}BrFe$ calc.: 277.9391.

3.5. Preparation of the biferrocenes 8 and 9

Ferrocene **3** or **7** (2 mmol) was thoroughly mixed with activated Cu (5 g) and the resulting mixture was heated at 120°C (oil bath) for 22 h. The solid was cooled to room temperature and then subjected to the Soxhlet process with dichloromethane for 4 h. The extract was evaporated at reduced pressure and the residue was chromatographed on a column of alumina (10 × 2 cm). Elution with hexane gave eluates (50 ml) containing some impurities which were was discarded. Continued elution with dichloromethane: hexane (1 : 4) gave eluates (50–250 ml) which yielded the desired biferrocenes. Recrystallization was from hexane–dichloromethane.

1,1'''-Dimethylbiferrocene [27] (**8**) (197 mg, (49.3%)) was obtained from 1'-methyl-1-bromoferrocene (560 mg, 0.2 mmol) as yellow–purple plates (m.p., 149–150°C). M^+ at *m/z* 398. ^1H NMR ($CDCl_3$): δ 1.75 (s, 6H,

Me), 3.85 (s, 4H, Cp), 3.88 (s, 4H, Cp) 4.13 (d, 4H, Cp), 4.26 (d, 4H, Cp) ppm.

1,1‴-Dimethoxymethylbiferrocene (**9**) (292 mg (63.5%)) was obtained from 1′-methoxymethyl-1-bromoferrocene (620 mg, 0.2 mmol) as yellow–purple rods (m.p., 86–88°C). M^+ at m/z 458. ^1H NMR ($CDCl_3$): δ 3.21 (s, 6H, Me), 3.96 (s, 4H, CH_2), 3.98 (d, 4H, Cp), 4.01 (d, 4H, Cp) 4.17 (t, 4H, Cp), 4.30 (t, 4H, Cp) ppm.

3.6. General procedure of 1′-substituted 1-methylferrocene

1′-Methyl-1-bromoferrocene (0.55 g, 2 mmol) was placed in a freshly oven-dried three-necked flask (50 ml) and then dried under vacuum at 2 Torr and 30°C for 4 h. Dried THF (10 ml), followed by butyllithium (1.2 ml; 1.6 M in hexane) was added under nitrogen. The resulting solution was stirred at −25°C for 30 min. Various electrophilic reagents (2 mmol) were added to the resulting solution and then stirred at −25°C for another 25 min. Water (10 ml) was added, and the resulting mixture was extracted with ether (10 ml × 2). The combined extracts were dried over sodium sulfate and evaporated at reduced pressure. The residue was chromatographed on a column of alumina (10 × 2 cm). Elution with hexane gave eluates (50 ml) containing some impurities which were discarded. Continued elution with dichloromethane : hexane (1 : 4) gave eluates (150–250 ml) which yielded the desired 1′-substituted 1-methylferrocene.

1′-Carbaldehyde-1-methylferrocene (**11**) (0.30 g (66.0%)) was obtained from DMF (0.16 ml, 2 mmol) as semireddish oil. M^+ at m/z 228. ^1H NMR ($CDCl_3$): δ 1.91 (s, 3H, Me), 4.14 (s, 2H, Cp), 4.16 (s, 2H, Cp), 4.54 (s, 2H, Cp), 4.70 (s, 2H, Cp), 9.96 (s, 1H.CHO) ppm. HRMS. Found: 228.0237. $C_{12}H_{12}OFe$ calc.: 228.0238.

1′-Carboxy-1-methylferrocene (**12**) (0.32 g (65.6%)) was obtained from excess of CO_2 and then concentrated HCl as purple–yellow plates (m.p., 144–145°C). M^+ at m/z 244. ^1H NMR ($CDCl_3$): δ 1.94 (s, 3H, Me), 4.11 (s, 4H, Cp), 4.41 (s, 2H, Cp), 4.78 (s, 2H, Cp) ppm. HRMS. Found: 224.0190. $C_{12}H_{12}O_2Fe$ calc.: 224.0187.

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