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Heterylferrocenes. Synthesis and use

M-G A Shvekhgeimer

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Abstract. Data on the synthesis of ferrocene derivatives containing heterocyclic substituents linked directly to the ferrocene system or separated from it by a chain of carbon atoms are described systematically and surveyed. Data on the biological activities and applications of these compounds are presented. The bibliography includes 229 references.

I. Introduction

In 1951, Kealy and Pauson[1] reported for the first time the synthesis of ferrocene and in the same year the first organic compound containing the ferrocenyl and heterocyclic groups was obtained.[2] Such compounds immediately attracted the attention of many investigators and in subsequent years ferrocene derivatives were synthesised in which there are various heterocyclic substituents both linked directly to the ferrocene system and separated from it by a chain of carbon atoms. The considerable interest in heterylferrocene was aroused not only by the unusual chemical behaviour of the ferrocene system, which enters into electrophilic and radical substitution reactions, but also by the unusual properties of the heterocyclic residue due to the presence of the ferrocene fragment. In addition, diverse biological activities of these compounds were observed. It is also significant that heterylferrocenes have found extensive practical applications as medicinal preparations, as components of nonsilver photosensitive compositions and materials, as dyes, and also as additives improving the most important characteristics of rocket fuels and explosives.

The first review devoted to the synthesis of ferrocene derivatives with heterocyclic groups appeared in 1971.[3] It presented an analysis of studies published up to the middle of 1971. The literature data on the synthesis of compounds containing heterocyclic nuclei condensed with the ferrocene system were surveyed in a later communication.[4] The present author's previous review[5] was fully devoted to the chemistry of heterylferrocenes, but it dealt mainly with studies which had been published up to 1972.

The present review gives a systematic account and surveys data published after 1971. Earlier studies containing interesting and important results which were not reflected in subsequent publications are considered as an exception. The review includes data on the synthesis of compounds containing the ferrocenyl group linked directly to an atom of the heterocycle as well as compounds in which the ferrocenyl and heterocyclic groups are separated by a chain of carbon atoms. Compounds in which the ferrocenyl system is condensed with the heterocyclic nucleus, ferrocenophanes, as well as compounds containing the ferrocenyl and heterocyclic groups separated by heterocycles or chains incorporating heteroatoms are not considered. The review presents data on the biological activities and applications of heterylferrocenes.

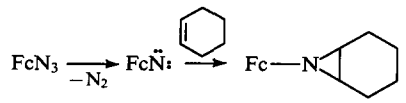
Sections II – VI present information about the synthesis of compounds containing heterocyclic nuclei with three, four, five, six, and more atoms. In each of these sections, the derivatives of ferrocene containing nitrogen, oxygen, and sulfur atoms in the heterocyclic nuclei are considered in succession. Next compounds with heterocycles containing simultaneously nitrogen and oxygen, nitrogen and sulfur, or oxygen and sulfur atoms are described. At the end of each section, data are presented on other heterocyclic systems. Each section deals at the beginning with compounds in which the ferrocenyl group is linked directly to an atom of the heterocycle and then with compounds containing the ferrocenyl and heterocyclic groups separated by a chain of carbon atoms. If the compound contains two or more heterocyclic nuclei (condensed or noncondensed), then its location in a particular section is determined by the heterocyclic system closest to the ferrocenyl nucleus.

II. Compounds containing three-membered heterocycles

When ferrocenyl azide is irradiated with UV light in cyclohexene, the aziridine derivative **1** is formed in a low yield.[6] The reaction evidently proceeds via the intermediate generation of the nitrene **2**, which adds to the double bond of cyclohexene. It has been noted that the aziridine **1** is formed both under nitrogen and under oxygen atmospheres. Consequently the nitrene **2** exists in the singlet state.[6]

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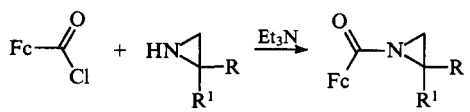
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Uspekhi Khimii **65** (1) 43 – 83 (1996); translated by A K Grzybowski



2 1

Here and henceforth Fc = ferrocenyl $(\eta^5\text{-}C_5H_4)Fe(\eta^5\text{-}C_5H_5)$.

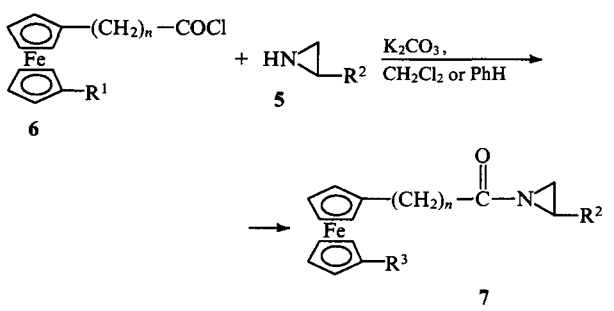
When the aziridine derivatives **4** interact with the chloride of ferrocenecarboxylic acid in the presence of triethylamine, *N*-ferrocenoylaziridines **3** are obtained.[7]



4 3

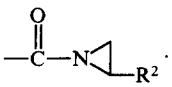
R, R^1 = H, Me.

On *N*-acylation of the monosubstituted aziridine derivatives **5** by the chlorides of ferrocenyl-substituted monocarboxylic and dicarboxylic acids **6** in the presence of potassium carbonate at 10–30 °C, compounds **7** are produced in 40%–90% yields.[8,9]

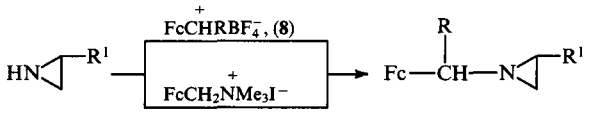


6 5 7

n = 0–3; R^1 = H, COCl; R^2 = H, Me, Et;

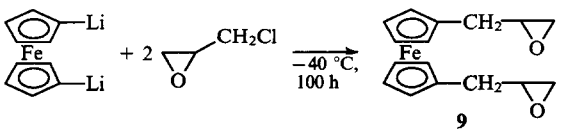
R^3 = H, .

The tetrafluoroborates of the α-ferrocenylcarbonium ions **8** and trimethylferrocenylmethylammonium iodide have been used recently for the *N*-alkylation of aziridine derivatives.[10]



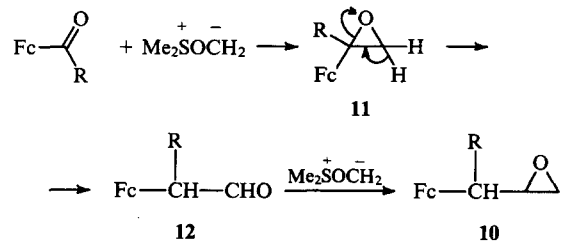
R = H, Me, Ph, Fc; R^1 = H, Me, Et.

Compound **9**, containing two epoxy-groups, has been synthesised in 44% yield by the reaction of 1,1′-dilithioferrocene with epichlorohydrin at −40 °C.[11]



9

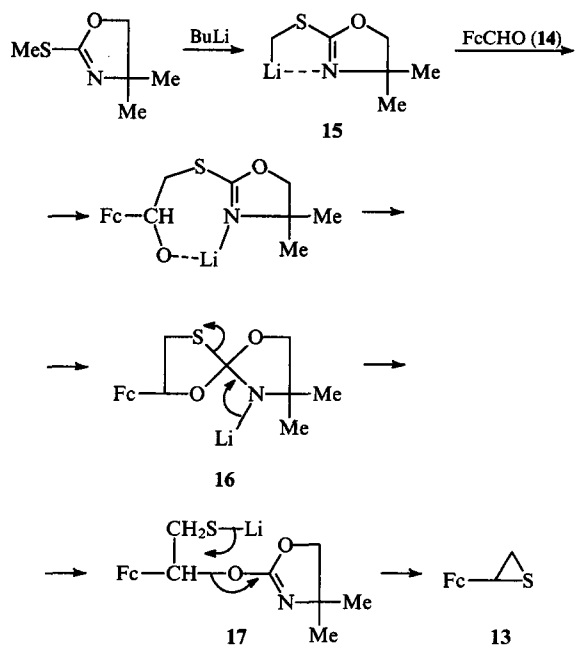
A novel method of synthesis of the epoxy-compounds **10** has been described.[12] The authors believe that, in the reactions of the carbonyl derivatives of ferrocene with dimethyloxosulfonium methylide, the epoxides **11** are formed in the first stage and are converted into the aldehydes **12** under the reaction conditions. The latter react with a further molecule of the methylide and are converted into compound **10**.



11 12 10

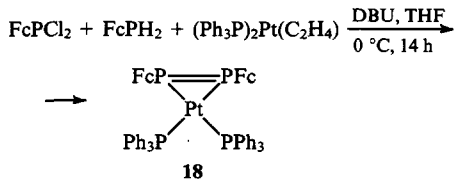
R = H, Me.

A mechanism involving the lithiation of the methyl group attached to the sulfur atom, the interaction of the aldehyde **14** with the lithio-derivative **15**, the conversion of the reaction product into the spiro-compound **16**, and the rearrangement of the latter to a new oxazoline derivative **17** and its cleavage to the thiirane **13** has been put forward for the synthesis of ferrocenylthiirane **13** from formylferrocene **14** and 2-methylthio-4,4-dimethyloxazoline.[13,14]



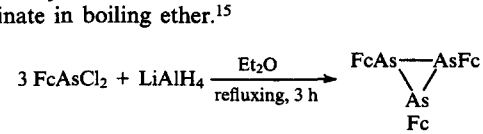
15 16 17 13

German investigators[15] synthesised unusual heterocyclic compounds containing ferrocenyl groups. Thus the reaction of $FcPCl_2$, $FcPH_2$, and $(Ph_3P)_2Pt(C_2H_4)$ in the presence of diazabicycloundecene (DBU) resulted in the formation of (diferrocenyldiphosphene)bis(triphenylphosphine)platinum(0) **18** in a quantitative yield.



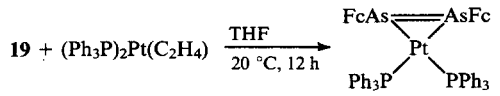
18

Triferrocenyltriarsirane (**19**) has been synthesised in 66% yield by the reduction of $FcAsCl_2$ with lithium tetrahydroaluminate in boiling ether.[15]



19

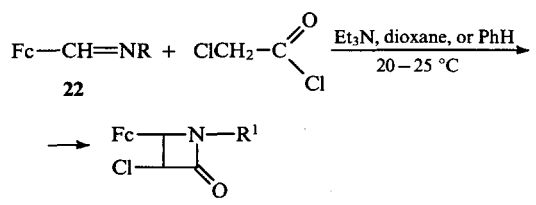
The latter was made to react with $(Ph_3P)_2Pt(C_2H_4)$ at room temperature, which led to compound **20** in 68% yield.



20

III. Compounds containing four-membered heterocycles

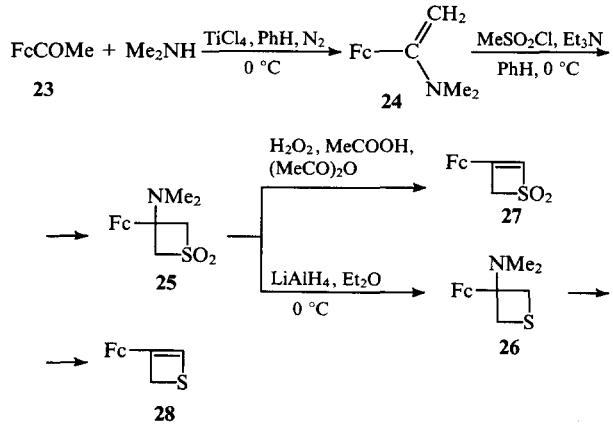
Numerous derivatives of 4-ferrocenylazetidin-2-ones **21** have been synthesised by the addition of chloroketene (synthesised from chloroacetyl chloride) to ferrocenylmethylideneimines **22**.[16-20] The reactions were carried out in dioxane at 20–25 °C, the reaction time (ranging from several hours to several days) depending on the structure of the initial imine **22**. The reaction products and their yields are listed in Table 1.



21

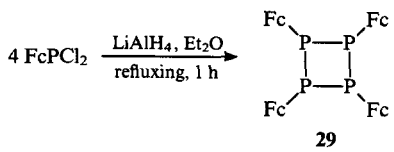
There are no literature data on the derivatives of ferrocene containing four-membered heterocyclic rings with oxygen atoms in the ring.

A series of 3-ferrocenylthiete derivatives have been synthesised from acetylferrocene **23**.[21] Thus its treatment with dimethylamine in the presence of $TiCl_4$ leads to α-dimethylaminovinylferrocene **24** (yield 89%), which affords the sulfone **25** (yield 46%) on treatment with methanesulfonyl chloride in the presence of triethylamine. The sulfone may be reduced to the thietane **26** (yield 78%) and also deaminated by treatment with H_2O_2 in an acid medium to 3-ferrocenyl-2*H*-thiete dioxide **27** (yield 34%). Compound **26** was converted in two stages into 3-ferrocenylthiete **28** (yield 36%).[21]



23 **24** **25** **26** **27** **28**

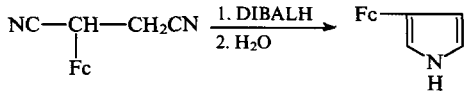
On heating ferrocenyldichlorophosphine with lithium tetrahydroaluminate in ether, tetraferrocenyltetraphosphetane **29** is formed in 11% yield.[15]



29

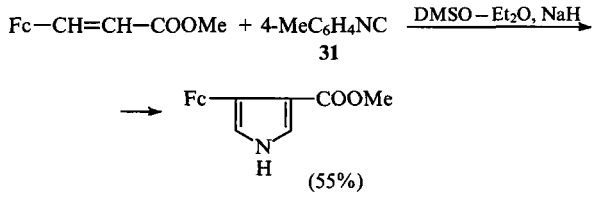
IV. Compounds containing five-membered heterocycles

3-Ferrocenylpyrrole is formed in 21% yield on reduction of the dinitrile of 2-ferrocenylsuccinic acid **30** with diisobutylaluminium hydride (DIBALH) and subsequent hydrolysis.[22]



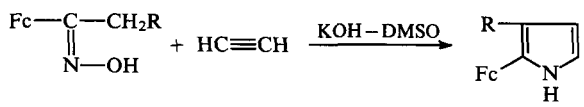
30

In the presence of sodium hydride, methyl 3-ferrocenylacrylate reacts with the isonitrile **31**, affording 3-ferrocenyl-4-methoxycarbonylpyrrole.[23]



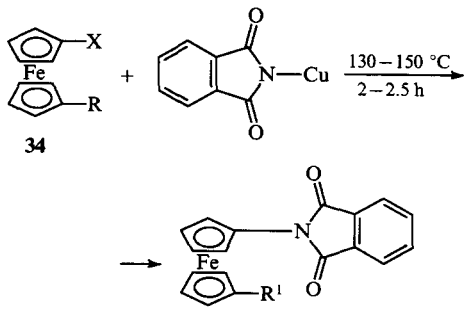
31

The cyclocondensation of the oximes of the acylferrocenes **32** with ethyne on treatment with alkali leads to the pyrrole derivatives **33**.[24] It has been noted that, when the reaction is carried out in a microwave oven, the yield of the reaction products increases appreciably.



32 **33**

Ferrocene derivatives containing a phthalimide residue have been synthesised by heating the halo-derivatives **34** with copper phthalimide.[25-27]



34

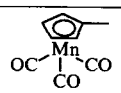
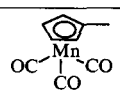
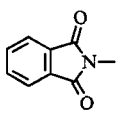
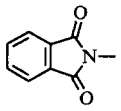
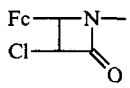
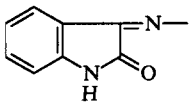
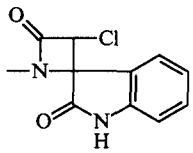
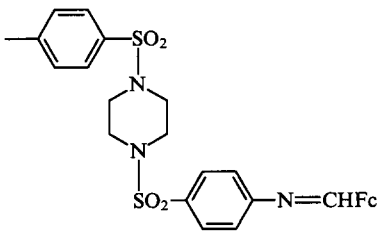
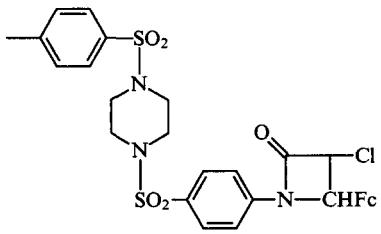
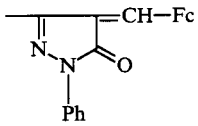
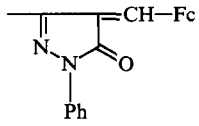
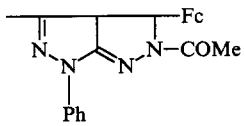
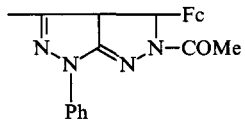
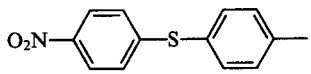
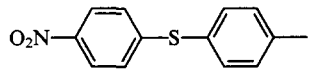
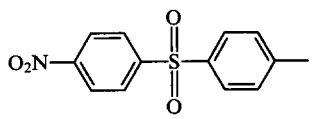
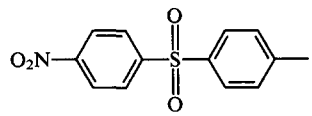
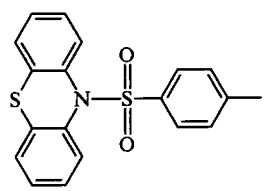
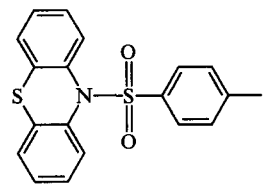
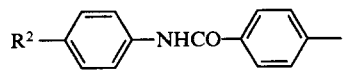
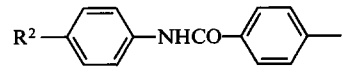
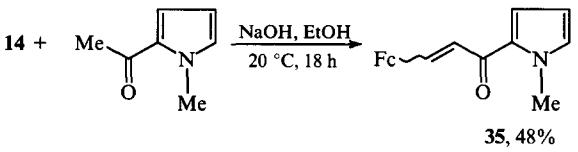
X	R	R^1	Yield (%)
Br			37
Cl	Ph	Ph	49
Br	Br	H	8.5
Br	Br		47
I	H	H	73
I	I		35

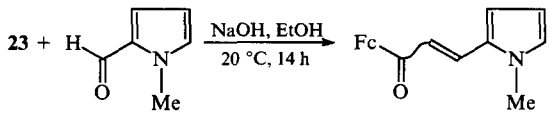
Table 1. The initial imines **22** and the 4-ferrocenylazetidin-2-one derivatives **21**.

R	R^1	Yield of **21** (%)	Ref.
2-Py	2-Py	12	16
FcCH=N–		10	16
H_2NCONH–	H_2NCONH–	22	16
H_2NCSNH–	H_2NCSNH–	18	16
		14	16
		15	16
		50	17
		70	17
		32	18
		100	18
		40	19
 (R² = H, Cl)	 (R² = H, Cl)	70	20

In the presence of an alcoholic solution of NaOH, the aldehyde **14** condenses with 2-acetyl-1-methylpyrrole, while the ketone **23** condenses with 2-formyl-1-methylpyrrole to form the corresponding chalcones **35** and **36**.[28]

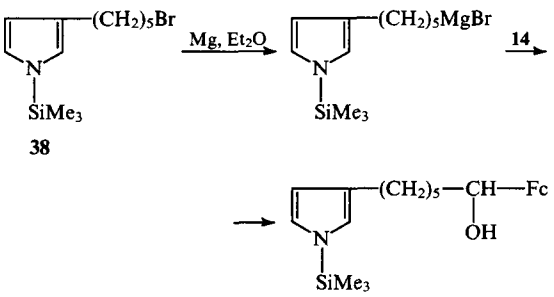


35, 48%



36, 40%

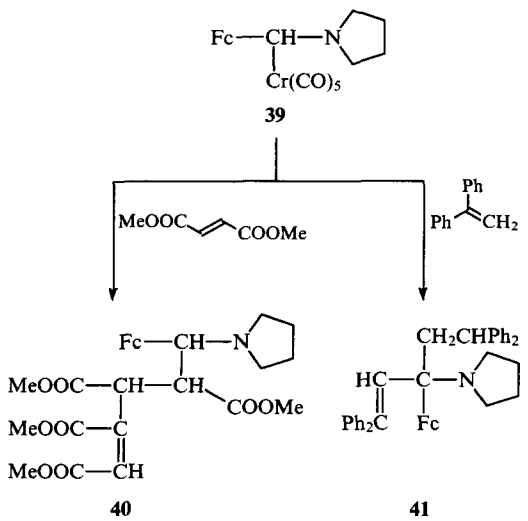
The alcohol **37** has been synthesised from the bromo-derivative **38** and FcCHO **14**.[29]



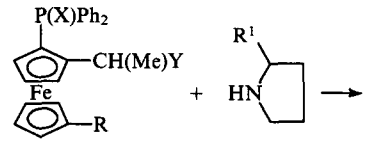
The synthesis of *N*-(2-ferrocenylethyl)pyrrole from 2-hydroxyethylferrocenyl toluene-*p*-sulfonate and potassium pyrrolide has been described.[30]

Two procedures have been proposed for the synthesis of *N*-ferrocenylmethylpyrrolidine: the interaction of ferrocenylmethyl(trimethyl)ammonium iodide with pyrrolidine in the presence of aqueous sodium hydroxide[31,32] and condensation of ferrocene with formaldehyde and pyrrolidine (yield 50%).[33]

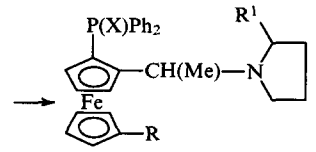
Unusual compounds have been obtained by the reactions of complex **39** with unsaturated compounds.[34] The interaction with fumaric acid ester affords the tetraester **40** (solvent – pyridine, refluxing for 2.5 h, yield 44%), while the reaction with 1,1-diphenylethene gives rise to the derivative **41** (inert atmosphere, in the dark, heating up to 136 °C for 3.5 h, yield 7%).



The group Y in compound **42** is substituted on treatment with pyrrolidine or its derivatives (refluxing in methanol for 5 – 8 h or maintenance in acetonitrile at 20 °C for 12 h); the yields of the products **43** are 55% – 88%.[35,36]



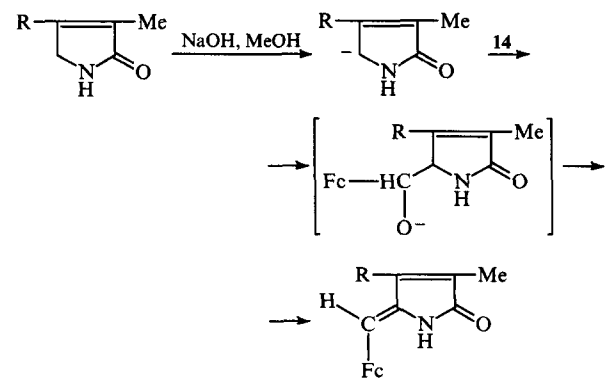
42



43

X	Y	R	R^1
O	NMe_2	H	H
—	OAc	H	CH_2NMe_2
—	OAc	H	Me
—	OAc	PPh_2	H
—	OAc	H	H

The reaction of 3,4-dimethylpyrroline-2-one with FcCHO results in the formation of the product **44** of the kinetically controlled addition almost exclusively in the form of the (*Z*)-isomer.[37]

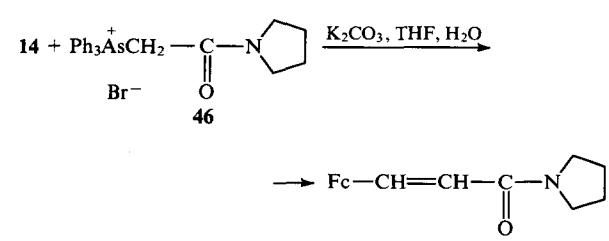


44

R = H, Me.

If 3-methylpyrrolin-2-one is made to react with the aldehyde **14**, then the product **44** (R=H) is formed as a 1 : 1 mixture of the (*Z*)- and (*E*)-isomers.[38]

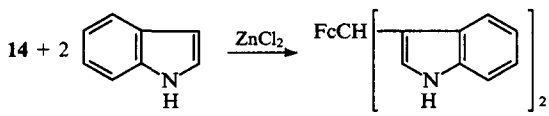
In the synthesis of the amide **45**, the reaction of FcCHO with the arsonium salt **46** was carried out in the presence of potassium carbonate in aqueous tetrahydrofuran (THF).[39]



46

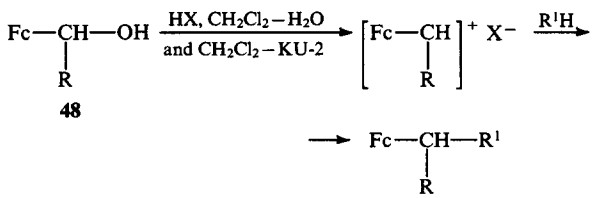
45

In the presence of $ZnCl_2$, the aldehyde **14** reacts with two molecules of indole, producing the ferrocene derivative **47**.[40]



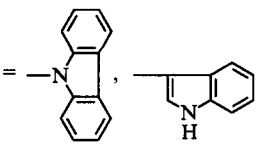
47

When the ferrocenyl carbinols **48** are treated with strong acids, highly reactive α-carbonium ions are formed. However, when strong acids are employed, the reaction is complicated by oxidation– reduction processes due to the presence of the ferrocene fragment in the substrate. In order to suppress these processes, the reaction is carried out in the $CH_2Cl_2-H_2O$ two-phase system and the KU-2 cation-exchange resin is employed instead of strong acids.[41-45] The $[Fc-CHR]^+$ cations readily react with nitrogen heterocycles, affording the ferrocene derivatives **49** in 60%–80% yields.



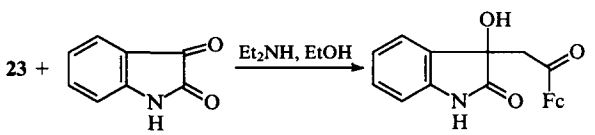
48 **49**

R = H, Me, Ph, FcCH=CH; R^1 =



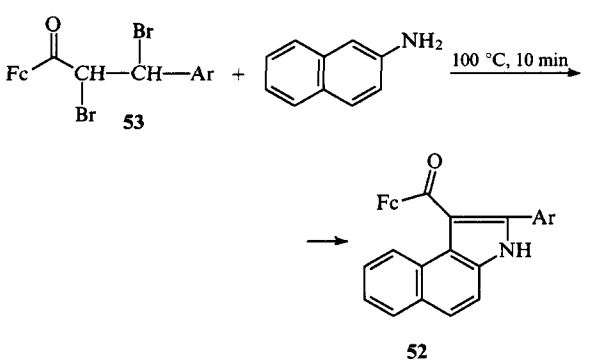
$X = BF_4^-, ClO_4^-$.

Refluxing of an alcoholic solution of FcCOMe **23** and isatin **50** in the presence of diethylamine for 1 h and subsequent standing at room temperature for several days led to the synthesis of compound **51** in 93% yield.[46]



50 **51**

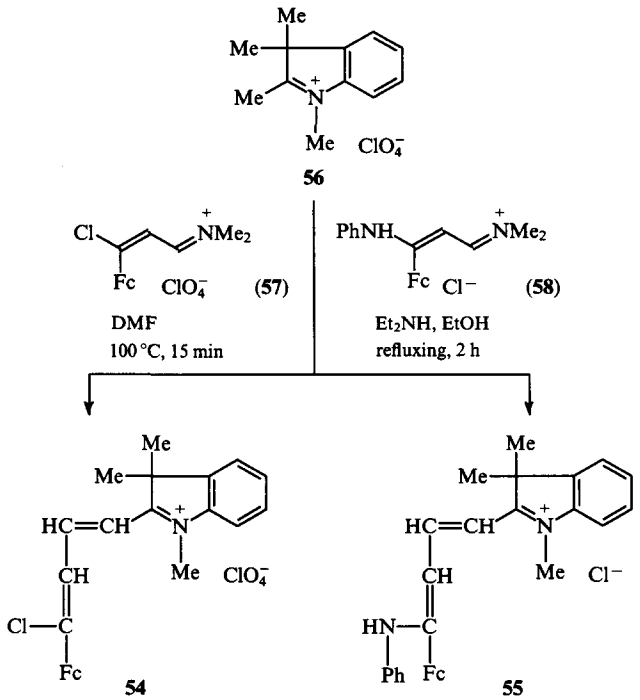
The naphthopyrrole derivatives **52** have been obtained in 80%–85% yields by heating the dibromo-derivative **53** with 2-aminonaphthaline.[47]



53 **52**

Ar = Ph, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

The dyes **54** and **55**, containing the ferrocenyl group, are formed as a result of the condensation of the perchlorate **56** with the immonium salts **57** and **58**.[48]

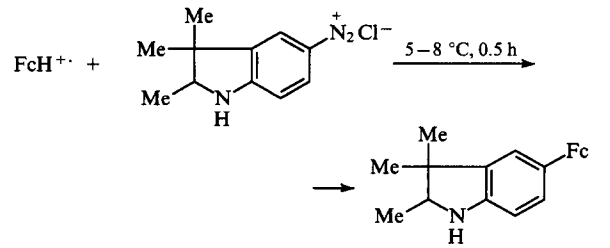


56 **(57)** **(58)**

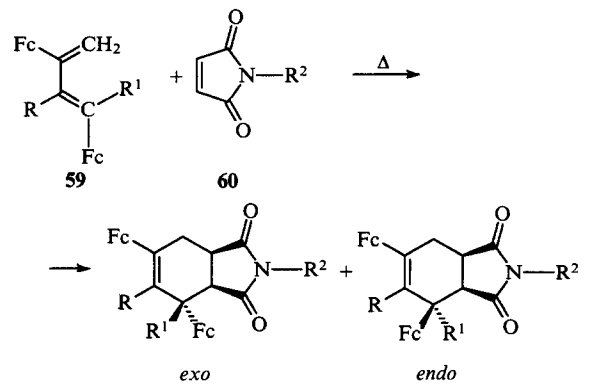
DMF, 100 °C, 15 min; Et_2NH, EtOH, refluxing, 2 h

54 **55**

The ferrocenium cation, arising on interaction of ferrocene with concentrated sulfuric acid, reacts with diazotised 5-amino-2,3,3-trimethylindolenine, which results in the formation of 5-ferrocenyl-2,3,3-trimethylindolenine in 23% yield.[49]



The 1,3-dienes **59**, containing a ferrocenyl substituent, are capable of undergoing the diene synthesis reaction with *N*-substituted maleic acid imides **60**.[50,51] A mixture of the *endo*- and *exo*-isomers is formed as a rule and the *endo*-isomer has been obtained exclusively only in the case of the diene **59** (R = Me, R^1 = H).

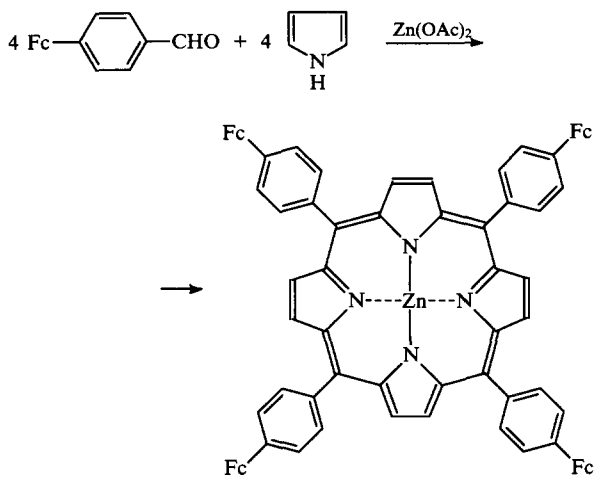


59 **60**

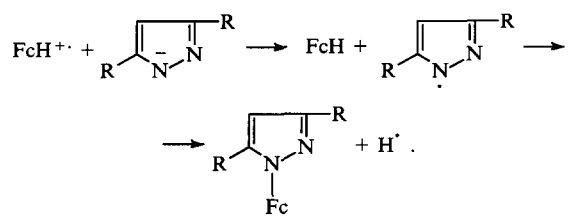
exo *endo*

R	R^1	R^1
H	H	Ph
H	H	$PhCH_2$
Me	H	Ph
H	Me	Ph

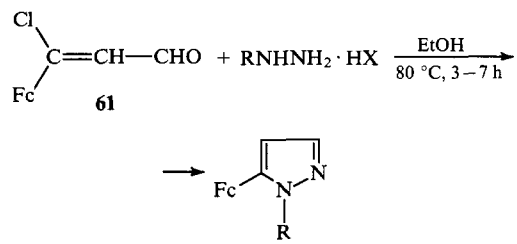
Schmidt et al.[52] synthesised *meso*-tetrakis(4-ferrocenylphenyl)porphyrin by condensing 4-ferrocenylbenzaldehyde with pyrrole.



The direct conversion of ferrocene into a heteryl derivative has been achieved by treating ferrocenium hexafluorophosphate with the sodium derivatives of pyrazole or 3,5-dimethylpyrazole.[53] 1-Ferrocenylpyrazole and 1-ferrocenyl-3,5-dimethylpyrazole were synthesised. The following process mechanism has been put forward:



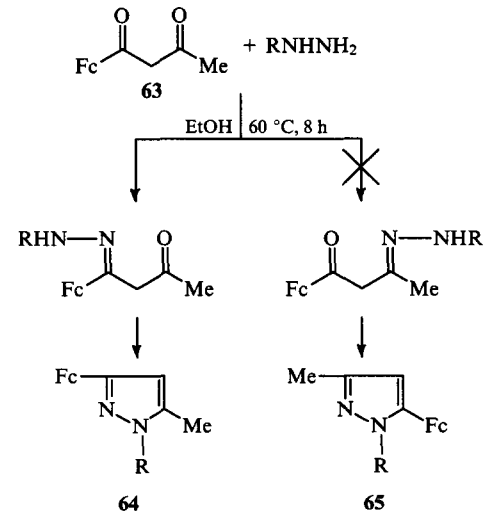
3-Chloro-3-ferrocenylacrylic aldehyde **61** and 3-chloro-3-ferrocenylacrylonitrile **62** are convenient starting compounds for the synthesis of ferrocenylpyrazoles. Thus the condensation of the aldehyde **61** with hydrazine hydrate or phenylhydrazine hydrochloride leads to the formation of 5-ferrocenylpyrazole and 5-ferrocenyl-1-phenylpyrazole respectively.[54]



R	HX	Yield (%)
H	H_2O	18
Ph	HCl	41

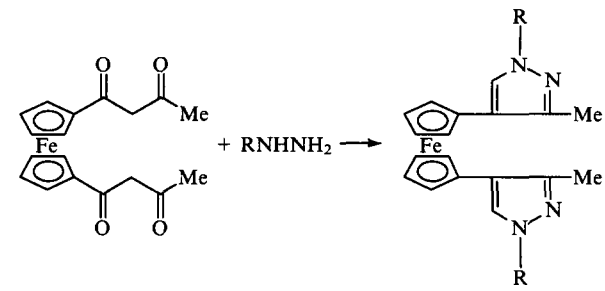
If the nitrile **62** is introduced into the reaction with hydrazine hydrate, then the product is 3-amino-5-ferrocenylpyrazole (yield 68%).

The reactions of acetoacetylferrocene **63** with hydrazine and its derivatives may lead to the formation of the two isomeric pyrazoles **64** and **65**. However, only the isomers **64** have been isolated from the reaction mixture.[55] The author explained this by the smaller steric hindrance in the cyclisation stage.



R	H	Me	Ph	2,4-$(O_2N)_2C_6H_3$	$CONH_2$
Yield (%)	81	30	70	21	90

A similar situation is observed in the condensation of the tetraketone **66** with hydrazine and its derivatives. Out of the three possible regioisomers, only the isomer **67** is formed. Together with steric factors, the stability of the corresponding intermediate hydrazones apparently plays a no less important role.[55]

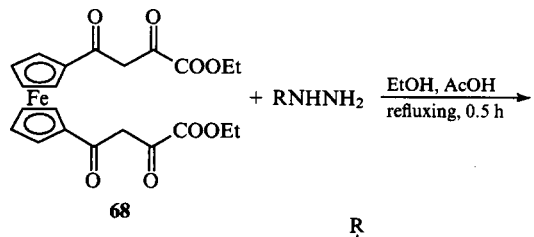


Compound	R	Yield (%)
a	H	60
b	$CONH_2$	80

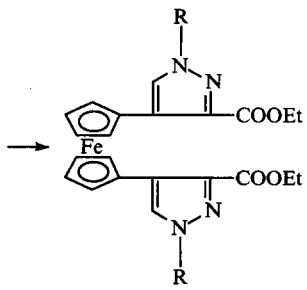
1-Benzoyl-1′-(5-trifluoromethylpyrazol-3-yl)ferrocene has been synthesised by condensing 1-benzoyl-1′-(4,4,4-trifluoro-3-oxobutanoyl)ferrocene with hydrazine.[56]

An unusual method of synthesis of 3-ferrocenylpyrazol has been described.[57] Acetylferrocene **23** was treated with ethyl formate in the presence of sodium ethoxide in toluene, after which the reaction mixture was treated initially with hydrazine hydrochloride in water and then with hydrazine hydrate in methanol. The yield of 3-ferrocenylpyrazole reached 61%.

α,γ-Diketoacids of the ferrocene series and their esters have been used successfully as the starting compounds in the synthesis of ferrocenylpyrazoles. Thus condensation of the diester **68** with hydrazine (in the presence of acetic acid) or with phenylhydrazine afforded the corresponding pyrazole-containing diesters **69** (the yields of compound **69a** and **69b** were 56% and 52% respectively).[58] It was shown in the same study that the dihydrazide **71** is formed in 76.5% yield after brief refluxing of the dicarboxylic acid **70** with an excess of hydrazine.

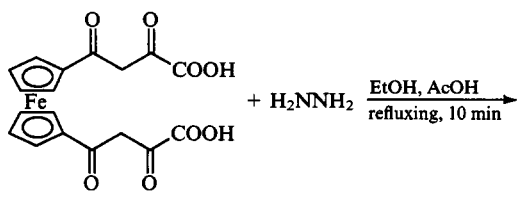


68

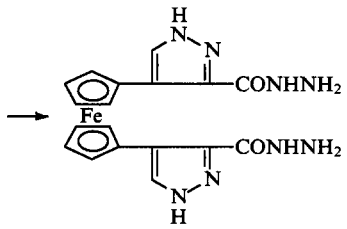


69a, b

R = H (a), Ph (b)

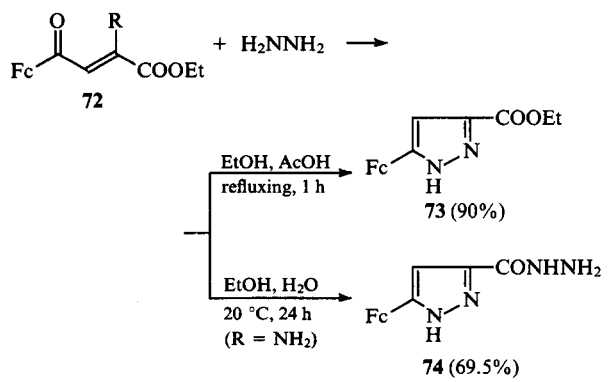


70



71

Depending on the reaction conditions, either 3-ethoxycarbonyl-5-ferrocenylpyrazole **73** or the hydrazide of 5-ferrocenylpyrazole-3-carboxylic acid **74** may be obtained from the ethyl esters of α-hydroxy- or α-amino-β-ferrocenoylacrylic acids **72** and hydrazine.[59]



72

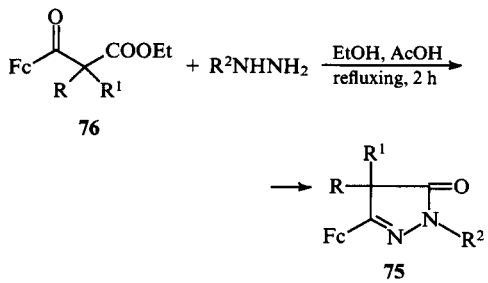
73 (90%)

74 (69.5%)

R = NH_2, OH, NHMe, NHEt, $NHPr^i$, NHPh, NHC_6H_4Cl-*m*, NHC_6H_4OMe-*o*.

It is of interest that the reaction of β-ferrocenoyl-α-hydroxyacrylic acid with semicarbazide in the presence of sodium acetate and sodium bicarbonate afforded 5-ferrocenylpyrazole-3-carboxylic acid.[59] Consequently semicarbazide serves as a source of hydrazine under these conditions.

Derivatives of ferrocenylpyrazolones **75** are formed when the esters of the ketoacids **76** interact with hydrazine or phenylhydrazine in the presence of acetic acid.[60]

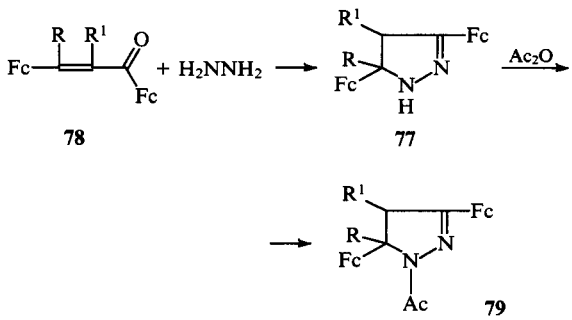


76

75

R, R^1 = H, Me; R^2 = H, Ph.

The most general method of synthesis of ferrocenylpyrazolines involves the reaction of the vinyl ketones $FcCR{=}CR^1{-}COR^2$ or $FcCO{-}CH{=}CHR$ with hydrazine or its derivatives. As a rule, ferrocenylpyrazolines with a hydrogen atom at the N(1) atom are unstable and are therefore converted into the *N*-acetyl derivatives. For example, when the pyrazoline derivatives **77**, obtained from the vinyl ketones **78** and hydrazine, were treated with acetic anhydride, the *N*-acetyl derivatives **79** were isolated in 72%–75% yields.[61]



78

77

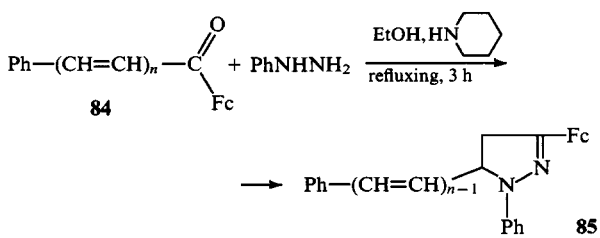
79

R, R^1 = H, Me.

The reactions of the vinylketones **80** with hydrazine and its derivatives have been investigated in a series of studies;[62–67] the pyrazoline derivatives **81** (Scheme 1) were obtained in 60%–95% yields. When the reaction was carried out in the presence of acetic acid, the reaction products were the *N*-acetyl derivatives. For R^1 = Ph, the reaction was carried out in the presence of piperidine.

The pyrazoline derivatives **82** with a different disposition of the substituents have been synthesised by the cyclocondensation of the vinyl ketones **83** with hydrazine and its derivatives;[47,62,64,65] the yields were 60%–95% (Scheme 2).

The behaviour of polyene ketones in their reactions with hydrazine and its derivatives has been studied in fair detail. The ketones **84**, containing two or three conjugated double bonds, react regiospecifically with phenylhydrazine in the presence of piperidine, affording the pyrazoline derivatives **85** in 86%–91% yields.[68]

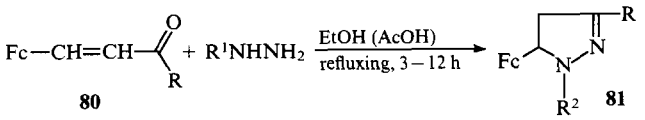


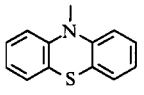
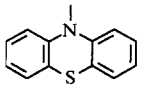
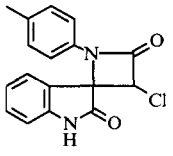
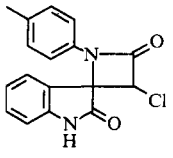
84

85

n = 2, 3.

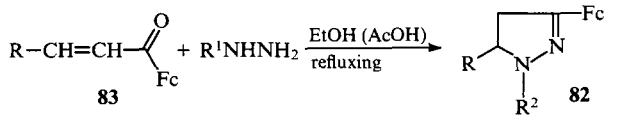
Scheme 1

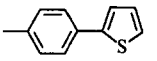
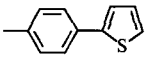


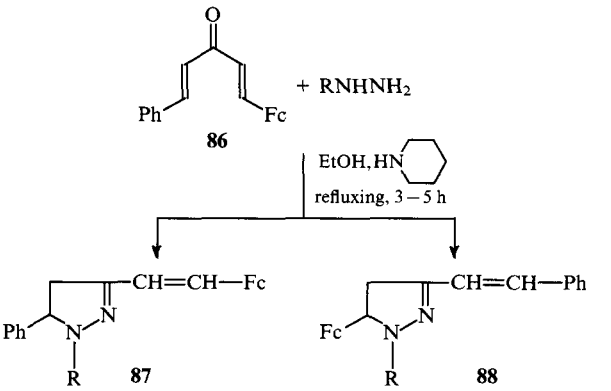
R	R^1	R^2	Ref.
Me	H	Ac	62
Me	Ph	Ph	62
Et	H	Ac	62
Et	Ph	Ph	62
Ph	H	Ac	62
Ph	H	H	65
Ph	Ph	Ph	62, 65
C_6H_4Et-4	H	Ac	62
C_6H_4Et-4	Ph	Ph	62
Ph	SO_2Ph	SO_2Ph	63
C_6H_4Ph-4	SO_2Ph	SO_2Ph	63
C_6H_4Br-4	SO_2Ph	SO_2Ph	63
C_6H_4Cl-4	SO_2Ph	SO_2Ph	63
C_6H_4OMe-4	SO_2Ph	SO_2Ph	63
C_6H_4Me-4	SO_2Ph	SO_2Ph	63
C_6H_4Et-4	SO_2Ph	SO_2Ph	63
Ph	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4Ph-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4Br-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4Cl-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4OMe-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4Me-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
C_6H_4Et-4	$SO_2C_6H_4NHAc$-4	$SO_2C_6H_4NHAc$-4	63
$(\eta^5\text{-}C_5H_4)Mn(CO)_3$	H	H	64
Fc	H	H	64, 65
Fc	Ph	Ph	64, 65
$(\eta^5\text{-}C_5H_4)Mn(CO)_3$	Ph	H	64
C_6H_4OMe-4	H	H	65
C_6H_4OMe-4	Ph	Ph	65
C_6H_4Br-4	Ph	Ph	65
Ph	Fc	Fc	65
	H	Ac	66
	Ph	Ph	66
	Ph	Ph	67
	H	H	67

The addition of $RNHNH_2$ (R = H, Ph) to the divinyl ketone derivative **86** leads to a mixture of the isomeric pyrazolines **87** and **88**.[68] The regioselectivity of the reaction in favour of the formation of compound **88** has been noted and has been explained by the greater electron-donating capacity of the ferrocenyl substituent compared with the phenyl substituent.

Scheme 2

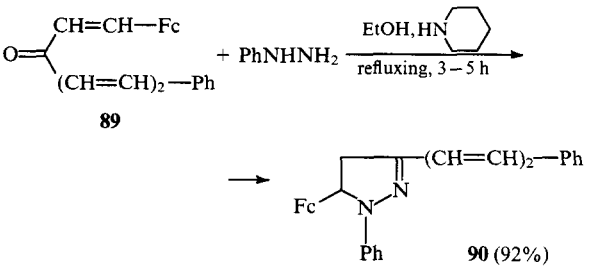


R	R^1	R^2	Ref.
Ph	H	Ac	62
C_6H_4OH-4	H	Ac	62
Ph	Ph	Ph	47, 62, 65
C_6H_4OH-4	Ph	Ph	62
$(\eta^5\text{-}C_5H_4)Mn(CO)_3$	H	H	64
$(\eta^5\text{-}C_5H_4)Mn(CO)_3$	Ph	Ph	64
C_6H_4OMe-4	H	H	65
C_6H_4Br-4	H	H	65
C_6H_4Br-4	Ph	Ph	65
Ph	Fc	Fc	65
Ph	H	H	65
Ph	H	Ac	47
C_6H_4Cl-4	H	Ac	47
$C_6H_4NO_2$-3	H	Ac	47
$C_6H_4NO_2$-4	H	Ac	47
C_6H_4Me-4	H	Ac	47
C_6H_4Fc-4	H	Ac	47
	H	Ac	47
C_6H_4Cl-4	Ph	Ph	47
$C_6H_4NO_2$-3	Ph	Ph	47
$C_6H_4NO_2$-4	Ph	Ph	47
C_6H_4Me-4	Ph	Ph	47
C_6H_4Fc-4	Ph	Ph	47
	Ph	Ph	47

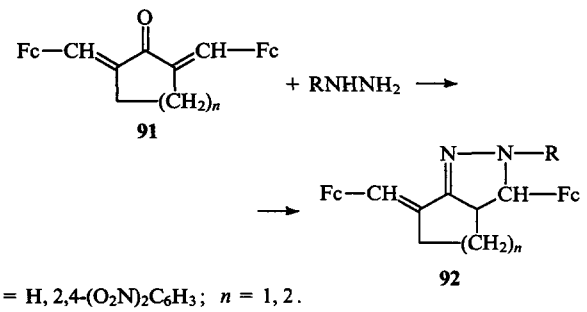


R = H, Ph

In the case of the ketone **89**, the addition of hydrazine takes place regiospecifically,[68] whereupon the pyrazoline **90** is formed. Apart from the electronic factors quoted above, the proximity of the carbonyl group and the Fc fragment apparently plays a role.



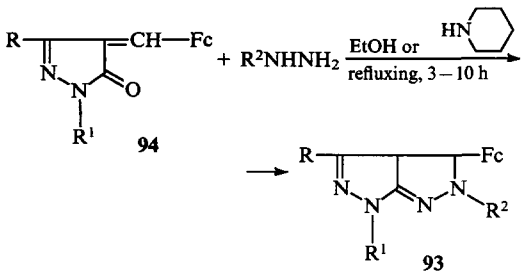
The ferrocenylmethylidene-substituted cyclic ketones **91** are converted into the bicyclic compounds **92** on condensation with hydrazine or its derivatives.



91 **92**

R = H, 2,4-$(O_2N)_2C_6H_3$; n = 1, 2.

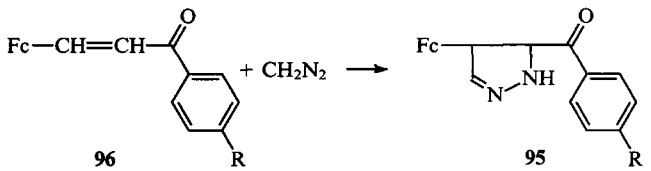
The ferrocene derivatives **93** with two condensed pyrazoline rings have been synthesised by the reaction of the ferrocenylmethylidenepyrazolones **94** with hydrazine or phenylhydrazine (in the presence of piperidine) in alcohol (10 h) or dioxane (3 h), the product yield amounting to 50%–70%.[17,69]



94 **93**

R	R^1	R^2
Me	Ph	H
Me	2,4-$(O_2N)_2C_6H_3$	H
Me	Ph	Ph
Me	2,4-$(O_2N)_2C_6H_3$	Ph
FcCH=N–	Ph	Ph

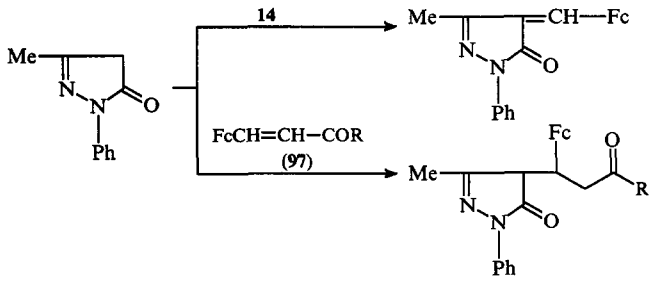
A series of pyrazoline derivatives **95** have been synthesised by the cycloaddition of the vinyl ketones **96** to diazomethane.[63]



96 **95**

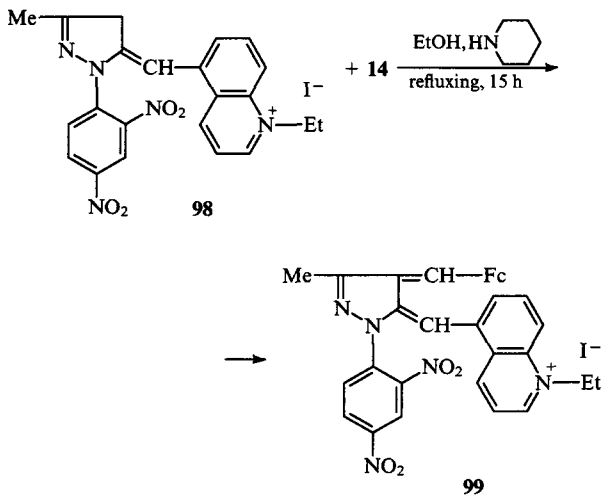
R = H, Cl, Br, Me, Et, OMe, Ph.

Two methods of synthesis of pyrazolone derivatives containing the ferrocenyl group in the side chain have been described: by the condensation of formylferrocene **14** with 3-methyl-1-phenylpyrazol-5-one or by the addition of the latter to the double bond of the vinyl ketones **97**.[69]



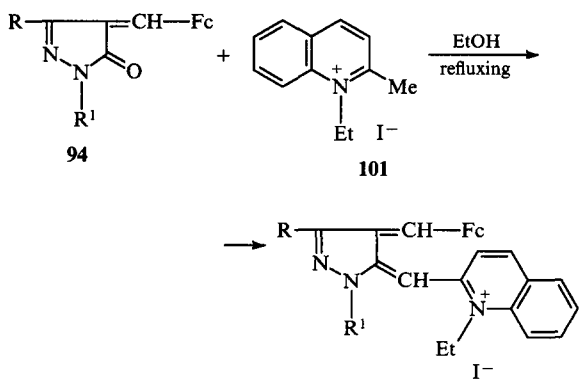
R = 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-PhC_6H_4.

When the aldehyde **14** is heated with the salt **98** in alcohol in the presence of piperidine, the monomethinecyanine **99** is formed in 50% yield.[70]



98 **99**

The cyanine dyes **100** have been synthesised by condensing the pyrazolone derivatives **94** with 1-ethyl-2-methylquinolinium iodide **101** in the presence of piperidine.[17,69]

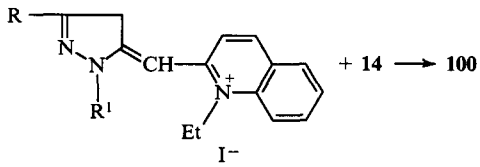


94 **101** **100**

R = Me, R^1 = Ph, 2,4-$(O_2N)_2C_6H_3$; R = FcCH=N–, R^1 = Ph.

An analogue of the salt **100** (R = Me, R^1 = Ph), with a pyridine instead of a quinoline ring, has been obtained by the same procedure.[69]

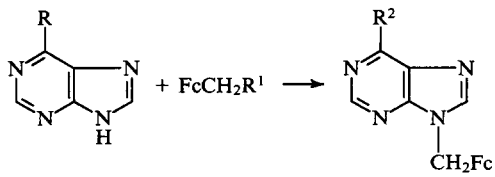
Compounds **100** are also formed as a result of the condensation of the salts **102** with FcCHO.[69]



102

R = Me; R^1 = Ph, 2,4-$(O_2N)_2C_6H_3$.

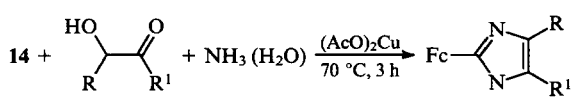
The ferrocenylmethyl group can also be introduced into the 9-position in the purine nucleus in two ways: as a result of the alkylation of 6-X-purines (X = NH_2, Cl) by ferrocenylmethyl(trimethyl)ammonium iodide or aminomethylferrocene.[71]



R	R^1	R^2	Conditions	Yield (%)
NH_2	$N^+Me_3I^-$	NH_2	H_2O, refluxing, 6 h	47
Cl	NH_2	$NHCH_2Fc$	$MeOCH_2CH_2OH$, refluxing, 3 h	21

N-Ferrocenylimidazole has been synthesised by treating the sodio-derivative of the imidazole with ferrocenium hexafluorophosphate.[53]

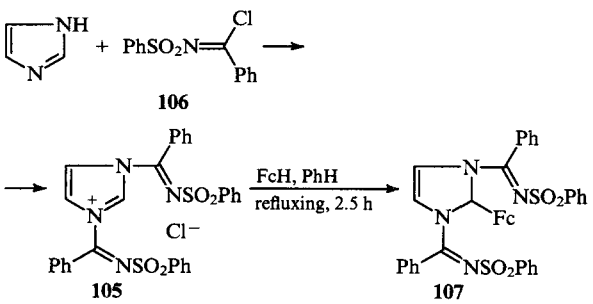
2-Ferrocenylimidazole and its derivatives **103** are formed in 15%–50% yields as a result of the condensation of FcCHO **14** with the α-hydroxycarbonyl compounds **104** and ammonia in the presence of copper acetate.[72]



104 **103**

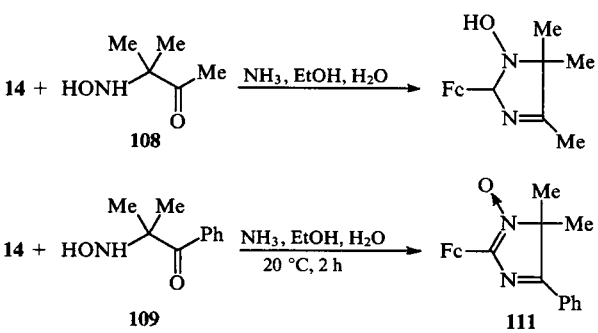
R = H: R^1 = H, Me, Ph;
R = Me: R^1 = Me, Ph;
R = R^1 = Ph; R + R^1 = $-(CH_2)_4-$.

The salt **105**, which is obtained from imidazole and benzenesulfonylbenzimidoyl chloride **106**, is converted into 1,3-bis(benzenesulfonylbenzimidoyl)-2-ferrocenylimidazoline **107** on heating with ferrocene in benzene.[73]

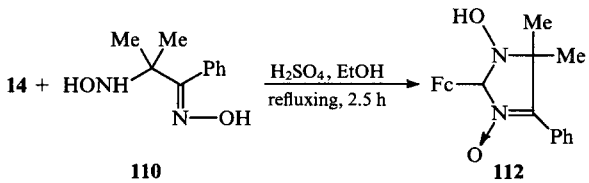


106 **105** **107**

The selectivity of the reaction of FcCHO with the hydroxylamine derivatives **108**–**110** is influenced by the nature of the substituent at the keto-group:[74] 2-ferrocenyl-1-hydroxy-4,5,5-trimethylimidazoline is formed from the methyl ketone **108** (the reaction was carried out at 0 °C for 0.5 h with subsequent maintenance at 20 °C for 0.5 h; the yield was 30%); the *N*-oxides **111** and **112** were obtained from the phenyl ketone **109** and the oxime **110** (in 25% and 60% yields respectively). It has been suggested that compound **111** is formed as a result of the rapid oxidation in solution of the intermediate hydroxyimidazoline.[74]

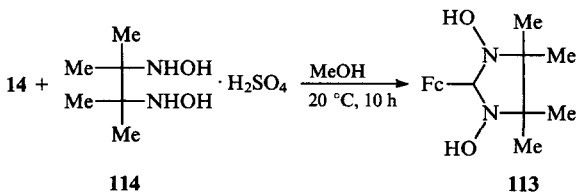


108 **109** **111**



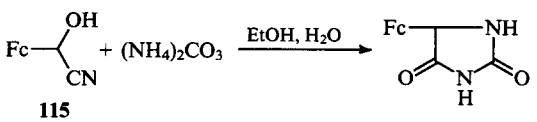
110 **112**

The salt **114** was used as the starting material for the synthesis of 2-ferrocenyl-1,3-dihydroxy-4,4,5,5-tetramethylimidazoline **113**.[75]



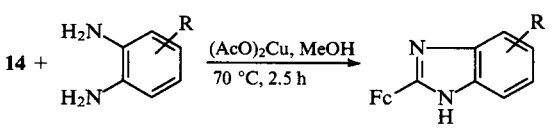
114 **113**

5-Ferrocenylhydantoin has been obtained in 85% yield from the cyanohydrin **115** and ammonium carbonate in aqueous alcohol (the reaction was carried out at 50 °C for 2 h with subsequent maintenance at 20 °C for two days).[76]



115

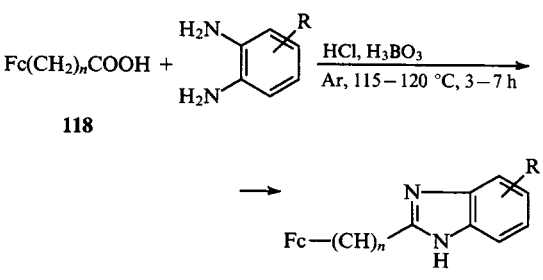
German investigators[72] synthesised a series of derivatives of 2-ferrocenylbenzimidazole **116** (in 70%–90% yield) by condensing FcCHO **14** with substituted 1,2-diaminobenzenes in the presence of copper acetate.



116

R = H, 4-Me, 5-Me, 5,6-Me_2, 4-Cl, 5-Cl, 5-Br, 4-NO_2, 5-NO_2, 5-CN, 5-OMe, 5-NH_2, 4,5-(−CH=CH−CH=CH−).

The benzimidazole derivatives **117**, containing the ferrocenyl group linked directly to the heterocycle or separated from it by a chain of 1–5 carbon atoms, are formed in 45%–98% yields on heating ferrocenyl-substituted carboxylic acids **118** with substituted 1,2-diaminobenzenes under an argon atmosphere in the presence of hydrochloric and boric acids.[72]



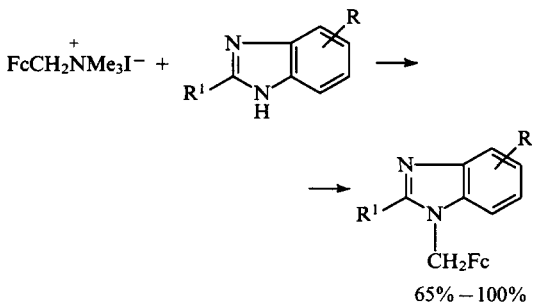
118 **117**

R = H (*n* = 1–5), 4-Me (*n* = 0, 1), 5-Me (*n* = 1), 5,6-Me_2 (*n* = 1), 4-Cl (*n* = 1), 5-Cl (*n* = 1), 5-OMe (*n* = 1), 4,5-(−CH=CH−CH=CH−) (*n* = 1).

Their analogues **117**, methylated at the N(1) atom, have been obtained under similar conditions from the acids **118** (*n* = 0, 1) and 1-amino-2-methylaminobenzene, while the *N*-phenylated

analogue **117** has been obtained from the acid **118** (n = 1) and 1-amino-2-phenylaminobenzene.[72] The yields of compounds **117** were 54%–81%.

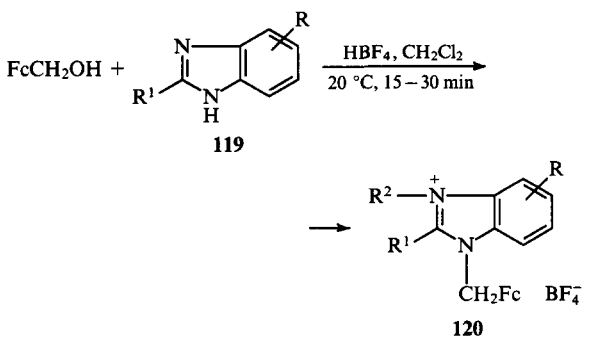
When benzimidazoles are treated with ferrocenylmethyl(trimethyl)ammonium iodide, the N(1) atom is ferrocenylmethylated.[77,78]



65%–100%

R = H: R^1 = H, Me, Ph;
R = 5-NO_2: R^1 = H, Me.

The $FcCH_2$ substituent can also be introduced at the nitrogen atoms of the benzimidazole derivatives **119** by the reaction with hydroxymethylferrocene in the presence of tetrafluoroboric acid. Depending on the ratios $FcCH_2OH$: **119** : HBF_4, one or both nitrogen atoms of the heterocycle are alkylated. The monoalkylated products **120** (R^2 = H) are obtained for the ratios 1:1:2, while the dialkylated products **120** (R^2 = $FcCH_2$) are formed for the ratios 2:1:2.[78]

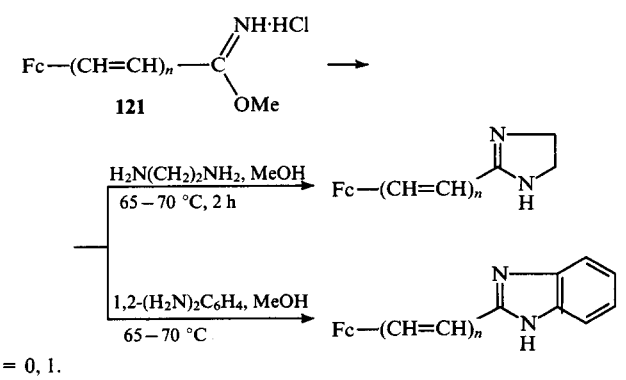


119

120

R	R^1	R^2	Yield (%)
H	Me	H	55
H	Me	$FcCH_2$	68
6-NO_2	H	H	71
6-NO_2	Me	H	75
6-NO_2	H	$FcCH_2$	65
6-NO_2	Me	$FcCH_2$	62

Ferrocene-containing imidazolines and benzimidazoles are formed in high yields (80%–93%) on condensation of the iminoester hydrochlorides **121** with ethylenediamine or 1,2-diaminobenzene.[79,80]

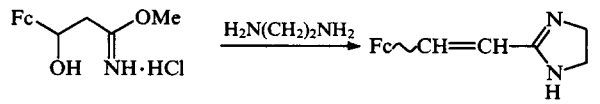


121

n = 0, 1.

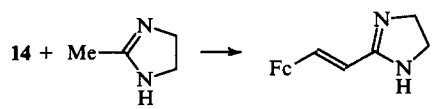
The configuration of the ethene fragment in the product is the same as in the initial iminoester **121** (n = 1).[81,82]

The reaction of ethylenediamine with the hydrochloride of the iminoester of 3-ferrocenyl-3-hydroxypropionic acid results in the formation of 1-ferrocenyl-2-(2-imidazolinyl)ethene **122** in the form of a mixture of the *cis*- and *trans*-isomers.[82]



122 (95%, *cis* + *trans*)

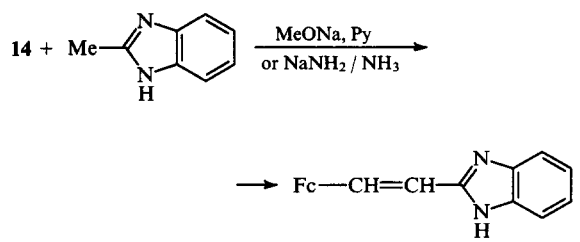
The condensation of the aldehyde **14** with 2-methylimidazoline constitutes a stereoselective method of synthesis of the *trans*-isomer of the imidazoline **122**.[82–84]



trans- **122**

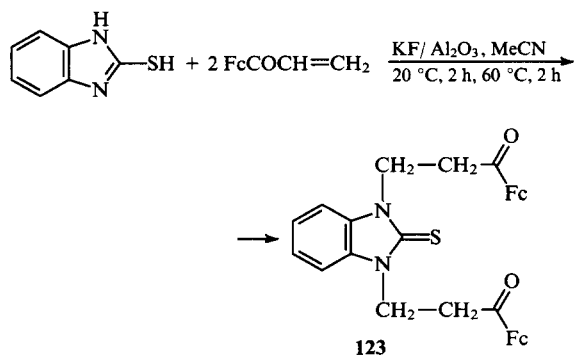
Conditions	Yield of **122** (%)
RONa, ROH (R = Me, Et)	54
KU-2, PhH	32

2-(2-Benzimidazolyl)-1-ferrocenylethene has been obtained similarly from 2-methylbenzimidazole.[83,84]



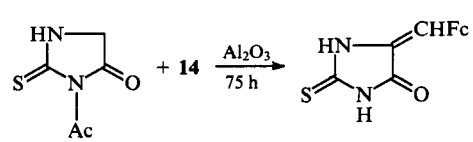
31%

2-Mercaptobenzimidazole reacts in the thiono-form with two molecules of ferrocenyl vinyl ketone in the presence of potassium fluoride, affording the adduct **123** in 94% yield.[85]



123

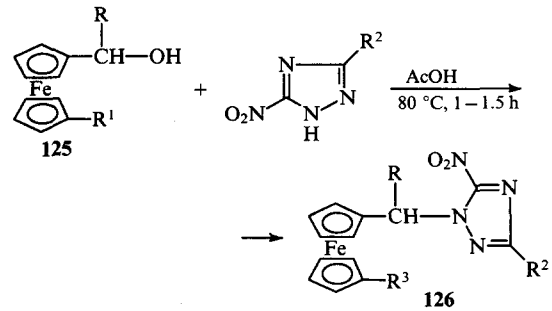
In the reaction of 3-acetyl-2-thiohydantoin with FcCHO on aluminium oxide, deacetylation takes place together with ferrocenylmethylation; the reaction product is compound **124** (yield 75%).[86]



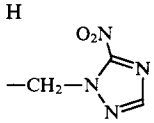
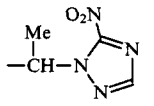
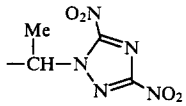
124

The synthesis of 2-ferrocenyl-5-mercapto-4-phenyl-1,2,4-triazoline by the condensation of phenyl isothiocyanate with the hydrazide of ferrocenecarboxylic acid has been described.[87]

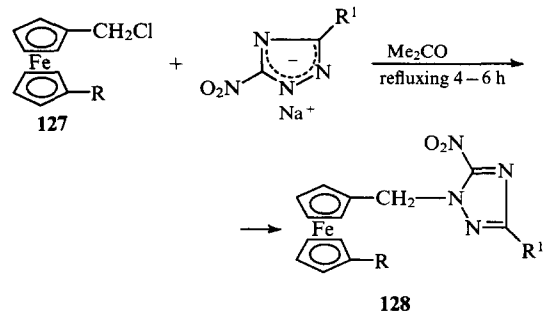
In the presence of acetic acid, the ferrocenylcarbinols **125** react regiospecifically with 5-nitro- and 3,5-dinitro-1,2,4-triazoles, forming the products of alkylation at the N(1) atom.[88] The ferrocene derivatives **126** with heteryl-containing substituents in both rings can be obtained under these conditions.



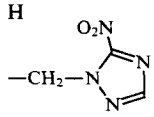
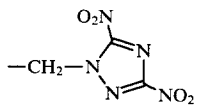
125 **126**

R	R^1	R^2	R^3	Yield (%)
H	H	H	H	42
Me	H	H	H	57
Ph	H	H	H	18
H	H	NO_2	H	12
Me	H	NO_2	H	14
H	CH_2OH	H		60
Me	CH(Me)OH	H		53
Me	CH(Me)OH	NO_2		14

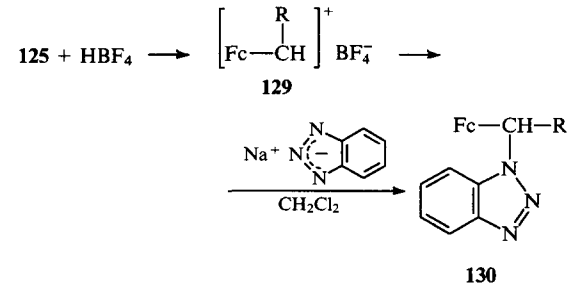
The alkylation of the sodio-derivatives of 5-nitro- and 3,5-dinitro-1,2,4-triazoles by chloromethyl- and 1,1'-di(chloromethyl)-ferrocenes **127** also takes place regiospecifically at the N(1) atom. The yields of the products **128** are 50%–80%.[89,90]



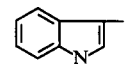
127 **128**

R	R^1	R^2
H	H	H
H	NO_2	H
CH_2Cl	H	
CH_2Cl	NO_2	

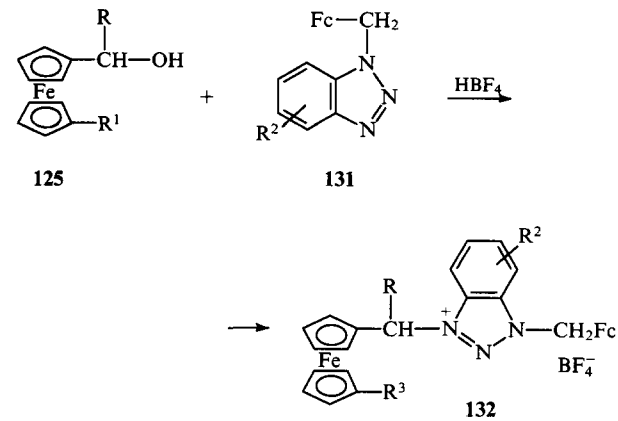
The reaction of the sodio-derivative of benzotriazole with the salts **129**, formed from the ferrocenylcarbinols **125** and HBF_4, leads to *N*-substituted benzotriazoles **130** in 54%–96% yields.[43] According to the authors, the reaction proceeds via a stage involving the one-electron oxidation of the benzotriazole anion.



130

R	H	Me	Ph	FcCH=CH	Fc	
Reaction time/h	0.25	1.25	1.75	20	0.5	0.5

The alkylation of the substituted benzotriazoles **131** by treatment with the ferrocenylcarbinols **125** in 48% aqueous HBF_4 in the course of 3–5 min leads to the salts **132** in 92%–96% yields.[91]



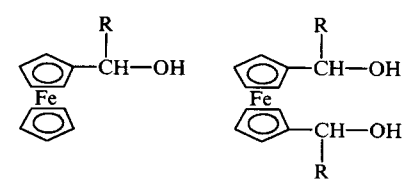
125 **131**

132

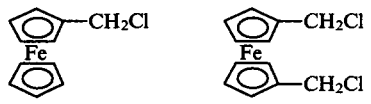
R = H, Me; R^1 = H, CH_2OH; R^2 = H, Me, Br, NO_2;

R^3 = H, 

The alkylation of tetrazole and its derivatives **133** by various cationoid ferrocene-containing reagents has been investigated.[88,92] The reagents employed were the alcohols **125** of the ferrocene series, which readily generate α-ferrocenylcarbonium ions in an acid medium, as well as α-haloalkylferrocenes **127**. In these reactions, electrophilic functional groups were present in only one as well as in both rings of the ferrocene system.

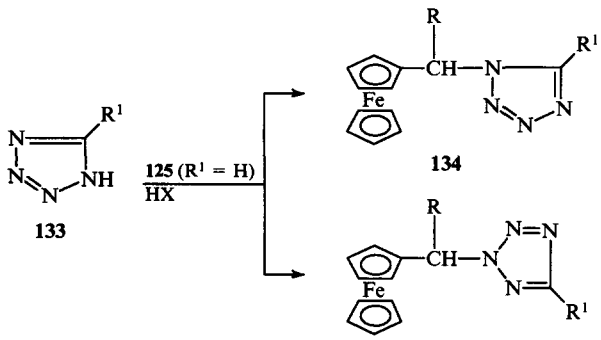


125 (R^1 = H) **125** [R^1 = CH(R)OH]



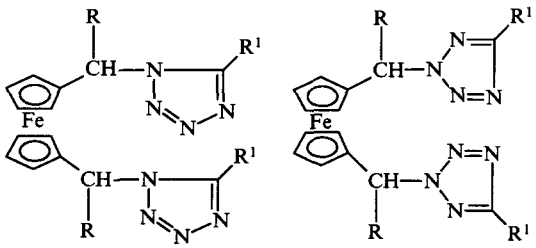
127 (R = H) 127 (R = CH_2Cl)

Treatment of tetrazole (or 5-R^1-tetrazole) **133** or of its sodio-derivative by the above reagent gave the products of alkylation at the N(1) atom (compound **134**) or the N(2) atom of the tetrazole ring (compound **135**).

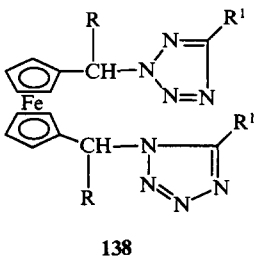


133 **134** **135**

It has been observed that tetrazole and its alkyl derivatives (R^1 = H, Alk) are alkylated nonselectively, which results in the formation of a mixture of regioisomers (compounds **134, 135,** and **136–138**). The introduction of electron-accepting or aromatic substituents (R^1 = Ar, NO_2) into the tetrazole ring promotes substitution at the N(2) atom. In the case of 5-nitrotetrazole, only the *N*(2)-alkylated derivatives are obtained (compounds **135** and **137**).



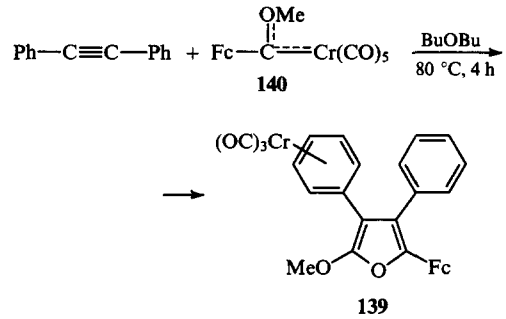
136 **137**



138

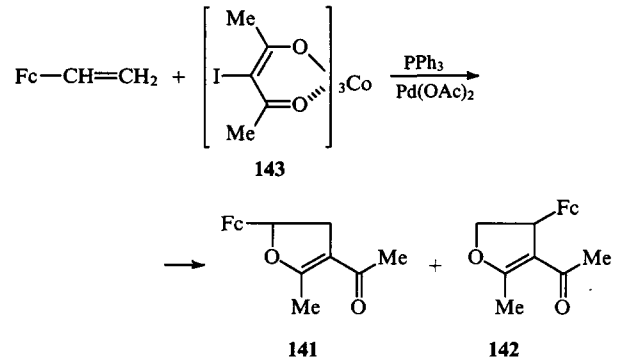
The influence of the acidity of the medium on the selectivity of the alkylation of tetrazole by the alcohols **125** has been investigated.[93] It was found that alkylation at the N(1) atom predominates in an acid medium.

The ferrocenylfuran derivative **139** has been obtained in 45% yield by heating a mixture of diphenylethyne with pentacarbonyl[ferrocenyl(methoxy)carbene]chromium(0) **140** in dibutyl ether.[94]



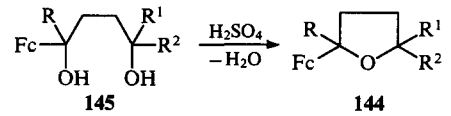
140 **139**

A mixture of the two dihydrofuran derivatives **141** and **142** is formed as a result of the reaction of vinylferrocene with tris(3-iodopentane-2,4-dionato)cobalt **143** in the presence of palladium acetate and triphenylphosphine.[95]



143 **141** **142**

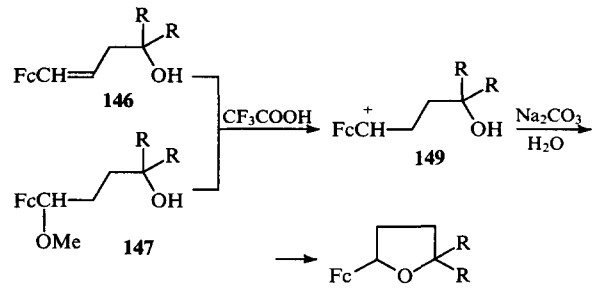
2-Ferrocenyltetrahydrofuran and its derivatives **144** have been synthesised in 90%–95% yields by the dehydrocyclisation of the corresponding 1,4-diols **145** on treatment with sulfuric acid or on heating in vacuo.[96,97]



145 **144**

R	R^1	R^2
H	H	H
Ph	Me	Me
Ph	Me	Et
Ph	Pr	Pr
Ph	$-(CH_2)_n-$ (n = 4, 5)	

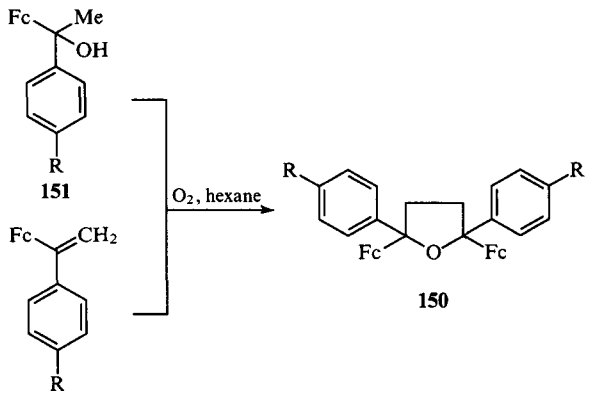
The unsaturated alcohols **146** or the 1,4-diol monoethers **147** are converted into the tetrahydrofuran derivatives **148** by the reaction with trifluoroacetic acid and subsequent treatment with an aqueous solution of sodium carbonate. According to the authors,[98] the reaction proceeds via a stage involving the formation of the carbonium ions **149**. The yields of compounds **148a, b** were 84% and 88% respectively.



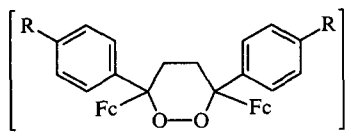
146 **147** **149**

R = H (**a**), Me (**b**) **148a,b**

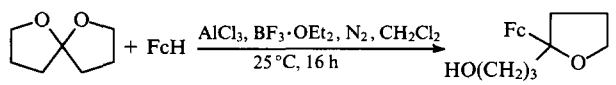
Japanese investigators have described a new method of synthesis of 2,5-diferrocenyltetrahydrofuran derivatives **150**.[99,100] They treated the alcohols **151** or the alkenes **152** with oxygen in hexane in the presence of silica gel or acid aluminium oxide.



The authors believe that the reaction proceeds via the intermediate formation of a peroxide as a result of the oxidative dimerisation of the initial compounds.

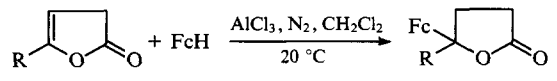


When 1,6-dioxaspiro[4.4]nonane **153** is activated by Lewis acids ($AlCl_3$, BF_3), it is capable of alkylating ferrocene with the opening of one of the rings of the spiro-system.[101,102] After treatment with water, 2-ferrocenyl-2-(3-hydroxypropyl)tetrahydrofuran **154** is formed in 55%–89% yield.



153 **154**

Ferrocene adds to the dihydrofuranone derivative **155** under similar conditions.[103]



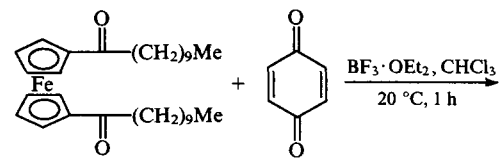
155

2-Ferrocenylfuran-5-carboxylic acid has been synthesised by the cyclocondensation of 3-chloro-3-ferrocenylacrolein **61** with glycolic acid. It was noted that, when the reaction is carried out in a microwave oven, the yield of the cyclocondensation product increases appreciably.[24]

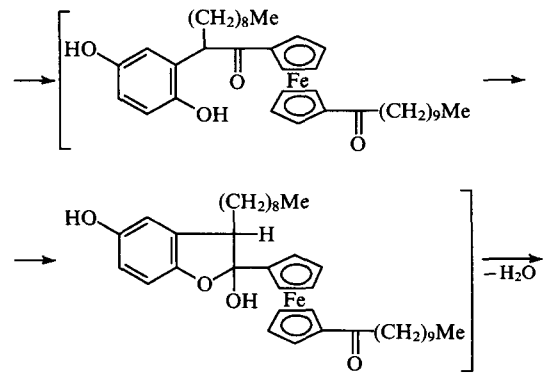
The interaction of the diketone **156** with benzoquinone in the presence of $Et_2O \cdot BF_3$ results in the formation of the benzofuran derivative **157** in 30% yield.[104]

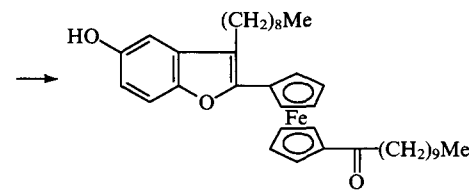
The alcohols obtained from 3-ferrocenoylpropionic acid or its methyl ester cyclise to the tetrahydrofuranone derivative **158** on treatment with MeMgI or $NaBH_4$ in situ.[98,105]

The acylation of ferrocene by the chloride of 5-(2-furoyl)-valeric acid in the presence of aluminium chloride is accompanied by the intramolecular crotonic condensation; the final reaction product is 2-ferrocenyl-1-(2-furoyl)cyclopentene **159**.[106]

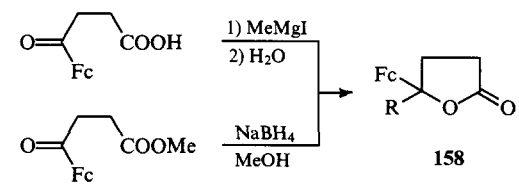


156



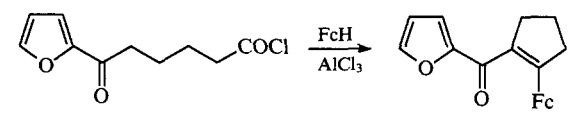


157



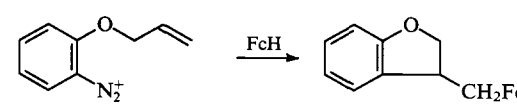
158

R = H, Me.



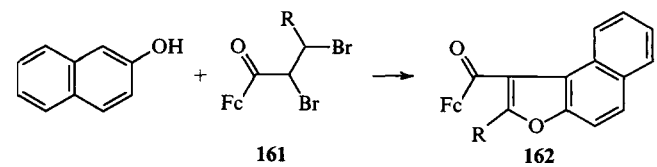
159

Australian investigators[107] described a novel method of synthesis of 3-ferrocenylmethyl-2,3-dihydrobenzofuran by the cyclocondensation of ferrocene with the diazonium cation **160**.



160

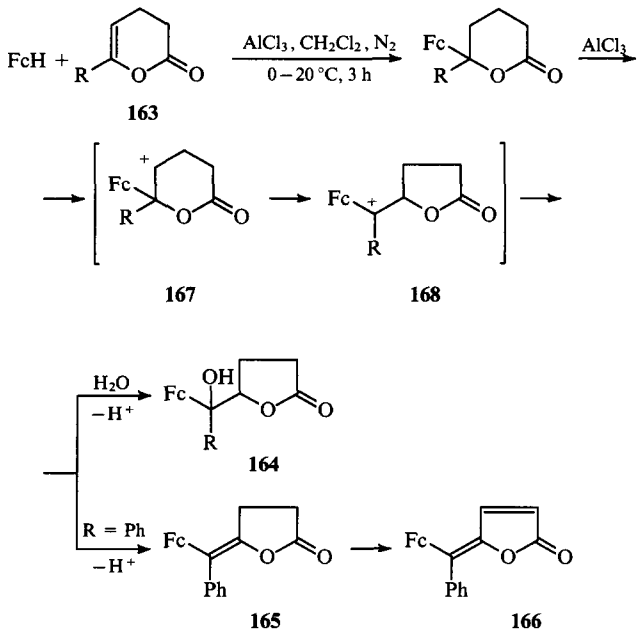
The naphthofuran derivatives **162** have been synthesised in 70%–78% yields by heating a mixture of β-naphthol and the dibromo-derivatives **161** above the melting point.[47]



161 **162**

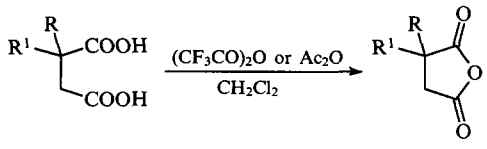
R = Ph, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

The reaction of ferrocene with the lactones **163** in the presence of aluminium chloride[103] leads to compounds **164–166** with five-membered rings, which are formed as a result of the carbonium ion rearrangement **167** → **168**.



163 **167** **168** **164** **165** **166**

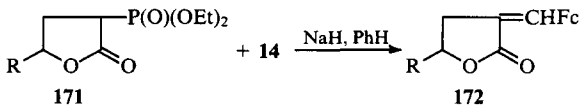
The synthesis of the ferrocenyl-substituted succinic anhydrides **170** from the corresponding acids **169** on treatment with Ac_2O or $(CF_3CO)_2O$ has been described.[108–110]



169 **170**

R	R^1	Yield (%)	Ref.
H	$FcCH_2$	80–88	109
Fc(Me)C=		100	108
Fc(Ph)C=		90	108
FcHC=		53	110

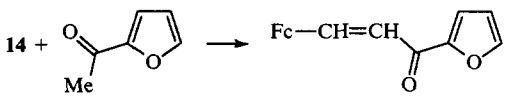
The Horner–Emmons interaction of FcCHO **14** with the phosphonates **171** leads to the unsaturated lactones **172**.[111]



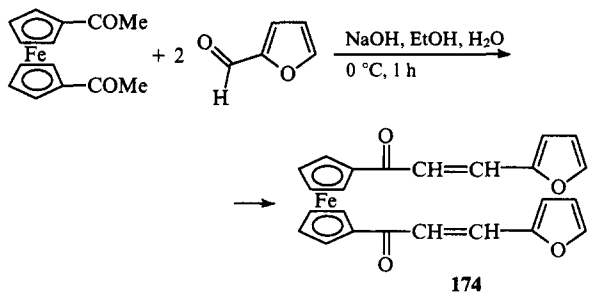
171 **172**

R = H, Me.

The ferrocene-containing chalcones **173** and **174** have been obtained[112,113] by condensing compound **14** with 2-acetylfuran (on treatment with aqueous alkali at 20 °C for 24 h or on treatment with piperidine in methanol) and also by condensing 1,1′-diacetylferrocene with furfural.

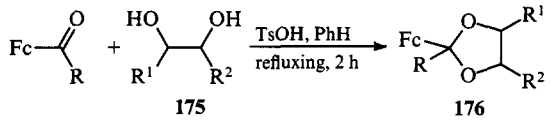


173



174

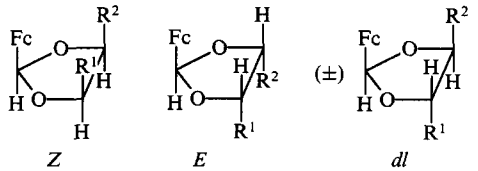
On treatment with the glycols **175** in the presence of toluene-*p*-sulfonic acid, the aldehyde **14** and acetylferrocene **23** afford the corresponding dioxolanes **176** (yield 68%–77%).[114,115]



175 **176**

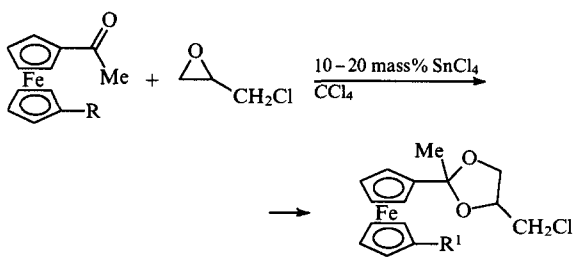
R	R^1	R^2	Ref.
Me	H	H	114
H	Me	H	115
H	Me	Me	115

It has been established by ^1H NMR spectroscopy[115] that the reaction with aldehyde **14** proceeds stereoselectively: for R^1 = Me and R^2 = H, a 6:5 mixture of (*Z*)- and (*E*)-isomers is formed; the *dl*- and (*E*)-isomers are formed in proportions of 6:1 from the symmetrical diol, where $R^1 = R^2$ = Me.

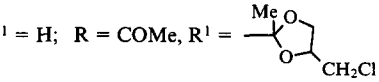


Z *E* *dl*

The introduction of the dioxolane fragment into the ferrocene system is also possible on treatment with epichlorohydrin in the presence of tin(IV) chloride.[114,116] The maximum yields of the products **177** have been obtained for the ratio ferrocene derivative : epichlorohydrin = (1:2)–(1:4).



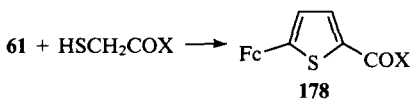
177



A method of synthesis of 1,1′-bis(2-thienyl)ferrocene, involving the reaction of 1,1′-dibromoferrocene with an excess of (2-thienyl)magnesium iodide has been patented.[117]

The cyclocondensation of 3-chloro-3-ferrocenylacrolein **61** with thioglycolic acid in the presence of triethylamine [60–80 °C, dimethylformamide (DMF)][24,118] leads not only to the expected 2-ferrocenylthiophene-5-carboxylic acid (yield 12%) but also to its decarboxylation product — 2-ferrocenylthiophene (yield 20%).

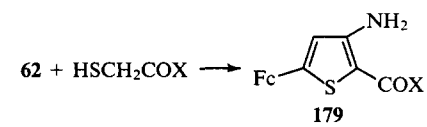
The condensation of ethyl thioglycolate proceeds without complications[118] and the corresponding thiophene derivative **178** (X = OEt) has been isolated in 63% yield. The amide **178** (X = NHPh) has been obtained in 36% yield from the anilide of thioglycolic acid.



178

X = OEt, NHPh.

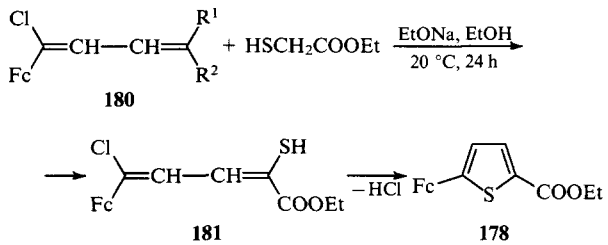
The same communication reports the synthesis of the amino-derivatives **179** (X = OEt, yield 49%; X = NHPh, yield 65%) when the 3-chloro-3-ferrocenylacrylonitrile **62** is condensed with thioglycolic acid derivatives.



179

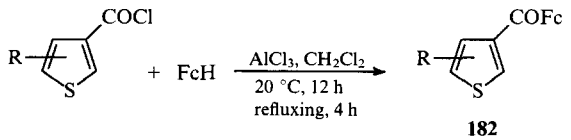
X = OEt, NHPh.

In a basic medium, the diene derivative **180** undergo transcondensation with ethyl thioglycolate. This leads to the product **181**, unstable under the reaction conditions, which cyclises to the thiophene derivative **178** (X = OEt).[119]



180 **181** **178**

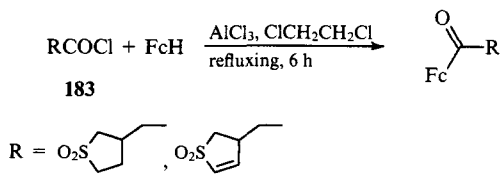
When ferrocene is acylated by the chlorides of thiophene-3-carboxylic acids, the ketones **182** are formed in low yields (14%–20%).[120]



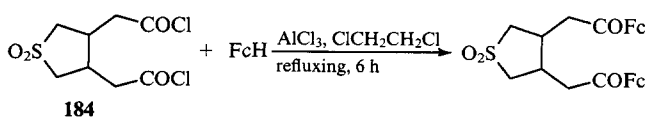
182

R = 2-COOMe, 4-COOMe.

The acylation of ferrocene by the acid chlorides **183** and **184**, containing a sulfolane or sulfolene fragment, is also ineffective for preparative purposes (the product yields are 14%–20%).[121]

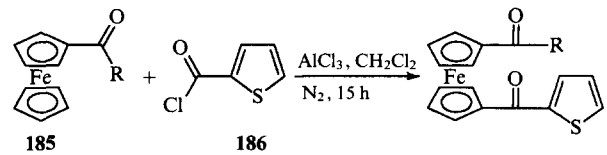


183



184

When the acylferrocenes **185** are acylated by the chloride of thiophene-2-carboxylic acid **186**, the attack by the electrophile is directed to the unsubstituted cyclopentadienyl fragment.[122]

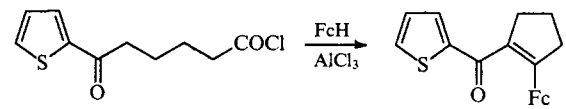


185 **186**

R = Me (80%), Et (83%), Ph (81%), $PhCH_2$ (85%).

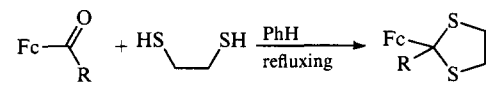
When 1-acetyl-1'-ethylferrocene is used as the substrate, substitution takes place in the ring with the alkyl substituent (the yield of the acylation product is 16%).[122]

The acylation of ferrocene by the chloride **187** under the conditions of the Friedel–Crafts reaction is accompanied by cyclisation with formation of the ketone **188**.[106]



187 **188**

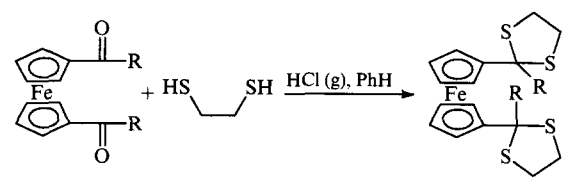
The 1,3-dithiolanes **189** have been synthesised in 51%–81% yields by the thioketalisation of the acylferrocenes **185** on treatment with the 1,2-dithiols **190** in the presence of acid catalysts.[115]



185 **190** **189**

R = H, Me, Ph.

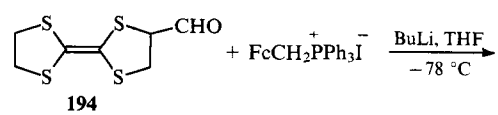
More severe conditions are required for the synthesis of the bisthioketals **191** from 1,1'-diacylferrocenes **192**, the product yields being 29%–31%.



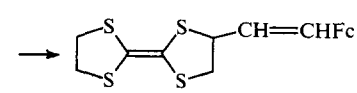
192 **191**

R = Me, Ph.

The vinylferrocene derivative **193** has been synthesised by the Wittig reaction from the aldehyde **194** and ferrocenylmethyl-(triphenyl)phosphonium iodide in 58% yield.[123]

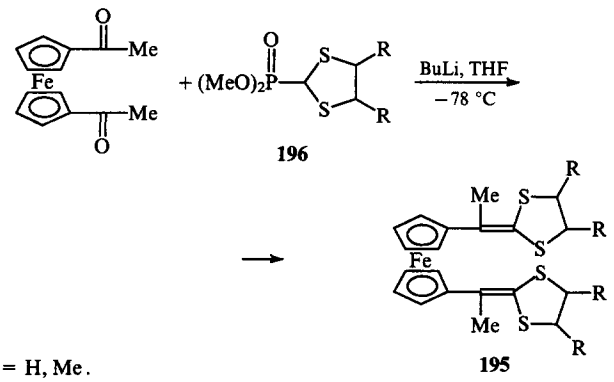


194



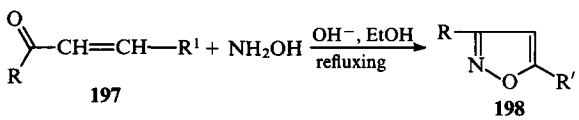
193

Compounds **195** have been obtained from 1,1'-diacetyl-ferrocene and the reagents **196** by the Horner–Emmons method in 60%–70% yields.[123]



R = H, Me.

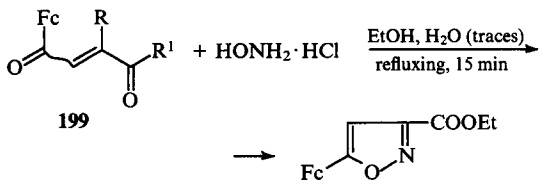
On heating the unsaturated ketones **197** with hydroxylamine in the presence of alkali, the adduct was unexpectedly readily aromatised, the isoxazoles **198** being obtained instead of the isoxazolines.[124]



R = Fc; R^1 = Fc, Ph, ; R = *p*-FC_6H_4, R^1 = Fc.

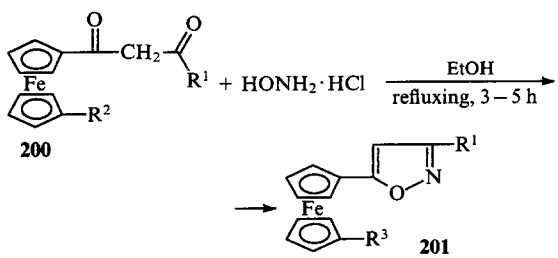
5-Ferrocenylisoxazole has been synthesised in 25% yield by heating the aldehyde **61** with the hydrochloride of hydroxylamine in methanol. On treatment with hydroxylamine in the presence of sodium ethoxide, the nitrile **62** affords a 56% yield of 3-amino-5-ferrocenylisoxazole.[54]

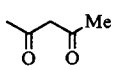
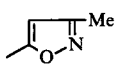
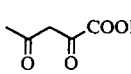
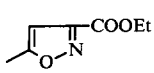
The ethyl ester of 5-ferrocenylisooxazole-3-carboxylic acid is formed in 61%–86% yield in the reaction of 3-ferrocenoylacrylic acid derivatives **199** with hydroxylamine hydrochloride.[59]



R = NH_2, R^1 = OEt; R = OH, R^1 = OH.

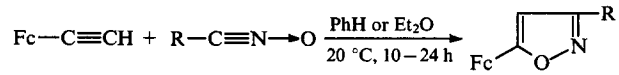
The ferrocene derivatives **201**, containing isoxazole fragments in one or both cyclopentadienyl rings, have been obtained in 47%–81% yield by the cyclocondensation of the diketo-derivatives **200** on refluxing with $HONH_2 \cdot HCl$ in alcohol.[55,58] For R^1 = Me in the initial diketo-derivative **200**, the reaction is carried out in the presence of pyridine.



R^1	R^2	R^3
Me	H	H
Me		
COOEt		

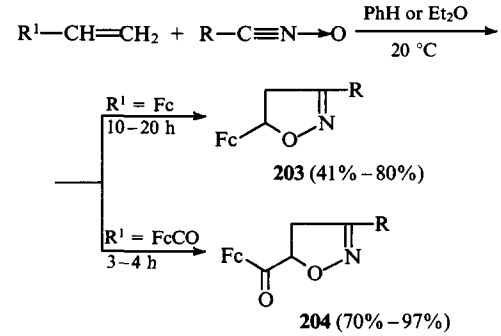
3-(10-Phenothiazinyl)-5-ferrocenylisoxazoline has been synthesised in 40% yield by refluxing a mixture of 10-(3-ferrocenyl-1-oxoprop-2-en-1-yl)phenothiazine with hydroxylamine in ethanol for 6 h.[66]

The 1,3-dipolar addition of the *N*-oxides of carboxylic acid nitriles to unsaturated ferrocene derivatives is a convenient method of synthesis of 5-ferrocenylisoxazole and 5-ferrocenyl-isoxazoline derivatives. Ferrocenylethyne, vinylferrocene, and ferrocenyl vinyl ketone have been used as the dipolarophiles. Their cycloaddition to the *N*-oxides of aliphatic and aromatic acid nitriles led to the series of derivatives **202**–**204**.[125]



202 (23%–94%)

R = Me, Et, COMe, COOEt, Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

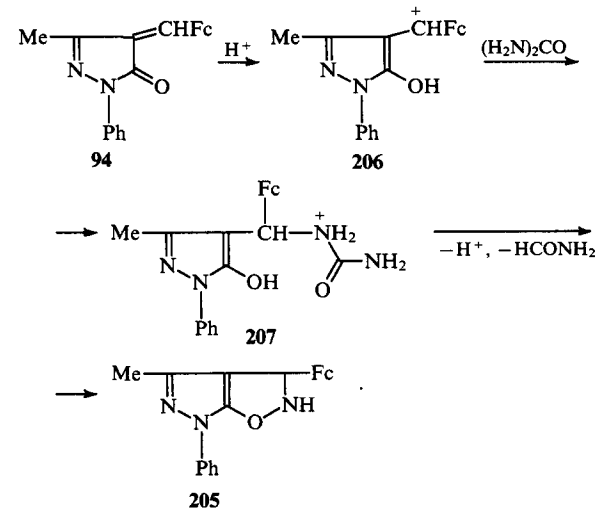


203 (41%–80%)

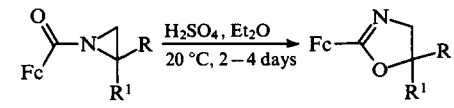
204 (70%–97%)

R = Me, Et, COMe, COOEt, Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

Compound **205** with two condensed heterocyclic rings is formed in 60% yield as a result of the interaction of the pyrazolone derivative **94** (R = Me, R^1 = Ph) with urea in boiling acetic acid.[69] The following reaction mechanism has been proposed:



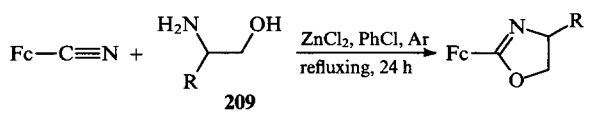
Treatment of 1-ferrocenoylaziridines **3** with sulfuric acid in the dark leads to the expansion of the ring and the formation of the oxazoline derivatives **208** (yields 24%–58%).[7]



R = R^1 = H (**a**); R = H, R^1 = Me (**b**); R = R^1 = Me (**c**).

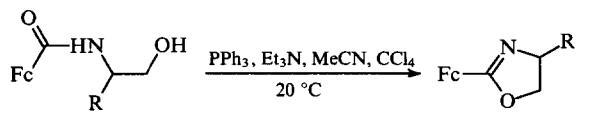
A further two methods of synthesis of the oxazolines **208** have been patented: by the reaction of FeCN with 1-aminopropan-2-ol (compound **208b** is obtained) or by the reaction of FeCOCl with 2,2-dimethylaziridine (compound **208c** is obtained).[126]

A method has been proposed recently for the synthesis of 4-substituted 2-ferrocenyloxazolines from cyanoferrocene and the aminoalcohols **209** in the presence of zinc chloride (yields 15%–38%).[127] Best results are achieved when the β-hydroxyamides **210** are cyclised on treatment with triphenylphosphine (yield 77%–92%).[128]



209

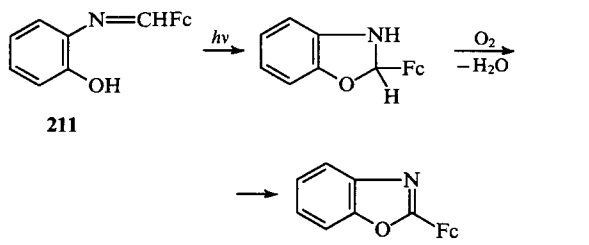
R = Me, Pr^i, Bu^i, Bu^t, Ph, PhCH$_2$.



210

R = H, Pr^i.

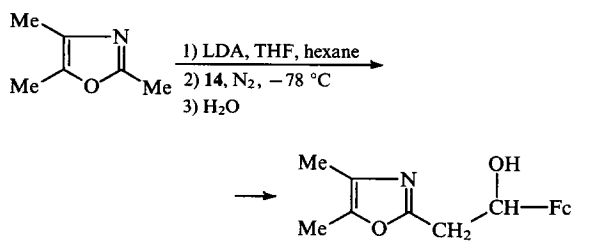
Cyclocondensation of the hydrochloride of the methyl iminoester of ferrocenecarboxylic acid with *o*-aminophenol in boiling methanol leads to 2-ferrocenylbenzoxazole in 84% yield.[79] The latter has also been obtained in 70% yield by irradiating the imine **211** with light of 348 nm wavelength in boiling toluene for 10 s.[129] The unstable 2-ferrocenylbenzoxazoline, which is rapidly oxidised, is formed as an intermediate.



211

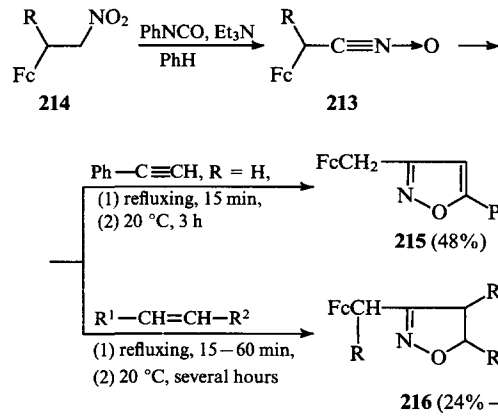
An alternative route to 2-ferrocenylbenzoxazole involves the treatment of the imine **211** with lead tetraacetate in glacial acetic acid.[129]

The lithium derivative, formed on deprotonation of 2,4,5-trimethyloxazole by treatment with lithium diisopropylamide (LDA), reacts with FcCHO **14**, affording (after hydrolytic treatment) the alcohol **212** (yield 57%).[130]



212

The *N*-oxides of the carboxylic acid nitriles **213**, generated by the dehydration of the primary nitro-compounds **214** by phenyl isocyanate in the presence of triethylamine, were made to undergo the 1,3-dipolar cycloaddition to phenylethyne or alkenes.[131,132] This resulted in the synthesis of 3-ferrocenylmethyl-5-phenylisoxazole **215** or of the isoxazoline derivatives **216**.



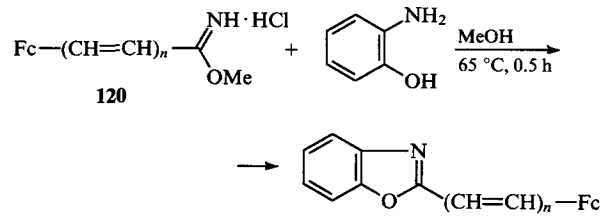
214 **213**

215 (48%)

216 (24%–88%)

R	R^1	R^2
H	H	CN
H	H	Ph
H	H	n-C_5H_{11}
H	H	cyclo-C_6H_{11}
H	H	$SiMe_3$
H	H	OAc
H	H	$CH_2OCO(CF_2)_2CF_3$
H	H	$COOCH_2(CF_2)_5CF_3$
Me	H	CN
Me	H	OAc
OEt	COOMe	*trans*-COOMe
Ph	COOMe	*trans*-COOMe
OMe	COOMe	*trans*-COOMe

Interaction of the hydrochlorides of the iminoesters **120** with *o*-aminophenol results in the formation of the benzoxazole derivatives **217** in 84%–100% yields.[82,133]



120

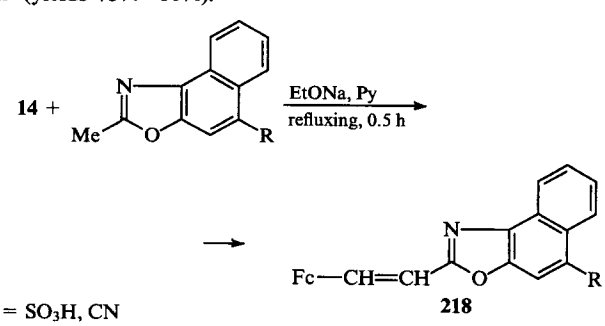
217

n = 0, 1.

It has been found that the cyclocondensation does not affect the configuration of the double bond.[81] The individual *cis*- and *trans*-iminoesters **120** (*n* = 1) afforded the corresponding diastereoisomers **217** in 90%–93% yields.

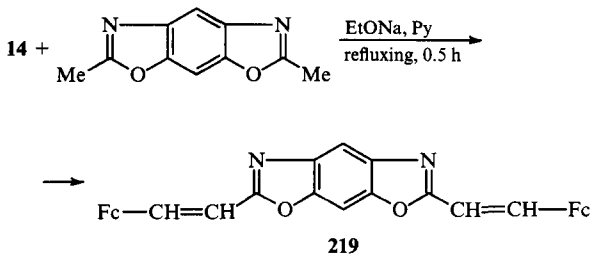
Compound **217** (*n* = 1) has been synthesised by condensing the aldehyde **14** with 2-methylbenzoxazole in the presence of bases (MeONa, $NaNH_2$).[83,84,133] If the substrate is 2,3-dimethylbenzoxazolium iodide, the condensation product is the corresponding salt of the *N*-methyl derivative **217**.

A condensation of the same type has been used to synthesise the more complex ferrocene-containing benzoxazoles **218** and **219** (yields 75%–80%).[84]



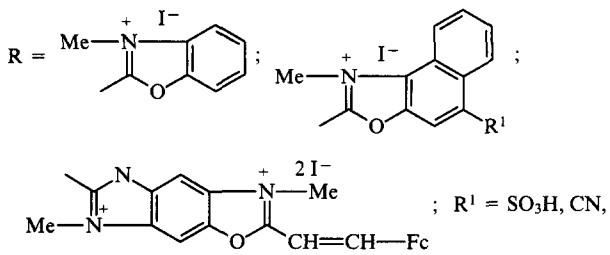
R = SO_3H, CN

218



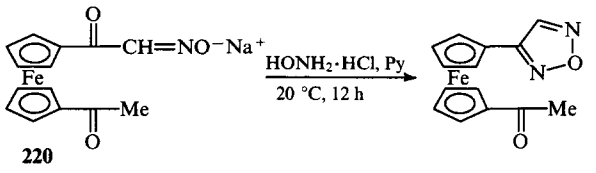
219

Ferrocene-containing cyanines having the general formula FcCH=CHR have been synthesised from the aldehyde **14** and the methiodides of 2-methylbenzoxazole and its derivatives.[84] The compounds with



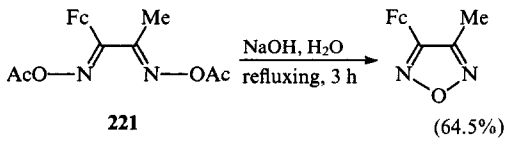
have been described.

The condensation of the salt **220** with hydroxylamine results in the formation of 1-acetyl-1′-(1,2,5-oxadiazol-4-yl)ferrocene in 73% yield.[134]

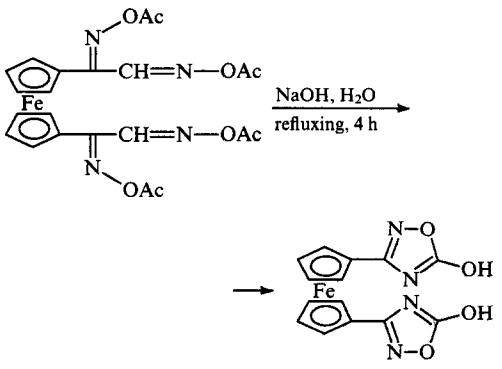


220

Refluxing of the diacetate of 1-ferrocenyl-2-methylglyoxime **221** in aqueous alkali leads to 5-ferrocenyl-4-methyl-1,2,5-oxadiazole.[135] On the other hand, when there is a hydrogen atom attached to the carbonyl carbon atom in the glyoxime derivative, the 1,2,4-oxadiazole derivative **222** is formed under the same conditions.

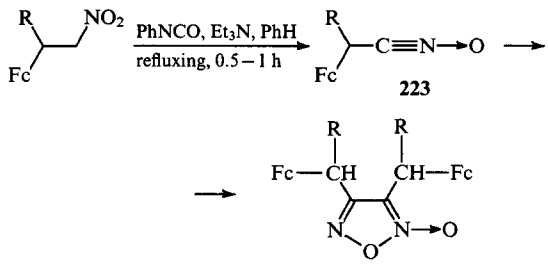


221 (64.5%)



222 (68%)

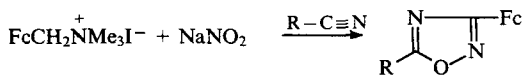
The *N*-oxides of the nitriles **223**, generated from primary nitro-compounds on treatment with phenyl isocyanate in the presence of triethylamine, dimerise in the absence of dipolarophiles and are converted into the furoxanes **224**.[131,132]



223

224: R = H (42%), Me (80%).

The 1,2,4-oxadiazole derivatives **225** have been obtained[136] by the reaction of ferrocenylmethyl(trimethyl)ammonium iodide with sodium nitrite in acetonitrile or propionitrile.

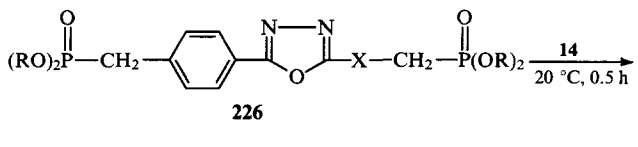


225

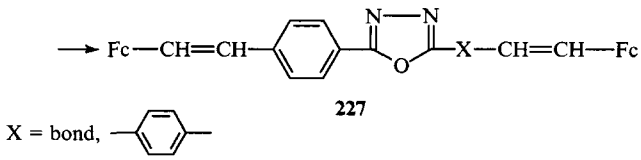
R = Me, Et.

Apparently the *N*-oxide of the nitrile FcC≡N → O is formed as an intermediate, undergoing subsequently the 1,3-dipolar cycloaddition reaction with the nitrile group.

The phosphonic acid derivatives **226**, containing the 1,3,4-oxadiazole ring, react under very mild conditions with the aldehyde **14** to form compounds **227**.[137]



226

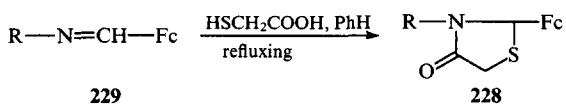


227

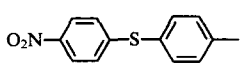
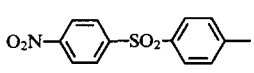
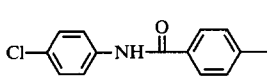
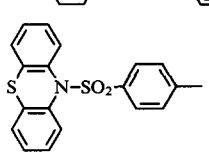
X = bond,

5-Ferrocenylisothiazole has been synthesised from the aldehyde **61** on treatment with ammonium thiocyanate (refluxing in acetone for 20 min; yield 42%).[54]

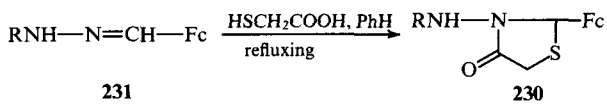
The cyclocondensation of the imines **229** with thioglycolic acid is frequently used to synthesise 2-ferrocenylthiazolin-4-one **228**.[16,18-20]



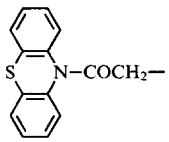
229 **228**

R	Yield (%)	Ref.
	14	16
	54	18
	100	18
	—	20
	—	19

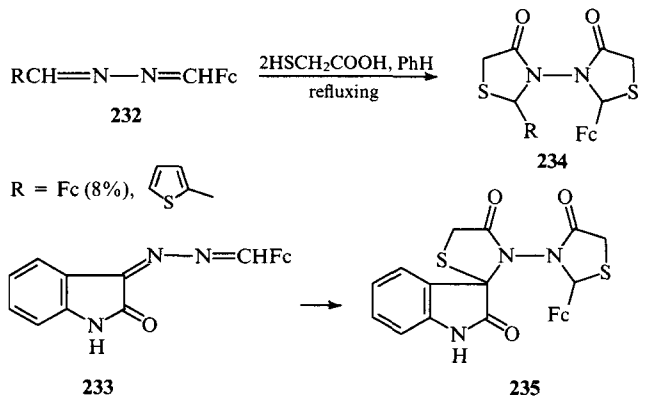
The 3-aminothiazolin-4-one derivatives **230** have been synthesised by the cyclocondensation of the hydrazones **231** with thioglycolic acid.[16,138]



231 **230**

R	Yield (%)	Ref.
$CONH_2$	11	16
$CSNH_2$	13	16
	—	20, 138

The same reaction involving the azines **232** and **233** leads to compounds **234** and **235** containing two thiazoline rings in the molecule.[16,139]

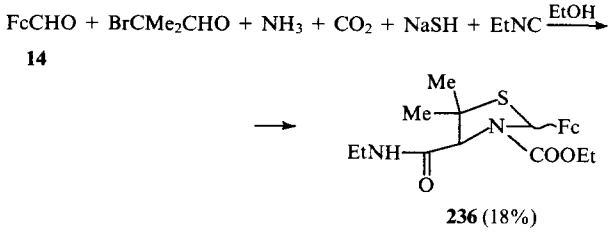


232 **234**

R = Fc (8%),

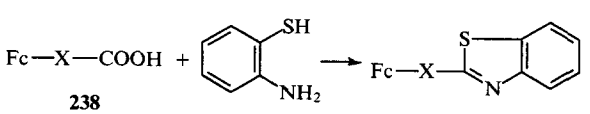
233 **235**

A procedure has been proposed for the synthesis of thiazolidine derivatives **236**,[140] in which the aldehydes **14** and $BrCMe_2CHO$ are treated with sodium hydrogen sulfide in alcohol at −10 °C. This is followed by the passage of a stream of ammonia for 15 min, the addition of EtNC, and the maintenance of the reaction mixture under a CO_2 pressure for six days.



14 **236** (18%)

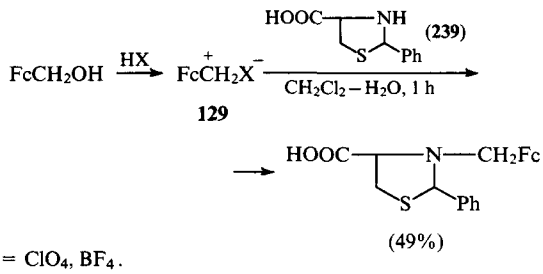
Benzothiazole derivatives **237** have been obtained by the cyclocondensation of the carboxylic acids **238** with *o*-aminothiophenol.[141]



238 **237**

X = bond, $—CO(CH_2)_3—$, $—CO(CH_2)_4—$.

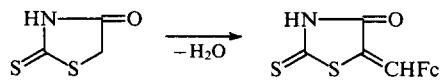
2-Phenylthiazolidine-4-carboxylic acid **239** is alkylated at the N atom of the heterocycle on treatment with ferrocenylmethyl perchlorate or tetrafluoroborate **129**, which are generated from ferrocenylmethanol under phase-transfer conditions.[41,44]



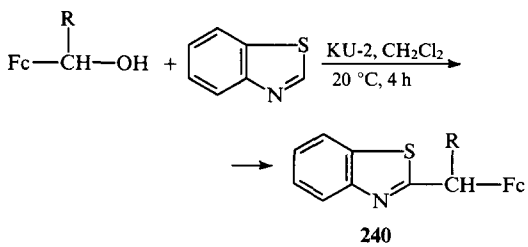
129

X = ClO_4, BF_4.

The condensation of the aldehyde **14** with rhodanine yields 5-ferrocenylmethylidene-4-oxo-2-thionothiazolidine.[142]



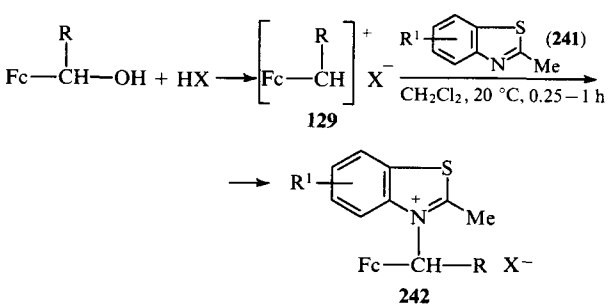
The α-carbonium ions, formed from ferrocenylcarbinols on treatment with the KU-2 cation-exchange resin (in the H-form), add electrophilically to benzothiazole, affording the derivatives **240**.[45]



240

R	Me	Ph	FcCH=CH
Yield (%)	63	80	81

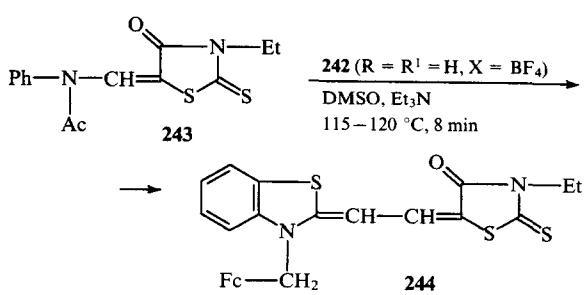
When the α-carbonium ion salts **129** were allowed to react with the 2-methylbenzothiazole derivatives **241**, the nitrogen atom of the heterocycles was alkylated and the corresponding salts **242** were formed in 77%–100% yields.[143,144]



129 **242**

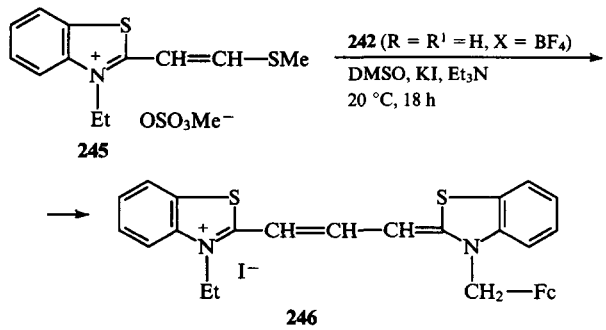
R = H, Me; R^1 = H, 5-Fc, 6-Fc; X = BF_4, ClO_4.

The methyl group at the C(2) atom of the heterocycle in 3-ferrocenylmethyl-2-methylbenzothiazolium tetrafluoroborate **242** (R = R^1 = H, X = BF_4) contains mobile hydrogen atoms and is able to condense with 5-acetylphenylaminomethylene-3-ethylrhodanine **243** to form dimethinemerocyanine **244** (yield 39%).[42]

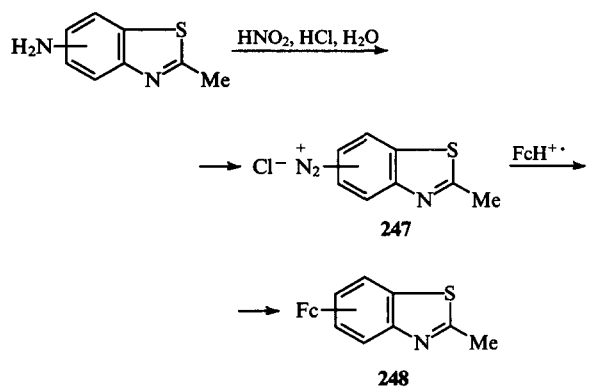


243 **244**

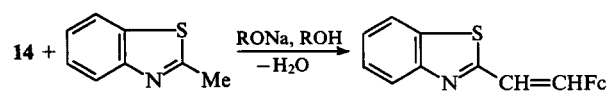
The carbocyanine **246** has been obtained in 64% yield by treating 3-ethyl-2-(2-methylthiovinyl)benzothiazolium methosulfate **245** with the reagent **242** (R = R¹ = H, X = BF_4).[42]



Compounds **248** have been synthesised (yields 7%–9%) by the reaction of the ferrocenium cation, formed when ferrocene is treated with concentrated sulfuric acid, and 5- and 6-diazo-2-methylbenzothiazolium chloride **247**.[49]



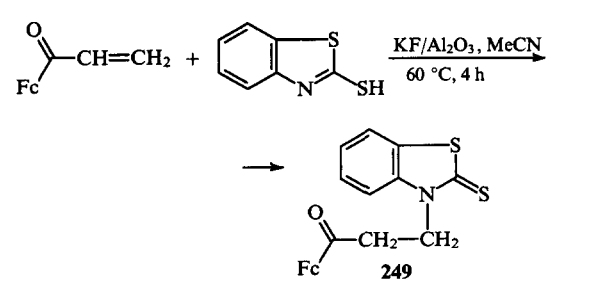
It has been shown[83,84] that in the presence of bases 2-methylbenzothiazole condenses with FcCHO **14** to form 2-(2-ferrocenylvinyl)benzothiazole.



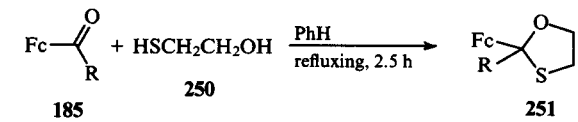
Solvent	Reaction time/h	Yield (%)	Ref.
MeOH	0.5	65	83
EtOH	12	65	84
EtOH, Py	0.5	97	83, 84

2,3-Dimethylbenzothiazolium iodide, in which the mobility of the H atoms of the methyl group at the C(2) atom is greater, reacts more readily with FcCHO[83] and 2-(2-ferrocenylvinyl)-3-methylbenzothiazolium iodide is formed in a virtually quantitative yield in the presence of piperidine.

Ferrocenyl vinyl ketone is a Michael acceptor in relation to 2-mercaptobenzothiazole.[85] When the radiation is carried out on aluminium oxide, a 96% yield of the adduct **249** is attained.

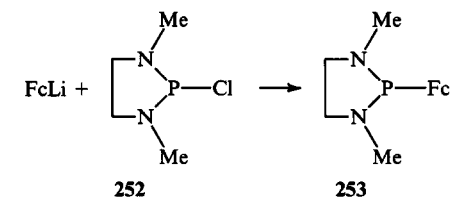


The acylferrocenes **185** react with 2-mercaptoethanol **250** to form the 1,3-oxathiolane derivatives **251**. It has been established[115] that, depending on the nature of R, various catalysts are required for the successful synthesis.

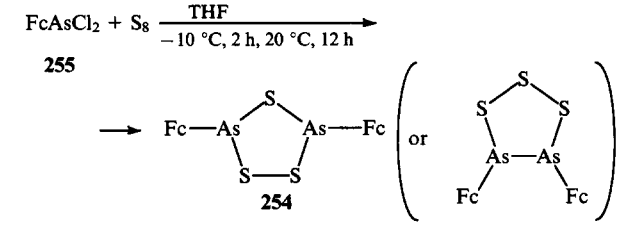


R	Catalyst	Yield (%)
H	$ZnCl_2$	55
Me	TsOH	55
Ph	$BF_3 \cdot OEt_2$	35

On treatment with ferrocenyllithium, the chlorine atom in compound **252** is substituted by the ferrocenyl group, whereupon 1-ferrocenyl-2,5-dimethyl-1,2,5-diazaphospholane **253** is formed.[145]

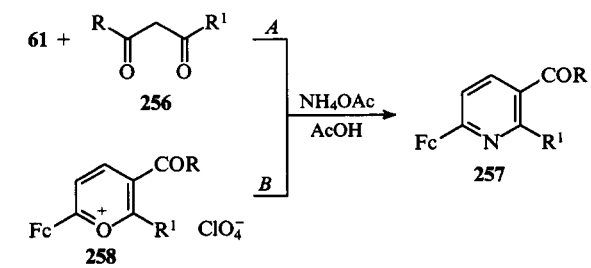


Compound **254** has been obtained in 49% yield as a result of the reaction of dichloro(ferrocenyl)arsine **255** with sulfur in the presence of 2,4,6-tris(*tert*-butyl)phenylphosphine and diazabicycloundecene.[15]



V. Compounds containing six-membered heterocycles

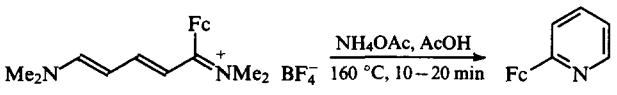
Condensation of the aldehyde **61** with the β-dicarbonyl compound **256** in the presence of ammonium acetate leads to the 3-acyl-6-ferrocenylpyridine derivatives **257**;[146] the same result has been achieved by treating the pyrilium salts **258** with ammonium acetate.[147]



R	R^1	Yield (%)	
		A	*B*
Ph	Ph	34	25
Me	Me	27	10
Me	EtO	43	
EtO	Me		43
$-CH_2-CMe_2-CH_2-$		45	21

4-Ferrocenyl-2,6-dimethylpyridine is formed in 63% yield on treatment of 4-ferrocenyl-2,6-dimethylpyrylium perchlorate with aqueous ammonia.[148] A similar transformation of 6-ferrocenyl-2,4-diphenylpyrylium perchlorate into 6-ferrocenyl-2,4-diphenylpyridine requires more severe conditions: refluxing with an alcoholic solution of ammonium for 10 min (yield 45%–51%)[149] or heating with an alcoholic solution of ammonia in a sealed tube at 100 °C for 7 h (yield 27%).[150]

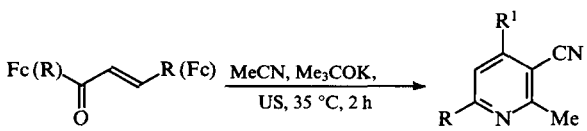
When the salt **259** was heated with ammonium acetate in aqueous acetic acid, 2-ferrocenylpyridine **260** was obtained in 57% yield.[151]



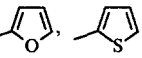
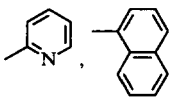
259 **260**

3,5-Dicyano-4-ferrocenyl-2,6-dimethyl-1,4-dihydropyridine, formed as a result of the condensation of FcCHO with diacetonitrile (refluxing for 1 h in acetic acid under a nitrogen atmosphere), is converted into 3,5-dicyano-4-ferrocenyl-2,6-dimethylpyridine on oxidation with chloranil.[152]

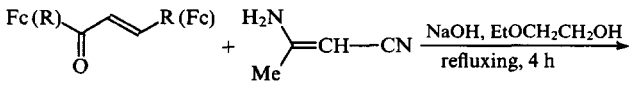
The accelerating effect of ultrasound on chemical reactions has been demonstrated by Japanese investigators.[153] They showed that the sonolysis of unsaturated ferrocenyl-substituted ketones **261** in acetonitrile at 35 °C for 2 h leads to the pyridine derivatives **262** in 60%–85% yields. The authors[153] believe that diacetonitrile, generated from acetonitrile under the reaction conditions, participates in the formation of the pyridines.



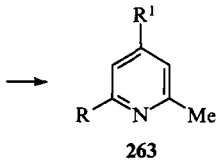
261 **262**

R = R¹ = Bu^t, Ph, 4-ClC6H4, 4-MeOC6H4, , .

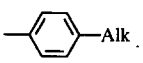
In the presence of bases, the unsaturated ketones **261** react with 3-aminocrotononitrile. If the reaction is carried out in 2-ethoxyethanol,[154] then the products are the substituted pyridines **263**.



261

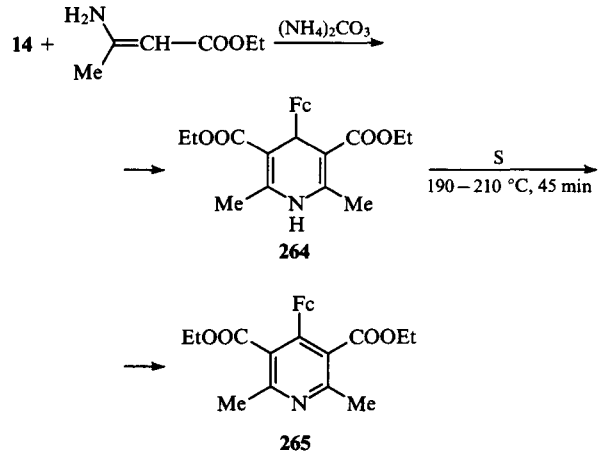


263

R = Ph, , , .

When the condensation is carried out in butanol with subsequent heating of the reaction products with water, substituted nicotinamides are obtained.[154]

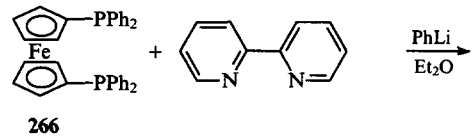
The condensation of the aldehyde **14** with ethyl 3-aminocrotonate in the presence of ammonium carbonate leads to the 1,4-dihydropyridine derivative **264**, which is oxidised by sulfur and is converted into 3,5-bis(ethoxycarbonyl)-4-ferrocenyl-2,6-dimethylpyridine **265**.[155]



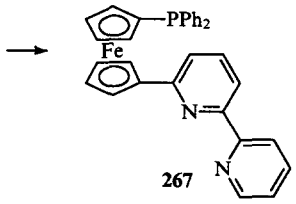
264

265

In the diphosphine **266**, one of the PPh_2 groups is substituted by the 2,2′-bipyridyl group on treatment with the lithium derivative formed from 2,2′-bipyridyl and phenyllithium.[156]

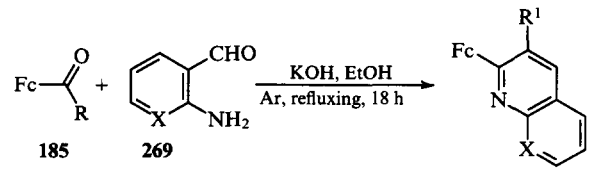


266



267

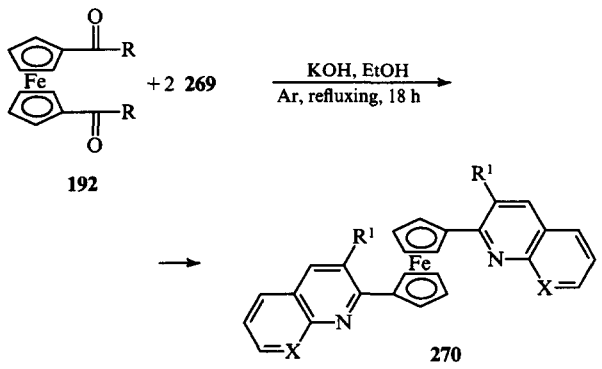
A series of quinoline and naphthyridine derivatives **268**, containing the ferrocenyl group, have been synthesised by the Friedlaender reaction from acylferrocenes **185** and the aminoaldehydes **269**.[157]



185 **269** **268**

R	R¹	X	Yield (%)
Me	H	CH	53
Me	H	N	85
Me	H	COMe	75
Et	Me	CH	67
Et	Me	N	43
Et	Me	COMe	34

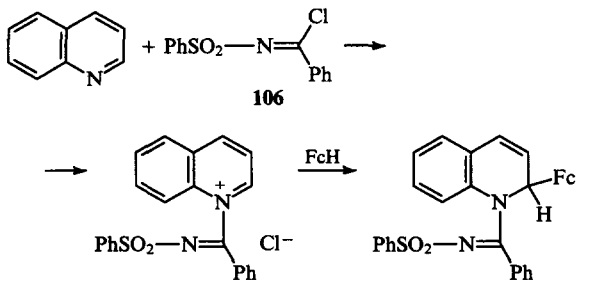
Compounds **270** are obtained under similar conditions from the 1,1′-diacylferrocenes **192** and 2 mol of the aminoaldehydes **269**.

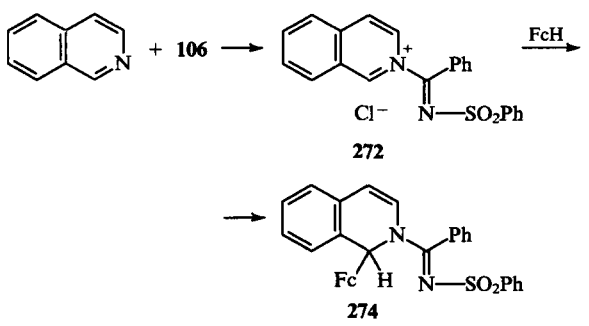


192 270

R	R^1	X	Yield (%)
Me	H	CH	75
Me	H	N	75
Me	H	COMe	62
Et	Me	CH	26
Et	Me	N	40
Et	Me	COMe	24

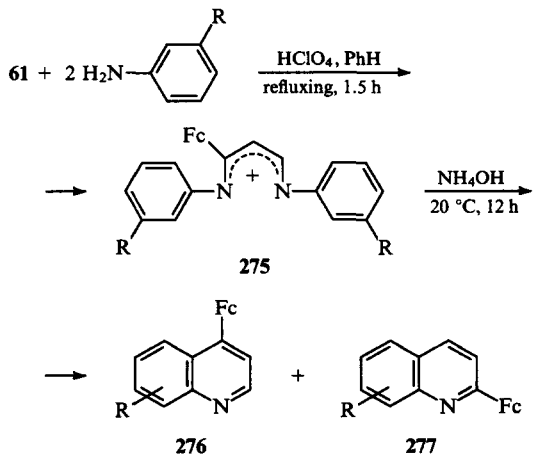
Benzenesulfonylbenzimidoyl chloride **106** adds to quinoline or isoquinoline with formation of the salts **271** or **272**, which alkylate ferrocene (refluxing in benzene for 2.5 h), affording compounds **273** or **274** in 42% or 51% yields respectively.[73]



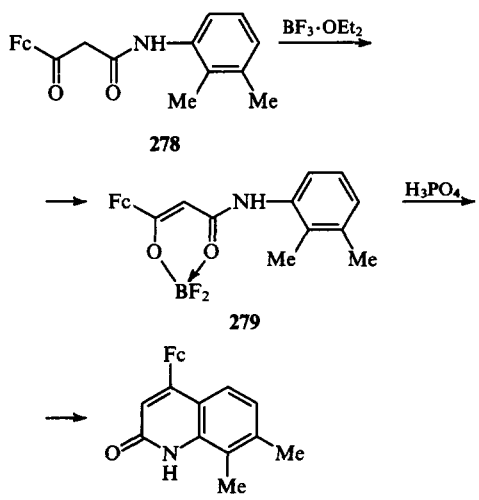


The aldehyde **61** reacts with two molecules of 3-hydroxy- or 3-methoxyaniline with formation of the salts **275**, the subsequent treatment of which with aqueous ammonia leads to cyclisation to the quinoline derivatives **276** and **277**.[146] ^{1}H NMR data revealed the regioselectivity of the cyclisation in favour of compound **277**. In the case of unsubstituted aniline, the reaction stops at the stage involving the formation of the salt **275** (R = H).

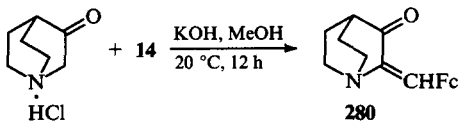
On treatment with boron trifluoride etherate, the amide **278** gives rise to the chelate **279**, which cyclises on heating with orthophosphoric acid and is converted into 4-ferrocenyl-7,8-dimethyl-2-quinolone.[158]



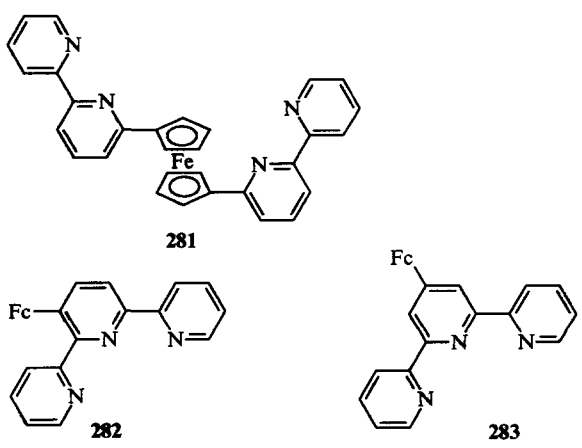
R = OH (15%), OMe (44%).



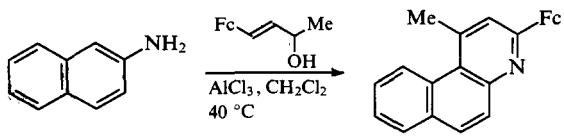
In the presence of alkali, the aldehyde **14** condenses with the hydrochloride of quinuclidin-3-one, which affords 2-ferrocenylmethylidenequinuclidin-3-one **280**.[159]



Methods for the synthesis of a series of ferrocene-containing derivatives of bipyridyl (compounds **281**) and terpyridyl (compounds **282** and **283**) have been developed based on the carbonyl derivatives of ferrocene.[160–162]

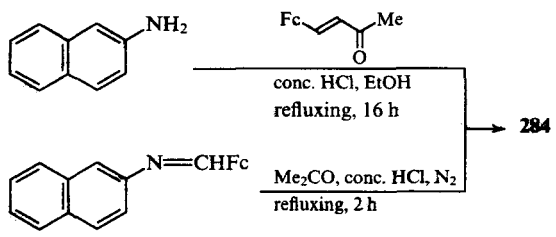


The method of synthesis of 2-ferrocenyl-4-methyl-5,6-benzoquinoline **284**, proposed in a patent,[163] involves the condensation of 4-ferrocenylbut-3-en-1-ol with β-naphthylamine in the presence of aluminium chloride.

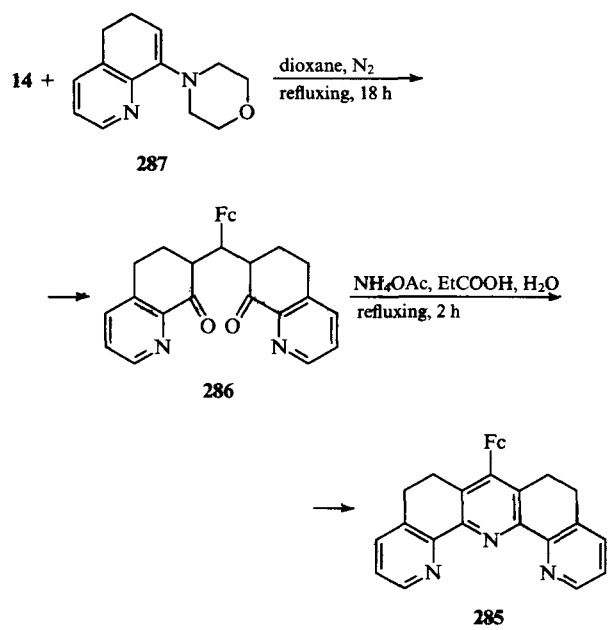


284

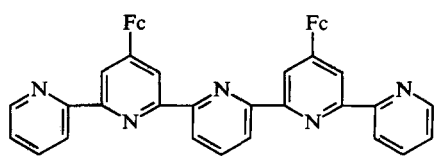
Two other methods of synthesis of compound **284** are based on the acid-catalysed condensation of carbonyl compounds with β-naphthylamine or *N*-ferrocenylmethylidene-β-naphthylamine.[164]



Compound **285**, in which condensed pyridine and cyclohexadienyl rings alternate, has been synthesised in 26% yield by treating with ammonium acetate the product **286** formed when the aldehyde **14** reacts with the enamine **287**.[165]

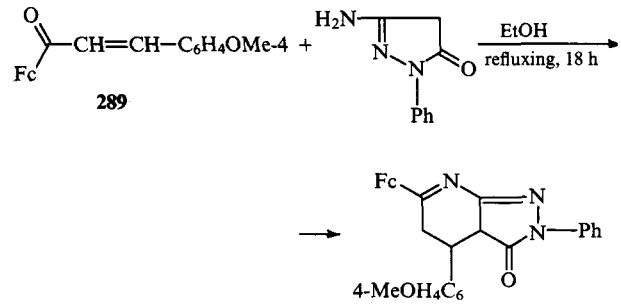


Compound **288**, containing two ferrocenyl groups and five pyridine rings, has been obtained by a two-stage synthesis from the aldehyde **14** and 2,6-diacetylpyridine.[166]



288

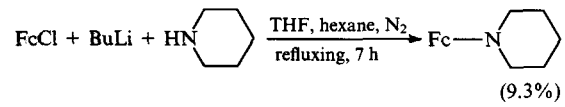
The pyridopyrazole derivative **290** is formed in 70% yield on refluxing the chalcone **289** with 3-amino-1-phenylpyrazol-5-one in ethanol.[167]



289

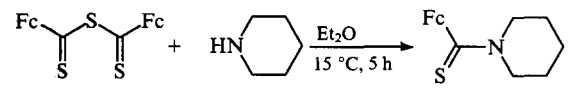
290

A single example of the synthesis of 1-ferrocenylpiperidine by the reaction of chloroferrocene with piperidine in the presence of butyllithium has been described.[168]



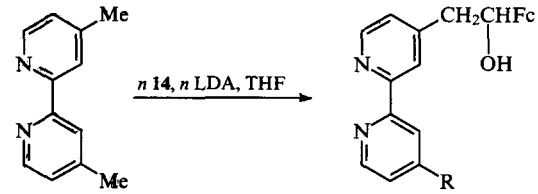
(9.3%)

Bis(ferrocenylcarbothionyl) sulfide thioacylates piperidine, affording *N*-(ferrocenylcarbothionyl)piperidine **291**.[169]



291 (83%)

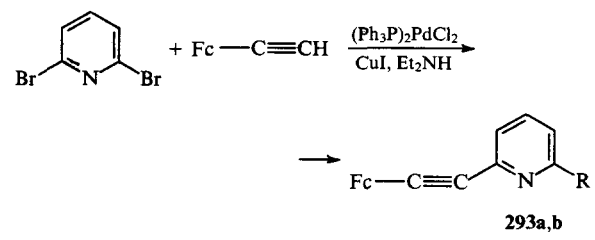
The mono- and di-lithio-derivatives of 4,4′-dimethyl-2,2′-bipyridyl, generated by treatment with LDA, add to the carbonyl group of compound **14**, which leads to the alcohol **292a** or the diol **292b**.[170]



292a,b

292a: n = 1, R = Me (77%);
292b: n = 2, R = $CH_2CH(OH)Fc$ (55%).

Bis(triphenylphosphine)palladium dichloride catalyses the nucleophilic substitution of the halogen atoms in 2,6-dibromopyridine on treatment with ferrocenylethyne in the presence of bases and copper(I) salts.[171] After reaction for 1.5 h, the monosubstitution product **293a** is formed in 78% yield. When the reaction is carried out over a period of 24 h, the disubstitution product **293b** is formed in 90.4% yield.

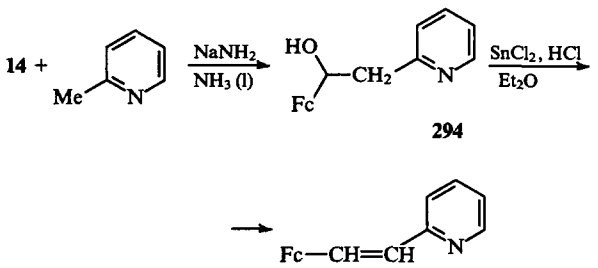


293a,b

R = Br (**a**), C≡C—Fc (**b**).

It was shown in the same investigation that both bromine atoms in 3,3′-dibromo-2,2′-bipyridyl are substituted by the FcC≡C group [the yield of 3,3′-bis(2-ferrocenylethynyl)-2,2′-bipyridyl was 89% after 48 h].

The condensation of the aldehyde **14** with 2-methylpyridine on treatment with sodium in liquid ammonia leads to the alcohol **294** in 57% yield.[83] It may be dehydrated to 2-(2-ferrocenylvinyl)pyridine **295** by treatment with tin(II) chloride.

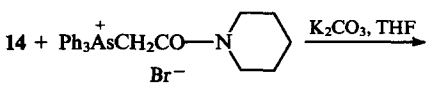


294

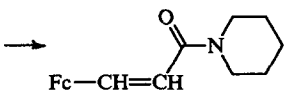
295 (90%)

When an excess of sodium amide[83] or sodium alkoxide in pyridine[84] is used, the alkene **295** is formed in 51% yield. 2-(2-Ferrocenylvinyl)quinoline has been obtained similarly (yield 94%).

The amide **297** has been synthesised by converting the aldehyde **14** into an alkene by treatment with the arsonium salt **296** in the presence of potassium carbonate in THF containing traces of water.[39]

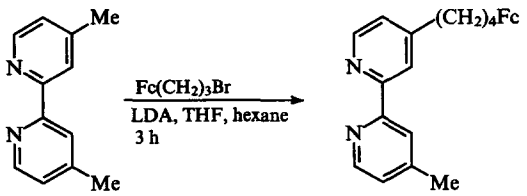


296



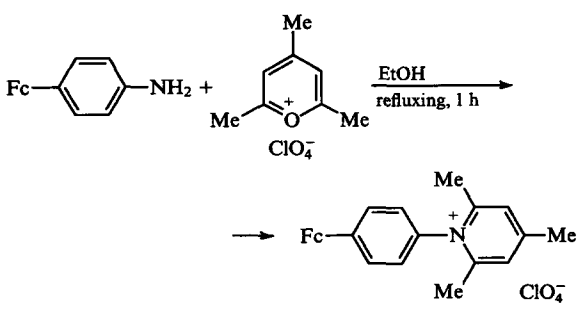
297

The alkylation of the lithio-derivative of 4,4'-dimethyl-2,2'-bipyridyl with 3-bromopropylferrocene affords compound **298**.[172]



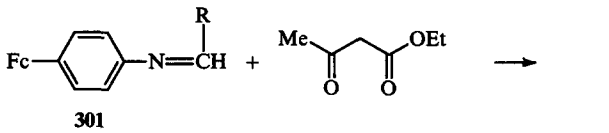
298 (37%)

N-(4-Ferrocenylphenyl)-2,4,6-trimethylpyridinium perchlorate **299** has been obtained in 65% yield as a result of the substitution of the oxygen atom in the heterocyclic nucleus of 2,4,6-trimethylpyrylium perchlorate on treatment with *p*-ferrocenylaniline.[155]

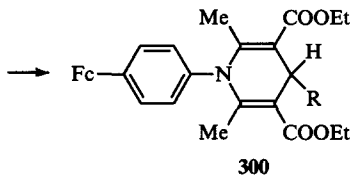


299

The 1,4-dihydropyridine derivative **300** is formed on cyclocondensation of the imines **301** with acetoacetic ester.[155]



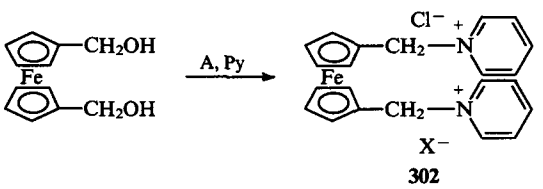
301



300

R = 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 4-HOC_6H_4, 4-$Me_2NC_6H_4$.

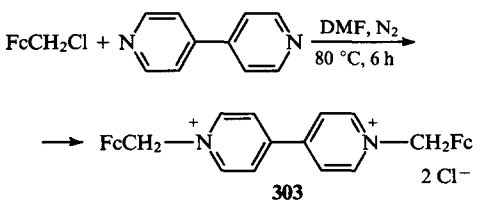
1,1'-Bis(hydroxymethyl)ferrocene is able to alkylate pyridine at the nitrogen atom on activation with toluene-*p*-sulfonyl chloride or thionyl chloride.[173] The mixed salt **302** (X = OTs) and a dichloro-derivative are formed in the first and second cases respectively.



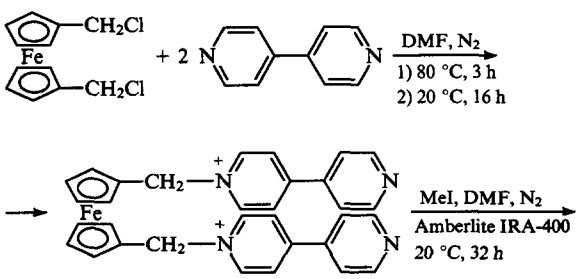
302

A = 4-$MeC_6H_4SO_2Cl$, X = $OSO_2C_6H_4Me$-4;
A = $SOCl_2$, X = Cl.

The synthesis of compounds with fragments of viologens (*N,N'*-dialkyl-4,4'-bipyridyls) linked covalently to photosensitive groups constitutes a complex task. The study[174] in which a method was described for the preparation of the viologen-metallocenes (ferrocenyl-containing viologens) **303** and **304**, capable of displacing hydrogen from water in the presence of catalysts, is therefore of significant interest.



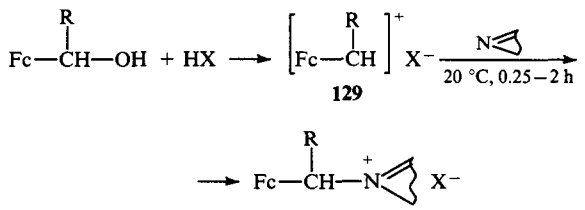
303



304

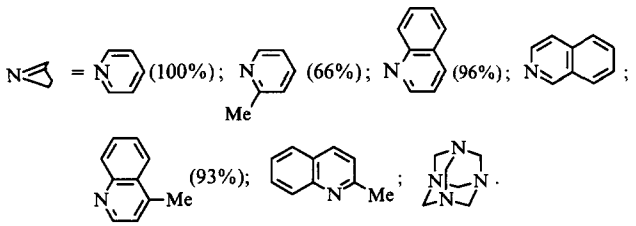
Boev and coworkers[42,45,143,144] investigated the reactions of hydroxymethylferrocene and 1-ferrocenylethanol with six-membered nitrogen heterocycles in the presence of HBF_4 or $HClO_4$.

It was found that the reaction proceeds via a stage involving the formation of the salts **129**, which attack the heterocyclic nucleophiles. This is confirmed by the finding that salts of the heterocycles with HX obtained beforehand do not react under the conditions investigated with the alcohols FcCH(R)OH.[144]

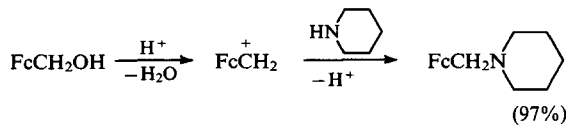


129

R = H, Me; X = BF_4, ClO_4;

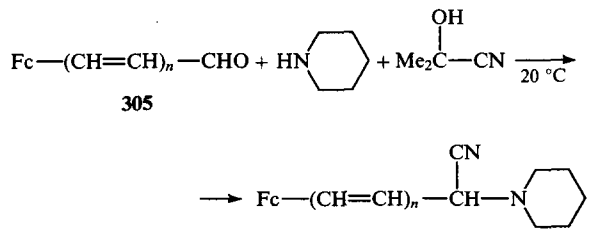


Piperidine is alkylated similarly by hydroxymethylferrocene in the presence of an acid.[175]



(97%)

The aminals formed from the aldehydes **305** and piperidine undergo transcondensation with acetone cyanohydrin, affording the aminonitriles **306**.[176]

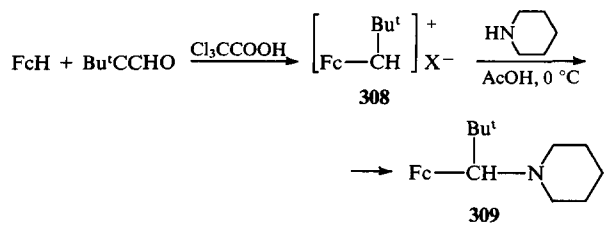


305

306: (95%, n = 0); (87%, n = 1).

When the aldehyde **14** or the ketone **23** interacts with phosphorous acid esters and piperidine, the α-aminophosphonates **307** are formed.[177] Of the two possible mechanisms (*A* and *B*, Scheme 3), the first is preferable since it has been shown[177] that piperidine does not displace phosphorous acid esters from specially prepared α-ferrocenyl-α-hydroxyalkylphosphonates (150–160 °C, 10–12 h).

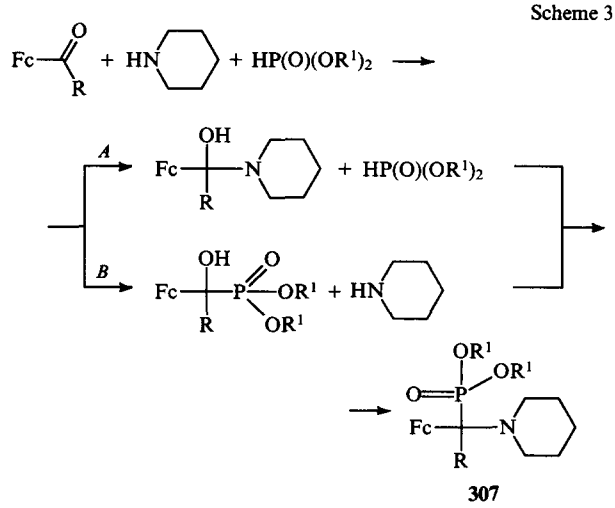
In the presence of trichloroacetic acid, electrophilic substitution in the ferrocene nucleus by treatment with



308

309

Scheme 3

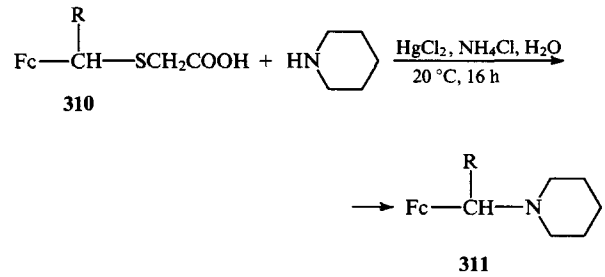


307

R	R^1	Yield (%)
H	Me	55
Me	Me	50
H	Et	76
Me	Et	56
H	Pr	80
Me	Pr	52
Me	Pr^i	43
Me	Bu	45
Me	Bu^i	45

trimethylacetaldehyde and subsequent protonation and dehydration lead to the salt **308**, which is converted into *N*-(1-ferrocenyl-2,2-dimethylpropyl)piperidine **309** in 68% yield on treatment with piperidine.[178]

The alkylation of piperidine by α-carbonium ion intermediates (generated from the sulfides **310** on treatment with mercury salts), leading to the amines **311**, takes place similarly.[179]

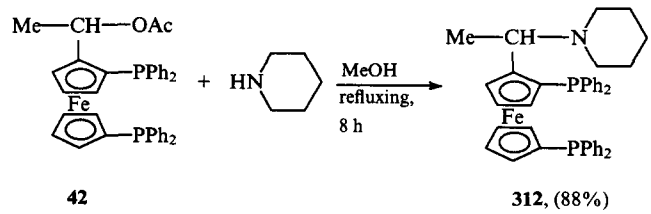


310

311

R = H (30%), Me (90%).

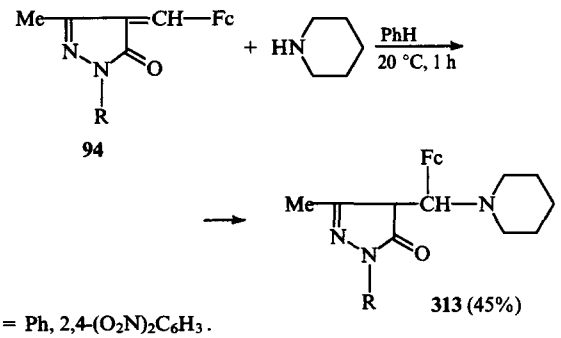
On refluxing in methanol, piperidine substitutes the acetoxy-group in compound **42**.[35]



42

312, (88%)

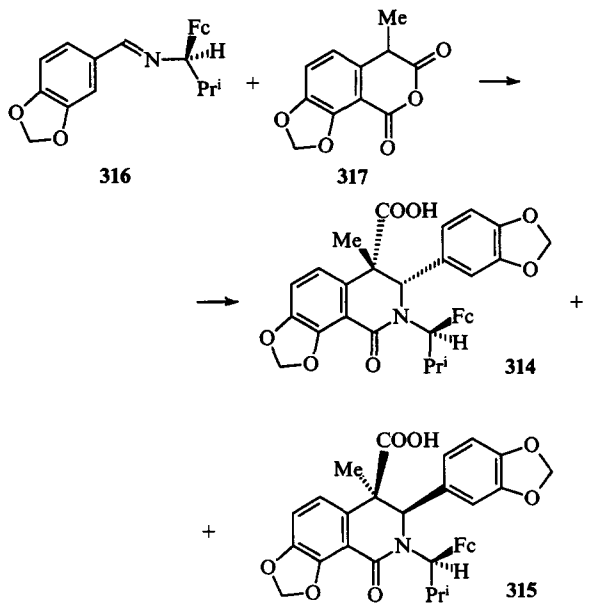
Another method for the introduction of the piperidinyl group into ferrocene derivatives involves the Michael addition of piperidine to the pyrazolones **94**, which leads to compound **313**.[69]



94 **313** (45%)

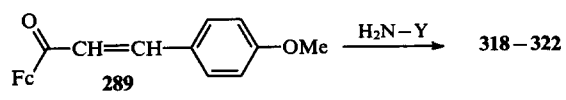
R = Ph, 2,4-$(O_2N)_2C_6H_3$.

A mixture of the two isomeric tetrahydroisoquinolinone derivatives **314** and **315** has been obtained (in 10% and 81% yields respectively) by refluxing the imine **316** and compound **317** in benzene for 82 h.[180]



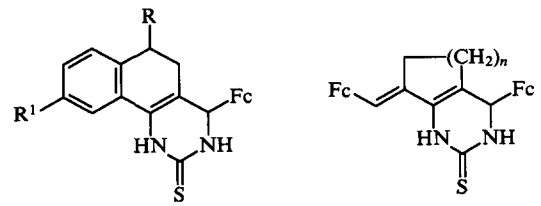
316 **317** **314** **315**

Indian investigators[167,181] made a detailed study of the reaction of 1-ferrocenoyl-2-(*p*-methoxyphenyl)ethene with primary heterocyclic amines and guanidine. The structures of the products and the yields of compounds **318**–**322** are presented in Table 2.



289 **318**–**322**

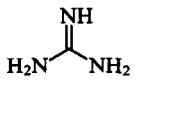
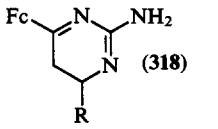
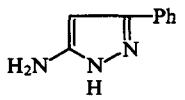
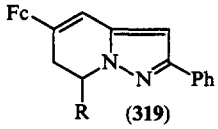
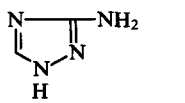
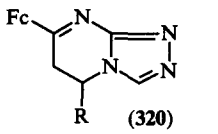
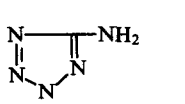
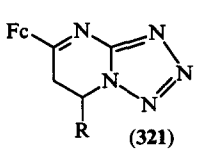
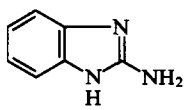
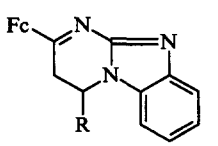
The derivatives of dihydropyrimidine-2-thione **323**–**326** have been synthesised by condensing α,β-unsaturated cyclic ferrocene-containing ketones with thiourea in the presence of alkali in ethanol.[182]



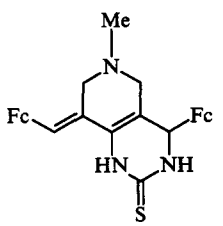
323a: R = R¹ = H (95%);
323b: R = H, R¹ = OMe (95%);
323c: R = OMe, R¹ = H (90%).

324, *n* = 1 (95%), 2 (75%).

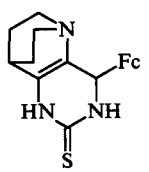
Table 2. The reactions of 1-ferrocenoyl-2-(*p*-methoxyphenyl)ethene with nitrogen-containing heterocyclic compounds and guanidine.

H_2N-Y	Product	Yield (%)	Ref.
	 **(318)**	50	167
	 **(319)**	51	181
	 **(320)**	65	167
	 **(321)**	56	181
	 **(322)**	75	167

Note. The reactions were carried out in boiling ethanol for 18–24 h. The group R in the reaction product is 4-$MeOC_6H_4$.

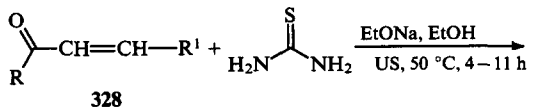


325 (76%)

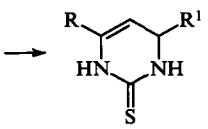


326 (65%)

A series of similar compounds (compounds **327**) have been synthesised from the ketones **328** and thiourea with irradiation by ultrasound (US).[183]



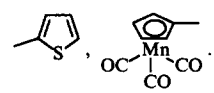
328



327 (58%–79%)

R = Fc: R¹ = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$(OCH_2O)C_6H_3$;
R = 4-$MeOC_6H_4$, R¹ = Fc.

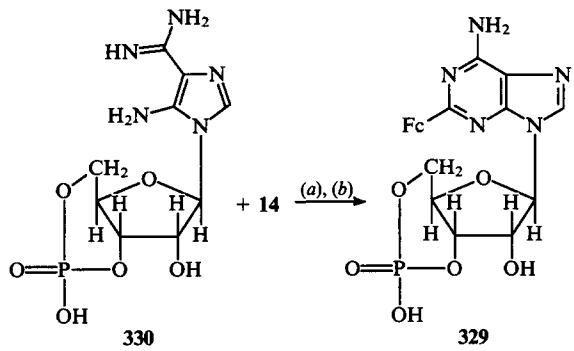
A wider range of the ketones **328** were later involved in this reaction[184,185] and conditions were found under which the products **327** are obtained in yields from 70% to 95%. Here

R = Fc, R^1 = 4-$Me_2NC_6H_4$;
R^1 = Fc, R = Ph, 4-FC_6H_4, 4-IC_6H_4, 

The synthesis of 5-ferrocenylmethylidenebarbituric acid (yield 94%) by condensing barbituric acid with the aldehyde **14** has been patented.[186]

The coupling of ferrocenylethyne with 5-chloromercurio-derivatives of uracil, cytosine, and adenine, as well as the corresponding nucleosides, which leads to compounds having the general formula FcC≡C–R, where R is a group derived from a heterocyclic base or a nucleoside, has been described.[187]

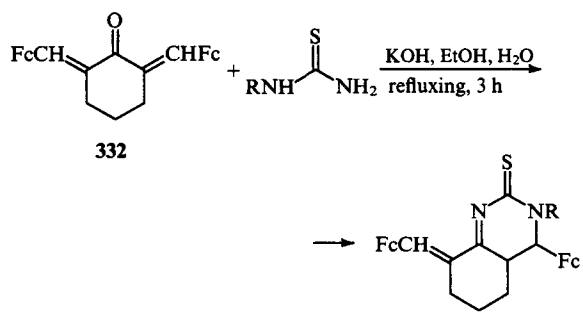
The adenosine derivative **329** has been obtained in 19% yield as a result of the condensation of the aldehyde **14** with compound **330** and subsequent aromatisation under the influence of palladium.[188,189]



330 **329**

a: NaOH, MeOH, 20 °C, 3 days; *b*: Pd/C, EtOH, H_2O, 80 °C.

The dihydropyrimidine–2-thione derivatives **331** are formed in 58%–79% yield on interaction of the ketone **332** with thiourea or phenylthiourea.[62]



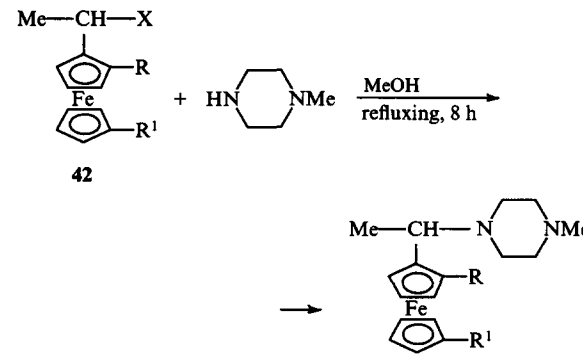
332 **331**

R = H, Ph .

High-molecular-mass compounds containing quinoxaline nuclei have been obtained by the polycondensation of 1,2,4,5-tetraaminobenzene or 3,4,3′,4′-tetraaminobiphenyl with 1,1′-bis-(glyoxalyl)ferrocene.

The chloride of ferrocenecarboxylic acid acylates piperazine or 1-(2-aminoethyl)piperazine (at 25 °C for 24 h) with formation of 1,4-bis(ferrocenoyl)piperazine or 1-(2-ferrocenoylaminoethyl)-4-ferrocenoylpiperazine.[190]

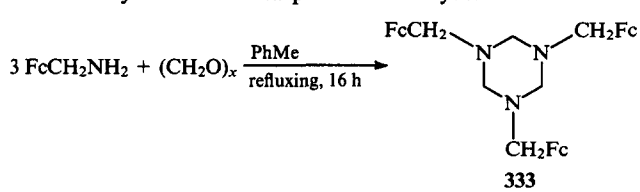
Ferrocene derivatives containing piperazine fragments have been synthesised by the nucleophilic substitution of the $N^+Me_3I^-$ or OAc groups in compound **42** on treatment with *N*-methylpiperazine.[35,36]



42

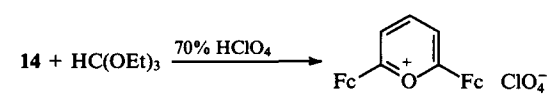
R	R^1	X	Ref.
$P(O)Ph_2$	H	$N^+Me_3I^-$	35
PPh_2	PPh_2	OAc	35, 36

1,3,5-Tris(ferrocenylmethyl)hexahydro-1,3,5-triazine **333** has been obtained in 85% yield by the cyclocondensation of aminomethylferrocene with paraformaldehyde.[191]



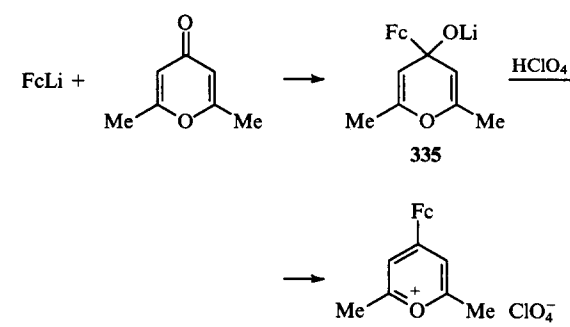
333

Two methods of synthesis of ferrocenylpyrylium salts have been patented.[148] 2,6-Diferrocenylpyrylium perchlorate **334** has been synthesised by the reaction of the aldehyde **14** with orthoformic ester in the presence of perchloric acid.



334 (82%)

4-Ferrocenyl-2,6-dimethylpyrylium perchlorate has been synthesised by another method—treatment of the lithio-derivative **335**, obtained from 2,6-dimethyl-4-pyrone and ferrocenyllithium, with perchloric acid.

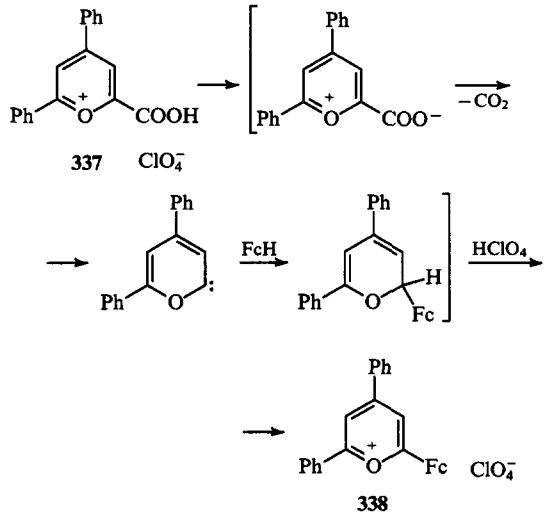


335

336 (48%)

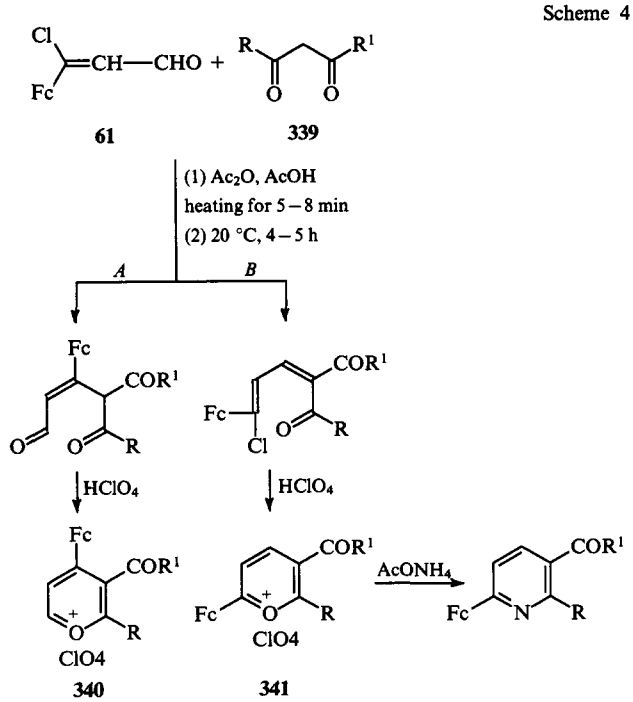
The thermal decarboxylation of the acid salt **337** in boiling acetic acid in the presence of ferrocene leads to the formation of the ferrocenylpyrylium salt **338** (yield 47%).[150] The authors postulate a mechanism involving the insertion of a carbene intermediate in the Fc–H bond.

The salt **338** has also been obtained as a result of the interaction of acetylferrocene with the chalcone PhCH=CH–COPh in the presence of perchloric acid.[150]



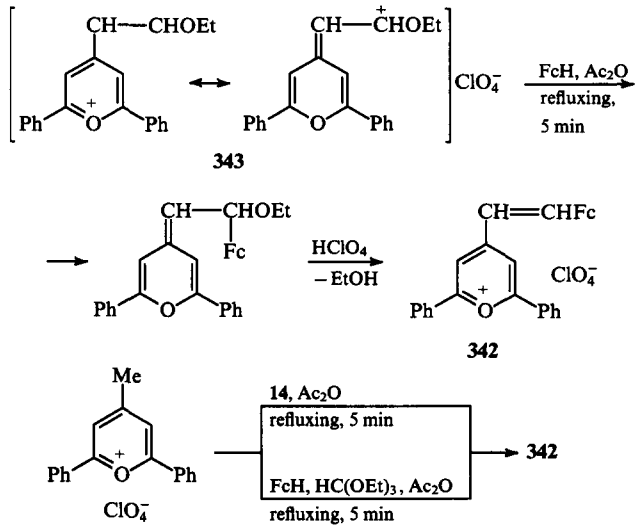
The interaction of the aldehyde **61** with the β-dicarbonyl compounds **339** on treatment with acetic anhydride in acetic acid can lead to various intermediates, which should be converted into the pyrylium salts **340** or **341** on treatment with perchloric acid (Scheme 4). It was found that treatment of the primary reaction product with ammonium acetate affords 3-acyl-6-ferrocenylpyrylium derivatives, which may be formed only from the salts **341**, demonstrating that the reaction proceeds via route *B*.[147]

Scheme 4



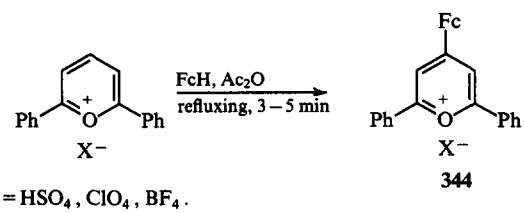
R	R¹	Yield (%)
Ph	Ph	100
Me	Me	100
Me	OEt	68
$-CH_2-CMe_2-CH_2-$		72

4-(2-Ferrocenylvinyl)-2,6-diphenylpyrylium **342** has been synthesised by three procedures:[149] by the reaction of the salt **343** with ferrocene (yield 55%), by the condensation of 4-methyl-2,6-diphenylpyrylium perchlorate with the aldehyde **14** (yield 88%), or by the condensation with ferrocene and orthoformic acid ester (yield 46%).

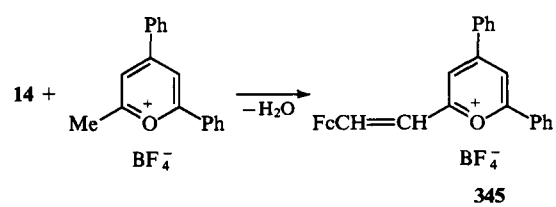


4-(2-Ferrocenylvinyl)-2,6-dimethylpyrylium perchlorate has been obtained by the last method from 2,4,6-trimethylpyrylium perchlorate (in 52% yield).[149]

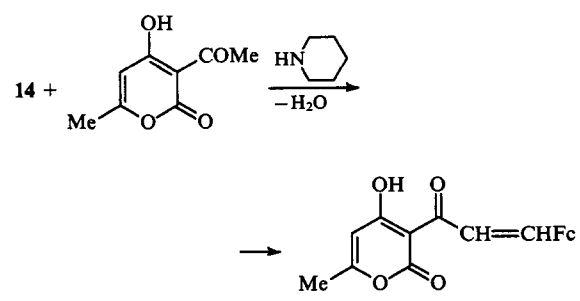
The 4-ferrocenylpyrylium salts **344** are formed in 81%–82% yields on refluxing the corresponding 2,6-diphenylpyrylium salts with ferrocene in acetic anhydride.[149]



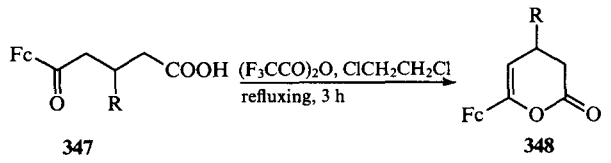
The methyl group in 2-methyl-4,6-diphenylpyrylium tetrafluoroborate exhibits an enhanced reactivity and condenses with the aldehyde **14** to form the derivative **345**.[192]



In the presence of piperidine, the aldehyde **14** reacts with 3-acetyl-4-hydroxy-6-methyl-2-pyrone, affording the vinyl ketone **346**.[193]



3-Aryl-5-ferrocenyl-5-oxovaleric acids **347** are dehydrated by trifluoroacetic anhydride and are converted into the dihydropyrone derivatives **348** in 92%–98% yields.[194]

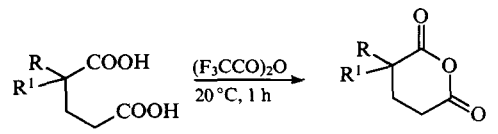


347 348

R = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$.

The cyclodehydration of 1-ferrocenylpentane-1,5-diol results in the formation of 2-ferrocenyltetrahydropyran.[96]

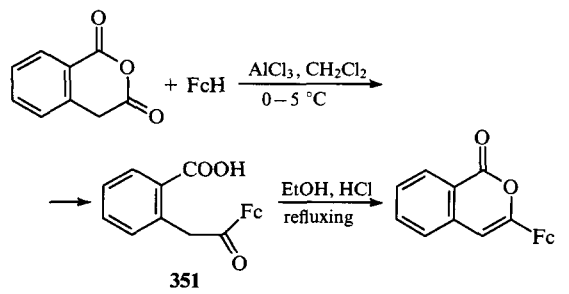
The dehydration of the glutaric acid derivatives **349** by treatment with trifluoroacetic anhydride in CH_2Cl_2[109] or dichloroethane[195] with formation of the derivative **350** has been described.



349 350

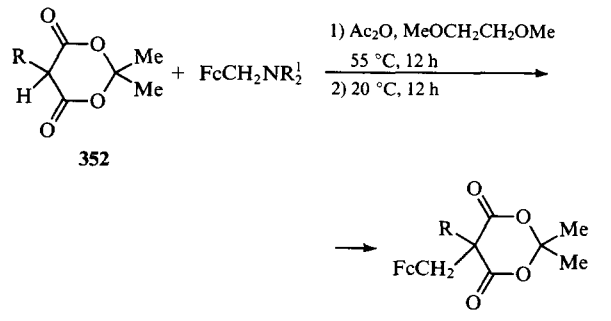
R	R^1	Yield (%)	Ref.
$FcCH_2$	H	70	109
FcCH=		98	196

The ketoacid **351**, obtained as a result of the acylation of ferrocene with homophthalic anhydride, is converted into 3-ferrocenylisocoumarin on refluxing with a solution of HCl in ethanol.[196]



351

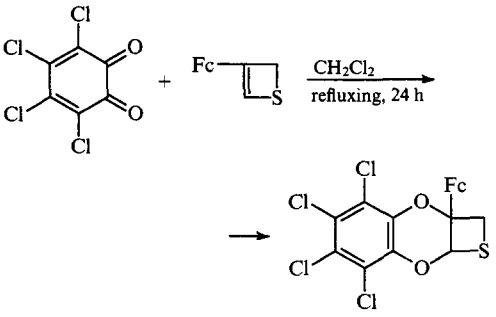
The substitution of a hydrogen atom in compounds **352** by the ferrocenylmethyl group has been achieved by treatment with dialkylaminomethylferrocene derivatives in the presence of acetic anhydride.[197]



352

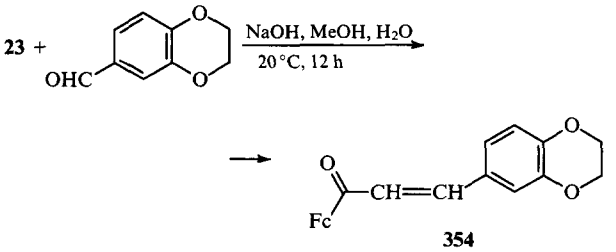
R = Me (70%), Et (66%), Ph (92%); R^1 = Me, Et.

The tricyclic compound **353**, containing a 1,4-dioxane fragment, has been synthesised by heating 3,4,5,6-tetrachloro-*o*-benzoquinone with 3-ferrocenylthiete.[198]



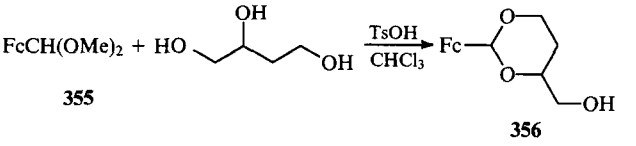
353 (59%)

The condensation of the ketone **23** with 6-formyl-1,4-benzodioxane leads to compound **354** in 54% yield.[112]



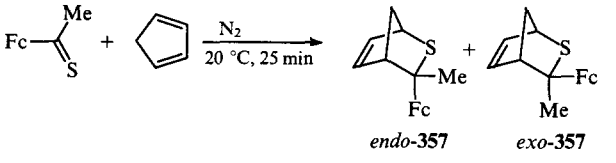
354

The acid-catalysed transesterification[199] of the acetal **355** leads to the 1,3-dioxane derivative **356**.



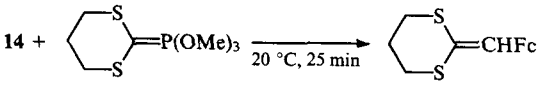
355 356

Thioacetylferrocene plays the role of the dienophile in relation to cyclopentadiene.[200] The adduct **357** is obtained even at room temperature in the form of a mixture of the *endo*- and *exo*-isomers.



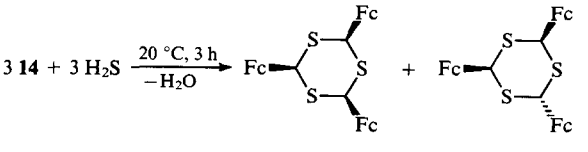
endo-357 *exo*-357

The reaction involving the conversion of the aldehyde **14** into an alkene by the ylide **358** afforded 2-ferrocenylmethylidene-1,3-dithiane **359** in 63% yield.[201]



358 359

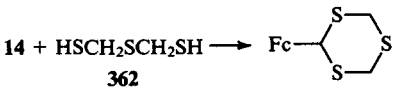
The preparation and certain properties of the isomeric *cis*- and *trans*-1,3,5-trithiacyclohexanes **360**, containing ferrocenyl substituents, have been described.[202]



cis-360 *trans*-360

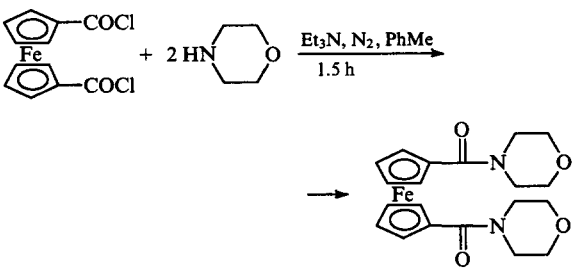
The ratio of the *cis*- and *trans*-isomers depends on the medium in which the reaction is carried out. The ratio is 5:1 in EtOH–HCl and 1:4 in concentrated HCl. When the reaction is carried out in concentrated HCl in the presence of $Na_2S_2O_3 \cdot 5H_2O$, mainly the *cis*-trithiane (yield 35%) and traces of the *trans*-isomer are formed.[202]

The synthesis of 2-ferrocenyl-1,3,5-trithiane **361** from the aldehyde **14** and bis(mercaptomethyl) sulfide **362** has been reported recently.[203]



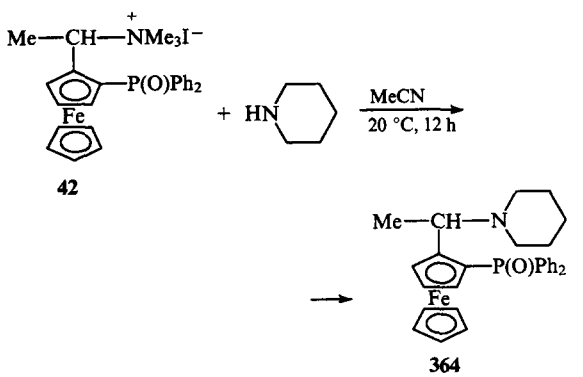
362 **361**

The *N*-acylation of morpholine by the chloride of ferrocene-1,1'-dicarboxylic acid affords the dimorpholide **363** (yield 83%).[204]



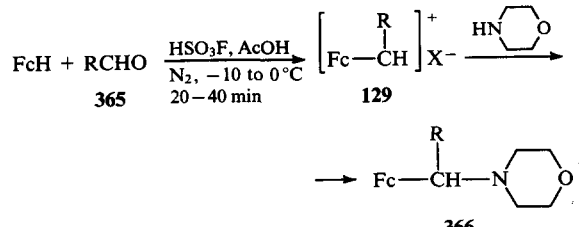
363

The quaternary ammonium salt **42** alkylates morpholine, whereupon the $N^+Me_3I^-$ group is substituted by the heterocyclic group. The product **364** is formed in 92% yield.[35]



42 **364**

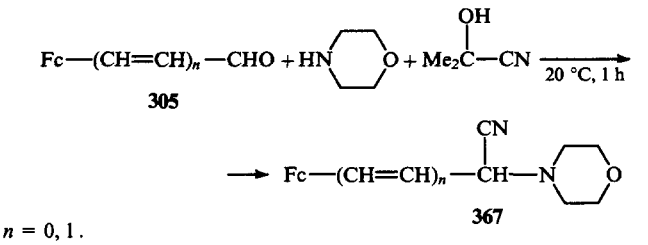
Electrophilic substitution in the ferrocene nucleus on treatment with the aldehydes **365** under superacid conditions leads to the salts **129** (formed as a result of the acid-catalysed dehydration of the intermediate carbinols), which are converted on treatment with morpholine into α-morpholino-derivatives of ferrocene **366**, with yields of 49% to 59%.[178]



365 **129** **366**

R = Pr^i, Bu^t.

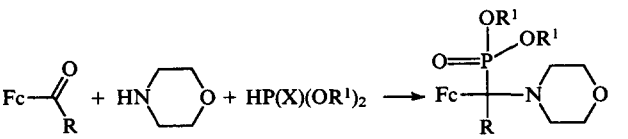
The aldehydes **305** react with acetone cyanohydrin and morpholine, which affords the aminonitriles **367** (yields 93%–96%).[176]



305 **367**

n = 0, 1.

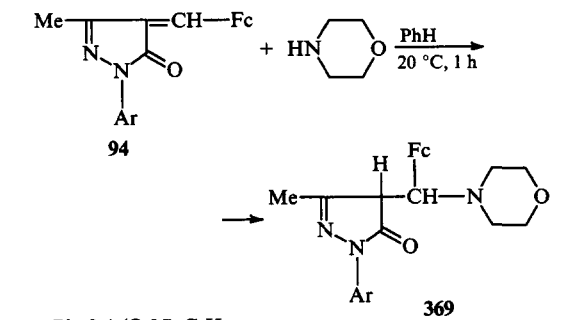
Compounds **368** have been synthesised by condensing carbonyl compounds of the ferrocene series with morpholine and phosphorous or phosphorothious acid esters.[177,205]



368

R	R^1	X	Yield (%)	Ref.
H	Et	S	60	205
H	Me	O	55	177
H	Et	O	81	177
Me	Et	O	33	177

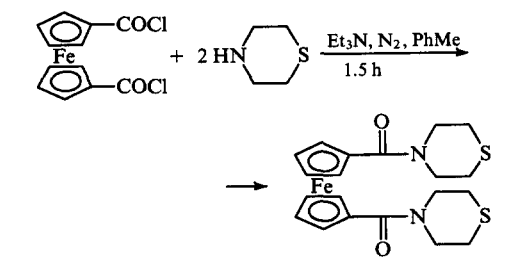
The addition of morpholine to the enones **94** leads to the pyrazolone derivatives **369** in 47%–57% yields.[69]



94 **369**

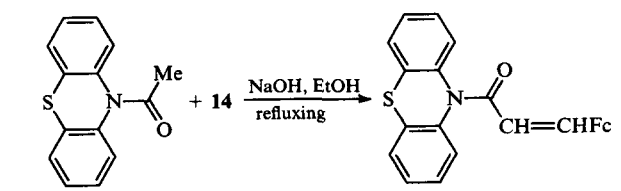
Ar = Ph, 2,4-$(O_2N)_2C_6H_3$.

The chloride of ferrocene-1,1'-dicarboxylic acid acylates thiomorpholine with formation of the product **370** (yield 85%).[204]



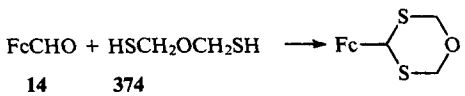
370

In the presence of alcoholic alkali, 10-acetylphenothiazine **371** condenses with the aldehyde **14**; the reaction product is the unsaturated amide **372**.[66]



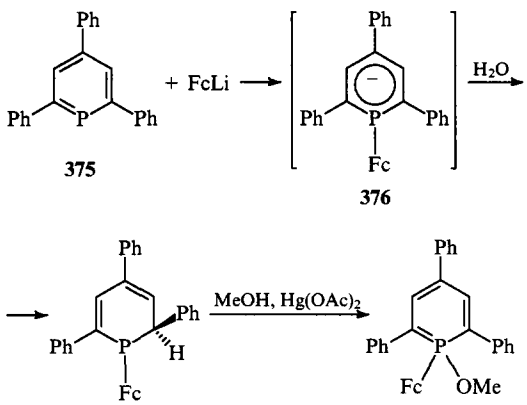
371 **372**

2-Ferrocenyl-1,3-dithia-5-oxacyclohexane **373** has been synthesised from FcCHO and di(mercapto)ether **374**.[203]



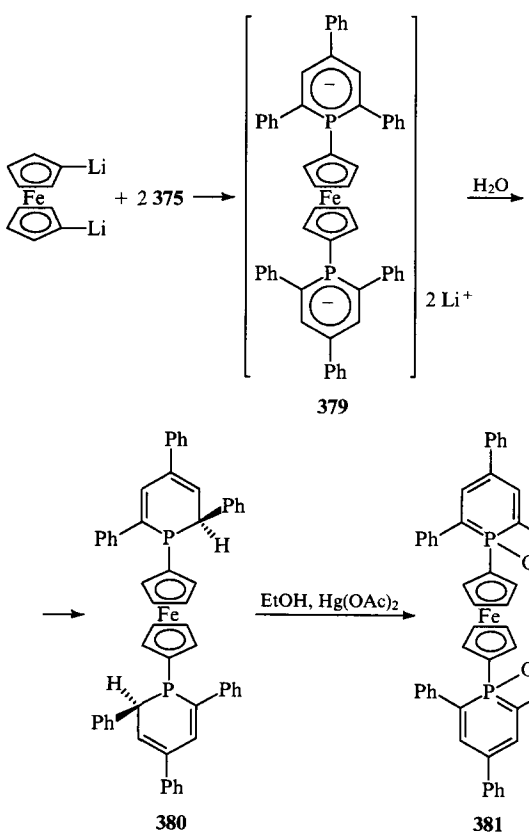
14 **374** **373**

On treatment with ferrocenyllithium, 2,4,6-triphenylphosphinine **375** gives rise to the anion **376**, which, on treatment with water, is converted into 1-ferrocenyl-2,4,6-triphenyl-1,2-dihydrophosphinine **377**. As a result of oxidative alkoxylation, the latter affords 1-ferrocenyl-1-methoxy-2,4,6-triphenylphosphinine **378**.[206]



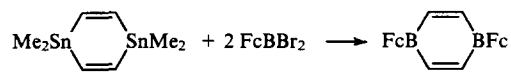
375 **376** **377** **378**

The interaction of the phosphorine **375** with 1,1'-dilithioferrocene takes place similarly.[206] The diphosphorylated ferrocene **379** is converted on treatment with water into the dihydrophosphinine **380**, which is converted into compound **381** after treatment with mercury acetate in ethanol.



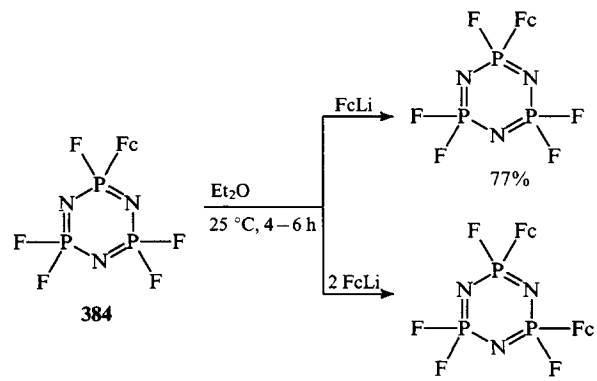
379 **380** **381**

The transmetallation of 1,1,4,4-tetramethyl-1,4-distannacyclohexa-2,5-diene **382** on treatment with dibromo(ferrocenyl)borane leads to 1,4-diferrocenyl-1,4-diboracyclohexa-2,5-diene **383**.[207]



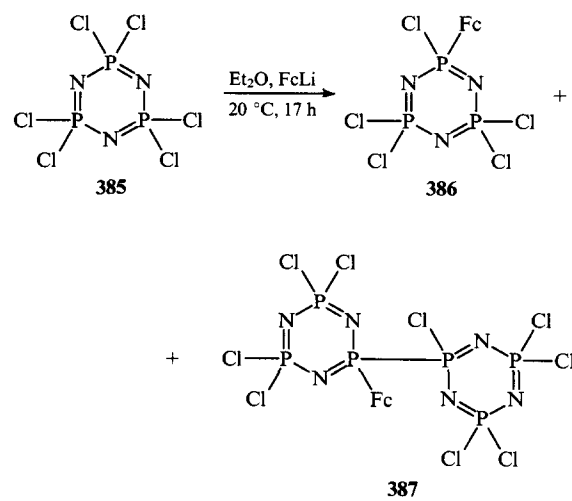
382 **383**

One[208] or two[209] fluorine atoms in 2,2,4,4,6,6-hexafluorocyclotriphosphazene **384** can be substituted by ferrocenyl groups on treatment with ferrocenyllithium.



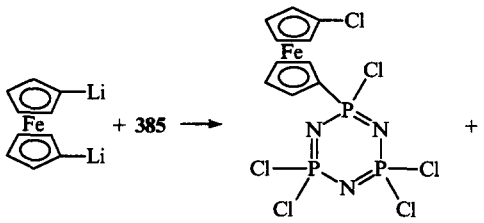
384 77%

Apart from the monosubstitution product **386** (yield 31%), compound **387** was obtained (yield 20%) in the reaction of ferrocenyllithium with 2,2,4,4,6,6-hexachlorocyclotriphosphazene **385**. Compound **387** is evidently formed as a result of the interaction of the product **386** with the initial cyclophosphazene **385**.[209]

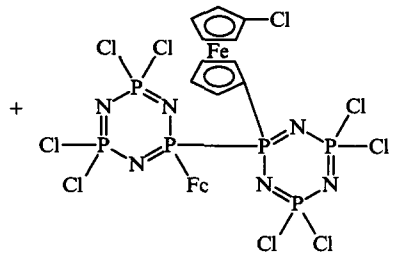


385 **386** **387**

The interaction of the hexachloro-derivative **385** with 1,1'-dilithioferrocene proceeds in a more complex manner: the reaction products **388** and **389** contain a heterocyclic substituent only in one of the ferrocene rings.[209]

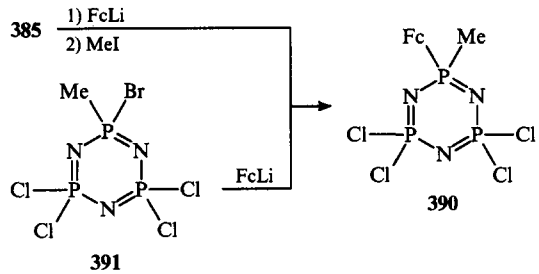


388, 11%



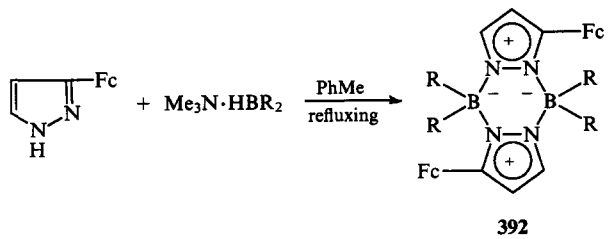
389 (40%)

Two methods of synthesis of 2,2,6,6-tetrachloro-4-ferrocenyl-4-methylcyclotriphosphazene **390** were described in the same investigation: by treatment with iodomethane of the product of the reaction of FcLi with the hexachloro-derivative **385** or by the reaction of 4-bromo-2,2,6,6-tetrachloro-4-methylcyclotriphosphazene **391** with FcLi.



391

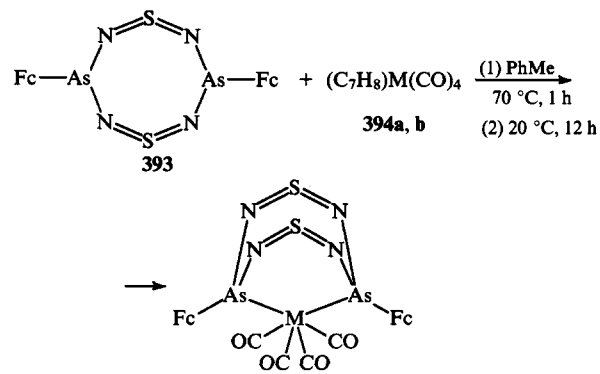
Interesting and unusual heterocyclic compounds—pyrazaboles **392**—have been synthesised by the reaction of 3-ferrocenylpyrazole with trimethylamine–borane or trimethylamine–diethylborane in boiling toluene.[57]



392

R	Reaction time/h	Yield (%)
H	1	—
Et	8	35

The interaction of diferrocenyldithiatetraazadiarsocine **393** with norbornadienechromium tetracarbonyl **394a** or norbornadienemolybdenum tetracarbonyl **394b** results in the formation of the complex tetracarbonyl(diferrocenyldithiatetraazadiarsocine)-chromium(0) **395a** and the corresponding molybdenum(0) complex **395b**.[15]



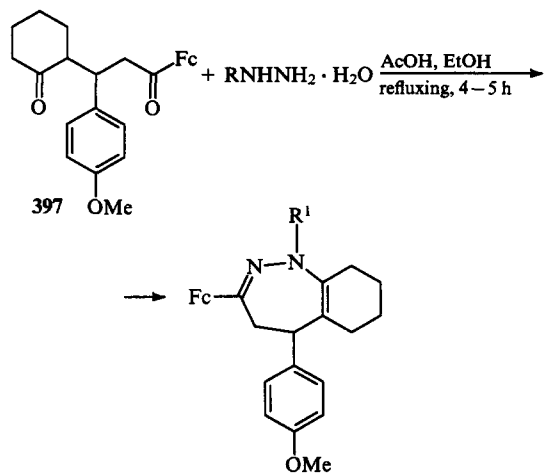
393

394a, b

395a: M = Cr (61%);
395b: M = Mo (57%).

VI. Compounds containing heterocycles with more than six atoms

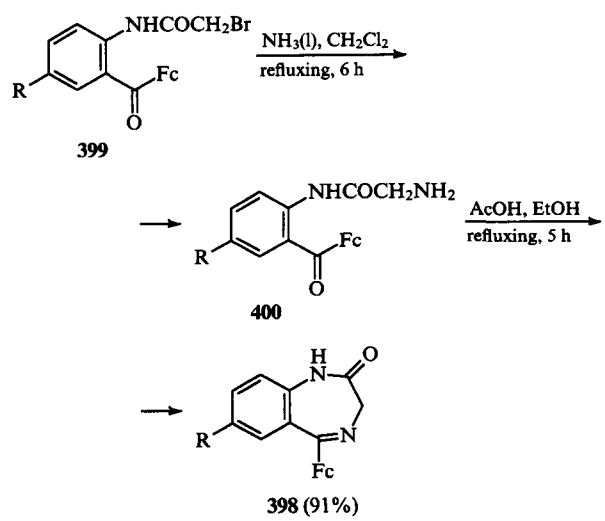
The synthesis of dihydro-1,2-diazepine derivatives **396a, b** from the diketone **397** on treatment with hydrazine or phenylhydrazine has been described.[181]



397

396a: R = H, R¹ = Ac (50%);
396b: R = R¹ = Ph (55%).

The 1,3-dihydrobenzo-1,4-diazepin-2-one derivatives **398** have been synthesised in two stages: by treating the ketoamides **399** with liquid ammonia and the subsequent cyclisation of the aminoketones **400** formed.[210]



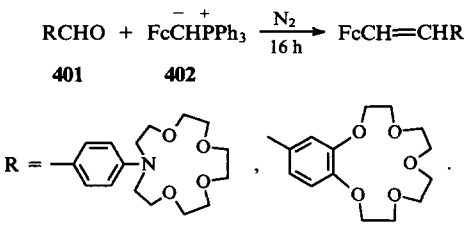
399

400

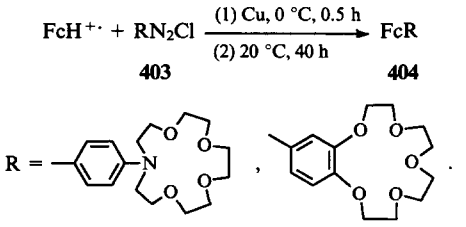
398 (91%)

R = H, I.

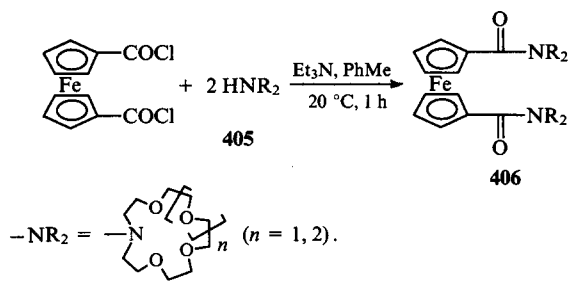
The Wittig insertion of the ferrocenylvinyl fragment into the crown-ether derivatives **401** has been achieved[211] by treatment with the ylide **402** under an inert atmosphere in the absence of light.



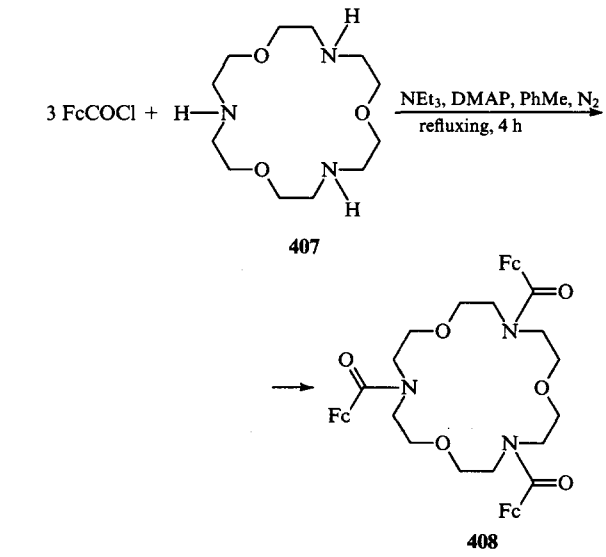
The crown-ethers **404**, containing a ferrocenyl substituent, have been synthesised (yields 25%–30%) by coupling the ferrocenium cation with the diazonium salts **403**.[212]



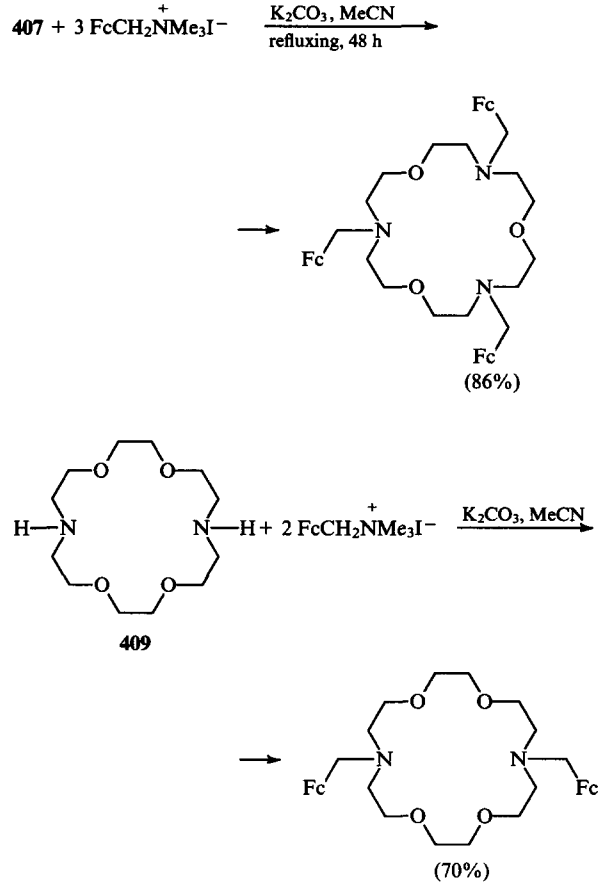
The ferrocene derivatives **406**, containing two crown-ether fragments in the molecule, are formed in 80%–85% yields as a result of the acylation of the aza-crown-ethers **405** by the dichloride of ferrocene-1,1′-dicarboxylic acid in the presence of triethylamine.[213]



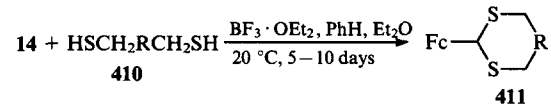
Three ferrocenoyl groups have been introduced into the triaza-crown-ether **407** by treatment with the ferrocenecarboxylic acid chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) (the yield of the product **408** was 85%).[214]



The aza-crown-ethers **407** and **409** are smoothly alkylated by ferrocenylmethyl(trimethyl)ammonium iodide, affording the corresponding ferrocenylmethyl-substituted macrocycles.[214]



The ferrocenyl-substituted crown-ethers **411**, containing oxygen and sulfur atoms in the ring, have been obtained from the aldehyde **14** by its conversion into an acetal with the aid of the bismercapto-derivatives **410** in the presence of Lewis acids.[203,215,216]

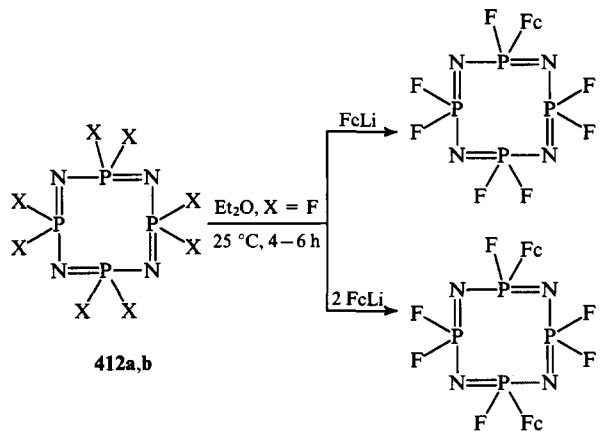


R	Yield (%)
$OCH_2CH_2SCH_2CH_2O$	—
CH_2OCH_2	84
$CH_2OCH_2CH_2OCH_2$	72
$CH_2O(CH_2CH_2O)_2CH_2$	92
$CH_2O(CH_2CH_2O)_3CH_2$	62
$CH_2O(CH_2CH_2O)_4CH_2$	64
CH_2SCH_2	31
$CH_2OCH_2CH_2SCH_2CH_2OCH_2$	78
$CH(OH)CH(OH)(CH_2)_2$	—
CH_2SCH_2	—

The reaction of 2,2,4,4,6,6,8,8-octafluorocyclotetraphosphazene **412a** with ferrocenyllithium results in the formation of the products of the substitution of one or two fluorine atoms by the Fc groups (Scheme 5).[208,209]

Treatment of a mixture of hexachlorocyclotriphosphazene **385** and octachlorocyclotetraphosphazene **412b** with ferrocenyllithium leads to the formation of compounds **413**, containing cyclotriphosphazene and cyclotetraphosphazene fragments in the molecule.[217]

Scheme 5

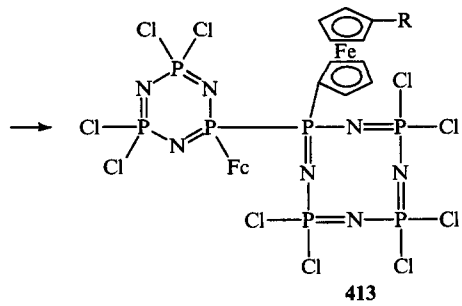


412a,b

X = F (a), Cl (b)

(57%)

385 + 412b + FcLi ⟶



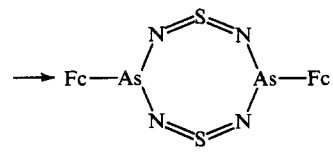
413

R = H, Cl.

Diferrocenyldithiatetraazadiarsocine **414** has been synthesised in 73% yield from dichloro(ferrocenyl)arsine and compound **415**.[15]

$$2\ FcAsCl_2 + 2\ Me_3SiNSNSiMe_3 \xrightarrow[20\ °C,\ 14\ h]{Et_2O}$$

415



414

VII. Biological activities and applications of heterylferrocenes

It has been found that many heterylferrocenes exhibit a biological activity. Thus ferrocenyl-containing derivatives of 6-aminopenicillanic or 7-aminocephalosporanic acids have been recommended as effective antibiotics and inhibitors of β-lactamase.[218,219] The tetrafluoroborates and perchlorates of benzothiazolium derivatives inhibits the growth of staphylococci and streptococci as well as the yeast fungi of the genus *Candida*.[143] Derivatives of ferrocene-containing fragments of the diethyl esters of phosphonic and phosphonothioic acids and morpholine[177] or 1,3,4-triazole[205] as well as thiophene and 1,3-thiazolidin-2-one rings[139] in the molecule exhibit an antimicrobial activity against both Gram-positive and Gram-negative microorganisms.

3-Ferrocenyl-1-(2-furyl)cyclopent-1-ene has been patented as an agent counteracting the anaemia induced by iron deficiency in the organism.[106] The product of the condensation of 2,4,6-trichloro-1,3,5-triazine with the disodium salt of ferrocene-1,1'-dicarboxylic acid is active against a series of bacteria.[220]

The nonsilver photosensitive compositions and materials frequently include charge-transfer complexes (CTC). It has been stated that CTC based on the copolymer of vinylferrocene with *N*-vinylcarbazole and 2,4,7-trinitrofluorenone[221] as well as the copolymer based on 4-cyano(or phenyl)-3-ferrocenylisoxazolines and CBr_4 have been synthesised.[131,222] The products of the condensation of FcCHO with benzothiazole derivatives or with 1,3-diazolidine-2,4-dione have been recommended as components of nonsilver photosensitive compositions.[192] Compounds containing the FcCH=CH groups and 1,3,4-oxadiazole rings may be used as electrophotographic materials.[137] Derivatives of 2,3-bis(2-ferrocenylvinyl)quinoxaline are electrophotographic semiconductors and are used in compositions for the preparation of effective and long-lived printing plates, which make it possible to obtain many thousands of impressions.[223]

2-Ferrocenyl-1,4-dimethyl-5,6-benzoquinolinium iodide is a dye for polyamide and polyester fibres.[164] Derivatives of ferrocene-containing quinoline and pyrazoline rings have been recommended as cyanine dye-sensitisers.[17,69,70] Ferrocenyl-containing cyanine dyes with an indole ring fragment in the molecule have been described.[48]

Heterylferrocenes are used as modifying agents which improve the operational characteristics of rocket fuels and explosive compositions. *N*-Ferrocenylmethylpyrrolidine has been used as an additive improving the ballistic and mechanical characteristics of rocket fuels.[31,32] 1,4-Bis(*N*-ferrocenoyl)piperazine and analogous compounds,[190] 2-ferrocenyltetrahydrofuran,[224] and 2-ferrocenoyl-1-isopropenylcarbaborane[225] may be used to regulate the rate of combustion of rocket fuels based on NH_4ClO_4. 2-Ferrocenyl-2-(hydroxypropyl)tetrahydrofuran has been proposed as a catalyst for the combustion of rocket fuel.[102] 2-Ferrocenyltetrahydrofuran increases the rate of combustion of rocket fuel and its efficiency.[226] 5-Ferrocenylmethylenebarbituric acid is a catalyst of the combustion of explosive compositions based on nitramines.[186]

Crown-ethers containing a ferrocenyl group are interesting as regards practical use.[212,213,216]

The polymers obtained by condensing furfural with ferrocene in the presence of $AlCl_3$ have been proposed as thermostable and radiation-resistant coatings, adhesives, and insulators.[228] 6-(2-Ferrocenylvinyl)-2,4-diphenylpyrylium tetrafluoroborate has been patented as a dye-hardening agent for gelatin in photographic compositions.[192] The polymer formed on heating ferrocenyldihydrobenzofuranone in the presence of $ZnCl_2$ or $AlCl_3$ exhibits an effective thermal stability and may be used in many fields: as a coating, as an adhesive, as an insulator, as an ion-exchange resin, as a combustion catalyst, as films resistant to irradiation, and as an inhibitor of the ageing of silicone rubbers and other elastomers.[228]

Isoxazoline derivatives containing ferrocenylalkyl groups in the 3-position exhibit pesticidal, herbicidal, acaricidal, and fungicidal activities and are plant growth regulators.[131] It has been reported[229] that the 4,5-diphenyloxazole derivative containing the NHN=CHFc group in the 2-position may be used to combat plant viruses.

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