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DIRECTED METALATION REACTIONS

II*. DEMONSTRATION OF DIRECTED LITHIATION AT THE 2-POSITION OF METHOXY- AND CHLOROFERROCENE

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SUMMARY

Unequivocal demonstration that the position of lithiation of chloro- and methoxyferrocene is the 2-position is provided. 2-Methylchloroferrocene and 2-(methoxymethyl)methoxyferrocene were prepared from the respective 2-lithio intermediates. These derivatives were shown to be identical to samples of these compounds prepared by the lithiation of [(dimethylamino)methyl]ferrocene, a procedure well documented to produce 1,2-disubstituted ferrocenes.

Lithiation of methoxy[1]- and chloroferrocene[2,3] has been suggested to occur at the 2-position in each of these molecules; however direct proof of this contention is lacking. We now wish to report the unequivocal demonstration of the 1,2-disposition of substituents in the products formed by metalation of these respective molecules.

The basis of this proof, outlined in Scheme 1, lies in the already documented[4] 2-metalation of [(dimethylamino)methyl]ferrocene (I) with n-butyllithium. Since the 2-chloro derivative of amine (I) can be prepared via this 2-metalation technique[5,6] and readily transformed into 2-chloromethylferrocene (III), the 1,2 orientation of the substituents in (III) is established (Scheme 1). Treatment of chloroferrocene (IV) itself with n-butyllithium and subsequent addition of methyl iodide to the resulting lithio-intermediate produced after workup a chloromethylferrocene with elemental analyses signifying a molecular formula of $C_{11}H_{11}ClFe$**. The IR and NMR spectra of this compound were identical to those of 2-chloromethylferrocene (III) prepared by the metalation of amine (I). The synthesis of (III) by these two independent routes establishes that chloroferrocene (IV) undergoes metalation at the 2-position.

2-Deuterochloroferrocene (V), prepared by the deuterolysis of the lithio-intermediate, (IV'), of chloroferrocene, was converted to the corresponding 2-deutero-methoxy- derivative (VII) via the acetate (VI) by a known procedure[7]. Metalation of

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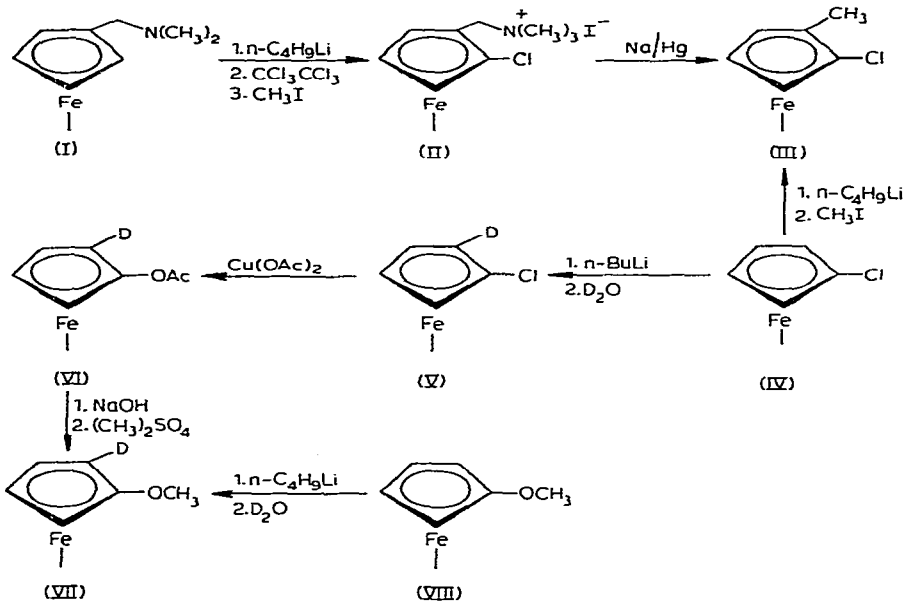
* For part I see ref. 17.

** GLC analysis of the product mixture indicated an additional species present. Although the amount of this species was too small for isolation, we feel this was probably a dimethylated chloroferrocene which arose via dimetalation of (IV).



Scheme 1. 2-Metalation of methoxy- and chloroferrocene.

methoxyferrocene (VIII) with n-butyllithium and subsequent deuterolysis also afforded a deuterated methoxyferrocene. The NMR spectrum of this compound exhibited three well resolved resonances which were identical to those of 2-deuteromethoxyferrocene (VII) prepared from the 2-deuterochloroferrocene (V) precursor. Both spectra in comparison with the spectrum of methoxyferrocene (VIII) itself exhibited attenuation of the ring proton resonance at δ 3.91 ppm along with an expected change in the splitting of the substituted ring proton resonances at δ 3.91 and 3.65 ppm. These results unequivocally demonstrate that the deuterium introduced into methoxyferrocene (VIII) via directed metalation is indeed at the 2-position to the ether moiety.

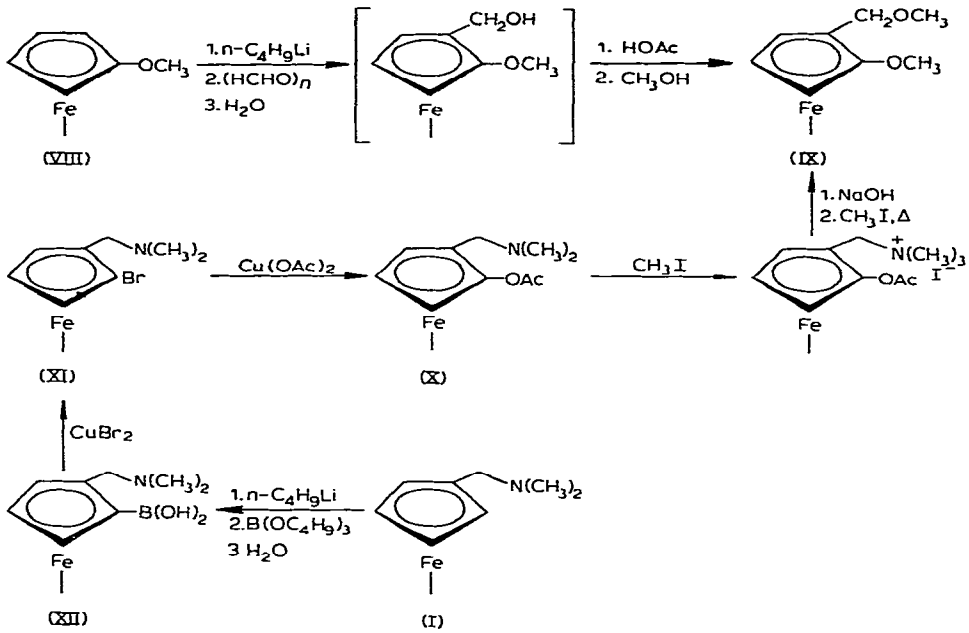
The deuterium contents of (V)–(VII), analyzed both by NMR and mass spectral analysis, are summarized in Table 1. The integration of the NMR spectra

TABLE 1

DEUTERIUM ANALYSIS OF SUBSTITUTED FERROCENES

Substituted ferrocene		*Method of analysis*	
		Mass spectrum[a]	*NMR spectrum*
(V)	2-Deuterochloro-	1.05	0.9
(VI)	2-Deuteroacetoxy-	1.12	1.1
(VII)	2-Deuteromethoxy-[b]	1.14	1.1
(VII)	2-Deuteromethoxy-[c,d]	0.94	1.0

[a] Average of two spectra. [b] Prepared via the chloroferrocene procedure. [c] Prepared via directed metalation of methoxyferrocene (VIII). [d] A determination of the deuterium content of this molecule by the falling drop method yielded a value of 1.02 D/molecule[15].

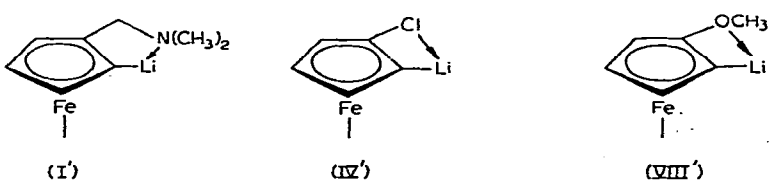


Scheme 2. Correlation of syntheses of 2-(methoxymethyl)methoxyferrocene (IX).

is based on the methyl resonances of (VI) and (VII) and on the $H_{3,4}$ proton resonance of (V). Agreement is observed in all cases for the deuterium content calculated by these two methods. The deuterium content in excess of 1.0 D/molecule of (V)–(VII) probably arose via dimetalation of (V).

In addition to the spectroscopic evidence for 2-metalation of methoxyferrocene, authentic sample identification has been made for a methoxyferrocene derivative. This reaction sequence is shown in Scheme 2. Methoxyferrocene (VIII) was metalated and condensed with paraformaldehyde. The resulting alcohol-ether was not isolated, but was immediately converted to the dimethyl ether (IX) by the method of Nesmeyanov, Perevalova and Ustynyuk[8]. Diether (IX) was then compared with the ether prepared through the route involving the directed metalation of [(dimethylamino)-methyl]ferrocene (I). Condensation of the lithiated intermediate of (I) with $B(OC_4H_9)_3$ afforded the amino-acid (XII) which was converted to the acetate (X) via the bromoamine (XI). Treatment of (X) with *a*) methyl iodide, *b*) 50% NaOH, and *c*) methyl iodide gave 2-(methoxymethyl)methoxyferrocene (IX) whose IR and NMR spectra were superimposable on those of the sample prepared via the metalation of methoxyferrocene directly, thereby confirming 2-metalation of methoxyferrocene.

Although the mechanisms of directed metalation reactions in general have not



been fully delineated, it is possible that coordinated lithio-intermediates (IV') and (VIII') intervene in the metalation of chloro- and methoxyferrocene, respectively. A somewhat similar coordinated lithio-intermediate (I') has been postulated in the 2-lithiation of [(dimethylamino)methyl]ferrocene[4]. Such coordinated structures may involve oligomer structure of the alkyllithium reagent[9], so that these formulae are probably simplifications.

It is significant that although the methoxy group is known to promote directed lithiation in benzene[10], the chloro substituent does not. Other reactions intervene when chlorobenzene is treated with metalating agents[11]. Thus far, five substituent systems have been demonstrated to promote directed metalations in ferrocenes. These include: $-CH_2NMe_2$[4], $-CH_2OCH_3$[13], $-CR_2OH$[14], and now $-Cl$ and $-OCH_3$.

EXPERIMENTAL

The NMR spectra of the reported compounds were obtained on a Varian A 56/60 Spectrometer with TMS as internal standard. Mass spectra were run on a Consolidated Electrodynamics Model 21-104 Spectrometer operating at 70 eV using a heated inlet system at 250°. Mass spectral analysis of the deuterium content was obtained by comparison of the relative intensities of the molecular ion peak of the deuterated molecule and the undeuterated molecule under identical instrumental conditions. The IR spectra were obtained on a Perkin–Elmer 137 Recording Spectrophotometer. All melting points were obtained on a Thomas Hoover Apparatus and all reported uncorrected. The melting points of the deuterated compounds were compared to those of the undeuterated analogs cited in the literature. Microanalysis were performed by Galbraith Laboratories Inc., Knoxville, Tennessee.

Preparation of 2-deuterochloroferrocene (V)

Chloroferrocene (1.10 g, 0.005 mole) was dissolved in 15 ml of sodium-dried ether. After flushing the system with argon, 5 ml of n-butyllithium (1.6 *M*, 0.008 mole) was added at room temperature to the stirring ethereal solution. After stirring for 5 h, excess deuterium oxide (0.40 ml, 0.022 mole) was added and the reaction mixture was allowed to stir for an additional 0.5 h. Ether (30 ml) was added and the hydrolyzed mixture was dried with anhydrous $MgSO_4$. Evaporation of the solvent afforded 1.06 g of 2-deuterochloroferrocene (V), m.p. 58–59°. An NMR spectrum (CCl_4) of the recovered material exhibited a 2.0 proton multiplet at $\delta(H_{3,4})$ 3.91 ppm, a 4.9 proton singlet at $\delta(H_{1'})$ 4.11 ppm and a 1.2 proton multiplet at $\delta(H_{2,5})$ 4.27 ppm.

Total deuterium content of the molecule calculated on the basis of NMR integration was 0.9 D/molecule with 88% of this total at the 2,5-positions. A mass spectrum of the product exhibited a molecular ion peak at *m/e* 221 in accord with $C_{10}H_8ClDFe$. Analysis of the relative intensities of the molecular ion peaks gave a deuterium content of 1.05 D/molecule.

Preparation of 2-deuteroacetoxyferrocene (VI)[7]

2-Deuterochloroferrocene (0.60 g, 0.0027 mole), cupric acetate monohydrate (1.99 g, 0.01 mole), 4 ml of 95% ethanol and 4 ml of H_2O were placed together in a round bottom flask. The reaction mixture was heated and allowed to relux for 2 h after which time it was cooled to room temperature and diluted with 200 ml of water.

This aqueous solution was extracted with ether repeatedly. The ether extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum afforded a dark yellow oil which solidified upon cooling. After washing of this solid with petroleum ether, a small residue remained which the previous authors[7] have identified as biferrocenyl; however attempted identification of this material led to decomposition. The petroleum ether extracts were evaporated and the resulting solid was chromatographed on Silica Gel (60–100 mesh). Elution with petroleum ether afforded a very small fraction which was identified as ferrocene. Further elution with a 50/50 mixture of petroleum ether/dichloromethane afforded a yellow fraction. Evaporation of the solvent yielded 0.20 g (31%) of 2-deuteroacetoxyferrocene (VI), m.p. 64–66° (lit.[7] 64.5–66.5°). An NMR spectrum (CCl_4) of (VI) exhibited a 3.0 proton singlet at $\delta(CH_3)$ 2.07 ppm, a 1.9 proton multiplet at $\delta(H_{3,4})$ 3.80 ppm, a 4.9 proton singlet at $\delta(H_{1'})$ 4.07 ppm and a 1.2 proton multiplet at $\delta(H_{2,5})$ 4.32 ppm. Total deuterium content based upon NMR integration was calculated to be 1.0 D/molecule with 80% of this total at the 2,5-positions.

A mass spectrum of acetate (VI) exhibited a parent peak at *m/e* 245 corresponding to $C_{12}H_{11}DFeO_2$. Calculation of the deuterium content based on mass spectral analysis was found to be 1.12 D/molecule.

Preparation of 2-deuteromethoxyferrocene (VII) from 2-deuteroacetoxyferrocene (VI)[7]

2-Deuteroacetoxyferrocene (0.10 g, 0.0004 mole), 0.5 ml of dimethyl sulfate and 1 ml of methanol were placed together in a round bottom flask. Sodium hydroxide (1 ml; 50%) was added slowly to the above solution. The reaction mixture was then heated at reflux for 1.5 h. Without cooling, the reaction mixture was poured into 75 ml of water and the resulting solution extracted repeatedly with ether. The ether extracts were combined, dried over anhydrous $MgSO_4$ and stripped of the solvent under vacuo affording 55 mg (64%) of 2-deuteromethoxyferrocene (VII), m.p. 39–41° (lit.[7] 29.5–40.5).

An NMR spectrum (CCl_4) of the product exhibited a 3.0 proton singlet at $\delta(OCH_3)$ 3.50 ppm, a 1.9 proton multiplet at $\delta(H_{3,4})$ 3.65 ppm, a 1 proton multiplet at $\delta(H_{2,5})$ 3.91 ppm and a 4.9 proton singlet at $\delta(H_{1'})$ 4.03 ppm. Total deuterium content of the ether was calculated from this spectrum to be 1.1 D/molecule with 82% of this total at the 2,5-positions.

The mass spectrum of (VII) exhibited a parent peak at *m/e* 217 corresponding to $C_{11}H_{11}DFeO$. Total deuterium content based on mass analysis was calculated to be 1.20 D/molecule.

Preparation of 2-deuteromethoxyferrocene (VII) via directed metalation

Methoxyferrocene (1.08 g, 0.005 mole) was placed into an oven-dried flask along with 40 ml of sodium-dried ether. n-Butyllithium (7 ml, 1.6 *M*, 0.10 mole) was then added slowly with stirring at room temperature under an argon atmosphere. The reaction was allowed to stir at room temperature for 6 h at which time excess deuterium oxide (0.5 g, 0.028 mole) was added dropwise. After an additional 2 h of stirring, the hydrolyzed solution was diluted with ether and dried with anhydrous $MgSO_4$. Evaporation of the ether under vacuum afforded 0.98 g (91%) of 2-deuteromethoxyferrocene, m.p. 38–40°, after recrystallization from 95% ethanol. Additional purification of this material by column chromatography on Alumina 1 was necessary.

A very small amount of ferrocene (< 50 mg) was eluted with petroleum ether. Elution with an ether/petroleum ether solution (25/75) afforded a yellow band containing the methoxyferrocene. Recrystallization of this material from methanol yielded the 2-deuteromethoxyferrocene (VII), m.p. 40–41° (lit.[7] 39.5–40.5°).

The NMR spectrum (CCl_4) of (VII) exhibited a 3.0 proton singlet at $\delta(OCH_3)$ 3.52 ppm, a 2.0 proton multiplet at $\delta(H_{3,4})$ 3.68 ppm, a 1.0 proton multiplet at $\delta(H_{2,5})$ 3.94 ppm and a 5.0 proton singlet at $\delta(H_{1'})$ 4.03 ppm. The total deuterium content was 1.0 D/molecule and existed entirely at the 2,5-positions.

The mass spectrum of the deuterated derivative (VII) exhibited a molecular ion fragment at *m/e* 217. Mass analysis for deuterium content was calculated to be 0.94 D/molecule.

Elemental deuterium analysis by the Falling Drop technique[15] gave an excess deuterium abundance of 1.02 D/molecule.

2-Chloromethylferrocene (III) via chloroferrocene metalation

Chloroferrocene (3.30 g, 0.015 mole) was placed in an oven-dried 100 ml round bottom flask along with 30 ml of sodium-dried ether. n-Butyllithium (19 ml, 1.6 *M*, 0.03 mole) was added to this stirring ethereal solution slowly at room temperature under an argon atmosphere. After stirring at room temperature for 3.5 h, the reaction mixture was condensed with methyl iodide (7.10 g, 0.05 mole) and allowed to stir for an additional hour. Water (10 ml) was added and the organic layer separated from the aqueous layer. The aqueous layer was extracted twice with ether and the ether extracts combined, dried over anhydrous $MgSO_4$ and stripped of the solvent. The resulting oil was distilled with collection of the fraction distilling between 58–67°/0.1 mm. This fraction crystallized upon standing. After repeated recrystallizations from hexane, 2.50 g (72%) of yellow crystals of 2-chloromethylferrocene, m.p. 53–54.5°, were obtained.

An NMR spectrum ($CDCl_3$) of this compound exhibited a 1 proton multiplet at δ(ring proton adjacent to Cl) 4.32 ppm, a 5 proton singlet at $\delta(C_5H_5)$ 4.13 ppm, a 2 proton multiplet at δ(protons adjacent to CH_3) 3.98 ppm and a 3 proton singlet at $\delta(-CH_3)$ 2.03 ppm.

An IR spectrum of (III) was superimposable on that of 2-chloromethylferrocene prepared via the metalation of [(dimethylamino)methyl]ferrocene[6].

Microanalysis of (III) confirmed the elemental formula for 2-chloromethylferrocene. (Found: C, 56.35; H, 4.73; Cl, 15.24; Fe, 23.75. $C_{11}H_{11}ClFe$ calcd.: C, 56.33; H, 4.74; Cl, 15.12; Fe, 23.81%.)

Preparation of (2-methoxymethyl)methoxyferrocene (IX) by metalation of methoxyferrocene (VIII); condensation with paraformaldehyde and subsequent reaction with methanol and acetic acid

Methoxyferrocene (VII) (2.16 g, 0.01 mole) was placed in 10 ml of dry ether under an argon atmosphere and 10 ml (0.016 mole) of 1.6 *M* n-butyllithium in hexane was added. The mixture was stirred for 3 h after which time 0.33 g (0.011 mole) of paraformaldehyde was added. This mixture was stirred for 5 h and hydrolyzed with 20 ml of water. The ether layer and the ether extracts of the aqueous layer were combined, washed with water and dried over $MgSO_4$. The ether was stripped and the resulting oil was dissolved in a mixture of 2 ml glacial acetic acid and 80 ml of dry

methyl alcohol. Refluxing of this solution was continued for 5 h after which period it was cooled and then made basic with a saturated solution of KOH. The alcohol was evaporated. The residue was extracted with ether, the ether dried over $MgSO_4$ and removed by evaporation. The resulting oil was chromatographed on Alumina 2 with petroleum ether as eluent. Three fractions were isolated.

Fraction 1 was identified as ferrocene (yield: 0.05 g, 0.6%); fraction 2 as methoxyferrocene (VIII) (recovery: 0.85 g, 39.2%). Fraction 3 gave a yellow oil upon removal of solvent which was assigned the structure of (IX).

An NMR spectrum ($CDCl_3$) of fraction 3 exhibited a 10.0 proton multiplet at δ(ring protons and methylene) 4.60–3.70 ppm, a 3.0 proton singlet at δ(methoxy group on ring) 3.68 ppm, a 2.9 proton singlet at δ(methoxy group on methylene) 3.38 ppm.

An IR spectrum was superimposable on that of 2-(methoxymethyl)methoxyferrocene prepared via metalation of [(dimethylamino)methyl]ferrocene[4].

Microanalysis of (IX) confirmed the elemental formula for 2-(methoxymethyl)-methoxyferrocene. (Found: C, 60.25; H, 6.21. $C_{13}H_{16}O_2Fe$ calcd.: C, 60.03; H, 6.20%.)

Preparation of 2-(methoxymethyl)methoxyferrocene (IX) via 2-metalation of [(dimethylamino)methyl]ferrocene (I)[4]

2-Bromo[(dimethylamino)methyl]ferrocene[16] (1.6 g, 0.005 mole) and cupric acetate monohydrate (10 g, 0.05 mole) were placed in an erlenmeyer flask with 150 ml of water and 10 ml of ethanol. This mixture was stirred and heated at 50–60° for 20 min. The reaction mixture was made basic with $NaHCO_3$ and extracted with ether. Methyl iodide (2 g, 0.0074 mole) was added. The ether was evaporated and the resulting salt washed into a flask with 30 ml of methanol. Sodium hydroxide (50%, 10 ml) was added (the mixture turned dark) along with 2 g (0.0074 mole) of methyl iodide. This mixture was heated on a steam bath for 30 min, cooled, more methyl iodide added and then allowed to stand for 30 min. The reaction mixture was stripped, extracted with ether, the ether dried and stripped and the resulting oil chromatographed on Alumina 3 using methylene chloride/petroleum ether as eluent. Rechromatography of the compound isolated gave 0.2 g (2%) of a compound whose NMR and IR spectra were consistent with the structure (2-methoxy)methoxymethylferrocene (IX). The compound was evidently destroyed upon attempted isolation which accounts for the low yield.

An NMR spectrum ($CDCl_3$) of this compound exhibited a 10.0 proton multiplet at δ(ring protons and methylene) 4.60–3.70 ppm, a 2.9 proton singlet at δ(methoxy group on ring) 3.68 ppm and 3.1 proton singlet at δ(methoxy group on methylene) 3.37 ppm.

These spectral data completely match those of compound (IX) prepared via metalation of methoxyferrocene.

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