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STUDIES ON FERROCENE DERIVATIVES

XIX *. THE ACYLATION OF [*m*]-FERROCENOPHANES AND 1,1′-DIETHYLFERROCENE AND THE DIRECT CONVERSION OF THE ACYLFERROCENES TO ETHERS AND ALKENES

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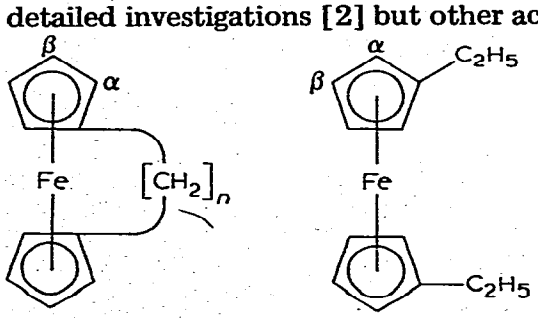
Summary

The Vilsmeir formylation of 1,1′-diethylferrocene, [3]- and [4]ferrocenophane has been shown to produce mainly, but not exclusively, the β-isomer and the ratio of β/α for the acetylation of [3]-ferrocenophane depends on the reagent used in the reaction. These aldehydes are directly converted to ethers by reduction with sodium borohydride in alcohol and also to alkenes via the Wittig reaction.

Introduction

The acetylation of [*m*]-ferrocenophanes has been the subject of several detailed investigations [2] but other acylation reactions have not received the



(I) a ; $n = 3$
b ; $n = 4$

(II)

* For Part XVIII see ref. 1.

same scrutiny. Since our work on α-ferrocenyl carbenium ions [1] required the synthesis of several 2- and 3-substituted ferrocenophanes we undertook a study of the formylation of [3]-ferrocenophane (Ia), [4]-ferrocenophane (Ib) and 1,1′-diethylferrocene(II), and the separation of the various isomeric aldehydes.

Discussion

Compounds Ia, b and II have two reactive sites, α and β, which are susceptible to electrophilic substitution and simple calculations [3,4] predict that the α site should be preferrred. However, acetylation studies have shown that the major product results from β-substitution to give the 3-isomer. This study, using Sato's modification of the Vilsmeir reaction [5] shows an even greater preference for β attack. Table 1 summarizes the results and includes data from related acetylation studies for comparison. If we consider first the data for the acetylation of Ia it is clear that the β/α ratio is greatly affected by the catalyst used and remains essentially constant with $AlCl_3$ but the selectively becomes much greater with the Brönsted acid, H_3PO_4. The interesting point is that the yield of the β isomer hardly varies, the variation in the β/α ratio is essentially due to a decrease in the amount of the α isomer formed. Barr et al. [12] also looked at the effect of increasing the length of the polymethylene chain 3 → 4 → 5 and concluded that the preference for β-substitution increased but their data show that the yield of the β isomer was essentially constant (51, 56 and 55% respectively). Here again the important feature was the variation in the yield of α-isomer (32, 33 and 25% respectively) as the bridging element increases and we may conclude that the α-position becomes more sterically constrained and so the reagent becomes more selective. Using a Brönsted acid as catalyst, α-substitution is further suppressed, and the reagent is either bulkier or less electrophilic. It is possible that attack at the α position requires formation of the more reactive acylium ion and that β attack can be accomplished by the bulkier

TABLE 1

ACYLATION OF 1,1′-DISUBSTITUTED FERROCENES

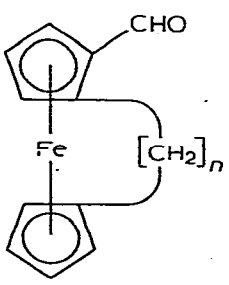
Precursor	Reaction	Products (% yield)	β/α	Reference
Ia	Ac_2O/H_3PO_4	VIIa(21.5), VIIIa(53.4)	2.48 [a]	
Ia	$AcCl/AlCl_3/CH_2Cl_2$	VIIa(32), VIIIa(51)	1.57	12
Ia	$AcCl/AlCl_3/CH_2Cl_2$	VIIa(28.5), VIIIa(46.9)	1.65	9
Ia	$Ac_2O/AlCl_3/CH_2Cl_2$	VIIa(26), VIIIa(44)	1.60	10
Ia	DMF [b]/$POCl_3/CH_2Cl_2$	IIIa(4), Va(80)	20 [a]	
Ia	MFA [c]/$POCl_3$	Va(60) [d]		6
Ib	$Ac_2O/BF_3/CH_2Cl_2$	VIIIb(34), VIIIb(56)	1.64	11
Ib	DMF [b]/$POCl_3/CH_2Cl_2$	IIIb(19.5), Vb(64.3)	3.3 [a]	
II	DMF [b]/$POCl_3/CH_2Cl_2$	IV(18), VI(70)	3.9 [a]	
II	MFA [c]/$POCl_3/CH_2Cl_2$	IV, VI [e] (70)		6
II	MFA [c]/$POCl_3$	IV(8), VI(92)	11.5	7
II	$Ac_2O/AlCl_3/CH_2Cl_2$	IX(30.7), X(79.8)	2.6	8

[a] Measured by GLC and confirmed by column chromatography. [b] DMF: *N,N*-dimethylformamide. [c] MFA: *N*-methylformamide. [c] Only one product isolated and it was assumed to be the 3 isomer. [c] Isomers not separated but β/α = 7 from the approximate ratio of isomers obtained on reduction of the cyclisation product derived from the isomeric mixture of substituted ferrocenylpropionic acids.

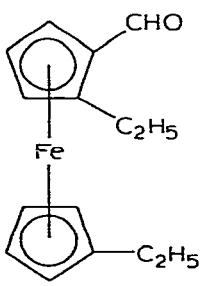
oxonium ion complex RCOCl : $AlCl_3$. A point that should be made is that the α-position in these substituted ferrocenes is much more reactive than the related carbocyclic systems, tetralin and indane, which are attacked exclusively in the β position [13].

It would be predicted that the Vilsmeir complex $CH_3\overset{+}{N}(CH_3)CHOPCl_2\ Cl^-$ would have a larger steric requirement than the acetylating reagents and that it would be more selective in forming the β isomer. In earlier work, Schögl isolated only one isomer from the reaction of [3]-ferrocenophane and presumed that substitution had taken place in the 3 position. The present work confirmed that β substitution predominated and only 4% of the α isomer was detected in the crude reaction. Unlike acetylation, increasing the polymethylene bridge 3 → 4 caused a dramatic change in the product distribution: the yield of the α-isomer increased 5 fold with a concommitant reduction in the yield of the β isomer. In the case of Ib formylation and acetylation give roughly the same amount of the α isomer but formylation of Ia in the α position is almost totally inhibited. The Vilsmeir reaction of II had previously been studied by several groups [6,7, 14]; the latter group reported that only the 3-isomer was formed while the others had great difficulties in separating the isomers and thus obtaining accurate β/α ratios. A combination of GLC and column separations gave a β/α value of 3.9 which indicates a high selectivity in this reaction but is much more in line with [4]-ferrocenophane than Ia. Acylation studies on II show similar high β/α values [7,8,12] and that of Bublitz [8] is probably the most reliable. Again comparison with ethylbenzene shows that even although II shows considerable inhibition of attack at the α-position it is much more reactive than the corresponding *ortho* position which is not attacked by acylation reagents [13].

Acylation products were identified by a number of methods. It was found, as in previous studies [15,16] that the α-isomer eluted first in column chromatography and this was also the case with GLC. UV spectra agreed with Rinehart's observation [16] that the α isomer should exhibit the "slightly shorter 230 nm band" and have "the slightly higher extinction co-efficient" e.g. IIIb and Vb have the following maxima: 230 (16830), 271 (7640), 345 (565); and 233.5 (15270), 275 (6640), 347 (1180) respectively. The spectra probably



(III) a; $n = 3$
b; $n = 4$



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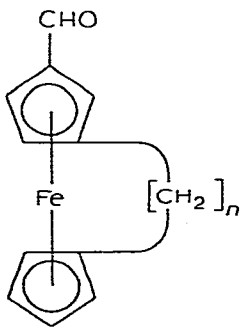

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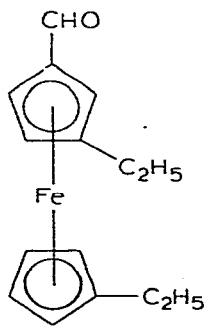


(VI)

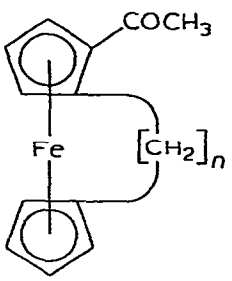
TABLE 2

NMR SPECTRA DATA

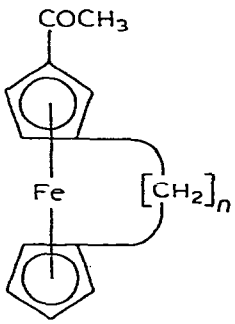
Compound	CHO	H_2	H_3	H_4	H_5	H_2'	H_3'	H_4'	H_5'	Methylene	Methyl
IIIa	9.97		4.62	4.37	4.37	4.24	3.97	3.97	3.97	2.02s(sh) (6H)	
Va	9.80	4.64		4.64	4.38	4.2	3.94	4.2	4.2	2.0m(6H)	
IIIb	10.15		4.6	4.6	4.6	4.04	4.04	4.25	4.25	2.4(4H) 1.9 (4H)	
Vb	9.89	4.72		4.72	4.52	4.22	4.03	4.22	4.22	2.2—2.7(4H) 2.2—1.7(4H)	
IV	10.15		4.63	4.44	4.44	3.73	3.73	3.73		2.84—3.43(4H) 7 lines	1.4—0.9m (6H)
V	9.93	4.65		4.65	4.47	4.08	4.08	4.08		2.65—2.1m (4H)	1.4—1.0m (6H)

reflect the fact that a formyl group in the β-position conjugates with the cyclopentadienyl ring whereas such interactions are sterically inhibited in the α isomer. ^{1}H NMR spectral assignments allow unambiguous differentiation between α and β isomers and the details are given in Table 2. Several important generalizations may be made: (1) Isomers can be identified by the low field formyl proton since the α isomer is most deshielded ca. δ 0.17 downfield from the β isomer. (2) All of the protons in the acylated ring are deshielded and the protons next the formyl group most. (3) The proton underneath the formyl group (eclipsed) is deshielded relative to the other protons in that ring. These results are in general agreement with those of McGuire et al. [17] on the corresponding acetyl derivatives.

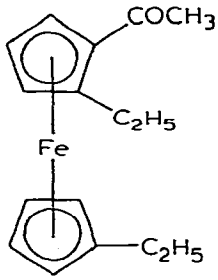
An additional proof of the stability of α-ferrocenylcarbenium ions was furnished by the remarkable reaction of these aldehydes with sodium borohydride in alcohol when the corresponding ether was obtained directly in 75—88% yield (Table 3). Reduction with $LiAlH_4$ in ether only gave the expected hydroxymethyl derivative when the reaction was carried out below 0°C; above that temperature bis(ferrocenyl)methyl ethers were obtained and were the sole product at room temperature. The only previous example of this type of behaviour involves the conversion of the carbinol (XIa) into its methyl ether (XIb) by boiling with



(VII) a; $n = 3$
b; $n = 4$



(VIII) a; $n = 3$
b; $n = 4$



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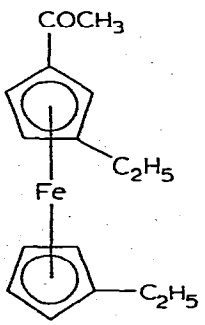

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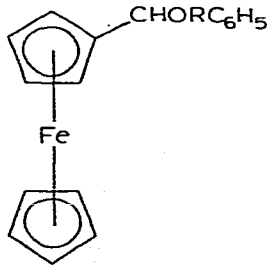
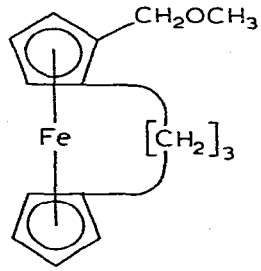


(XI) a; R = H
b; R = CH_3



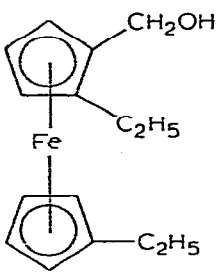
(XII)

TABLE 3

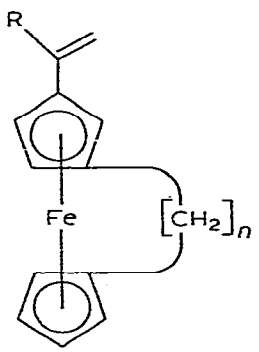
DIRECT CONVERSION OF ALDEHYDES TO ETHERS

Substrate	Alcohol	Yield (%)	Formula	m/e	Found (%)		Calcd. (%)	
					C	H	C	H
Va	C_2H_5OH	75	$C_{16}H_{20}OFe$	284	67.90	7.05	67.60	7.04
Va	CH_3OH	88	$C_{15}H_{18}OFe$	270	66.92	6.55	66.67	6.67
IIIa	CH_3OH	75	$C_{15}H_{18}OFe$	270	66.97	6.79	66.67	6.67
VI	CH_3OH	77	$C_{16}H_{22}OFe$	286	67.10	7.50	67.13	7.69

aqueous methanol [18]. The ^1H NMR of these ethers requires little comment except that the methylene group ($-CH_2O$) appears as an *AB* quartet δ 4.18 (J = 11 Hz) for XII as might be expected for a 1,2-disubstituted ferrocene [19] but



(XIII)



(XIV) a; $n = 3$, R = CH_3
b; $n = 3$, R = H
c; $n = 4$, R = H

the methylene group in XIII appears as a singlet δ 4.35. However the two ethyl groups are no longer of identical chemical shift as in the 1,3-isomer, but appear as two overlapping 4 line patterns due to either steric or inductive effects of the 2-hydroxymethyl group.

Previous work [20] has shown that ferrocenylalkenes are suitable precursors to α-ferrocenylcarbenium ions and it was also shown that these alkenes could

TABLE 4

YIELDS FROM WITTIG REACTION APPLIED TO FORMYL AND ACETYL SUBSTITUTED [m]-FERROCENOPHANES AND 1,1'-DISUBSTITUTED FERROCENES

Product	M.p.	Yield (%)	Formula	m/e	Found (%)		Calcd. (%)	
					C	H	C	H
XIVa	51.5–53	75	$C_{16}H_{18}Fe$	266	72.28	6.77	72.18	6.77
XIVb	40–41	61	$C_{15}H_{16}Fe$	252	71.76	6.43	71.50	6.35
XIVc	32.5–33	83	$C_{16}H_{18}Fe$	266	72.14	6.67	72.18	6.77

be prepared by the Wittig reaction [21]. Application of this reaction to formyl and acetyl substituted [*m*]-ferrocenophanes and 1,1′-disubstituted ferrocenes gave the corresponding alkenes XIV in high yield (Table 4). Additionally, all of these compounds (XIVa, b, c) showed olefinic absorption in the 1620—1625 cm^{-1} region and their ^1H NMR confirmed the presence of the vinyl protons.

This work has shown that the selectivity of acylation reactions with ferrocenophanes and related systems is a function of the catalyst used in the Friedel—Crafts reaction and that the Vilsmeir formylation reaction is even more selective but that the yields of the α-isomer in that reaction may be maximized by using DMF rather than MFA. The carbonyl compounds so formed mya be readily converted to alkenes by the Wittig reaction and directly to either alcohols or ethers by hydride reduction in ether or in alcohols.

Experimental

^1H NMR spectra were recorded on Varian A60, T60 and HA100 spectrometers. IR spectra were obtained on Beckman IR8 and Perkin Elmer 700 instruments. UV and Visible Spectra were recorded on a Cary 14. GLC analysis was carried out on a Varian Aerograph A90P instrument using a thermal conductivity detector,

1,1′-Diethylferrocene (II) was prepared by a modification of the literature procedures [15,22] as was [3]-ferrocenophane (Ia) [23,24] and [4]-ferrocenophane (Ib) was prepared by Rosenblum's method [9].

Acetylation of [3]-ferrocenophane (Ia)

Compound Ia (1.03 g), acetic anhydride (6 ml) and phosphoric acid (85%, 3 drops) were heated at 90°C under nitrogen for 1 h. The cooled mixture was poured onto icewater (100 cm^3) and neutralised (20% Na_2CO_4) and the products extracted into ether. The ethereal layer was washed, dried (Na_2SO_4) and the solvent removed leaving a red oil (1.1 g) shown to consist of three components by GLC with R_T 1.8, 4.0 and 5.6 min respectively on a 3 ft, 10% SE80 column at 195°C, flow rate 40 ml/min. Chromatographic separation on alumina gave (a) recovered Ia (0.05 g), (b) 2-acetyl-[3]-ferrocenophane (0.25 g; 21.5%), m.p. 68—70° lit. m.p. 78—78.5°C [10], (c) 3-acetyl-[3]-ferrocenophane (0.62 g; 53.4%), m.p. 94—96°, lit. m.p. 99—100°C [10]. Spectral data was also in accord with these assignments.

Formylation of Ia

Phosphoryl chloride (7.3 g) was added to an ice cold solution of Ia (4.45 g) and *N*,*N*-dimethylformamide (7 cm^3) in methylene chloride (29 cm^3) over 20 min; the solution was stirred for a further 15 mins before refluxing (6 h) and cooled overnight. The mixture was made alkaline by sodium carbonate, the products extracted into ether (4 × 50 cm^3) and solvent removed from the washed and dried extracts to leave a red solid. GLC analysis showed two products, R_T 5.1 and 4.2 min in the ratio 20 : 1. Separation by column chromatography gave (a) 2-formyl-[3]-ferrocenophane (IIIa) (0.2 g; 4%), m.p. 154—160°C on elution with 30% ether in Skelly F. (Found: C, 66.43; H, 5.60. $C_{14}H_{14}OFe$ calcd.: C, 66.2; H, 5.52%.) (b) Elution with 50% ether in Skelly F gave 3-

formyl-[3]-ferrocenophane (Va) (4.05 g; 80%), m.p. 60—61°C. (Found: C, 66.50; H, 5.57; $C_{14}H_{14}OFe$ calcd.: C, 66.2; H, 5.52%.)

Formylation of Ib

In a similar experiment Ib (0.6 g) was formylated using phosphoryl chloride (1 cm^3), *N,N*-dimethylformamide (1.3 cm^3) in methylene chloride (6 cm^3) to give a crude product (0.7 g) shown by GLC to be two components R_T 9.5 and 11.5 min resp. in the ratio 1 : 3.3. The minor component eluted with 20% ether in Skelly F as a red solid (0.13 g, 19.5%), m.p. 125—127°C was shown to be IIIb. Found: C, 67.03; H, 5.90. $C_{15}H_{16}FeO$ calcd.: C, 67.17; H, 5.97%, *m/e* 268, ν(C=O) 1675 cm^{-1} (CS_2). The second component eluted as an orange solid using 40% ether and was shown to be Vb (0.43 g, 64.3%), m.p. 51—52°C. Found: C, 66.93; H, 6.19; $C_{15}H_{16}FeO$ calcd.: C, 67.17; H, 5.97%, *m/e* 298, ν(C=O) 1675 cm^{-1} (CS_2).

Formylation of 1,1'-diethylferrocene (II)

Compound II (2.42 g) was formylated using phosphoryl chloride (3.7 cm^3), DMF (3.7 cm^3) in methylene chloride (5 cm^3) as previously described. The product was a red oil (2.4 g) consisting of two components R_T 12.4 and 12.9 min which were very difficult to separate. Elution with 30% ether in Skelly F gave 2-formyl-1,1'-diethylferrocene (0.5 g, 18%) while 50% ether gave 3-formyl-1,1'-diethylferrocene (1.9 g, 70%) as red oils.

Sodium borohydride reduction of Va

Sodium borohydride (0.2 g) was added to a solution of Va (0.2 g) in absolute ethanol (20 cm^3) and the mixture stirred for 2 h after which dilute HCl (1%) was added to decompose the excess $NaBH_4$ at ice-bath temperature. The mixture was diluted with water (100 cm^3) and ether extracted to obtain the product as a pale orange solid (0.15 g, 75%), m.p. 45—46°C which was assigned the structure, 3-ethoxymethyl-[3]-ferrocenophane. The ^1H NMR spectrum showed the presence of an ethoxy group as A_2X_3 centred on δ 3.5 (A, 2H q J = 7 Hz) and δ 1.2 (X, 3H, t J = 7 Hz). The methylene group (CH_2O) a singlet (2H, δ 4.17) and the methylene bridge (6H, δ 1.95) also a singlet.

3-Hydroxymethyl-1,1'-diethylferrocene

3-Formyl-1,1'-diethylferrocene (VI) (0.3 g) in dry ether (20 cm^3) was added over 15 min to an ice cold solution of $LiAlH_4$ (0.03 g) in ether (20 cm^3) and the mixture stirred for 20 min before quenching with wet ether. The solution was then dried and evaporated to give a crude product which was chromatographed on alumina, The hydroxymethyl derivative was eluted by Skelly F/ether (1 : 1) as a yellow oil (0.2 g, 67%). Found: C, 66.3; H, 7.26; $C_{15}H_{20}OFe$ calcd.: C, 66.17; H, 7.35% and ^1H NMR δ 4.28 (2H) s, δ 3.9—4.2 (7H) m, δ 2.35 (4H) q (J = 7 Hz), δ 1.57 (1H) s, δ 1.13 (6H) t (J = 7 Hz) which can be assigned to —(—CH_2—O)—, *cp* rings, —CH_2— of ethyl groups, OH, and CH_3 of the ethyl groups respectively while the hydroxyl group exchanged with D_2O.

3-Vinyl-[4]-ferrocenophane (XIVc)

Triphenylmethyl phosphonium bromide (1 g) dissolved in DMSO (3 cm^3)

was added to a solution of dimsyl sodium (0.0025 mole) in DMSO (3 ml) and stirred for 30 min. Vb (0.3 g) was added and the mixture stirred overnight under N_2 then poured into water (100 cm^3). The crude product was obtained by ether extraction and was then chromatographed on alumina using Skelly F as eluant. The vinyl derivative was obtained as a yellow solid (0.25 g, 83%) m.p. 32.5—33°C and GLC analysis showed one peak R_T 5.2 min.

Acknowledgements

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