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SUBSTITUTED (2-FERROCENYLETHYL) METHYL ETHERS

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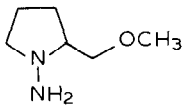
Summary

Ferrocene derivatives of the type $FcCH(X)CH_2OCH_3$ have been prepared and their structure is determined by their ^1H and ^{13}C NMR spectroscopy. Rearrangements in the presence of electrophiles and the methoxythallation reaction are interpreted in terms of carbocation stabilization.

Introduction

Asymmetric carbon–carbon bond formation is of growing importance in organic synthesis. Among the most useful chiral auxiliary reagents are hydrazines derived from natural occurring proline or glutamic acid, SAMP and RAMP [1].



(I)

SAMP, (*S*)-1-amino-2-methoxymethyl-pyrrolidine

RAMP, (*R*)-1-amino-2-methoxymethyl-pyrrolidine

On the other hand, chiral ferrocenylalkyl amines are useful chiral templates for asymmetric reduction of ketones [2] and for peptide synthesis by stereoselective four component condensation [3,4]. To combine the structural aspects of the two types of chiral auxiliaries we have begun to explore the chemistry of substituted (2-ferrocenylethyl)methyl ethers. The preparation and chemical behaviour of various compounds of this type will be described here.

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Results

The reaction of carbonyl compounds with ferrocene in the trichloroacetic acid/fluorosulfonic acid system is known to yield α-ferrocenylalkyl carbocations [5,6]. Thus, reaction of ferrocene II with 1,1,2-trimethoxyethane (methoxyacetaldehyde dimethyl acetal) III gives the 1-ferrocenyl-2-methoxy-ethylium ion IV, which is scavenged by nucleophiles to give the desired compounds V.

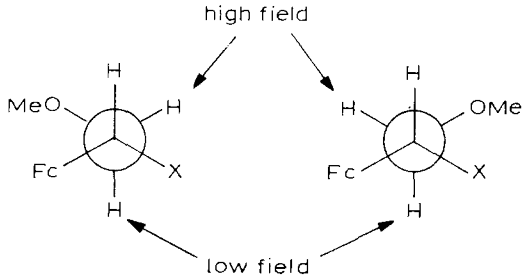
$$\underset{(II)}{FcH} + \underset{(III)}{MeOCH_2(OMe)_2} \xrightarrow{H^+} \underset{(IV)}{Fc\overset{+}{C}HCH_2OMe} \xrightarrow{X^-} \underset{(V)}{Fc\underset{X}{\underset{|}{C}}HCH_2OMe}$$

In this way have been prepared:
Va, X = OH, 1-ferrocenyl-2-methoxyethanol [7];
Vb, X = OMe, 1-ferrocenyl-1,2-dimethoxyethane;
Vc, X = O-i-Pr, 1-ferrocenyl-2-methoxy-1-methylethoxyethane;
Vd, X = SCH_2CO_2H, *S*-(1-ferrocenyl-2-methoxyethyl)-mercapto-ethanoic acid;
Ve, X = N_3, 1-ferrocenyl-2-methoxy-ethylazide.

Reduction of Ve yields 1-ferrocenyl-2-methoxy-ethylamine (Vf), which has been converted via *N*-(1-ferrocenyl-2-methoxyethyl)-formamide (Vg) into 1-ferrocenyl-2-methoxy-ethylisocyanide (Vh) [8]. For comparative purposes, 2-methoxyethylferrocene (VI) was prepared by Williamson methylation of 2-hydroxyethylferrocene [9,10].

The close structural relationship between the compounds V can clearly be seen from their ^{1}H NMR and ^{13}C NMR spectra (Tables 1 and 2).

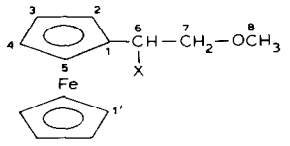
In the ^{1}H NMR spectra, doublets of doublets are observed for all three hydrogens at C^6 and C^7 (except compound Vg which has a spectrum of probably deceptive simplicity). This is due to hindered rotation around the C^6–C^7 bond. The vicinal coupling constant of the doublet at higher field is always 2–3 times higher than that of the other hydrogen at C^7. Considered together with the very similar chemical shifts in both ^{1}H and ^{13}C NMR for atoms separated by more than two bonds from the group X, this indicates not only analogous structures, but also very similar conformations in solution. Two possible conformations are shown below.



Treatment of the alcohol Va with methanol/HCl [7] or with iodotrimethylsilane gave a compound which was previously obtained by methoxythallation of ethenylferrocene [7]. From the data available this was previously suggested to be methoxy

TABLE 1

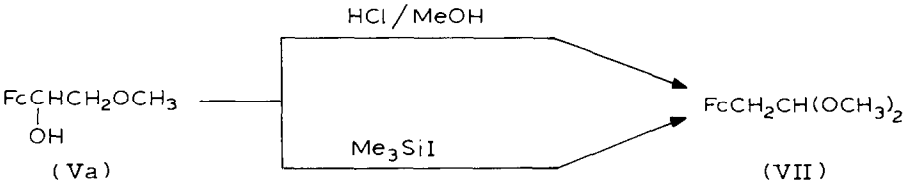
^{1}H NMR SPECTRA IN $CDCl_3$ (δ-values (ppm); J in Hz), AT 200 MHz



Compound	1′ (s, 5H)	2–5	6	7	8 (s, 3H)	X
VI	4.10	4.06(m)	2.60(tr, *J*7.2)	3.49(tr)	3.34	–
Va	4.15	4.10(m, 3H) 4.24(m, 1H)	4.56(dd, *J*8.0, 3.0)	3.41(dd, *J*8.0, 10.0) 3.43(dd, *J* 3.0, 10.0)	3.36	3.03(s, br, 1H)
Vb	4.15	4.00–4.20(m)	[a]	3.70(dd, *J* 8.2, 10.2) 3.88(dd, *J* 2.7, 10.2)	3.47	3.67(s, 3H)
Vc	4.13	4.13(m, 3H) 4.17(m, 1H)	4.37(dd, *J* 3.6, 7.4)	3.61(dd, *J* 7.4, 10.2) 3.76(dd, *J* 3.6, 10.2)	3.42	1.60("tr", *J* 6.0) 3.83(sept, *J* 6.0)
Vd	4.18	4.10–4.23(m)	3.73(m)	3.97(m)	3.45	3.33(s, 2H); 10.60(s, 1H)
Ve	4.12	4.08–4.18(m)	4.38(dd, *J* 3.0, 8.0)	3.50(dd, *J* 8.0, 10.0) 3.65(dd, *J* 3.0, 10.0)	3.37	
Vf	4.12	4.08(m, 3H) 4.21(m, 1H)	3.83(dd, *J* 3.5, 8.5)	3.23(dd, *J* 8.5, 9.0) 3.46(dd, *J* 3.5, 9.0)	3.33	1.73(s, br)
Vg	4.17	4.14–4.30(m)	5.16(m)	3.66(d, *J* 4.4)	3.39	6.14(m, 1H)
Vh	4.25	4.19(m, 3H) 4.34(m, 1H)	4.61(dd, *J* 5.4, 7.2)	3.54(m)	3.41	–

[a] Overlapped with ferrocene signals.

ether Vb, but the latter has obviously different spectral characteristics. We have identified Va as 2,2-dimethoxyethyl-ferrocene (ferrocenacetaldehyde dimethyl acetal) (VII).

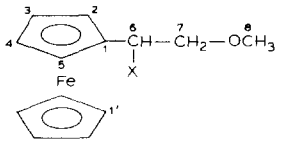


In the case of the methoxythallation, the formation of VII can be rationalized in terms of participation of the ferrocenyl group in the nucleophilic displacement of the thallium moiety. As VII is the only product observed, the tendency of the ferrocenyl group to undergo migration, implying anchimeric assistance, must considerably exceed that of the phenyl group, since in the methoxythallation of ethenylbenzene the products derived from both rearranged and unrearranged species are obtained [11].

The formation of VII from Va involves the α-ferrocenyl carbocation IV and its rearrangement to the α-methoxycarbocation XI. The ethers Vb and Vc do not react with iodotrimethylsilane, but Vc is converted to a mixture of Vb and VII by methanol/HCl. It is interesting to note that comparatively weak electrophiles seems

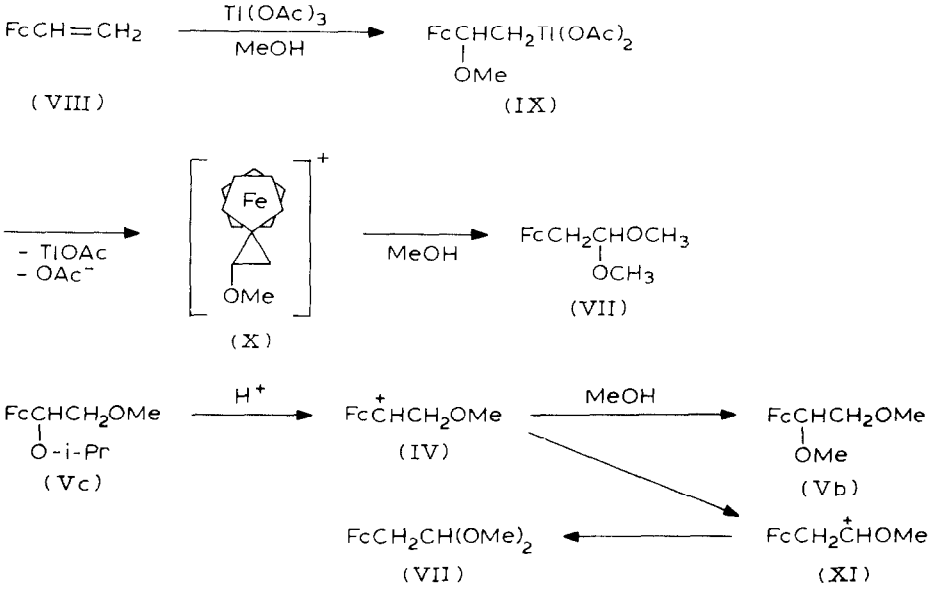
TABLE 2

^{13}C NMR SPECTRA IN $CDCl_3$ WITH TMS AS INTERNAL STANDARD (δ-values (ppm); 22.53 MHz)



Compound	1′	1	2–5	6	7	8	X
VI	68.50	85.32	67.27; 68.37	29.87	73.50	58.57	–
Va	68.12	83.32	65.93; 66.19; 67.37; 68.12 [a]	[a]	77.12	58.58	–
Vb	68.63	85.25	66.16; 67.40; 68.05; 68.37	78.31	76.16	59.09	56.88
Vc	68.57	87.53	66.10; 67.72 69.93; 67.70 [c]	74.09	77.08	59.09	22.27; 22.99 [c]
Vd	68.76	86.03	66.94; 67.66; 67.92	45.00	76.94	58.70	33.31; 176.03
Ve	68.83	84.80	66.49; 67.01; 68.05	61.23	75.97	59.02	–
Vf	68.05	90.45	65.52; 66.36; 67.14; 67.27	49.87	78.50	58.57	–
Vg [b]	68.70	87.40 86.49	66.36; 66.75; 67.14; 67.66; 67.79; 68.11 [a]	[a]	74.99 75.97	58.96 51.62	160.31; 164.28
Vh	69.09	82.66	65.84; 67.07 68.31	54.81	76.03	59.15	156.80

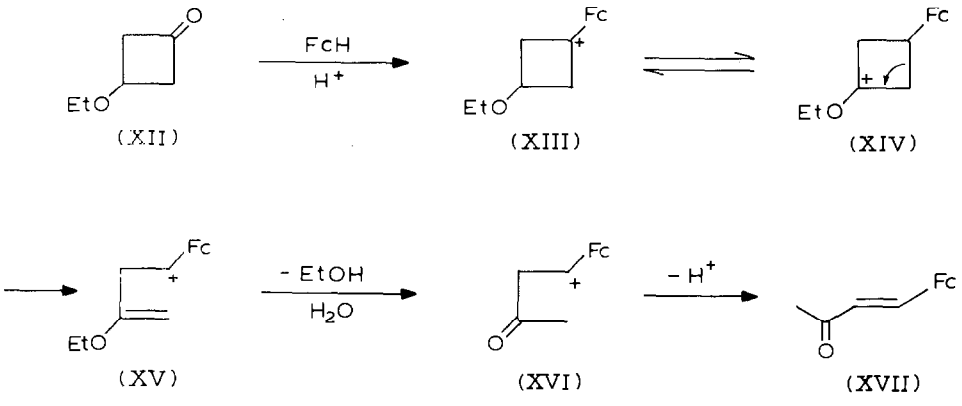
[a] Signal of CHX not clearly separated from ferrocene signals. [b] Complicated spectrum because of *E*/*Z*-isomers of the formamide. [c] Signal of $CHMe_2$ not clearly separated from ferrocene signals.



to promote the reaction. Under the strongly acidic conditions of the formation of the carbocation from ferrocene, no rearrangement is observed. However, it is known that iodotriphenylsilane forms a charge transfer complex with ferrocene [12] and so, iodotrimethylsilane may coordinate to ferrocene and reduce its electron donating capacity. In consequence, α-ferrocenyl carbocation IV will be less stabilized, and rearrangement to the α-methoxycarbocation XI seems possible. A low concentration of protons may produce the same effect by causing protonation of the ferrocene system.

There have been some reports [13,14] of the rearrangement of α-ferrocenyl carbocations to carbocations in which the positive charge is localized in positions other than α. They all involve ring-opening reactions of strained rings, and make use of the electron donating capacity of alkyl or aryl groups to stabilize the carbocationic centres not α to ferrocene. The reaction described below provides a bridge between the two types of rearrangements.

When 3-ethoxycyclobutanone (XII) was condensed with ferrocene in the trichloroacetic acid/fluorosulfonic acid system, *E*-4-ferrocenyl-3-buten-2-one was the main product. The reaction is assumed to involve the following steps:



The crucial step is the rearrangement XIII → XIV, which should occur only if ferrocenyl- and ethoxy-substituted carbocations have similar stabilities. The powerful ability of ferrocene systems to stabilize carbocations [15] suggests another explanation. Although X may exist in only very small amount in the equilibrium with IX, it is removed from the reaction by ring opening, which is favoured because of the release of ring strain [16] and formation of the α-ferrocenyl carbocation XVI.

Experimental

^{1}H NMR spectra were recorded on a Bruker WP 200 and ^{13}C NMR spectra on a JEOL FX 90 spectrometer. IR spectra were recorded on a Perkin–Elmer 157 spectrophotometer and mass spectra on a Varian CH 5 spectrometer.

Compounds Va–Ve

Ferrocene (0.1 mol, 18.6 g) and 1,1,2-trimethoxyethane (0.2 mol, 24.0 g) were added under nitrogen to a mixture of 80 g trichloroacetic acid and 15 ml acetic acid. The mixture was cooled to −10°C and 0.2 mol (15 ml) of fluorosulfonic acid were added dropwise with vigorous stirring. The mixture was stirred for 30 min at −10–0°C to complete the formation of the carbocation IV.

1-Ferrocenyl-2-methoxyethanol (Va)

The carbocation solution was neutralized carefully at 0°C with 30% aqueous sodium hydroxide. Water and ether were added and the organic phase was shaken several times with water. The ethereal layer was dried (Na_2SO_4) and evaporated, and the residue was purified by chromatography (silicagel, hexane/dichloromethane 3/1). Yield 15.3 g (59%), m.p. 30–33°C.

1-Ferrocenyl-1,2-dimethoxyethane (Vb) and 1-Ferrocenyl-2-methoxy-1-methyl-ethoxyethane (Vc)

The carbocation solution was added dropwise with stirring to a mixture of 200 ml of 2-propanol and 150 ml of triethylamine at −40°C. After warming to room temperature, ether and water were added and the mixture was worked up as above. Chromatography (silicagel, hexane) gave 10.5 g (35%) of Vc, followed by 6.8 g (25%) of Vb. The ethers were also the main product when attempts were made to bring the carbocation into reaction with weak nucleophiles (e.g. ammonia).

Vb: oil. Found: C, 61.85; H, 6.65. $C_{14}F_{18}FeO_2$ (274.15) calcd.: C, 61.34; H, 6.62%. MS: 274 (M^+), 229 (FcCHOMe).

Vc: oil. Found: C, 63.70; H, 7.32. $C_{16}H_{22}FeO_2$ (302.20) calcd.: C, 63.59; H, 7.34%. MS: 302 (M^+), 257 (FcCHO-i-Pr).

S-(1-Ferrocenyl-2-methoxyethyl)-mercaptoethanoic acid (Vd)

Vd was prepared from the carbocation solution as previously described [6]. Oil. Yield 12.9 g (36%). Found: C, 54.13; H, 5.57. $C_{15}H_{18}FeO_3S$ (334.22) calcd.: C, 53.85; H, 5.43%. MS: 334 (M^+), 289 ($FcCHCH_2SCH_2CO_2H$) 243 ($FcCHCH_2OMe$). Vd decomposes rapidly at room temperature.

1-Ferrocenyl-2-methoxy-ethylazide (Ve)

The carbocation solution was added dropwise with stirring at −30°C to a mixture of 150 ml of triethylamine with a solution of 25 g of NaN_3 in 200 ml of water. After warming to room temperature the mixture was worked up as above. Recrystallization of the residue from hexane gave Ve.

Ve: yield 25.6 g (90%), m.p. 27.0–27.5°C. Found: C, 54.92; H, 5.30; N, 14.25. $C_{13}H_{15}FeN_3O$ (285.13) calcd.: C, 54.76; H, 5.30; N, 14.74%. MS: 285 (M^+), 257 $(M - N_2)^+$, 243 ($FcCHCH_2OMe$). IR (KBr): 2090vs.

1-Ferrocenyl-2-methoxy-ethylamine (Vf)

To a solution of 14.3 g (50 mmol) of azide Ve in 250 ml of THF $LiAlH_4$ (2.0 g, 52 mmol) was added in small portions. The mixture was subsequently refluxed for 3 h, then cooled to room temperature and water and ether were added. The organic layer was shaken with 8% phosphoric acid, and the acid extracts were neutralized with 10% aqueous sodium hydroxide, the amine was extracted with ether. After drying

(Na_2SO_4) and evaporation of the solvent, the residue was purified by chromatography (silicagel, hexane/ether/dichloromethane 1/1/1).
Vf: oil, yield 10.1 g (78%). Found: C, 60.00; H, 6.64; N, 5.11. $C_{13}H_{17}FeNO$ (259.13) calcd.: C, 60.26; H, 6.61; N, 5.41%. MS: 259 (M^+), 212 ($FcCHN^+$).

N-(1-Ferrocenyl-2-methoxyethyl)formamide (Vg)

Amine Vg (5.2 g, 20 mmol) was refluxed for 30 h with 60 ml of ethyl formate. After evaporation of the volatile components, the residue was extracted with hexane to leave Vg as a dark brown oil, which crystallized reluctantly. Yield 4.0 g (70%), m.p. 58–59°C.
Found: C, 58.62; H, 6.27; N, 4.65. $C_{14}H_{17}FeNO_2$ (287.14) calcd.: C, 58.56; H, 5.97; N, 4.88%. MS: 243 ($FcCHCH_2OCH_3$).

1-Ferrocenyl-2-methoxyethylisocyanide (Vh)

Vh was prepared as previously described [8]. Yield 77%, m.p. 28–29°C.

2-Methoxyethylferrocene (VI)

VI was prepared by methylation of 2-hydroxyethylferrocene [10] using Na/dimethyl sulfate. Yield 63%, oil.
Found: C, 63.70; H, 6.50. $C_{13}H_{16}FeO$ (244.12) calcd.: C, 63.96; H, 6.61. MS: 244 (M^+), 199 ($FcCH_2$).

2,2-Dimethoxyethylferrocene (VII)

(a) To a solution of 1.30 g (5.3 mmol) of Va in 10 ml of acetonitrile and 2 ml of pyridine, were added 3.1 g of NaI and 2.6 ml of chlorotrimethylsilane. The mixture was stirred at room temperature under nitrogen for 40 h. The volatile components were evaporated off and the residue was treated with 30 ml of ether/dichloromethane 1/1. The solution was filtered, concentrated, and chromatographed (silica gel, hexane/ether 1/1).
VII: oil yield 0.69 g (47%). Found: C, 61.60; H, 6.35. $C_{14}H_{18}FeO_2$ (274.15) calcd.: C, 61.34; H, 6.62%. MS: 274 (M^+), 243 ($FcCH_2CHOMe$), 212 ($FcCH_2CH^+$), 199 ($FcCH_2^+$), 75 ($(MeO)_2CH^+$). ^1H NMR ($CDCl_3$): 2.57 (d, 2H, J 5.6 Hz, CH_2); 3.24 (s, 6H, OMe); 4.03 (s, 5H, Cp); 3.99–4.08 (m, 4H, Fc); 4.33 (tr, J 5.6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): 33.50 (CH_2); 52.85 (OMe); 68.37 ((Cp); 67.33, 67.72, 68.76, 82.98 (C_5H_4); 104.92 (CH).
(b) A solution of 1.50 g (5.0 mmol) of Vc in 40 ml of methanol containing 3 drops of conc. HCl was stirred under nitrogen for 40 h at room temperature. The solvent was evaporated off and the residue purified by chromatography (silicagel, hexane/ether 1/1). The first band contained VII (0.55 g, 49%) and the second Vb (0.58 g, 43%).

Reaction of 3-ethoxycyclobutanone XII with ferrocene

Ferrocene (1.86 g, 10 mmol) and 3-ethoxycyclobutanone [17] (2.00 g, 20 mmol) were dissolved under nitrogen in a mixture of 10.0 g trichloroacetic acid and 1.5 ml of dichloromethane. The solution was cooled to −10°C and fluorosulfonic acid (1.5 ml, 20 mmol) was added. Stirring was continued for 30 min at −10–0°C, then the mixture was carefully neutralized at 0°C with 20% aqueous sodium hydroxide.

Water and ether were added and the organic phase was shaken three times with water, then dried (Na_2SO_4) and evaporated. The residue is recrystallized from hexane to give 1.14 g (45%) of *E*-4-ferrocenyl-3-buten-2-one (XVII), with properties identical to those previously reported [18,19].

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