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APPLICATION OF INTERNAL MICHAEL ADDITION TO THE SYNTHESIS OF [*n*]FERROCENOPHANE DERIVATIVES

I. SYNTHESIS OF [3]-, [4]- AND [7]FERROCENOPHANE DERIVATIVES

Š. TOMA and M. SALIŠOVÁ

Department of Organic Chemistry, Faculty of Natural Sciences, Komensky University, Bratislava (Czechoslovakia)

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SUMMARY

The synthesis of [3]-, [4]- and [7]ferrocenophane derivatives is described. *Retro*- and *trans*-Claisen–Schmidt reactions were found to compete with internal Michael addition in the preparation of [3]- and [7]ferrocenophane derivatives. Cleavage of the acetyl group from the cyclopentadienyl ring and *trans*-Claisen–Schmidt reactions were observed on attempted closure of the three-membered homoannular bridge by internal Michael addition.

Ferroceneacetonitrile was found to condense readily with aromatic aldehydes.

INTRODUCTION

Syntheses of [5]ferrocenophane derivatives have almost exclusively involved internal Michael addition. The initial product of addition, *viz.* 1-acetyl-1′-cinnamoylferrocene, may have been an intermediate in the reaction of 1,1′-diacetylferrocene with benzaldehyde[1,2], and was synthesised by acylation of acetylferrocene with cinnamic acid chloride[3] and also by acetylation of cinnamoylferrocene[4]. The only example of an application of internal Michael addition for the preparation of [*n*]-ferrocenophanes where *n* is other than 5 is the preparation of 4-methyl-1-oxo[4]-ferrocenophane* by cyclization of 1-acetyl-1′-isopropenylferrocene[5]. The main goal of the present study was to examine the possibility of using internal Michael addition to synthesise other [*n*]ferrocenophanes.

RESULTS AND DISCUSSION

[3]*Ferrocenophanes*

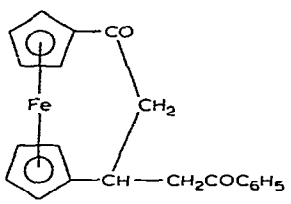
Acetylation of (3-oxo-3-phenyl-1-propenyl)ferrocene gave homo- as well as hetero-acetylation products[4]. We have examined the cyclization of both.

The cyclization of 1-acetyl-1′-(3-oxo-3-phenyl-1-propenyl)ferrocene by potas-

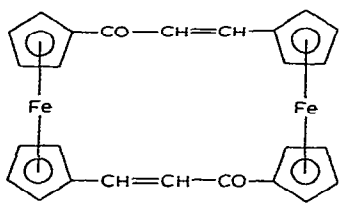
* The phane nomenclature proposed by Vögtle and Neumann[6] is used throughout.

sium hydroxide in boiling ethanol gives two products. The first is 1-oxo-3-phenacyl-[3](1,1')ferrocenophane (I), the product of internal Michael addition. The second is 1,15-dioxo[3.3](1,1')ferrocenophane-2,16-diene (II), which arises by auto-condensation of 1'-acetylferrocenecarbaldehyde; the latter was not detected or isolated, but could have been formed by a *retro*-Claisen–Schmidt reaction from the starting material. The yields of [3]ferrocenophane derivative (I) were small because of this side reaction. Exchange of ethanol for DMF slightly raised the yields of (I). The *retro*-Claisen–Schmidt reaction was the only reaction observed on attempted cyclization of the *p*-bromophenyl analogue of the starting material. An analogous *retro*-Claisen–Schmidt reaction was recently observed in the reaction of 1,1'-dicinnamoylferrocene with NaOH[7].

Cyclization of 1-acetyl-2-(3-oxo-3-phenyl-1-propenyl)ferrocene did not give any product having an homoannular bridge. Two other compounds were found, namely (3-oxo-3-phenyl-1-propenyl)ferrocene (IV), which is the main product of the reaction, and 1,15-dioxo[3.3](1,2)ferrocenophane-2,16-diene (III), which is formed in reactions of the type which gives (II). The removal of the acetyl group to give (IV) is a reaction of a type not previously observed in ferrocene chemistry, but such reactions are well known in benzene chemistry in the case of non-enolizable ketones[8–10]. Cleavage of enolizable ketones is rarer[10,11], and in the systems we studied it proceeded under milder conditions than those described for benzene derivatives. Replacement of EtOH by DMF as solvent had no effect on the reaction.



(I)



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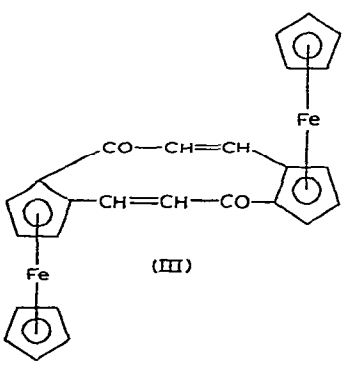

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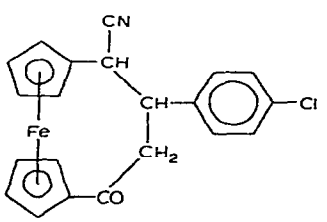


(VII)

[4]*Ferrocenophane*

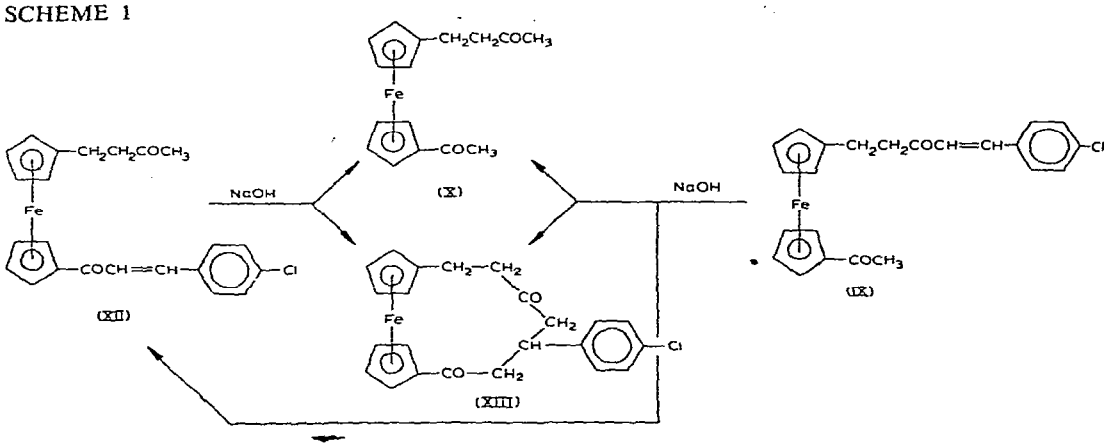
We intended to utilize ferroceneacetaldehyde, as the starting material for the synthesis of [4]ferrocenophane derivatives. As Schlögl's method[12] proved to be unsuitable for preparing larger quantities of the desired ferroceneacetaldehyde, we tried

to make it by a Wittig synthesis from (ferrocenylmethylene)triphenylphosphorane and ethyl formate, and also by reduction of ferroceneacetonitrile with Zn or Cr in acid medium, but neither of these methods was successful[13]. Thus we examined the condensation of ferroceneacetonitrile with *p*-chlorobenzaldehyde. The reaction proceeded smoothly, and the product, 2-ferrocenyl-3-(*p*-chlorophenyl)acrylonitrile (V), underwent Friedel–Crafts acetylation, to give excellent yields of 2-(1′-acetylferrocenyl)-3-(*p*-chlorophenyl)acrylonitrile (VI) from which 1-cyano-2-(*p*-chlorophenyl)-4-oxo[4]ferrocenophane (VII) was obtained in good yield. The existence of two stereoisomers of *vic*-disubstituted [5]ferrocenophane derivatives has been described[14] and so we tried to isolate a second isomer of (VII) but our attempts were unsuccessful, probably because the isomer we isolated is much the more stable thermodynamically.

[7] *Ferrocenophane*

We explored three possible routes to [7]ferrocenophane derivatives. Treatment of 3-oxybutylferrocene with *p*-chlorobenzaldehyde gave [5-(*p*-chlorophenyl)-3-oxo-4-pentenyl]ferrocene (VIII), which yielded 1-acetyl-1′-[5-(*p*-chlorophenyl)-3-oxo-4-pentenyl]ferrocene(IX) on acetylation. This was identical with the condensation product from 1-acetyl-1′-(3-oxobutyl)ferrocene (X) and *p*-chlorobenzaldehyde. A side-product was (XI), which was produced by condensation at both sides of the system. sides of the system.

SCHEME 1



Cyclization of (IX) gave only traces of the cyclizate (XIII) along with many side products; one was identified by TLC as the product, (X), of a *retro*-Claisen–Schmidt and the other, (XII), as the product of a *trans*-Claisen–Schmidt reaction.

Friedel–Crafts acylation of 3-oxybutylferrocene with cinnamic acid chloride gave moderate yields of 1-(*p*-chlorocinnamoyl)-1′-(3-oxobutyl)ferrocene (XII). This gave 3-(*p*-chlorophenyl)-1,5-dioxo[7]ferrocenophane (XIII) on treatment with NaOH in ethanol. The higher yields of (XIII) obtained by this method may be due to the higher thermodynamic stability of (XII) than of (IX), as there is conjugation of the benzene ring with the cyclopentadienyl ring of ferrocene in (XII), and this leads to a lower sensitivity of (XII) to side reactions.

Inspection of Dreiding stereomodels showed that there was no strain in the [4]ferrocenophane derivative or in 1,5-dioxo[5]ferrocenophane. There was strain caused by ring tilting in the [3]ferrocenophane derivative (I), and by interaction of the bridge hydrogens in the [7]ferrocenophane derivative (XIII), which may account for the lower yields of these products.

Steric strain was apparent in the model of (III), and possibly this is why the $[M-C_2H_2]^+$ ion is observed in the mass spectrum instead of the parent $[M]^+$ ion.

EXPERIMENTAL

M.p.'s were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on a Zeiss UR-20 instrument in the 700–3600 cm^{-1} region, the scale being calibrated with a polyethylene standard. The ^1H NMR spectra were recorded on a Perkin–Elmer 60 MHz or on a Tesla BS 487A 80 MHz instrument with tetramethylsilane as internal standard. The physical constants, analyses and IR spectra of products are shown in Tables 1 and 2. Yields are calculated with respect to the amount

TABLE 1

ELEMENTAL ANALYSES AND M.P.'S OF PRODUCTS

Compound	*Formula*	*Analyses found (calcd.) (%)*			*M.p. (°C) (solvent)*	*Yield (%)*
		Fe	*N*	*Cl*		
(I)	$C_{21}H_{18}FeO_2$	15.75 (15.59)			146–147 (benzene)	14.0
(II)	$C_{26}H_{20}Fe_2O_2$	22.82 (23.45)			> 360 (DMF)	14.0
(III)	$C_{26}H_{20}Fe_2O_2$	23.75 (23.45)			203–205 (benzene)	12.0
(IV)	$C_{19}H_{16}FeO$	18.03 (17.66)			137–138 (ethanol)	30.0
(V)	$C_{19}H_{14}ClFeN$	16.18 (16.07)	4.02 (4.09)	10.42 (10.20)	104–105 (acetone/petrol)	66.9
(VI)	$C_{21}H_{16}ClFeNO$	14.56 (14.33)	3.50 (3.59)	9.18 (9.01)	112–114 (benzene/petrol)	90.1
(VII)	$C_{21}H_{16}ClFeNO$	14.10 (14.33)	3.80 (3.59)	9.24 (9.01)	283–284 (dioxane)	82.0
(VIII)	$C_{21}H_{19}ClFeO$	15.01 (14.70)		9.37 (9.36)	90–92 (ethanol)	69.0
(IX)	$C_{23}H_{21}ClFeO_2$	13.16 (13.26)		8.41 (8.43)	89–95 (ethanol/petrol)	43.0
(X)	$C_{16}H_{19}FeO_2$	18.45 (18.67)			oil	30.0
(Xa)	$C_{16}H_{19}FeO_2$	17.87 (18.67)			oil	13.5
(XI)	$C_{30}H_{24}ClFe$	10.20 (10.02)		13.00 (13.02)	155–157 (ethanol/petrol)	3.7
(XII)	$C_{23}H_{21}ClFeO_2$	13.26 (13.26)		8.43 (8.43)	105–106 (acetone/petrol)	29.4
(XIII)	$C_{23}H_{21}ClFeO_2$	12.71 (13.26)		8.34 (8.43)	> 360 (benzene)	35.7

TABLE 2

CHARACTERISTIC IR FREQUENCIES OF PRODUCTS

Compound	*Cp ring*		$\nu_s(Cp-COCH_3)$ 1113–1118	$\gamma(C=C)$ C_6H_5	$\nu(CO)$	$\nu(CN)$
	1000–1023	1100–1107				
(I)					1661, 1680	
(II)				1590	1648	
(III)		1100		1570	1610, 1640	
(IV)	1011	1102		1588, 1595	1650	
(V)	1003	1106		1500, 1608		2227
(VI)	1012		1113	1500, 1590	1763	2218
(VII)	1018	1110		1612	1648	2249
(VIII)	1003	1108		1600, 1620	1693	
(IX)	1014	1106	1115	1595, 1620	1658, 1695	
(X)	1006	1109	1114		1682, 1728	
(Xa)	1005	1110	1115		1680, 1728	
(XI)	1015			1595, 1615	1658, 1692	
(XII)	1012	1108		1573, 1593	1657, 1718	
(XIII)	1017	1110		1500	1642, 1716	

All spectra were measured in Nujol; frequencies in cm^{-1}.

of ferrocene derivative initially taken.

Chromatography was carried out on Al_2O_3 (Brockman II-Reanal, Budapest) or SiO_2 (Kavalier, Votice), and products are given in the sequence of elution.

Cyclization of 1-*acetyl*-1'-(3-*oxo*-3-*phenyl*)-1-*propenylferrocene*

This compound[4] (1.8 g, 0.005 mole) was added to a solution of 3 g (0.05 mole) of KOH in 200 ml of ethanol. The mixture was refluxed one hour and then added to water. The solids were extracted with dichloromethane, and the extract was washed with water and dried over anhydrous Na_2SO_4. The residue left after evaporation of the solvent was extracted with benzene. The violet, insoluble material was filtered off and the benzene solution was chromatographed through Al_2O_3 with benzene as eluant, to give 0.25 g (14%) of the yellow 1-oxo-3-phenacyl[3]ferrocenophane (I). NMR 80 MHz ($CDCl_3$) (δ): 7.8 (m, 2 H); 7.4 (m, 3 H); 4.5 (t, 2 H); 4.25 (t, 2 H); 3.9 (m, 4 H); 3.7 (m, 2 H); 3.0 (m, 3 H).

The second band gave a small amount of a violet substance, identical with that filtered off before chromatography, and was found to be 1,15-dioxo[3.3](1,1')-

ferrocenophane-2,16-diene (II) (overall yield: 0.25 g, 14%). The NMR spectrum could not be taken because of the very low solubility of the product. Mass spectrum *m/e*-$[C_{26}H_{20}Fe_2O_2]^+$ 476.01512 → *m/e*$[C_{13}H_{10}FeO]^+$ 238.00814 → *m/e*$[C_{12}H_8]^+$ 152.06249.

Compound (I) was isolated in 21% yield as the sole product when the reaction was carried out in DMF/MeONa. Cyclization of [3-(*p*-bromophenyl)-3-oxo-1-propenyl]ferrocene in EtOH/KOH gave only (II).

Attempted cyclization of 1-acetyl-2-(3-oxo-3-phenyl-1-propenyl)ferrocene

Cyclization of 0.6 g of this compound was carried out as described above. Chromatography on Al_2O_3, with benzene as the eluant, gave 0.2 g (30%) of (3-oxo-3-phenyl-1-propenyl)ferrocene (IV) which was identical with a sample prepared by condensation of ferrocenecarbaldehyde with acetophenone. Mass spectrum *m/e*-$[C_{19}H_{16}FeO]^+$ 316.05228 → *m/e*$[C_{14}H_{11}FeO]^+$ 251.01418. NMR 60 MHz (CCl_4) (δ): 7.06 (1 H); 7.62 (1 H, AB quartet); 7.96 (m, 2 H); 7.45 (m, 3 H); 6.5 (t, 2 H); 6.35 (t, 2 H); 6.1 (s, 5 H). From the second band was isolated 0.07 g (12%) of 1,15-dioxo-[3.3](1,2)ferrocenophane-2,10-diene (III). Mass spectrum *m/e*$[C_{24}H_{18}Fe_2O_2 = M - C_2H_2]^+$ 450.0368. NMR 60 MHz (CS_2) (δ): 7.3 (2 H); 6.4 (2 H, AB quartet); 4.3 (m, 4 H); 4.2 (m, 4 H); 4.0 (s, 10 H). Similar results were obtained when the reaction was carried out in DMF/MeONa.

Preparation of 2-ferrocenyl-3-(p-chlorophenyl)acrylonitrile (V)

To a stirred solution of 0.4 g (0.01 mole) of NaOH in 50 ml of 50% ethanol were added 1.4 g (0.01 mole) of *p*-chlorobenzaldehyde and 2.25 g (0.01 mole) of ferroceneacetonitrile[16]. The mixture was stirred at 70° (bath temperature) for 4 h, then added to water. After the usual work-up, chromatography on SiO_2, with benzene as eluant, gave red crystals of 2-ferrocenyl-3-(*p*-chlorophenyl)acrylonitrile (V) (1.9 g, 66.9%) and of ferroceneacetonitrile (0.5 g, 22%).

Preparation of 2-(1'-acetylferrocenyl)-3-(p-chlorophenyl)acrylonitrile (VI)

To a stirred solution of 5.5 g (0.016 mole) of 2-ferrocenyl-3-(*p*-chlorophenyl)-acrylonitrile in 80 ml of dichloromethane was added during 30 min a solution of 1.6 ml (0.024 mole) of acetyl chloride and 6.28 g (0.047 mole) of anhydrous $AlCl_3$ in 80 ml of dichloromethane. The mixture was then stirred at room temperature for 4 h, and added to cold water and worked up as usual (see ref. 4). Chromatography on SiO_2, with benzene containing 3% of ethyl acetate as eluant, gave 5.5 g (90.1%) of deep violet crystals of 2-(1'-acetylferrocenyl)-3-(*p*-chlorophenyl)acrylonitrile (VI).

All the acylations below were carried out analogously.

(*i*). Acylation of [5-(*p*-chlorophenyl)-3-oxo-4-pentenyl]ferrocene (1.9 g) with acetyl chloride yielded 0.1 g (5.2%) of starting material and 0.9 g (43%) of 1'-acetylated product (IX).

(*ii*). Acylation of (3-oxobutyl)ferrocene (1.3 g) with acetyl chloride gave a trace of the starting material, 0.44 g (30%) 1'-acetylated product (X) as a red oil and 0.2 g (13.5%) of a deep red oil, which was probably the 3-acetylated product (Xa).

(*iii*). Acylation of (3-oxobutyl)ferrocene (1.7 g) with *p*-chlorocinnamic acid chloride gave a small amount of the starting material and 0.6 g (29.4%) of 1-(*p*-chlorocinnamoyl)-1'-(3-oxobutyl)ferrocene (XII).

Preparation of 3-(*p-chlorophenyl*)-4-*cyano*-1-*oxo*[4]*ferrocenophane* (*VII*)

A mixture of 0.95 g (0.0025 mole) of 2-(1'-acetylferrocenyl)-3-(*p*-chlorophenyl)acrylonitrile and 0.75 g (0.012 mole) of NaOH in 90 ml of ethanol was refluxed for 30 min. The orange-yellow precipitate was filtered off and washed with water until neutral. Yellow crystals of (VII) (0.7 g, 82%) were obtained after crystallisation.

Cyclization of 0.4 g (0.001 mole) of (VI) with 0.3 g (0.007 mole) of NaOH in 30 ml of ethanol at room temperature for 12 h gave the same material (VII). An attempt to cyclize (VI) by leaving it for 1 week on an Al_2O_3 column, according ref. 14, was unsuccessful.

Preparation of [5-(*p-chlorophenyl*)-5-*oxo*-4-*pentenyl*]*ferrocene* (*VIII*)

To a stirred solution of 0.8 g (0.02 mole) of NaOH in 40 ml of 50% ethanol 2 g (0.008 mole) of (3-oxobutyl)ferrocene and 1.1 g (0.008 mole) of *p*-chlorobenzaldehyde were added together. The mixture was stirred at room temperature for 4 h and then cooled in a refrigerator. The solid material was filtered off and washed with water. Crystallisation gave yellow crystals (2 g, 69%) of (VIII).

Condensation of 1-*acetyl*-1'-(3-*oxobutyl*)*ferrocene with p-chlorobenzaldehyde*

The condensation of 1.5 g starting material was carried out similarly. After 4 h of stirring, the mixture was poured into water and worked-up as usual. Chromatography on SiO_2, with benzene containing 5% of ethyl acetate as eluant, gave 0.1 g (3.7%) of 1-(*p*-chlorocinnamoyl)-1'-[5-(*p*-chlorophenyl)-3-oxo-4-pentenyl]ferrocene (XI) (as deep red crystals) and yellow crystals (0.7 g, 29.2%) which were shown by m.p., IR and TLC to be identical with (IX).

Cyclization of 1-(*p-chlorocinnamoyl*)-1'-(3-*oxobutyl*)*ferrocene*

A solution of 0.42 g (0.001 mole) of this compound and 0.3 g (0.007 mole) of NaOH in 35 ml of ethanol was refluxed for 1 h. The mixture was added to water and worked up as usual. Chromatography on SiO_2, with benzene containing 3% of ethyl acetate as eluant, gave 0.15 g (38.7%) of 3-(*p*-chlorophenyl)-1,5-dioxo[7]ferrocenophane (XIII), 0.07 g (16.6%) of the starting material and 0.13 g (43.4%) of (X) (identified by TLC and IR). There were small quantities of other substances which were not identified.

Because of the low solubility of (XIII), a good NMR spectrum could not be obtained, but it was clear that there was no singlet due to the $COCH_3$ group in the spectrum. (The NMR spectrum of (3-oxobutyl)ferrocene was used for comparison.)

Attempt to cyclize 1'-*acetyl*-1'-[5-(*p-chlorophenyl*)-3-*oxo*-4-*pentenyl*]*ferrocene*

From reaction under the conditions described above, 0.63 g of the starting material was isolated, along with 0.12 g (27.5%) of (X) (identified by TLC and IR), while traces of (XIII) and (XII) were detected by TLC among many other products.

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