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Lithiation of 2,5-dimethylazaferrocene

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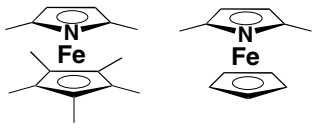
Abstract

Reaction of 2,5-dimethylazaferrocene with *sec*-BuLi/TMEDA in THF at −78 °C, followed by quenching with D_2O brought about incorporation of deuterium into the Cp ring (54%), methyl groups (38%) and the pyrrolyl β-position (8%). When benzyl chloride or *p*-methoxybenzaldehyde was used as quenchers products originated from the lateral lithiation were only formed, accompanied by recovered starting material. For this reaction a radical pathway is suggested.

Keywords: Azaferrocene; Lithiation

1. Introduction

Lithiation of methyl-substituted ferrocenes takes place at the Cp rings not at the methyl groups [1]. Ferrocenyl group does not seem to stabilize the negative charge in the α-position to an extent making CH_3 protons more acidic than those of the Cp rings [2,3]. However, it has been reported that *bis*-lithiation of 1,2,3,4,5-pentamethylferrocene proceeds at the Cp ring and at one of the methyl groups [4]. In contrast, it has recently been found that 1′,2,2′,3′,4′,5,5′,-heptamethylazaferrocene **1** undergoes lithiation at the methyl group of the pyrrolyl ligand [5]. The activating effect of the nitrogen atom can be compared to that observed in 2-methylpyridine, undergoing lateral lithiation more easily than toluene [6].



1 2

In contrast to **1**, 2,5-dimethylazaferrocene **2** contains three potential reaction sites: methyl groups, Cp- and pyrrolyl rings. We thought that determination of the preferential reaction site(s) of **2** and study of reactivities of resulting lithio compounds would be of interest for syntheses of specifically substituted azaferrocenes with possible applications in asymmetric syntheses [5,7] or in the study of photoinduced electron transfer reactions involving metalloporphyrins and metallophthalocyanines [8]. Herein, we report preliminary results of such a research.

2. Results and discussion

In our first attempts, we treated **2** with *sec*-BuLi/TMEDA in THF at −78 °C for 1.5 h and then quenched with D_2O. To determine the extent of deuteration the recovered metallocene was treated with neat methyl iodide, which transformed it quantitatively into the corresponding *N*-methyl iodide, [**2**-Me]$^+$ I^- [9]. The FAB mass spectrum of this complex in the positive peaks mode displays an intense peak corresponding to the mass of the cationic part of the complex. Comparison of this spectrum with that of the *N*-methyl iodide of the starting **2** led to conclusion that complete deuteration took place with some concomitant *bis*-deuteration (10–15%).

The deuteration sites were determined from the ^2H NMR spectrum of the reaction mixture (Fig. 1).

The most intense signal (4.25 ppm) corresponds to deuterium incorporated to the Cp ring, but the signal at

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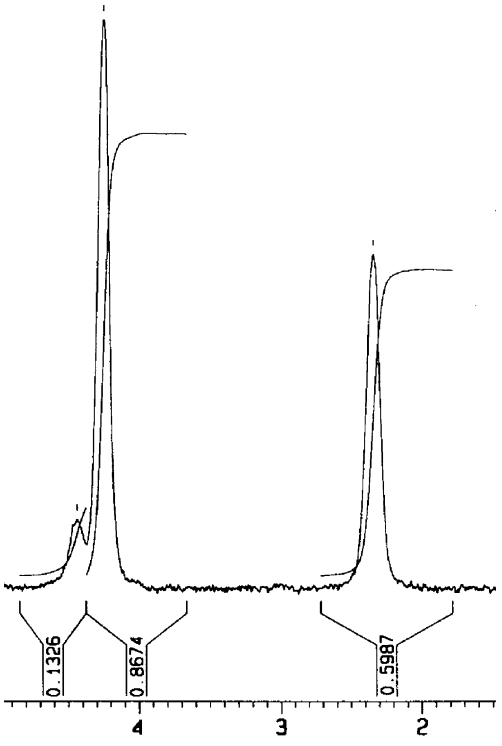
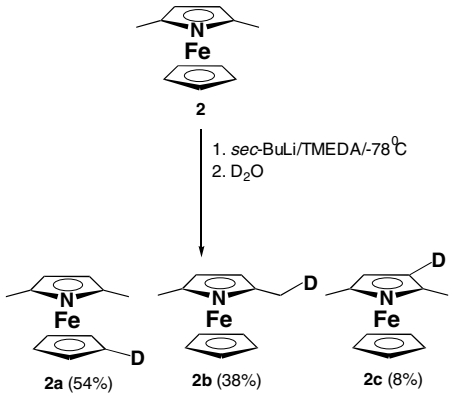


Fig. 1. ^{2}H NMR spectrum of deuterated **2**.

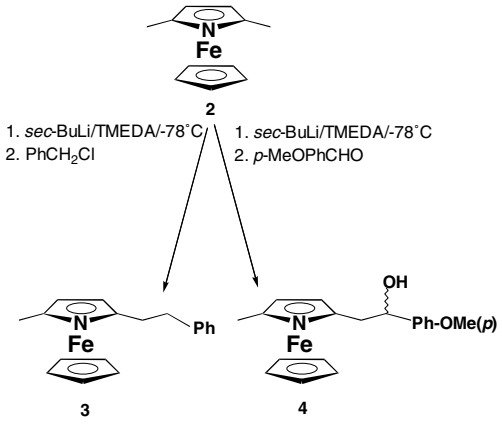
2.34 ppm must be assigned to the CH_2D group (the same chemical shifts are displayed by the corresponding protons in the ^{1}H NMR spectrum of nondeuterated **2**). There is also a weaker signal at 4.44 ppm, which we assigned to deuterium incorporated in the β-positions of the pyrrolyl ligand. Integration of these signals allowed determination of the yields of deuterated products **2a**–**c** (Eq. (1)).



(1)

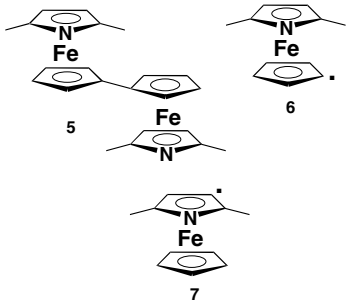
The above experiment confirms the presence in **2** of three competitive lithiation sites. Interestingly, lateral lithiation takes place to a significant extent even in the presence of reactive cyclopentadienyl C–H bonds. Moreover, lithiation of the pyrrolyl β-position is also observed (taking into account different numbers of C–H bonds in each site, relative reactivities of a single C–H bond can be estimated: Cp:Me:β-pyrrolyl = 2.7:1.6:1). It is interesting to compare these results with those obtained by Pyshnograeva et al. [10] for lithiation of parent, unsubstituted azaferrocene with *n*-BuLi. Using quenching with D_2O or methyl iodide, they found that lithiation occurs in the Cp ring and at the α-position of the pyrrolyl ligand at comparable rates.

In the following experiment, **2** was treated with *sec*-Buli-TMEDA in THF at −78 °C for 1.5 h and then quenched at the same temperature with benzyl chloride. Unexpectedly, the only azaferrocene product isolated was **3** (35%), along with a significant amount (55%) of recovered **2** (Eq. (2)). No other benzylated derivatives of **2** were detected in this reaction. Similarly, when *p*-methoxybenzaldehyde was used as a quencher, **4** (30%) was obtained along with **2** (50% recovery). According to ^{1}H NMR, only one diastereomer was formed.



(2)

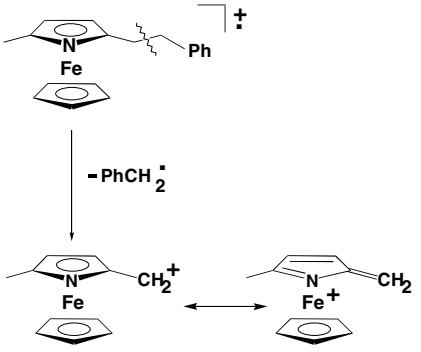
The separation of compounds **3** and **4** from recovered **2** was easily achieved by column chromatography. Apart from these compounds a nonpolar, colorless, purely organic fraction was also collected. GC–MS analysis revealed that it contains mainly (>90%) dibenzyl ($PhCH_2CH_2Ph$). In reaction quenched with benzyl chloride a small amount (3%) of bis-azaferrocene **5**, with the bond between Cp rings, was also isolated.



The formation of **3** and **4** indicates that **2** lithiated at the methyl group reacts efficiently with the alkylating reagent (note that the yields of **3** and **4** are close to that of **2b**) with formation of the C–C bond. On the other

hand, such a reaction does not appear to take place in the case of lithio derivatives of **2** metallated at the Cp or pyrrolyl rings. Formation of dibenzyl and **5**, as well as a significant recovery of **2**, suggest a radical pathway, leading to the benzyl radical, $PhCH_2^{\cdot}$ and **6** or **7**, undergoing subsequent abstraction of the $H^{\cdot}$ from the solvent or dimerization.

The mass spectrum (EI, 70 eV) of **3** presents a feature, which seems worthy to emphasize. The base peak is observed at m/e 214, which corresponds to azaferrocenyl carbenium ion (HR spectrum gave $m/e = 214.0319$; value calculated for $C_{11}H_{12}NFe$ is 214.0319) ion formed from the parent ion by the loss of benzyl radical as shown in Eq. (3).



(3)

So far attempts to generate azaferrocenyl carbenium ions in solution were unsuccessful [10b], suggesting low stability of such species. We now have evidence that an azaferrocenylmethyl cation can display (at least under conditions used in MS) a significant stability.

In conclusion, we have demonstrated that 2,5-dimethylazaferrocene possess three lithiation sites: Cp ring, methyl groups and pyrrolyl β-position. Despite competitive character of these sites, lithiation of 2,5-dimethylazaferrocene followed by reaction with an organic electrophile can be used in syntheses of 2,5-substituted azaferrocenes. Further studies on the scope and limitation of this reaction as well its mechanism are currently under investigation.

3. Experimental

All reactions were carried out under argon. Chromatographic separations were carried out using silica gel 60 (Merck, 230–400 mesh ASTM) using $CHCl_3$–MeOH (50:1) as eluent. NMR spectra were recorded on a Varian Gemini 200BB and Bruker AC 300 spectrometers. Mass spectra were run on a Finnigan MAT 95 spectrometer. 2,5-Dimethylazaferrocene was prepared according to the literature procedure [9]. Tetrahydrofuran was distilled over sodium benzophenone ketyl. Other solvents and reagents were of reagent grade and were used without prior purification.

3.1. Lithiation of 2,5-dimethylazaferrocene followed by quenching with D_2O

Sec-BuLi (1.4 M in cyclohexane, 1 ml, 1.4 mmol) was added to an argon-saturated THF (6 ml) solution of 2,5-dimethylazaferrocene (226 mg, 1.05 mmol) and TMEDA (30 μl, 0.20 mmol) at −78 °C. The orange coloration of the solution rapidly turned brown. The mixture was stirred for 1.5 h at −78 °C and quenched with D_2O in THF. Evaporation to dryness and flash chromatography afforded red oil which was dissolved in methyl iodide (5 ml). After 1 h, the precipitate of deuteriated [**2**-Me]$^+$I$^-$ was filtered off, washed with ether and dried under vacuum.

In a separate experiment non-deuteriated [**2**-Me]$^+$I$^-$ was prepared analogously from **1** and methyl iodide.

Spectral and analytical data: ^{1}H NMR δ (D_2O): 5.24 (s, 2H, β-pyrrolyl), 4.90 (s, 5H, C_5H_5), 3.50 (s, 3H, N^+–CH_3), 2.61 (s, 6H, CH_3-pyrrolyl). Anal. Calcd. for $C_{12}H_{16}NIFe$: C, 40.37; H, 4.52; N, 3.92. Found: C, 40.21; H, 4.56; N, 3.85. FAB (+ve) MS (nba) for the starting [**1**-Me]$^+$I$^-$ m/e 230.1 [M]$^+$, 231.1 [M]$^+$. FAB MS (+ve, nba) (nba) of [**1**-Me]$^+$I$^-$ after lithiation and quenching with D_2O m/e 231.1 [M]$^+$, 232.1 [M]$^+$.

3.2. Lithiation of 2,5-dimethylazaferrocene followed by reaction with benzyl chloride

Sec-BuLi (1.4 M in cyclohexane, 1 ml, 1.4 mmol) was added to an argon-saturated THF (6 ml) solution of 2,5-dimethylazaferrocene (226 mg, 1.05 mmol) and TMEDA (30 μl, 0.20 mmol) at −78 °C. The orange coloration of the solution rapidly turned brown. After the mixture was stirred for 1.5 h at −78 °C, benzyl chloride (167 μl, 1.46 mmol) was added and the stirring was continued for 1.5 h. The reaction mixture was warmed to room temperature and poured onto water. Extraction with dichloromethane, drying over $MgSO_4$ and solvent removal gave brown oil which was subjected to column chromatography.

The following fractions were collected:

(a) Colorless, containing according to GC–MS >90% of dibenzyl $m/e = 182$ [M]$^+$, 91 [M–CH_2Ph]$^+$, ^{1}H NMR δ ($CDCl_3$): 7.24 (m, 10H, C_6H_5), 2.96 (s, 4H, CH_2).

(b) Orange, containing **3**. Yield: 107 mg (35%). ^{1}H NMR δ ($CDCl_3$): 7.25 (m, 5H, C_6H_5), 4.37 (d, 1H, $J = 1.8$ Hz, β-pyrrolyl), 4.30 (d, 1H, $J = 1.8$ Hz, β-pyrrolyl), 4.16 (s, 5H, C_5H_5), 2.91 (m, 4H, CH_2), 2.31 (s, 3H, CH_3). EIMS (70 eV) $m/e = 305$ [M]$^+$, 240 [M–C_5H_5]$^+$, 214 [M–CH_2Ph]$^+$. HRMS of [M–CH_2Ph]$^+$: $m/e = 214.0319$ (Calcd. for $C_{11}H_{12}NFe$, 214.0319). Anal. Calcd. for $C_{18}H_{19}NFe$: C, 70.84; H, 6.27; N, 4.59. Found: C, 70.62; H, 6.31; N, 4.73.

(c) Orange containing recovered **2**. Yield: 124 mg (55%).

(d) Orange-red containing **5**. Yield: 7 mg (3%). ^{1}H NMR δ ($CDCl_3$): 4.30 (bs, 4H, C_5H_5), 4.25 (bs, 4H, C_5H_5), 4.14 (s, 4H, β-pyrrolyl), 1.99 (s, 12H, CH_3). EIMS (70 eV) $m/e = 428$ $[M]^+$, 334 $[M–C_6H_8N]^+$. HRMS $m/e = 428.0632$ (calcd. for $C_{22}H_{24}N_2Fe_2$: 428.0638).

3.3. Lithiation of 2,5-dimethylazaferrocene followed by reaction with p-methoxybenzaldehyde

Similar procedure, using *p*-methoxybenzaldehyde instead of benzyl chloride afforded **4** (Yield: 30%) along with recovered **2** (Yield: 50%). **4**: ^{1}H NMR δ ($CDCl_3$): 7.33 (AB d, 2H, $J = 8.6$ Hz, C_6H_4), 6.86 (AB d, 2H, $J = 8.6$ Hz, C_6H_4), 4.65 (dd, 1H, $J = 9.2$ Hz, $J = 4.0$ Hz, CH), 4.41 (d,1H, $J = 2.1$ Hz, β-pyrrolyl), 4.33 (d, 1H, $J = 2.1$ Hz, β-pyrrolyl), 4.17 (s, 5H, C_5H_5), 3.81 (s, 3H, OCH_3), 3.11 (dd, 1H, $J = 14.6$ Hz, $J = 9.2$ Hz, CH_2), 2.96 (dd, 1H, $J = 14.6$ Hz, 2H, $J = 4.0$ Hz, CH_2), 2.31 (s, 3H, CH_3-pyrrolyl). IR (KBr ν [cm^{-1}]): 3334 (OH). HRMS $m/e = 351.0915$ (calcd. for $C_{19}H_{21}O_2NFe$: 351.0921).

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