

A simple high-yielding synthesis of ferrocene-1,1'-diylbis-(methyltrimethylammonium iodide)

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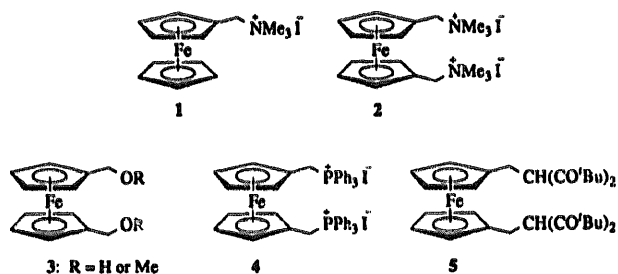
Abstract

A new simple, high-yielding procedure has been developed for the synthesis of ferrocene-1,1'-diylbis(methyltrimethylammonium iodide) **2**. Ferrocene is dilithiated using *n*-butyllithium/TMEDA and then reacted with Eschenmoser's salt to form the bis(dimethylaminomethyl) derivative **6** in good yield. Treatment with iodomethane gives rise to the corresponding ammonium salt **2** in excellent yield. Reaction of this bis-ammonium salt with sodium phenoxide affords the 1,1'-bis(phenoxymethyl) compound **10**.

Keywords: Ferrocene; Sodium phenoxide; Iodomethane

1. Introduction

Dimethylaminomethylferrocene and the corresponding methiodide salt **1** have long been established as extremely useful intermediates for preparing mono-substituted ferrocene derivatives [1–3]. The closely related bis-ammonium salt **2** [4] is also of interest because of its potential as a key intermediate in the synthesis of oligomeric and polymeric ferrocene-containing systems. Indeed **2** has been utilised in the formation of several interesting disubstituted ferrocenes **3–5** through nucleophilic displacement of trimethylamine [3,5].

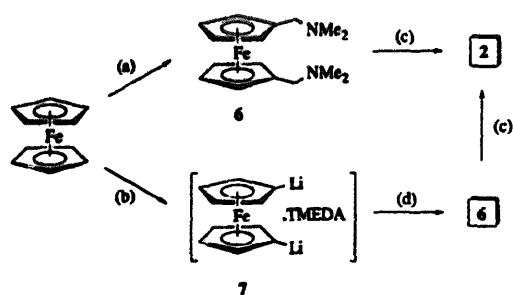


In comparison with the mono-quaternary ammonium salt **1**, the bis-system **2** undergoes nucleophilic substitution reactions more slowly [3,5], although the fact that it

has seen such little use in synthesis is still somewhat surprising. Undoubtedly, a principal reason for this has been the lack of a simple, reliable and high-yielding synthesis of **2**. Previous routes have all involved treatment of 1,1'-bis(dimethylaminomethyl)ferrocene **6** with iodomethane as the final stage of the preparation. This pivotal intermediate **6** has been prepared in a variety of ways: (a) by reduction of dimethylaminomethylferrocene with lithium metal then treatment with FeCl_2 [6]; (b) by lithium aluminium hydride reduction of α -dimethylaminofulvene then treatment with FeCl_2 [7]. The most successful method is the bis-dimethylaminomethylation of ferrocene under Mannich conditions (Scheme 1) [3]. This process works well in the case of mono-dimethylaminomethylation [3,8] but when extended to bis-dimethylaminomethylation invariably gives **6** in very poor yield (less than 17%). Clearly, a much-improved procedure is required.

The use of the di-lithium salt of ferrocene, as its TMEDA adduct [9,10], has rendered accessible a variety of 1,1'-disubstituted ferrocenes $\text{Fe}(\text{C}_5\text{H}_4\text{E})_2$ including the bis-aldehyde [9,11–13], the dicarboxylic acid [9,13], various di-alcohols ($\text{E} = \text{CR}'\text{R}'\text{OH}$) [9,13,14] and a range of bis-phosphines [15,16]; and simple carbon nucleophiles have been shown [17] to add smoothly and efficiently to Eschenmoser's salt, *N,N*-dimethylmethylethylammonium iodide [18]. We have now found that *in situ* reaction of the 1,1'-dilithioferrocene–TMEDA complex **7** with Eschenmoser's salt readily affords the desired bis-amine **6** in good yield. Quaternisation of the

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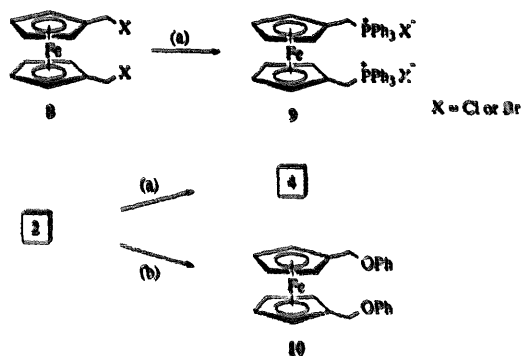


Scheme 1. Reagents: (a) $[\text{Me}_2\text{N}]_2\text{CH}_2$, H_3PO_4 ; (b) $n\text{BuLi}$, TMEDA; (c) MeI ; (d) $\text{H}_2\text{C}=\text{NMe}_2^+ \text{I}^-$.

two tertiary nitrogen atoms is then effected in the usual manner with iodomethane to give **2** in sufficient purity for direct use (Scheme 1). This represents a simple two-stage preparation from ferrocene in an overall yield of 57%. Unlike most other applications of dilithioferrocene [9–16], the reaction with Eschenmoser's salt involves no displacement of a covalently-bound leaving group, and requires no acidic work-up: purification of the product **6** therefore requires only minimal chromatography to remove the inevitable traces of by-products arising from incomplete dilithiation [12].

The trimethylammonium group is an excellent practical alternative to halide as a leaving group. Bis(halogenomethyl)ferrocenes **8**, which undergo reaction with triphenylphosphine analogous to that of **2** to form the corresponding phosphonium salts **9** [19,20] are obtained only after a laborious four-step transformation of 1,1'-diacetylferrocene [20,21].

The reactions of **2** with triphenylphosphine and the sodium salt of 2,2,6,6-tetramethylheptane-3,5-dione, to form **4** and **5** respectively, have already been described [5]. We have found that in order to achieve successful reaction with phenoxide ion it is necessary to employ non-aqueous conditions (Scheme 2). Thus, the bis-ether **10** was obtained in reasonable yield by treatment of **2** with sodium phenoxide in acetonitrile though, as in other cases, the rate of reaction was relatively slow. Attempts to make **10** via aqueous methods analogous to that used by Nesmeyanov et al. [1] for the preparation of phenoxymethylferrocene all failed; decomposition



Scheme 2. Reagents: (a) PPh_3 ; (b) PhOH , NaH .

occurred in each case. Further investigations into the synthetic utility of the bis-ammonium salt **2** are in progress.

2. Experimental

2.1. General

Hexane and diethyl ether were dried by storage over sodium wire prior to use. Methanol was dried by distillation from magnesium–iodine, and acetonitrile (Fisons HPLC grade) was used without further purification. Petroleum spirit had b.p. 60–80°C. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried by storage over solid KOH. *N,N*-Dimethylmethyleammonium iodide (Eschenmoser's salt) was purchased from Lancaster Synthesis Ltd.

2.2. 1,1'-Bis(*N,N*-dimethylaminomethyl)ferrocene **6**

n-Butyllithium (1.6 M in hexanes; 34 cm³, 54 mmol) was added dropwise to a stirred solution of ferrocene (4.84 g, 26 mmol) and TMEDA (6.28 g, 54 mmol) in hexane (250 cm³) under a nitrogen atmosphere. No external cooling was necessary, and approximately 4 h after addition of the BuLi was complete an orange precipitate was observed in the dark orange solution. Stirring was continued for a further 18 h at room temperature before the suspension was diluted with ether (250 cm³). Solid *N,N*-dimethylmethyleammonium iodide (10.00 g, 54 mmol) was added rapidly, in one portion, to the reaction mixture, which was then stirred at room temperature under nitrogen for a further 18 h, heated under reflux for 10 min, then allowed to cool — most of the precipitate had now dissolved. Water (50 cm³) was added dropwise and the two-phase system was stirred for 15 min before the flask was opened and a further portion of water (100 cm³) introduced. The layers were separated and the aqueous layer was extracted with ether (2 × 150 cm³). The organic layer was combined with the extracts, dried over MgSO_4 and concentrated (reduced pressure; water bath temperature 45°C to ensure removal of the TMEDA) to give an orange-brown liquid (7.10 g). This was purified by chromatography on neutral alumina (250 g) using petrol, to elute the unreacted ferrocene. 30% ether:petrol was used to elute the mono-dimethylaminomethyl derivative, and 3% methanol:ether was used to elute the desired product **6** ($R_f = 0.6$ streak, 10% methanol:ether) as an orange-brown liquid (5.28 g, 17.6 mmol, 68%) which was used directly in the next stage. NMR δ_{H} (300 MHz, CDCl_3) 2.17 (12H, s, 4 × Me), 3.26 (4H, s, 2 × CH_2), 4.07 and 4.11 (each 4H, m, 2 × Cp).

2.3. Quaternisation of **6** with iodomethane

Iodomethane (7.52 g, 3.3 cm³, 53 mmol) was added slowly (exothermic!) to a solution of 1,1'-bis(*N,N*-dimethylaminomethyl)ferrocene (5.28 g, 17.6 mmol) in methanol (50 cm³) and the resulting solution was heated under reflux for 10 min before being allowed to cool. Dry ether (250 cm³) was added and ferrocene-1,1'-diylbis(methyltrimethylammonium iodide) **2** precipitated as a pale yellow solid. This was collected by filtration, washed with dichloromethane (100 cm³) then ether (2 × 100 cm³) before being dried (8.74 g, 15 mmol, 85%). The salt **2** decomposed above 210 °C but does not melt below 300 °C (Ref. [5] 210 °C dec.); NMR δ_H (200 MHz, CD₃OD) 3.09 (18H, s, 6 × Me), 4.53 and 4.67 (each 4H, m, 2 × Cp), 4.80 (4H, s, 2 × CH₂); δ_C (50.3 MHz) 53.0 (6 × Me), 67.2 (2 × CH₂), 72.9 and 74.8 (8 × CP CH), 75.6 (1,1'-C).

2.4. Reaction of **2** with sodium phenoxide

A solution of sodium phenoxide was prepared by adding sodium hydride (60% w/w in oil-pretreated with petrol b.p. 40–60 °C; 0.09 g, 2.2 mmol) to phenol (0.21 g, 2.2 mmol) in acetonitrile (5 cm³). This was added to a solution of **2** (0.58 g, 1 mmol) in acetonitrile (60 cm³) and the resulting yellow solution heated under reflux for 48 h. The reaction mixture was cooled and the solvent evaporated under reduced pressure to leave a yellow solid residue. This was redissolved in ethyl acetate (100 cm³) and the solution washed with sodium hydroxide (2% w/w aqueous; 30 cm³) then with water until the aqueous phase had a pH = 7 (ca. 5 × 50 cm³) before the organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by chromatography on silica (15% ether:60–80 petrol) to give 1,1'-bis(phenoxymethyl)ferrocene **10** as a yellow solid (0.20 g, 50%) m.p. 146–147 °C (from toluene). Anal. Found: C, 72.65; H, 5.7. C₂₄H₂₂FeO₂. Calc.: C, 72.4; H, 5.6%. NMR δ_H (300 MHz, CDCl₃) 4.23 and 4.33 (each 4H, t, *J* 2 Hz, 2 × Cp), 4.80 (4H, s, 2 × CH₂), 6.89–6.99 (6H, m, 4 × Ph *o*- and 2 × *p*-H), 7.24–7.36 (4H, m, 4 × Ph *m*-H); δ_C (75.4 MHz) 66.1 (2 × CH₂), 69.0 and 69.4 (8 × CP CHs), 83.5 (CP C-1,1'), 114.6 (4 × Ph *o*-C), 120.7 (2 × Ph *p*-C), 129.4

(4 × Ph *m*-C), 158.7 (2 × Ph *iso*-C); *m/z* (EI) 398 (M⁺ 51%), 305 (45), 242 (9), 227 (66), 149 (100).

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