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Synthesis of *C*-vinylpyrroles

L N Sobenina, A P Demenev, A I Mikhaleva, B A Trofimov

Contents

I.	Introduction	563
II.	Synthesis of *C*-vinylpyrroles from acylpyrroles	563
III.	Synthesis of *C*-vinylpyrroles from functionalised aliphatic compounds	576
IV.	Addition of pyrroles to acetylenes	580
V.	Substitution reactions at the double bond	582
VI.	Other procedures for the introduction of the vinyl group into the pyrrole ring	584
VII.	Conclusion	588

Abstract. The latest advances in the synthesis of *C*-vinylpyrroles are generalised and systematised. Methods for the synthesis based on reactions of acylpyrroles and dicarbonyl compounds or their synthetic equivalents are still of most importance. New promising methods for the synthesis of *C*-vinylpyrroles are considered, among them the reactions of alkenyl ketone oximes with acetylene in the KOH – DMSO system and base-catalysed condensation of pyrrolecarbodithioates, which have recently become available, with CH-acids. The bibliography includes 195 references.

I. Introduction

The chemistry of pyrroles attracts continuing interest because of the enormous biological potential of these compounds and the possibility of their use in the design of new pharmaceuticals as well as of electro- and photoconducting materials. Functionalised vinylpyrroles occupy a special place as promising intermediates in the synthesis of new heterocyclic compounds,[1–4] valuable monomers[5–8] and also as ligands for new photocatalysts and biologically active complexes.[9]

Fragments of 2-vinylpyrroles are involved in life-supporting systems, such as porphyrins, vitamin B_{12}, bile pigments, chlorins, florins, oxoflorins, biliverdins and stercobilins. 3-Vinylpyrrole structures are present in haemoglobin and myoglobin, which are responsible for oxygen transport from the lungs to tissue cells of organisms and for oxygen storage, respectively, and also in chlorophyll which is responsible for photosynthesis. *C*-Vinylpyrroles bearing functional groups at the double bond (or deprived of these groups) serve as reactive intermediates for the directed synthesis of conjugated and fused heterocyclic compounds simulating natural pyrrole ensembles. This generates continuing interest in the development of new procedures for their synthesis and gives impetus to the examination of the reactivities and biological activities of *C*-vinylpyrroles.

1-Vinylpyrroles have been studied extensively and comprehensively in the last three decades. These compounds have become readily accessible owing to the discovery and development of a simple procedure for their synthesis from ketoximes and acetylene in the MOH – DMSO system, where M = Li, Na or K (Trofimov's reaction[10–16]). The data on the synthesis, structures, reactivities and biological activities of 1-vinylpyrroles were exhaustively surveyed in monographs[11,13] and reviews.[16–27]

Since the publication of the latest monographs[16,28,29] covering different aspects of the structures, reactivities and synthesis of *C*-vinylpyrroles, a substantial body of literature has evolved, which called for systematisation, analysis and generalisation of the new data.

The present review is devoted to procedures for the synthesis of *C*-vinylpyrroles, including those containing different functional substituents both in the vinyl group and pyrrole ring, and surveys the data, which were published in the last decade and were not covered in monographs and reviews.

Procedures for the synthesis of *C*-vinylpyrroles can be classified into several main categories: (1) syntheses based on acylpyrroles; (2) syntheses starting from functionalised aliphatic compounds; (3) addition of pyrroles to compounds with an activated triple bond (C-vinylation); (4) substitution at a double bond.

II. Synthesis of *C*-vinylpyrroles from acylpyrroles

Presently, 2- and 3-acylpyrroles (primarily, formylpyrroles) are the most commonly used starting compounds in the synthesis of *C*-vinylpyrroles.

1. Condensation of formylpyrroles with CH-acids

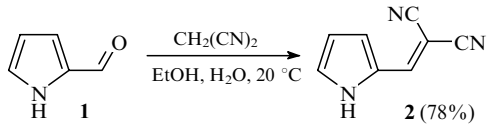
The ability of 2- and 3-formylpyrroles to be readily involved in condensation with different CH-acids is widely used in the synthesis of *C*-vinylpyrroles.

a. Condensation with malononitrile

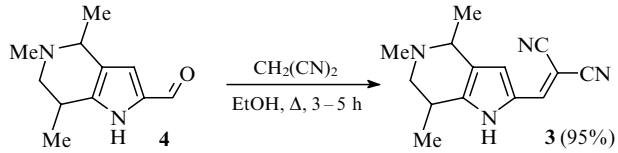
2-(2,2-Dicyanovinyl)pyrrole (**2**) was prepared from 2-formylpyrrole (**1**) and malononitrile in the presence of glycine.[30]

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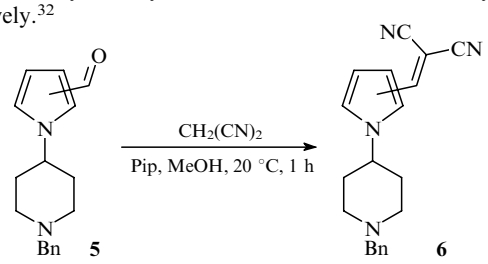
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Uspekhi Khimii **71** (7) 641 – 671 (2002); translated by T N Safonova



Tetrahydropyrollopyridine **3** was synthesised by refluxing 2-formyl derivative **4** with malononitrile.[31]

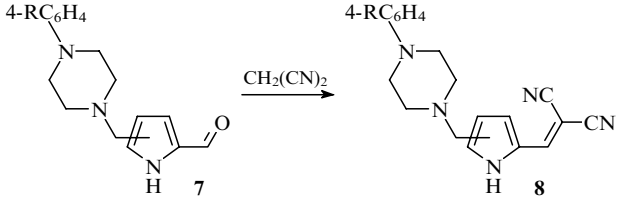


The reactions of 2- and 3-formylpyrroles **5** with malononitrile in the piperidine – methanol system afforded the corresponding 2- and 3-dicyanovinyl derivatives **6** in 87% and 75% yields, respectively.[32]



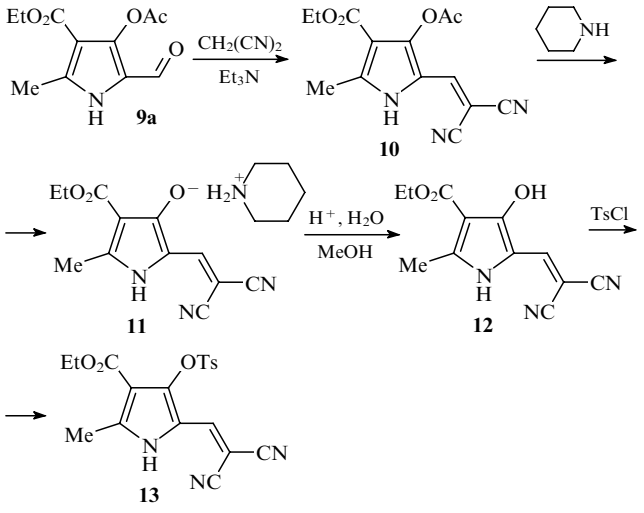
Pip is piperidine.

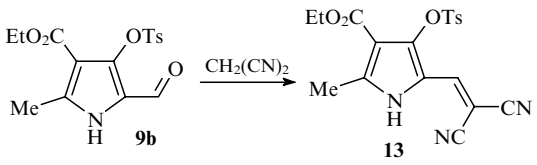
Under analogous conditions, 3-, 4- and 5-(piperazinylmethyl)-2-formylpyrroles **7** reacted with malononitrile to form the corresponding 2-(dicyanovinyl)pyrroles **8** in 49% – 90% yields.[33]



R = H, Cl.

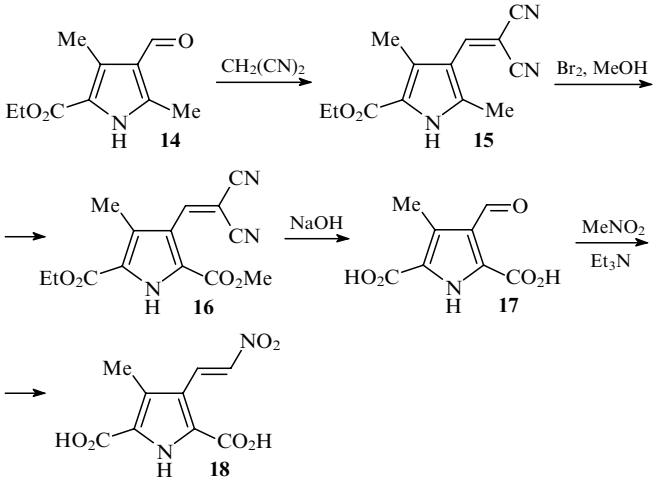
Condensation of 4-acetoxy-3-ethoxycarbonyl-5-formyl-2-methylpyrrole (**9a**) with malononitrile in the presence of triethylamine gave rise to derivative **10** in high yield,[34] and subsequent heating of the latter with piperidine led to elimination of the acetyl group to form the stable piperidinium salt of 4-hydroxypyrrole **11**. Subsequent acidification of the salt **11** produced 5-(2,2-dicyanovinyl)-3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole (**12**). Tosyl derivative **13** was generated both in the reaction of the pyrrole **12**



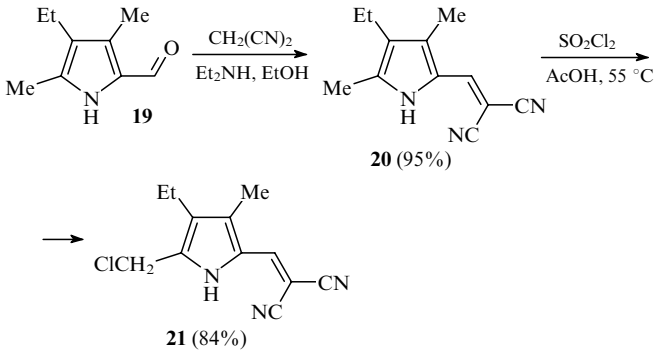


with *p*-toluenesulfonyl chloride and upon condensation of tosyloxy aldehyde **9b** with malononitrile.[34]

The reactions of formylpyrroles with malononitrile or cyanoacetic ester yielding the corresponding vinylpyrroles are often used for protection of the aldehyde function in the synthesis of porphyrins. The aldehyde group is readily regenerated upon treatment of these pyrroles with alkali. Thus Woodward *et al.*[35] performed the synthesis of chlorophyll starting from 2,4-di(ethoxycarbonyl)-3,5-dimethylpyrrole (Knorr pyrrole) through condensation of 4-formyl-substituted pyrrole **14** with malononitrile, oxidation of the methyl group in compound **15** to the corresponding methyl ester **16** and hydrolysis, which resulted in regeneration of the aldehyde group to give pyrrole **17**. The latter was transformed into 4-(2-nitrovinyl)pyrrole **18** upon refluxing with nitromethane in the presence of triethylamine. The pyrrole **18** was used as the starting compound in the synthesis of chlorophyll.



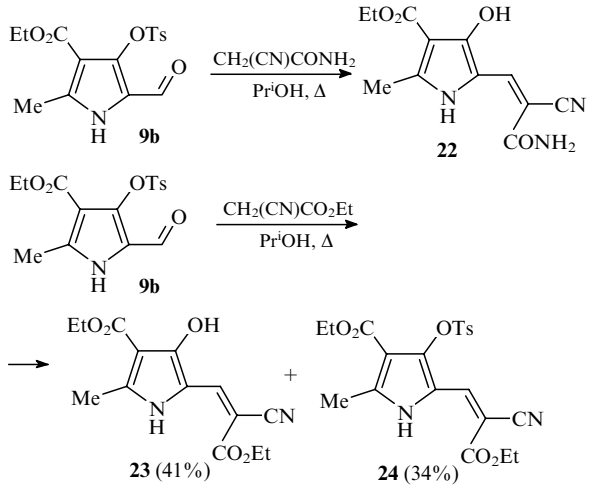
Analogously, the reaction of substituted 2-formylpyrrole **19** with malononitrile yielded 2-(2,2-dicyanovinyl)-4-ethyl-3,5-dimethylpyrrole (**20**) whose treatment with sulfuryl chloride afforded 5-chloromethyl-2-(2,2-dicyanovinyl)-4-ethyl-3-methylpyrrole (**21**).[35]



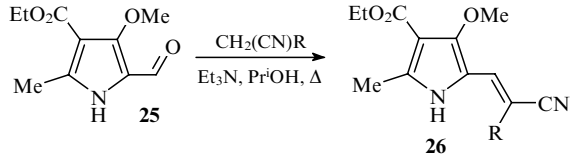
b. Condensation with alkoxycarbonyl- and amidomalononitriles

Condensation of the tosyloxy aldehyde **9b** with ethyl cyanoacetate and cyanoacetamide proceeded upon refluxing in isopropyl alcohol in the presence of piperidine. Water that was liberated hydrolysed the sulfonate group either partially or completely. The reaction with cyanoacetamide afforded 5-(2-carbamoyl-2-cyanovinyl)-4-hydroxypyrrole **22**, whereas the reaction of ethyl cyanoacetate gave rise to 5-(2-cyano-2-ethoxycarbonylvinyl)-3-

ethoxycarbonyl-4-hydroxy-2-methylpyrrole (**23**) along with compound **24** containing the *p*-toluenesulfonate group.[36]



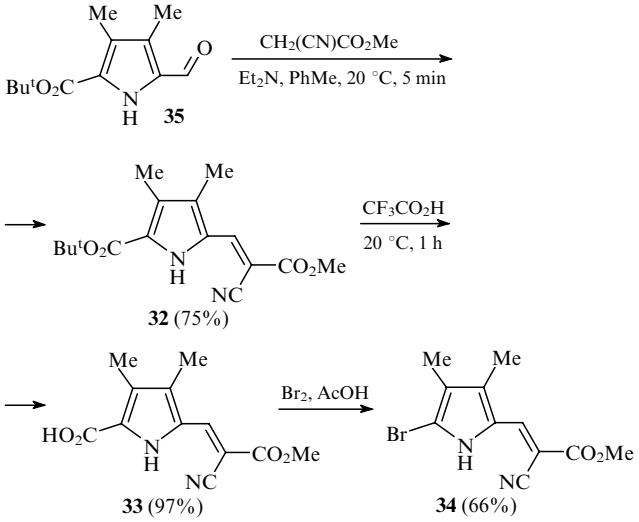
The reaction of 5-formyl-substituted pyrrole **25** with cyanoacetamide or ethyl cyanoacetate produced the corresponding 5-vinylpyrroles **26**.[37]



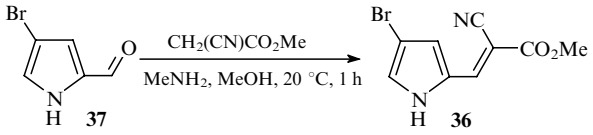
R = $CONH_2$, CO_2Et.

Condensation of aldehyde **27** with ethyl cyanoacetate was used for protection of the aldehyde group of pyrrole in the synthesis of the acetylene- and cumulene-containing porphyrinoid **28**.[38] Scheme 1 was employed for the preparation of functionalised vinylpyrroles **29**–**31**. Thus the 5-vinylpyrrole **29** generated in the first step was successively transformed into pyrrolecarboxylic acid **30** and then to iodopyrrole **31**, which gave 3,4-diethyl-2-formyl-5-iodopyrrole upon refluxing in methanol with NaOH. Subsequent cross-coupling and cyclisation afforded the porphyrinoid **28**.[38]

Functionalised vinylpyrroles **32**–**34** were prepared by treatment of 2-*tert*-butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (**35**) with methyl cyanoacetate. Hydrolysis of the ester group in the resulting vinylpyrrole **32** under the action of trifluoroacetic acid yielded vinylpyrrolecarboxylic acid **33**, which was transformed into 5-bromo-2-vinylpyrrole **34**.[39]

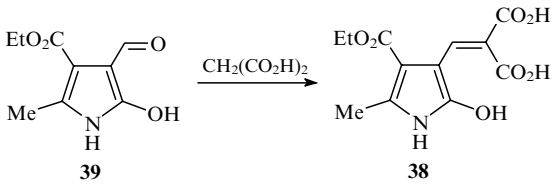


4-Bromo-2-(2-cyano-2-methoxycarbonylvinyl)pyrrole (**36**) was prepared by condensation of 4-bromo-2-formylpyrrole (**37**) with methyl cyanoacetate.[40]

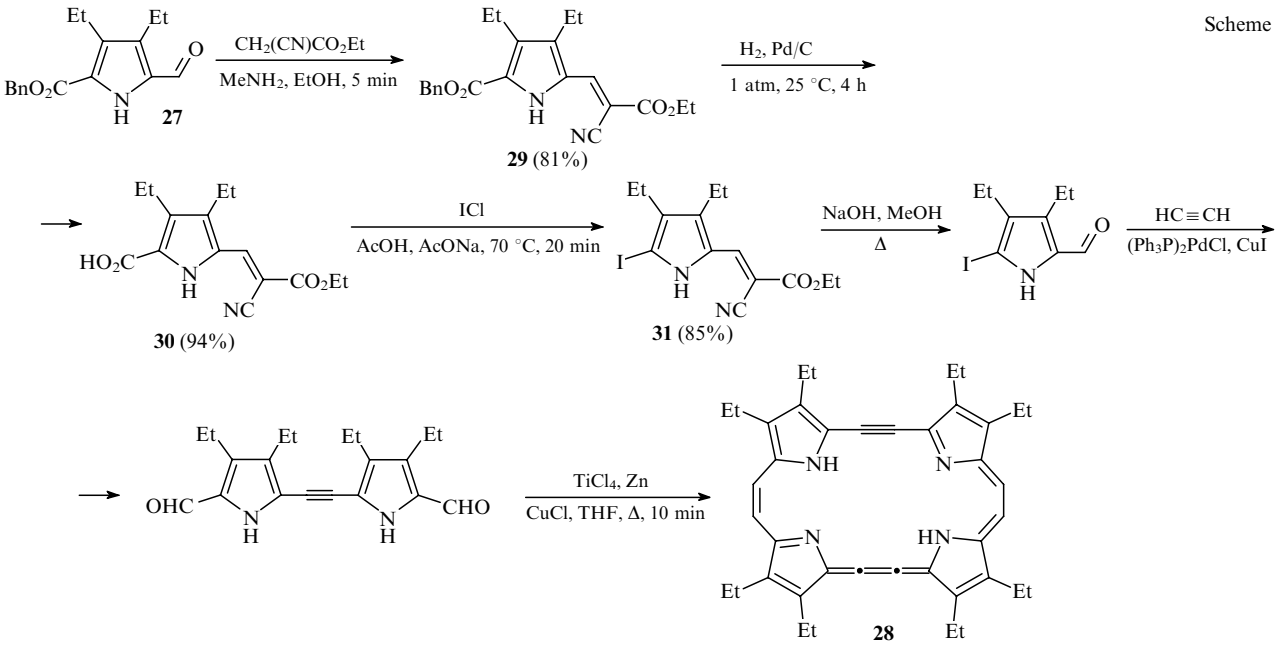


c. Condensation with malonic acid and its esters

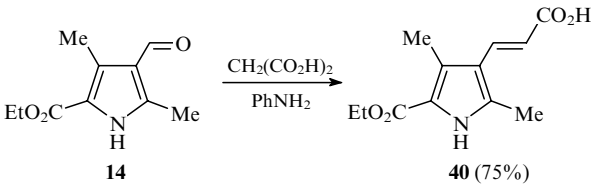
Functionalised 5-hydroxy-4-vinylpyrrole **38** was synthesised from 4-formyl-5-hydroxypyrrole **39** and malonic acid.[41]



Scheme 1

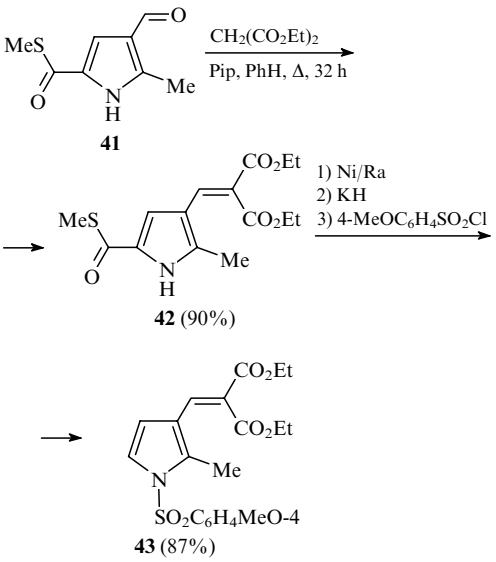


4-Vinylpyrrole **40** was prepared from the 4-formyl-substituted pyrrole **14** and malonic acid [35] by decarboxylating condensation in the presence of aniline.



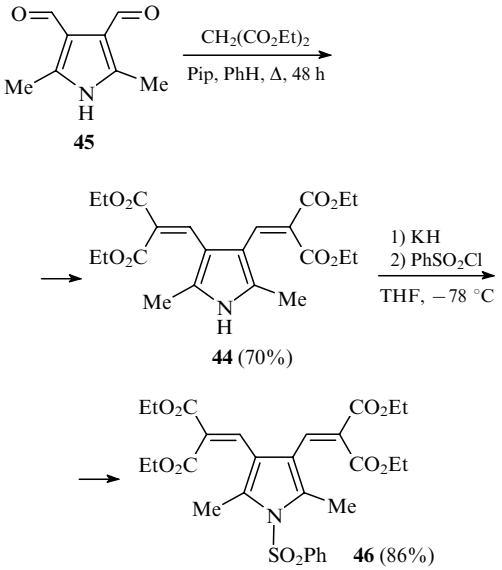
14 **40** (75%)

The reaction of 4-formyl-substituted pyrrole **41** with diethyl malonate afforded 4-vinylpyrrole **42**. Reductive elimination of the methylthiocarbonyl group from the pyrrole **41** under the action of Raney nickel (acetone, refluxing, 30 min) and successive treatment with potassium hydride and methoxybenzenesulfonyl chloride (THF, −78 °C) gave rise to pyrrole **43**.[42]



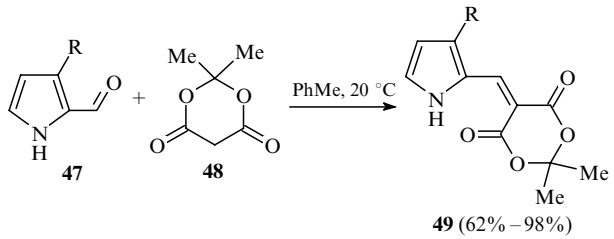
41 **42** (90%) **43** (87%)

Functionalised 3,4-divinylpyrrole **44** was synthesised by condensation of 3,4-diformylpyrrole **45** with diethyl malonate. Treatment of the potassium derivative, which was prepared by the reaction of compound **44** with potassium hydride, with benzenesulfonyl chloride afforded *N*-substituted divinylpyrrole **46**.[42]



45 **44** (70%) **46** (86%)

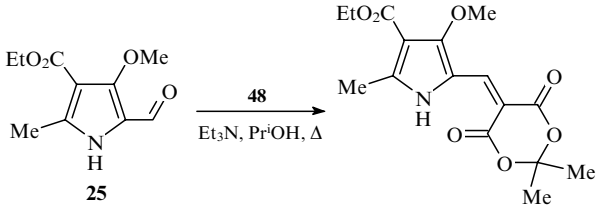
Classical Knoevenagel condensation of 2-formylpyrroles **47** with isopropylidene malonate (Meldrum's acid, **48**) in the presence of piperidinium acetate as a catalyst was used in the synthesis of 2-vinylpyrroles **49**.[43]



47 **48** **49** (62%–98%)

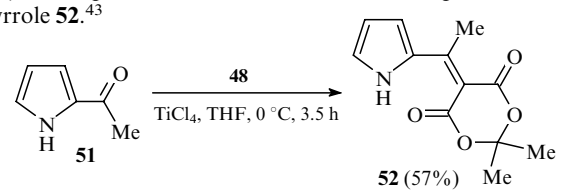
R = Me, MeO, CO_2Me.

The 5-formyl-substituted pyrrole **25** reacted with Meldrum's acid on refluxing in isopropyl alcohol in the presence of triethylamine to give 5-vinylpyrrole **50**.[37]



25 **50** (40%)

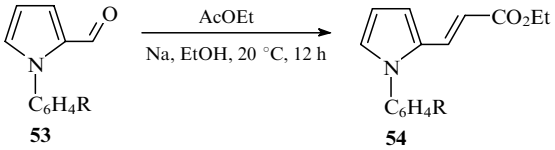
Condensation of 2-acetylpyrrole (**51**) with Meldrum's acid (**48**) in the presence of titanium tetrachloride produced 2-vinylpyrrole **52**.[43]



51 **52** (57%)

d. Condensation with acid derivatives containing the active methylene group

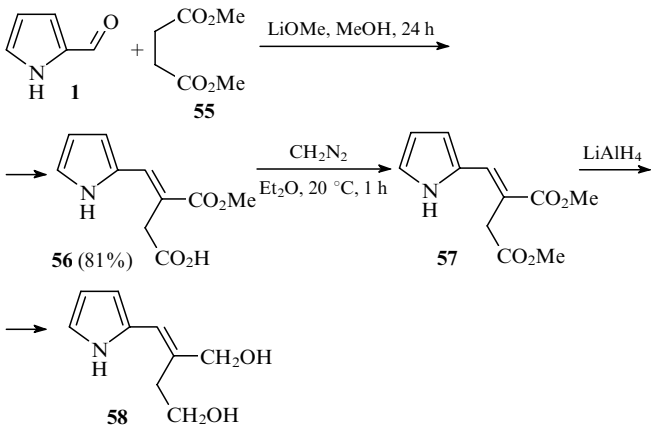
2-Vinylpyrroles **54** were synthesised by the Claisen reaction from 2-formylpyrroles **53** and ethyl acetate.[44]



53 **54**

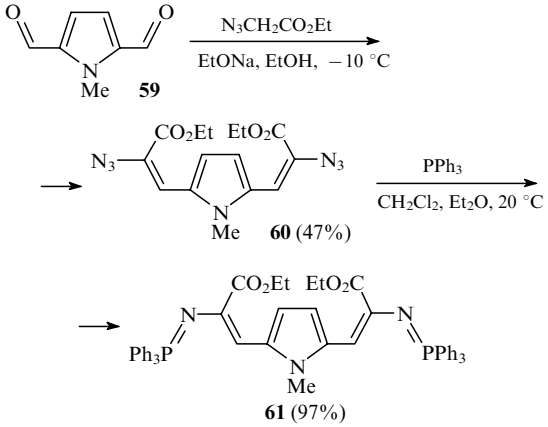
R = H, 4-MeO, 2-NO_2, 4-Cl.

Stobbe condensation of 2-formylpyrrole (**1**) with dimethyl succinate **55** afforded functionalised 2-vinylpyrrole **56** from which diester **57** was obtained in quantitative yield. Reduction of the latter gave rise to 1,4-diol **58**.[45]

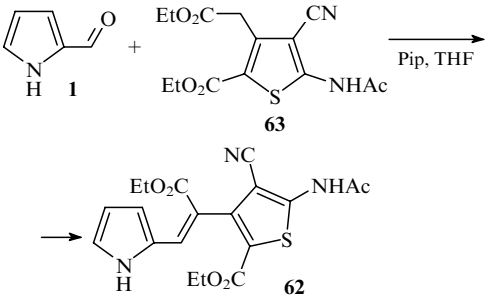


1 **55** **56** (81%) **57** **58**

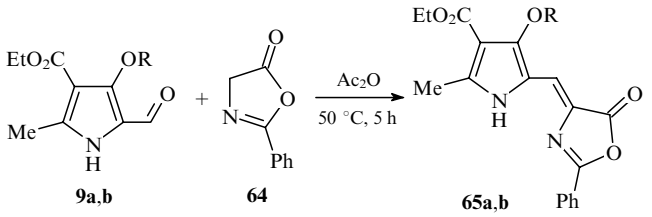
2,5-Diformyl-1-methylpyrrole (**59**) reacted with ethyl azidoacetate to form bis(azidovinyl)pyrrole **60**. Treatment of the latter with triphenylphosphine afforded divinylpyrrole **61** containing the iminophosphorane functional groups.[46]



Substituted 2-vinylpyrrole **62** was prepared by refluxing 2-formylpyrrole (**1**) with 5-acetylamino-4-cyano-2-ethoxycarbonyl-3-ethoxycarbonylmethylthiophene (**63**).[47]



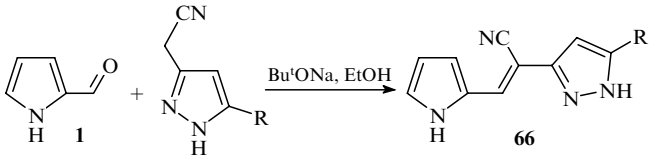
Heating of the formylpyrroles **9a**,**b** with hippuric acid (which was transformed into azlactone **64** under the reaction conditions) in acetic anhydride afforded 4-acetoxy- or 4-tosyloxy-5-pyrrolylmethyleneoxazolines **65a**,**b** containing the vinylpyrrole fragment.[48]



R = Ac (**a**), Ts (**b**).

e. Condensation with cyanomethylhetarenes and alkenes (hetaryl- and alkenylacetonitriles)

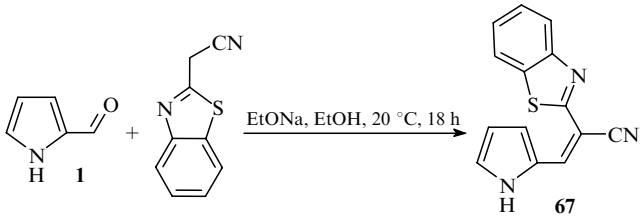
2-Formylpyrrole (**1**) undergoes condensation with nitriles of pyrazolylacetic acids to form the corresponding 1,2-dihetarylcyanoalkanes **66**. The ratio between the *Z* and *E* isomers of the compounds **66** depends on the temperature and reaction time.[49, 50]



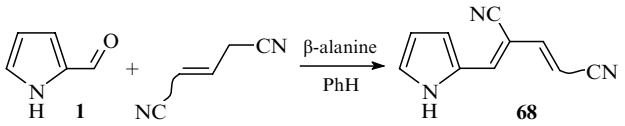
R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-BrC$_6$H$_4$.

At 20 °C, the *Z* isomers of the alkenes **66** were selectively generated during 4–5 h (the yields were 88%–95%). At 90–100 °C (20–24 h), the thermodynamically more stable *E* isomers were obtained as the major reaction products (the yields were 52%–60%). In the latter case, the yields of the *Z* isomers were no higher than 25%–30%. The ratio between the isomers remained unchanged as the duration of heating was increased, which indicates that an equilibrium was established. Attempts to transform the *Z* isomers of the compounds **66** into the *E* isomers by refluxing in methanol were unsuccessful. However, the degree of isomerisation reached 100% upon the addition of Bu^{t}ONa to the reaction mixture.[49]

2-Formylpyrrole (**1**) reacted with 2-cyanomethylbenzothiazole to give 2-vinylpyrrole **67** in 85% yield.[30]

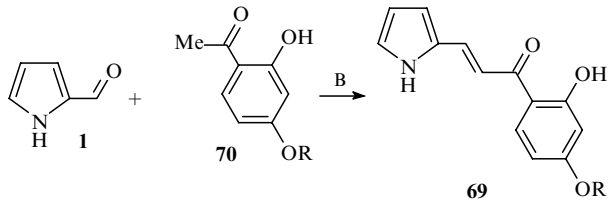


Condensation of 2-formylpyrrole (**1**) with glutacononitrile in the presence of β-alanine afforded butadiene derivative **68**.[51]



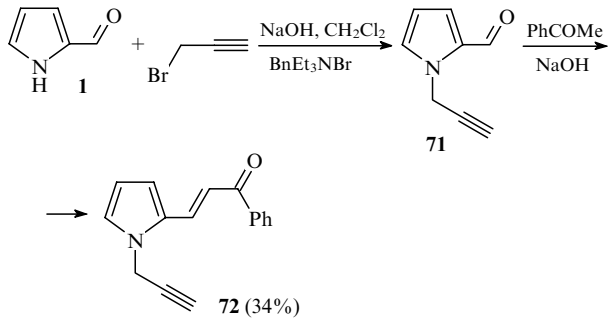
f. Condensation with ketones

2-Vinylpyrroles **69** were synthesised by base-catalysed condensation of 2-formylpyrrole (**1**) with aromatic ketones **70**.[52]

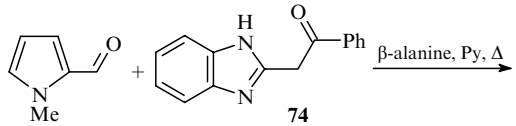


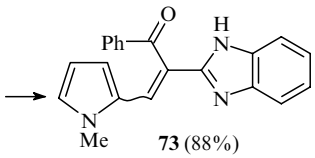
R = CH_2CO_2Et, $(CH_2)_2OH$.

2-Formyl-*N*-propargylpyrrole (**71**), which was prepared from 2-formylpyrrole (**1**) and propargyl bromide under the conditions of phase transfer catalysis, reacted with acetophenone in the presence of NaOH to give benzoylvinylpyrrole **72**.[53]



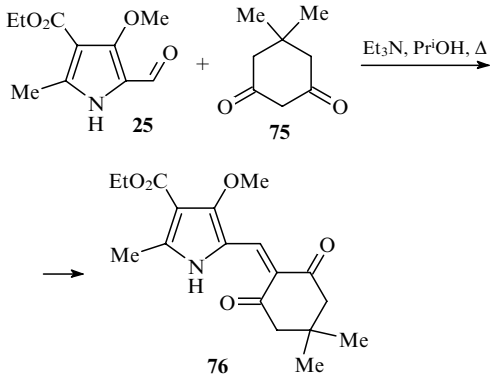
2-[2-Benzoyl-2-(benzoimidazol-2-yl)]vinylpyrrole (**73**) was prepared by condensation of 2-formyl-1-methylpyrrole with ketone **74** in the presence of β-alanine.[54]





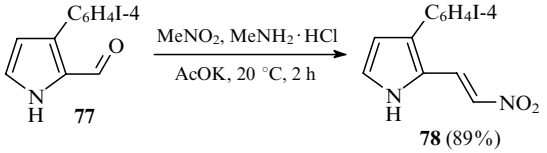
73 (88%)

5-Vinylpyrrole **76** was synthesised from 5-formylpyrrole **25** and dimedone (**75**).[37]



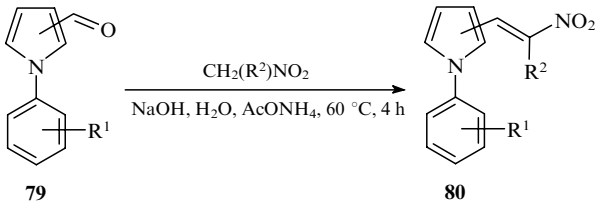
g. Condensation with nitroalkanes

The reaction of 2-formyl-3-(4-iodophenyl)pyrrole (**77**) with nitromethane in the presence of a small excess of methylamine hydrochloride afforded 2-(2-nitrovinyl)pyrrole **78**.[55]



78 (89%)

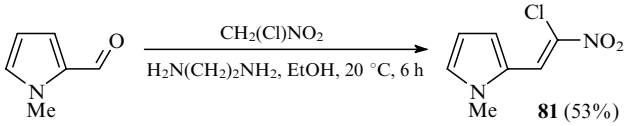
The reactions of *N*-aryl-2(3)-formylpyrroles **79** with nitroalkanes produced the *E* isomers of the corresponding 2- and 3-(2-nitrovinyl)pyrroles **80** in 64% – 78% yields.[44, 56]



79 **80**

R^1 = H, 4-MeO, 2-NO_2, 4-Cl; R^2 = H, Me, Et.

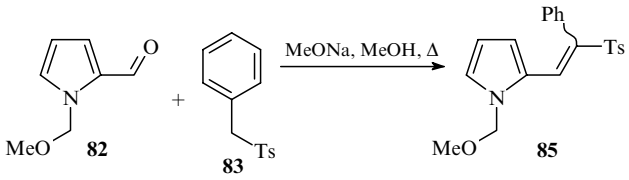
2-(2-Chloro-2-nitrovinyl)-1-methylpyrrole (**81**) was synthesised by condensation of 2-formyl-1-methylpyrrole with nitrochloromethane in the presence of catalytic amounts of ethylenediamine.[57]

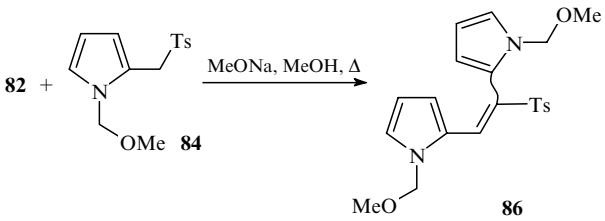


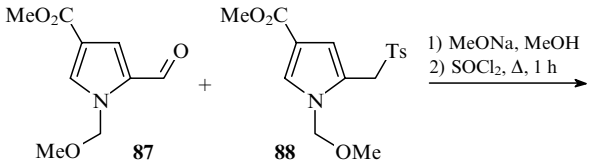
81 (53%)

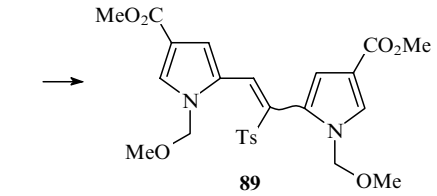
h. Condensation with sulfones

Condensation of 2-formyl-*N*-methoxymethylpyrrole (**82**) with sulfones **83** or **84** in the presence of 50 equiv. of sodium methoxide afforded 1,2-diaryl-1-sulfonylethenes **85** and **86** in 76% and 78% yields, respectively.[58] Under these conditions, aldehyde **87** underwent condensation with sulfone **88** to give a mixture of diester **89** and a product of its hydrolysis with water generated in the course of the reaction. The compound **89** was isolated in 89% yield after treatment of the resulting mixture with thionyl chloride.



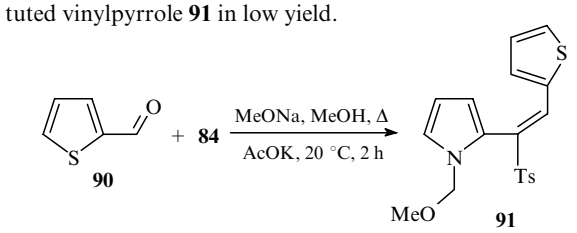






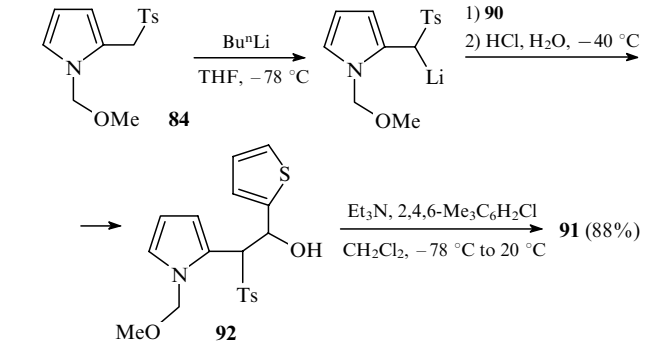
89

Under analogous conditions, the reaction of the sulfone **84** with thiophene-2-carbaldehyde (**90**) gave rise to thienyl-substituted vinylpyrrole **91** in low yield.



Apparently, the low yield is attributed to the Cannizzaro side reaction to which thiophenecarbaldehyde is more susceptible than aldehydes of the pyrrole series.

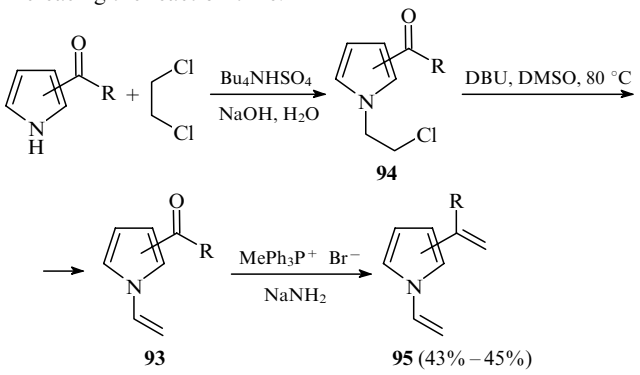
Condensation of thiophene-2-carbaldehyde (**90**) with the lithium derivative of sulfone **84** followed by hydrolysis with 10% HCl afforded a mixture of diastereomers of alcohol **92**. The latter was transformed into the alkene **91** by treatment with mesityl chloride.[58]



2. Wittig reaction

The reactions of formyl- and acetylpyrroles with alkylidenephosphoranes, which are generated upon dehydrohalogenation of quaternary phosphonium salts under the action of bases (Wittig reaction) is one of the most commonly used approaches to the synthesis of *C*-vinylpyrroles.[59–78]

Carbonyl derivatives of 1-vinylpyrroles **93**, which were prepared by dehydrohalogenation of 1-(2-chloroethyl)pyrroles **94** under the action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMSO at 80 °C, underwent methylenation upon treatment with methyltriphenylphosphonium bromide in the presence of sodium amide (the **93** : $CH_2=PPh_3$ ratio is 1 : 2) to give vinylpyrroles **95**. Dehydrohalogenation and methylenation of the chloroethyl derivatives **94** can be carried out in one step by using larger amounts of the phosphonium salt and sodium amide as well as by increasing the reaction time.[59]

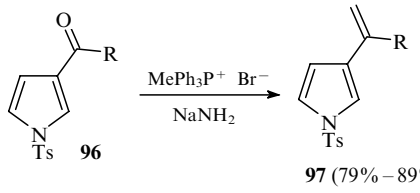


94

93 **95** (43% – 45%)

R = H, Me.

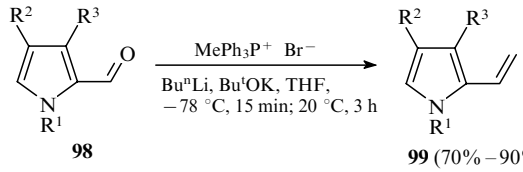
The analogous reactions of 3-acyl-1-tosylpyrroles **96** with methyltriphenylphosphonium bromide afforded 1-tosyl-3-vinylpyrroles **97**.[60]



96 **97** (79% – 89%)

R = Me, Pr^i, Ph.

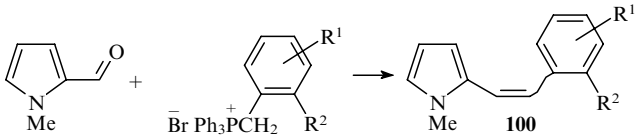
The same procedure was used for the synthesis of substituted 2-vinylpyrroles **99** from 2-formylpyrroles **98** and methyltriphenylphosphonium bromide.[61, 62]



98 **99** (70% – 90%)

R^1 = Me, Ts, CO_2Bu^t (Boc); R^2 = H, Me, NO_2;
R^3 = H, Me, $(CH_2)_2CN$.

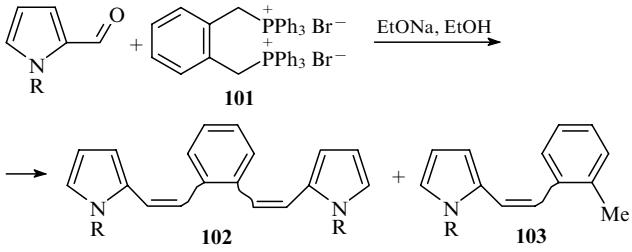
The reactions of 2-formyl-1-methylpyrrole with substituted benzyltriphenylphosphonium bromides produced (*E*)- and (*Z*)-*N*-methyl(styryl)pyrroles **100**.[63] In some cases, isomers were separated by column chromatography. Photochemical isomerisation of the initially formed *Z* isomers into *E* isomers was observed.[63]



100

R^1 = 4-Br, 3-CN, 4-CN, 3-NO_2, 4-Cl; R^2 = H, Cl.

The Wittig reaction of diphosphonium salt **101** proceeded with two 2-formylpyrrole molecules to give 2,2′-(1,2-phenylenedivinyl)dipyrroles **102** (a mixture of stereoisomers) in 32% (R = H) and 40% (R = Me) yields.[64]

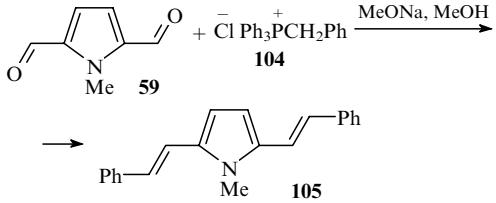


101 **102** **103**

R = H, Me.

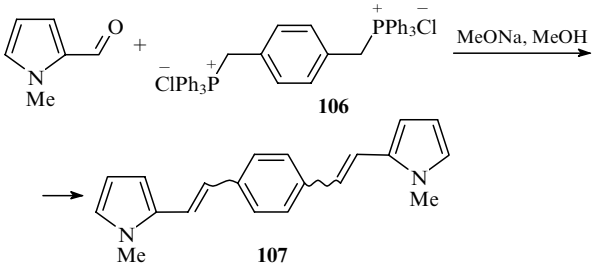
2-Styrylpyrroles **103** were generated as by-products due, apparently, to steric hindrances caused by the *o*-substituents in the diphosphonium salt **101**, which prevent the reaction of this salt with the second aldehyde molecule.[64]

The reaction of the dialdehyde **59** with phosphonium salt **104** proceeded at both aldehyde groups to yield 2,5-distyrylpyrrole **105**.[65]



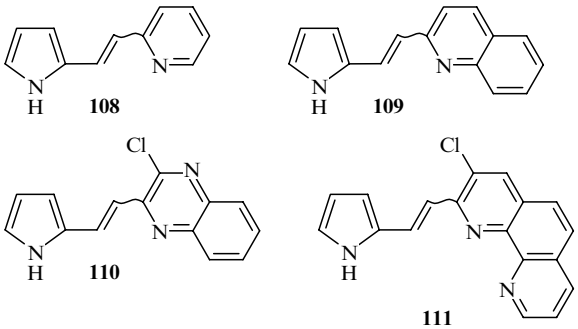
59 **104** **105**

Under the analogous conditions, the reaction of *p*-xylylenebis(triphenylphosphonium) chloride **106** with 2-formyl-1-methylpyrrole proceeded selectively to produce 1,1-dimethyl-2,2′-(1,4-phenylenedivinyl)dipyrrole (**107**) in 50% yield.[65] The initially formed mixture of the *E*,*E*, *E*,*Z* and *Z*,*Z* isomers of the compound **107** was isomerised into the pure *E*,*E* isomer upon refluxing in toluene in the presence of catalytic amounts of iodine.



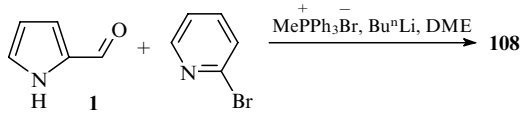
106 **107**

A series of studies performed by Arai and co-workers [66–70] was devoted to the examination of isomerisation of 2-(2-hetarylvinyl)pyrroles **108**–**111** containing the pyridine,[66, 67] quinoline,[66] quinoxaline [68] or phenanthroline substituents.[69]

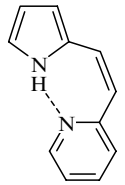


108 **109** **110** **111**

The compounds **108**–**111** were prepared by the reactions of 2-formylpyrrole (**1**) with ylides generated from the corresponding halogen-containing heterocycles and methylenetriphenylphosphorane. For example, the pyridine-substituted 2-vinylpyrrole **108** was synthesised from 2-formylpyrrole (**1**), 2-bromopyridine and methyltriphenylphosphonium bromide.[66]

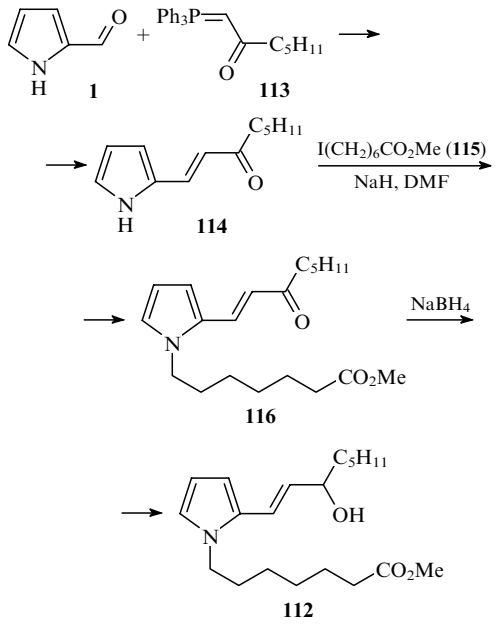


When irradiated with UV light (λ = 366 nm) in methanol, benzene or acetonitrile at 20 °C under an atmosphere of nitrogen, the initially formed *E* isomers of the compounds **108**–**111** were transformed into the *Z* isomers due, apparently, to intramolecular hydrogen bonding between the proton of the NH group of the pyrrole fragment and the nitrogen atom of the heterocycle. For example, the structure **A** was obtained in the case of 2-[2-(2-pyridyl)]vinylpyrrole **108**. The reverse transformation of the *Z* isomers into the *E* isomers proceeded in the presence of $NiCl_2$.[69]

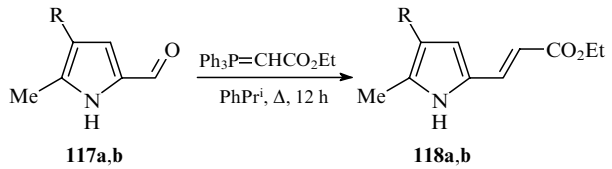


A

The pyrrole analogue of prostaglandins **112** was synthesised from 2-formylpyrrole (**1**) and phosphorane **113** followed by alkylation of the pyrrole fragment of compound **114** with methyl 7-iodoheptanoate (**115**) and reduction of the carbonyl group in the reaction product **116** with sodium borohydride.[71]

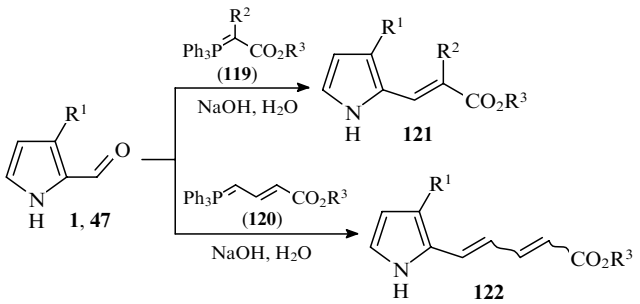


The reactions of 2-formyl-5-methylpyrrole (**117a**) and 3-acetyl-5-formyl-2-methylpyrrole (**117b**) with ethoxycarbonylmethylenephosphorane afforded 2-vinylpyrroles **118a**,**b** in 93% and 73% yields, respectively.[72]



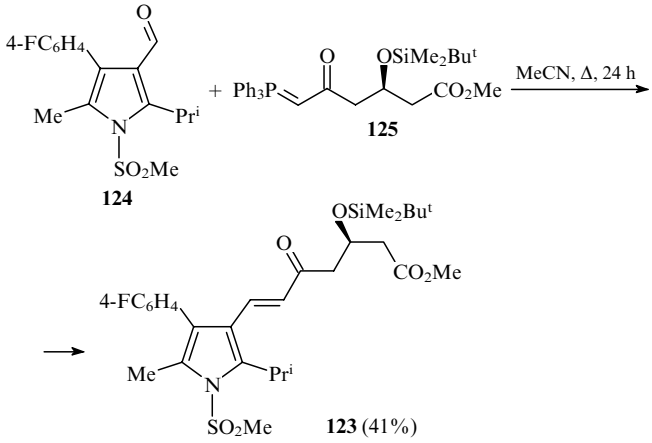
R = H (**a**), Ac (**b**).

2-Vinylpyrroles **121** and **122** (a mixture of the *E*,*E*, *E*,*Z* and *Z*,*Z* isomers) were synthesised by the reactions of 2-formylpyrroles **1** and **47** with phosphoranes **119** and **120**, respectively.[73]

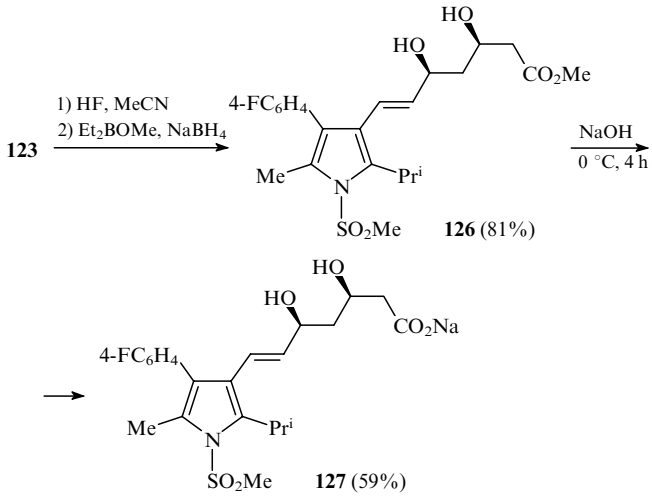


R^1 = H (**1**), Me (**47**); R^2 = H, Me, MeO, CO_2Me, CN; R^3 = Me, Et.

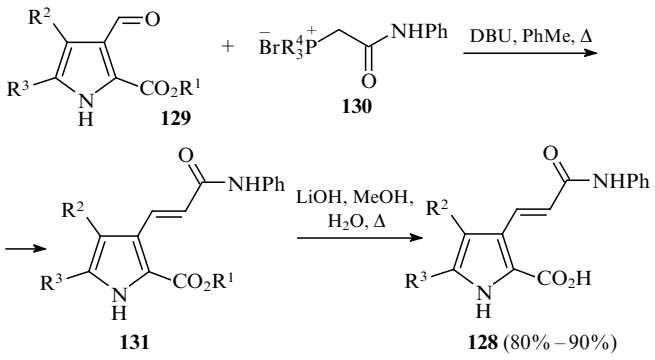
Optically active 3-vinylpyrrole **123** was prepared by refluxing unstable 3-formylpyrrole **124** with chiral Wittig reagent **125** in acetonitrile.[74]



The sodium salt of functionally substituted 3-vinylpyrrole **127**, which is a potential inhibitor of HMG-CoA reductase, was prepared by a series of transformations of the vinylpyrrole **123** involving removal of the silyl protective group, stereoselective reduction of the carbonyl group and hydrolysis of methyl ester **126**.[75]

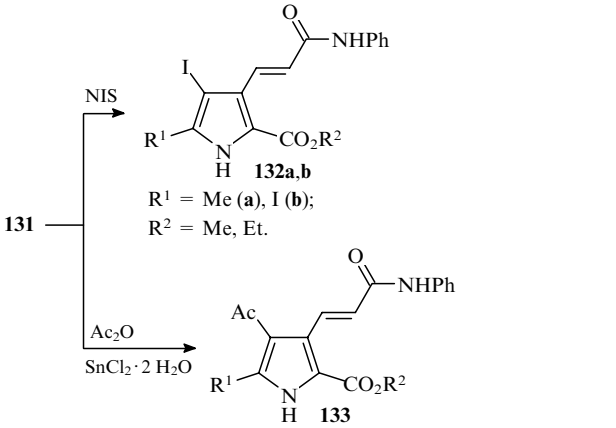


A broad spectrum of (*E*)-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrrole-2-carboxylic acids **128** containing various substituents at positions 4 or 5 of the pyrrole ring were synthesised by olefination of the corresponding 3-formylpyrroles **129** with phosphoranes, which were prepared from triphenyl- or tri-*tert*-butyl(*N*-phenylcarbamoyl)methylphosphonium bromides **130** followed by hydrolysis of the ester group in the resulting compounds **131**.[76,77]



R^1 = Me, Et; R^2 = H, Me, Et, Pr^i, OEt, OBn, Br, Cl;
R^3 = H, Me, Et, Pr^i, Ph, 2,4-$Cl_2C_6H_3$, Br; R^4 = Bu^t, Ph.

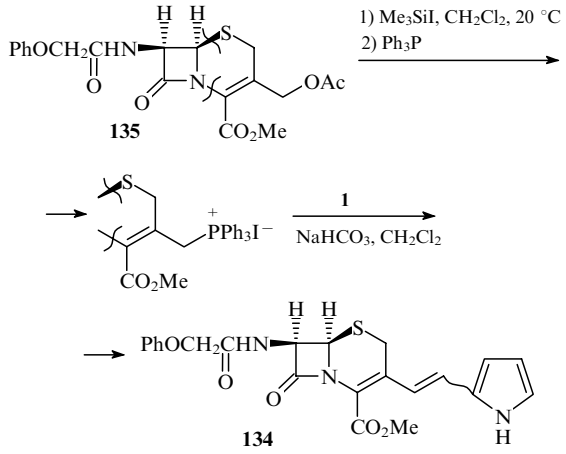
4-Iodo-5-methyl-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrroles (**132a**) and 4,5-diiodo-3-[2-(*N*-phenylcarbamoyl)vinyl]pyrroles (**132b**) were synthesised by iodination of the pyrroles **131** (R^2 = H, R^3 = H or Me) with one or two equivalents of *N*-iodosuccinimide (NIS). Vinylpyrroles **133** were prepared by Friedel–Crafts acylation of the pyrroles **131** (R^2 = H).[76]



R^1 = Me (**a**), I (**b**);
R^2 = Me, Et.

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

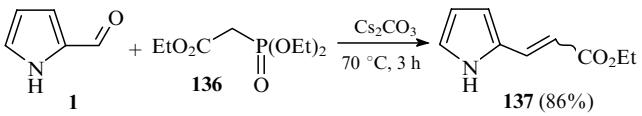
The active antibiotic, *viz*., 3-[2-(2-pyrrolyl)vinyl]cefalosporin **134**, was prepared as a mixture of *E* and *Z* isomers in a ratio of 1 : 3 in a total yield of 30% from 7-aminocefalosporanic acid **135**. The scheme for the synthesis involves the transformation of the acetoxymethyl group into the iodomethyl group, the formation of the phosphonium salt through the reaction of the 3-iodomethyl derivative with triphenylphosphine and its reaction with 2-formylpyrrole (**1**).[78]



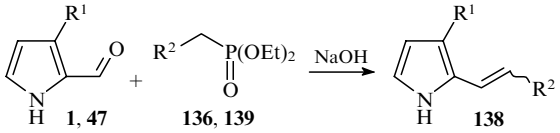
3. Horner reaction

Procedures for the synthesis of *C*-vinylpyrroles from acylpyrroles and dialkyl phosphonates in the presence of bases (Horner or Wittig–Horner reactions) are being extensively developed.[73,79–87]

Olefination of 2-formylpyrrole (**1**) with phosphonate **136** was carried out with the use of $Cs_2CO_3 \cdot 3H_2O$ (1.5-fold excess) as a base. The reaction was conducted in dioxane in a two-phase system to yield 2-[2-(ethoxycarbonyl)vinyl]pyrrole **137**.[79]

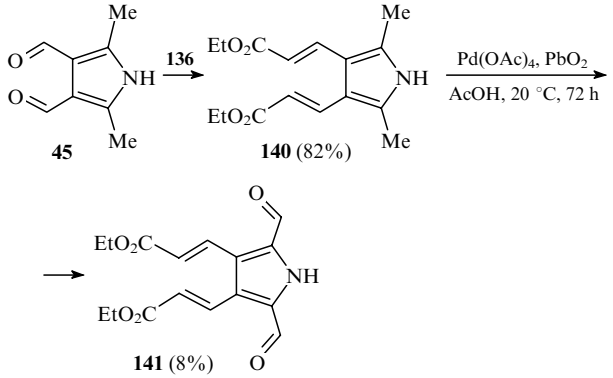


Functionalised 2-vinylpyrroles **138** (*E* and *Z* isomers) were prepared from the 2-formylpyrroles **1** and **47** and the phosphonates **136** and **139**.[73]

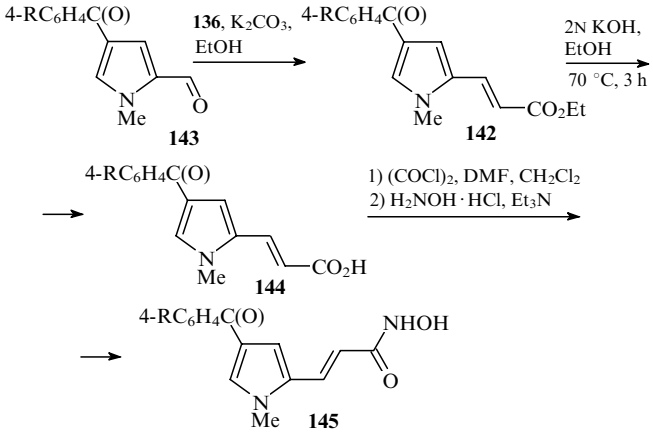


R^1 = H (**1**), Me, MeO, CO_2Me, CN (**47**);
R^2 = CO_2Et (**136**), CO_2Me (**139**).

Bis(ethoxycarbonylvinyl)pyrrole **140** was synthesised by the Horner reaction from 3,4-diformyl-2,5-dimethylpyrrole **45** and the phosphonate **136**. Oxidation of the methyl groups in the latter compound afforded 3,4-bis(2-ethoxycarbonylvinyl)-2,5-diformylpyrrole (**141**).[80]

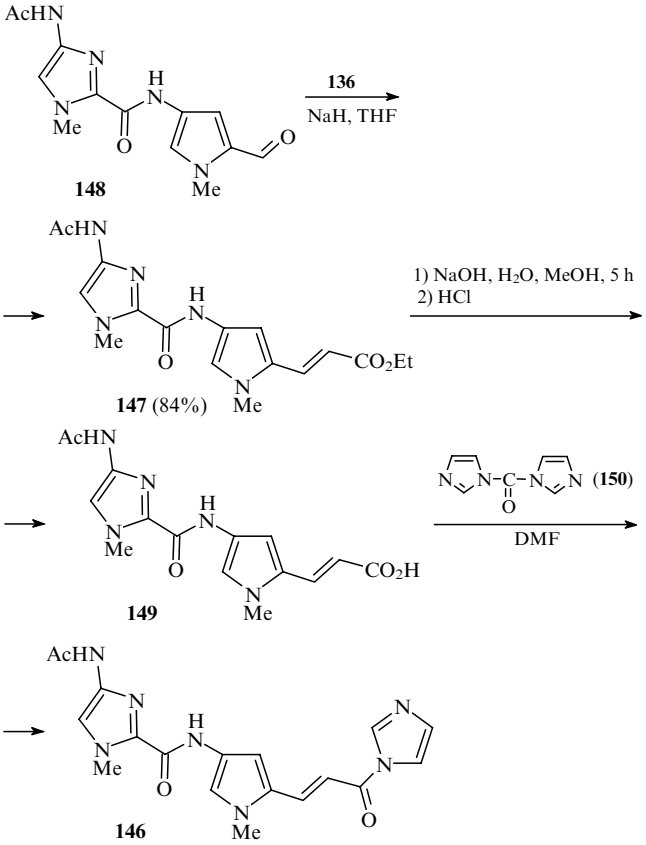


Ethyl (*E*)-3-[4-(4-R-benzoyl)-1-methylpyrrol-2-yl]acrylates **142** were prepared by the reactions of 4-(4-R-benzoyl)-2-formyl-1-methylpyrroles **143** with the phosphonate **136**. Alkaline hydrolysis of the esters **142** in ethanol afforded the corresponding acids **144**, which were transformed into [2-(*N*-hydroxyamido)vinyl]-pyrroles **145**.[81]

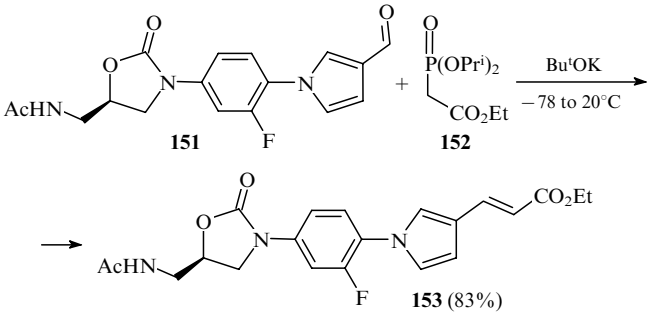


R = H, NO_2, Cl, F, MeO, NMe_2, imidazol-1-yl.

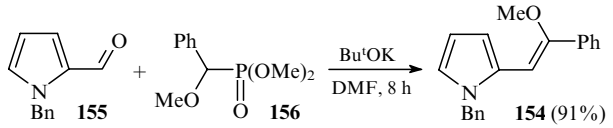
Substituted 2-vinylpyrrole **147**, which was prepared from 2-formylpyrrole **148** and the phosphonate **136**, served as the key intermediate in the synthesis of the precursor of the DNA-dialkylating agent, *viz*., activated amide **146**. Subsequent hydrolysis of the compound **147** followed by acidification with HCl gave rise to acid **149** in 67% yield. When treated with 1,1′-carbonyldiimidazole (**150**) in DMF, the latter was transformed into the target 2-vinylpyrrole **146**.[82]



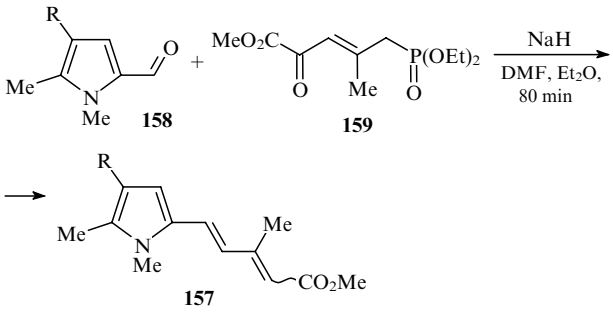
N-Substituted 3-formylpyrrole **151** reacted with phosphonate **152** in the presence of Bu^{t}OK to produce 3-ethoxycarbonylvinylpyrrole **153**.[83]



The scheme for the synthesis of the benzannelated analogue of the antibiotic CC-1065 involves the Horner reaction as the first step. *N*-Benzyl-2-(2-methoxy-2-phenylvinyl)pyrrole (*E*-**154**) was synthesised from 1-benzyl-2-formylpyrrole **155** and phosphonate **156** in dry DMF by the portionwise addition of Bu^{t}OK during 8 h.[84]

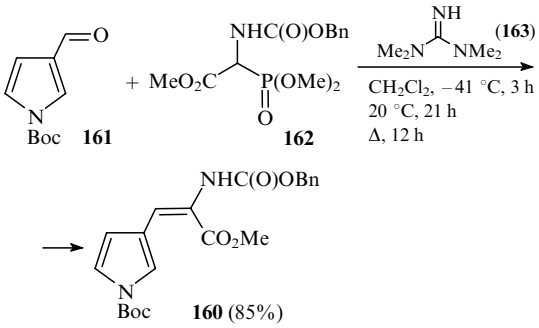


2-Butadienylpyrroles **157**, which are used in the synthesis of retinoids, were prepared as a mixture of the *E*,*E* and *E*,*Z* isomers in a ratio of 7 : 3 by the reactions of 2-formyl-1,5-dimethylpyrroles **158** with phosphonate **159**.[85]

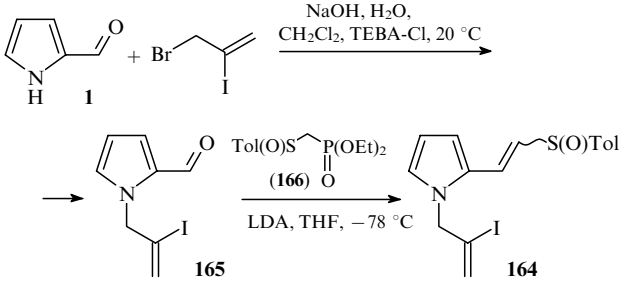


R = Ac (77%), CO_2Et (82%).

Functionalised 3-vinylpyrrole **160** was synthesised by the Horner–Emmons reaction from 3-formylpyrrole **161** and trimethyl *N*-(benzyloxycarbonyl)phosphonoglycine (**162**) in the presence of tetramethylguanidine **163**.[86]



The two-step synthesis produced a mixture of the *E* and *Z* isomers of 2-(4-tolylsulfinyl)vinylpyrrole **164** (in a ratio of 67 : 33) in a total yield of 82%.[87] The process involved *N*-allylation of 2-formylpyrrole (**1**) with 3-bromo-2-iodopropene followed by olefination of aldehyde **165** with phosphonate **166**.

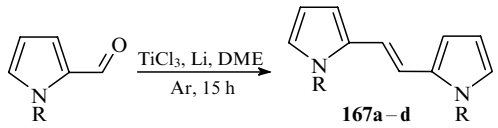


TEBA-Cl is benzyltriethylammonium chloride; LDA is Pr^i_2NLi; Tol is 4-MeC_6H_4.

4. Dimerisation of acylpyrroles

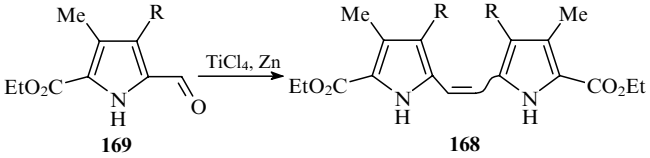
The intermediates in the synthesis of *meso*-substituted porphyrinoids, *viz*., 1,1- and 1,2-dipyrrolylethenes, are often prepared by reductive dimerisation of 2-formylpyrroles. In these reactions, titanium compounds are generally used as catalysts.[88–95]

Thus dipyrrolylethenes **167a–d** were prepared by refluxing *N*-substituted 2-formylpyrroles with $TiCl_3$ in dry dimethoxyethane in the presence of metal lithium in argon.[88] The yields of the reaction products depend on the nature of the substituent. The reactions of 2-formyl- and 2-formyl-1-methylpyrroles proceeded non-selectively to give complex mixtures of products, whereas dimerisation of 1-ethoxycarbonyl- and 1-acetyl-2-formylpyrroles afforded dipyrrolylethenes **167c**,**d** in 30% and 50% yields, respectively.[88]



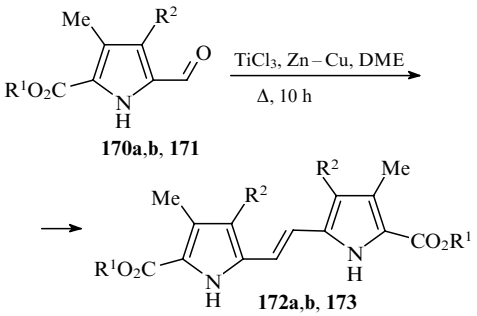
R = H (**a**), Me (**b**), COMe (**c**), CO_2Et (**d**).

1,2-Di(pyrrol-2-yl)ethenes **168** (*E* and *Z* isomers) were synthesised from pyrroles **169** in the presence of $TiCl_4$ and Zn.[89,90]



R = Et, COMe, CO_2Et, $CH_2CH_2CO_2Et$.

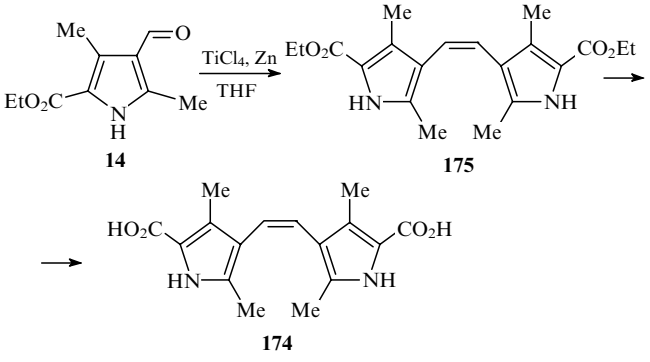
Refluxing of 2-formylpyrroles **170a–c** with the $TiCl_3 \cdot (DME)_{1.5}$ complex in dimethoxyethane in the presence of the Zn–Cu system (15 equiv.) afforded the *E* isomers of 1,2-di(pyrrol-2-yl)ethenes **171a–c**.[91,92] The lower yields of the pyrroles **171b,c** are apparently attributed to lability of the methoxycarbonylethyl and *tert*-butoxycarbonyl ester groups in the presence of the titanium reagent.



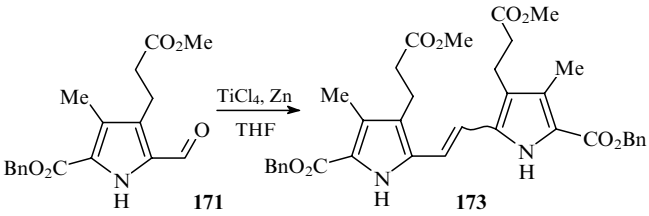
Compound	R^1	R^2	Yield (%)
172a	Bn	Me	81
172b	Bu^t	Et	22
173	Bn	$(CH_2)_2CO_2Me$	46

An attempt to perform cross-coupling of the pyrroles **170a** and **170c** to obtain mixed 1,2-di(pyrrol-2-yl)ethene failed; instead, the reaction afforded the pyrrole **171a** as the major product (20%).[91]

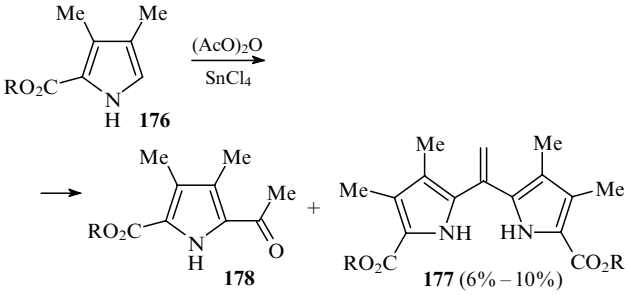
Treatment of ethyl 4-formyl-3,5-dimethylpyrrole-2-carboxylate (**14**) with the $TiCl_4$–Zn system in THF gave rise to a complex mixture of the reaction products. From this mixture, acid **174** was isolated in 10% yield through dimerisation of the 3-formylpyrrole **14** followed by hydrolysis of the ester groups in dimer **175**.[93]



However, the reaction of the 5-formylpyrrole **171** performed under the same conditions afforded reductive dimerisation product **173** (*E*:*Z* = 1:4) in 86% yield. In this case, hydrolysis of the ester groups did not take place.[93]

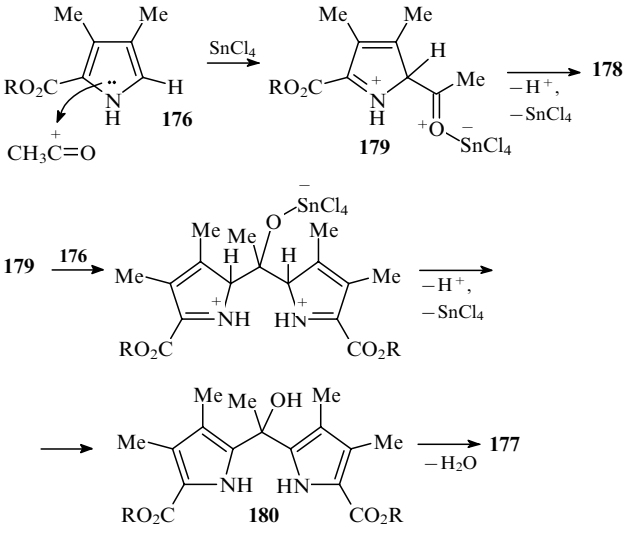


Friedel–Crafts acylation of 3,4-dimethylpyrrole-5-carboxylates **176** containing no substitutents at position 2 with acetic anhydride in the presence of tin chloride afforded symmetrical 1,1-di(pyrrol-5-yl)ethenes **177** as by-products due to condensation of ketones **178** with the starting pyrroles **176**, which proceeded under the reaction conditions.[91,94]

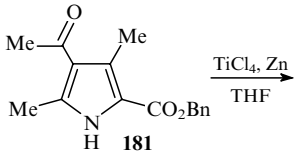


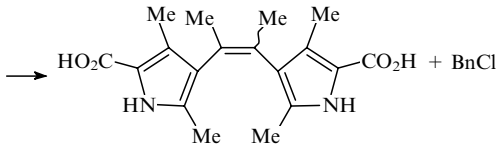
R = H, Et, Bn.

The proposed [91] reaction mechanism involves the electrophilic attack of the acylium ion on the pyrrole **176** giving rise to the cationoid intermediate **179**. The latter lost the proton at the α position to form the 2-acetylpyrrole **178**. The cation **179** can attack the second molecule of the pyrrole **176** to generate intermediate hydroxydipyrrolylethane **180** whose dehydration afforded the 1,1-di(pyrrol-2-yl)ethene **177**.[91]



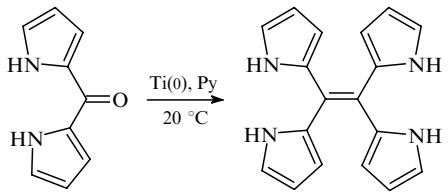
Ketone **181** reacted with the $TiCl_4$–Zn system to give 2,3-dipyrrolylbut-2-ene **182** in low yield. The reaction produced benzyl chloride rather than benzyl alcohol as a by-product. Cheng *et al.*[93] believed that this fact indicates that it is not the treatment that led to hydrolysis of the ester groups.





182

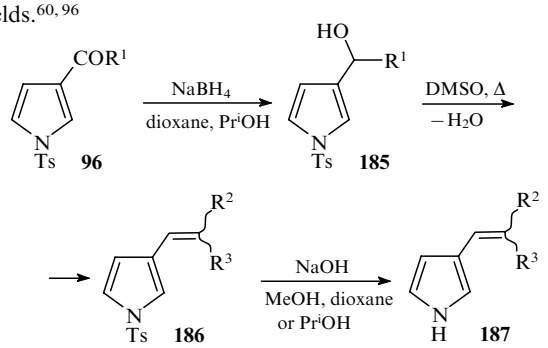
Reductive dimerisation of di(pyrrol-2-yl) ketone **183** in the presence of Ti(0) yielding 1,1,2,2-tetra(pyrrol-2-yl)ethene **184** may also be assigned to this type of reactions.[95]



183 **184** (56%)

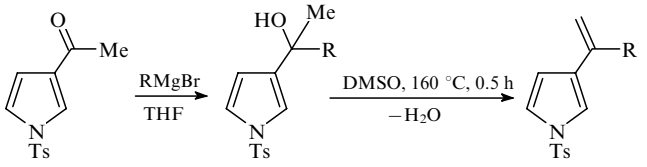
5. Other reactions involving acylpyrroles

Dehydration of 3-(1-hydroxyalkyl)-1-tosylpyrroles **185**, which were synthesised by reduction of 3-acylpyrroles **96** with sodium borohydride, afforded 3-vinylpyrroles **186**.[96] Detosylation of the latter with NaOH gave rise to 3-vinylpyrroles **187** in 66% – 87% yields.[60, 96]



R^1 = Me, R^2 = R^3 = H; R^1 = Et, R^2 = H, R^3 = Me;
R^1 = Bn, R^2 = H, R^3 = Ph; R^1 = Pr^i, R^2 = R^3 = Me.

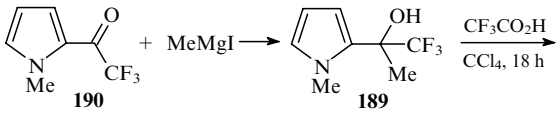
The reactions of 3-acetyl-1-tosylpyrrole (**96**) with Grignard reagents in THF produced 3-(1-hydroxyethyl)-1-tosylpyrroles **188**, which lost water upon heating in DMSO to give 3-(1-R-vinyl)pyrroles **97**.[60]



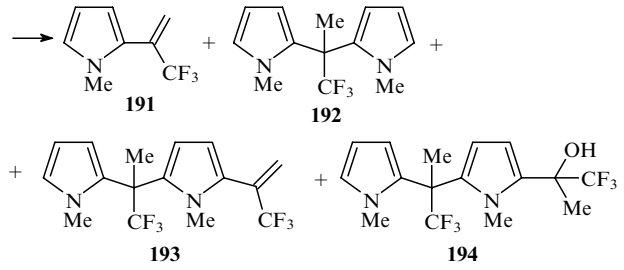
96 **188** (85% – 91%) **97** (60% – 93%)

R = Me, Pr^i, Ph.

The reaction of alcohol **189**, which was synthesised from 1-methyl-2-trifluoroacetylpyrrole **190** and methylmagnesium iodide, with trifluoroacetic acid (0.1 M solution in CCl_4) afforded a mixture of products from which pyrroles **191** – **194** were isolated by chromatography in a ratio of 4 : 7 : 8 : 74.[97]

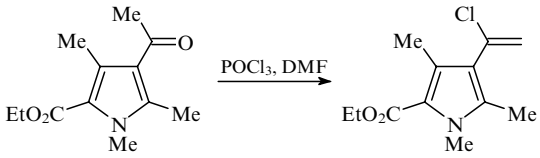


190 **189**



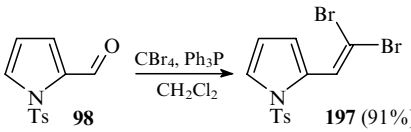
191 **192** **193** **194**

The reaction of 4-acetyl-2-ethoxycarbonyl-1,3,5-trimethylpyrrole (**195**) with $POCl_3$ gave rise to 3-(1-chlorovinyl)pyrrole **196**.[98]



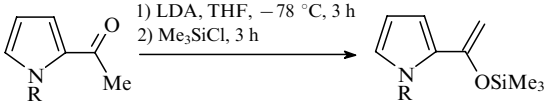
195 **196** (75%)

The reaction of 2-formyl-*N*-tosylpyrrole (**98**) with tetrabromomethane in the presence of triphenylphosphine yielded 2-(2,2-dibromovinyl)pyrrole **197**.[61]



98 **197** (91%)

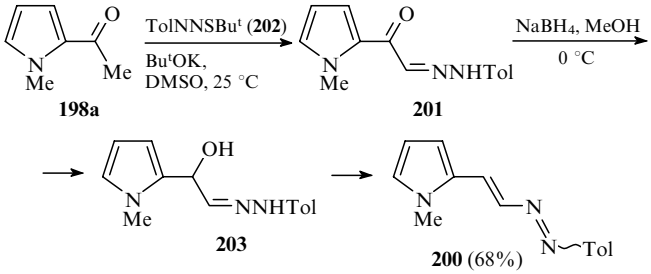
Successive treatment of 2-acetylpyrroles **198a** – **c** with lithium diisopropylamide and trimethylchlorosilane produced 2-[1-(trimethylsilyloxy)vinyl]pyrroles **199a** – **c**.[99] Silylation of 2-acetyl-1-ethoxycarbonylpyrrole **198d** in acetonitrile at 20 °C in the presence of triethylamine and catalytic amounts of $ZnCl_2$ afforded compound **199d**.[99]



198a – **d** **199a** – **d**

R = Me (**a**, 85%), Me_3Si (**b**), SO_2Ph (**c**, 85%), CO_2Et (**d**, 93%).

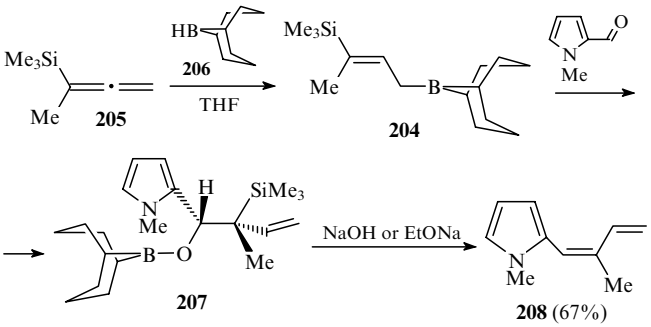
1-(1-Methylpyrrol-2-yl)-2-(*p*-tolylazo)alkene **200** (predominantly, the *E* isomer) was prepared from 2-acetyl-1-methylpyrrole **198a** in three steps.



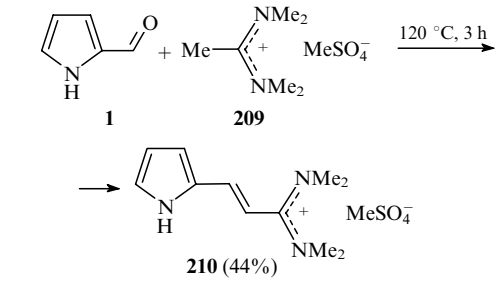
198a **201** **203** **200** (68%)

In the first step, diketone hydrazone **201** was prepared by the reaction of the enol form of 2-acetyl-1-methylpyrrole (**198a**) with *tert*-butyl *p*-tolylazo sulfide **202**. The second step involves selective reduction of the carbonyl group of the compound **201** with sodium borohydride. Hydrazone **203** was dehydrated to the diazadiene **200** either in a two-phase system (dilute sulfuric acid – diethyl ether) at 25 °C or in an acetic anhydride – pyridine mixture at 50 °C.[100]

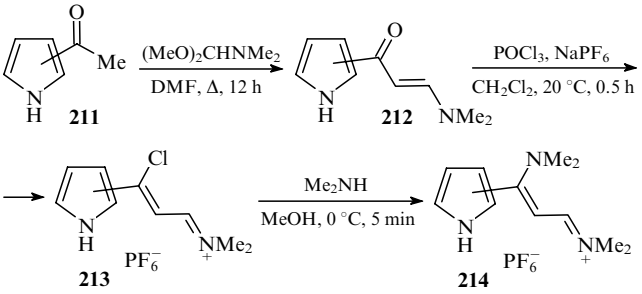
Condensation of γ-(trimethylsilyl)crotylborane **204**, which was prepared from trimethylsilylallene **205** and 9-borabicyclo[3.3.1]nonane (**206**), with 2-formyl-1-methylpyrrole afforded intermediate **207**. Treatment of the latter with a base (to initiate Peterson olefination) led to the virtually selective formation of the *Z* isomer of 1-(pyrrol-2-yl)isoprene **208**.[101]



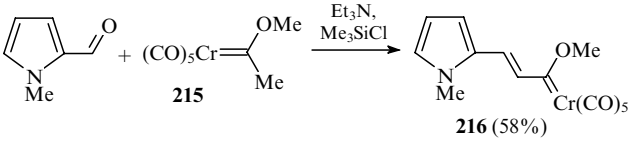
2-Formylpyrrole (**1**) smoothly reacted with *N*,*N*,*N*′,*N*′-tetramethylacetimidinium methyl sulfate **209** to produce *N*,*N*,*N*′,*N*′-tetramethyl-3-(2-pyrrolyl)acrylamidinium methyl sulfate **210**.[102]



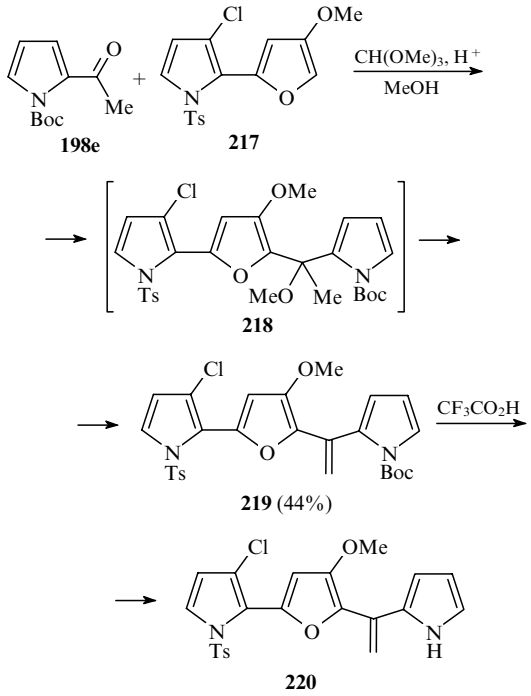
Aminomethylenation of 2- and 3-acylpyrroles **211** with dimethylformamide dimethyl acetal afforded 2- and 3-aminovinyl ketones **212** in 92% and 93% yields, respectively. The reactions of these ketones with $POCl_3$ in the presence of sodium hexafluorophosphate gave rise to (1-chlorovinyl)pyrroles **213** in 75% and 78% yields, respectively. The latter were transformed into (aminovinyl)pyrroles **214** (the yields were 64% and 69%, respectively) by treatment with dimethylamine.[103]



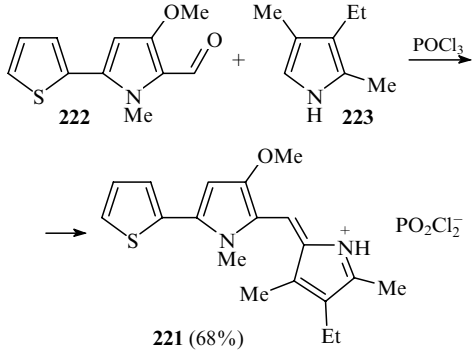
Condensation of the chromium carbene complex **215** with 2-formyl-1-methylpyrrole yielded product **216**.[104]



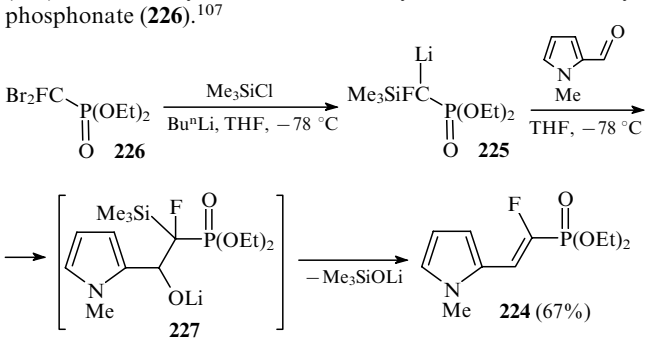
Protected 2-acetylpyrrole **198e** reacted with furylpyrrole **217** in the presence of methyl orthoformate and catalytic amounts of chlorosulfonic acid. The initially formed unstable compound **218** was transformed into 2-vinylpyrrole **219**, which was subsequently transformed into 2-vinylpyrrole **220** after removal of the *tert*-butoxycarbonyl protection.[105]



2-Vinylpyrrole **221**, which is an analogue of the natural antibiotic prodigiosin, was synthesised by condensation of formylpyrrole **222** with 3-ethyl-2,4-dimethylpyrrole (**223**) in the presence of $POCl_3$.[106]



2-(2-Diethoxyphosphoryl-2-fluorovinyl)-1-methylpyrrole (**224**, a mixture of the *E* and *Z* isomers in a ratio of 76 : 24) was prepared by condensation of 2-formyl-1-methylpyrrole with diethyl α-fluoro-α-lithio-α-(trimethylsilyl)methylphosphonate (**225**), which was synthesised from diethyl dibromofluoromethylphosphonate (**226**).[107]

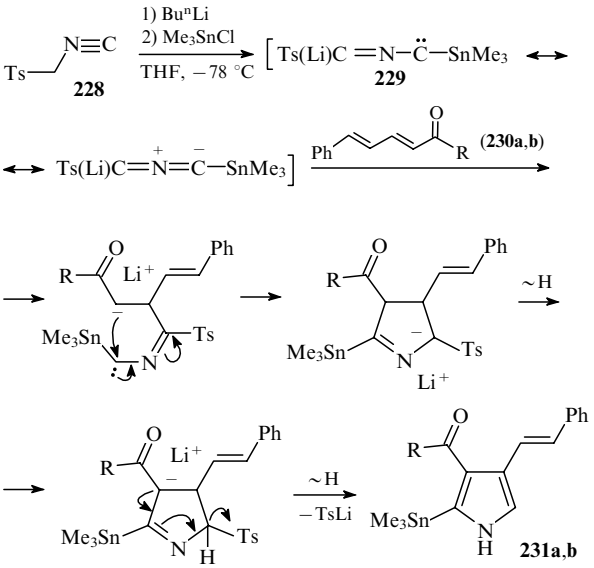


The reaction proceeded instantaneously in spite of the presence of the $(EtO)_2PO$ group stabilising the carbanion. Attempts to isolate the intermediate pyrrole after hydrolysis of alkoxide **227** failed. β-Elimination of the trimethylsilyloxy group from the initially formed intermediate **227** took place, *i.e.*, exclusively Peterson olefination (rather than the Wittig–Horner reaction) proceeded under these conditions.[107]

III. Synthesis of *C*-vinylpyrroles from functionalised aliphatic compounds

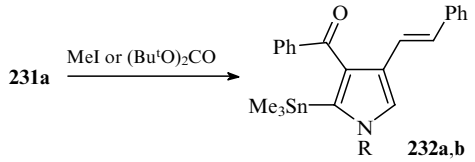
1. Synthesis from tosylmethyl isocyanide and activated alkenes

In the last decade, a procedure for the preparation of 4-vinylpyrrole derivatives containing no substituents at positions 1 and 5 has been extensively developed. This procedure relies on the base-catalysed addition of tosylmethyl isocyanide to activated alkenes.[22, 61, 108–115] The successive reactions of isocyanide **228** with Bu^nLi and then with an excess of Me_3SnCl afforded derivative **229**, which reacted with dienones **230a**,**b** to give 3-acetyl- (**231a**) or 3-benzoyl-4-(*E*)-styryl-2-(trimethylstannyl)-pyrroles (**231b**).[108] The reactions unexpectedly gave rise to 2-stannylpyrroles rather than to 5-stannylpyrroles, which are adducts of $TsCLi(SnMe_3)N{\equiv}C$ with dienones. In this process, the stannylated isocyanide derivative **229** serves, apparently, as the reactive species. In the study,[108] the possibility of the migration of the Me_3Sn group from position 5 to position 2 of the pyrrole ring was also not excluded.



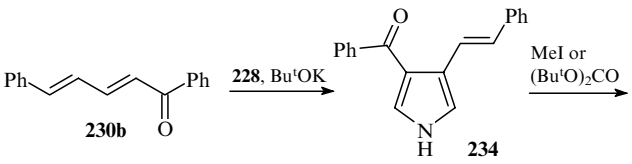
R = Me (**a**), Ph (**b**).

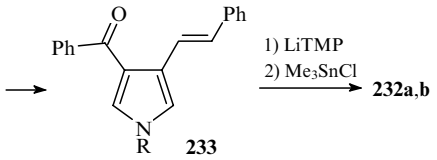
N-Substituted 2-(trimethylstannyl)pyrroles **232a**,**b** containing the styryl group at position 4 were prepared either by methylation of the pyrrole **231b** under the conditions of phase transfer catalysis or by acylation of di-*tert*-butyl carbonate.[108]



R = Me (**232a**), Boc (**232b**).

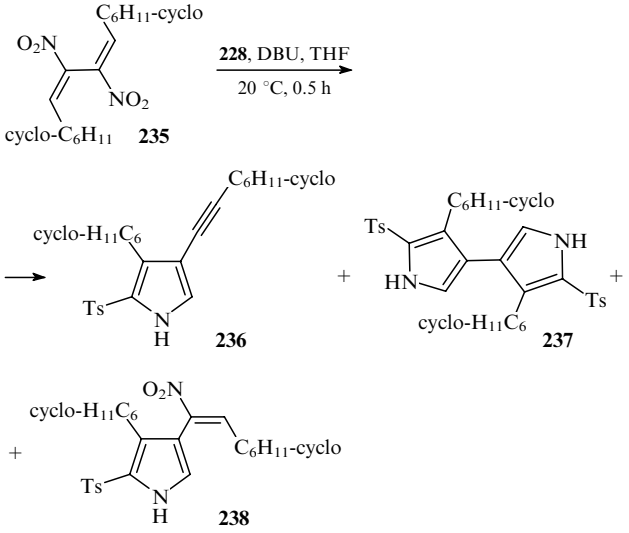
The compounds **232a**,**b** were also prepared by the introduction of the trimethylstannyl group into pyrroles **233**, which were synthesised by the reaction of the tosylmethyl isocyanide **228** with the dienone **230b** in the presence of Bu^tOK followed by alkylation or acylation of intermediate **234**.[108]



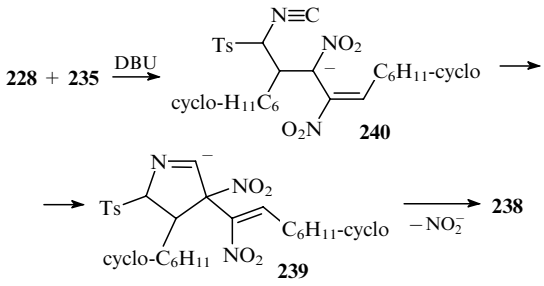


R = Me, Boc; LiTMP is lithium 2,2,6,6-tetramethylpiperidide.

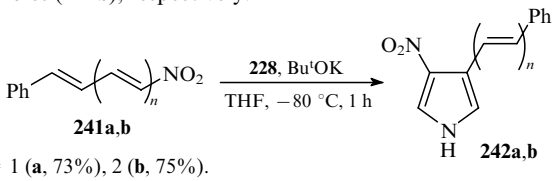
The reaction of the isocyanide **228** with an equimolar amount of 1,4-dicyclohexyl-2,3-dinitrobuta-1,3-diene (**235**) in THF in the presence of diazabicycloundecene afforded a mixture of ethynylpyrrole **236** (58%), 4,4′-bipyrrole **237** (9%) and nitrovinylpyrrole **238** (12%).[109]



Intermediate **239**, which is a precursor of the pyrrole **238**, was generated through the addition of the tosylmethyl isocyanide anion to one nitrovinyl group of the dinitrobutadiene system and intramolecular cyclisation of the resulting anion **240**.[109]

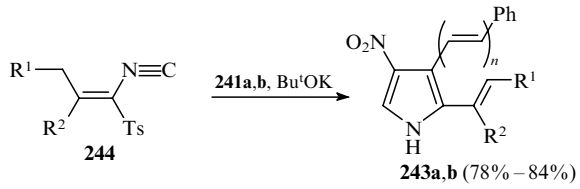


Conjugated nitrodiene **241a** and nitrotriene **241b** reacted with the isocyanide **228** in the presence of an excess of Bu^tOK in THF to form 4-styryl- (**242a**) and 4-(4-phenylbuta-1,3-dienyl)-3-nitropyrroles (**242b**), respectively.[110]



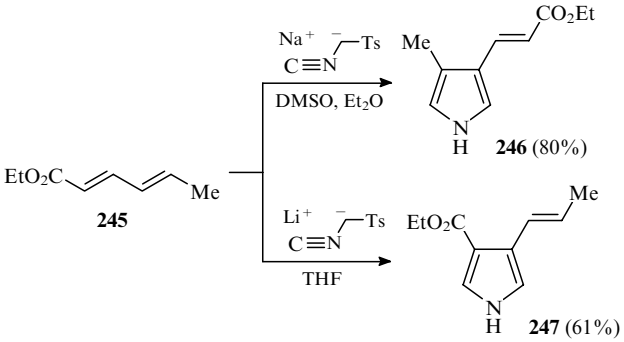
n = 1 (**a**, 73%), 2 (**b**, 75%).

2,3-Dialkenyl-4-nitropyrroles **243** were prepared by the analogous reactions of the nitrodiene **241a** or the nitrotriene **241b** with 1-isocyano-1-tosyl-2,2-disubstituted alkenes **244**, which are products of condensation of tosylmethyl isocyanide **228** with ketones.[110–112]

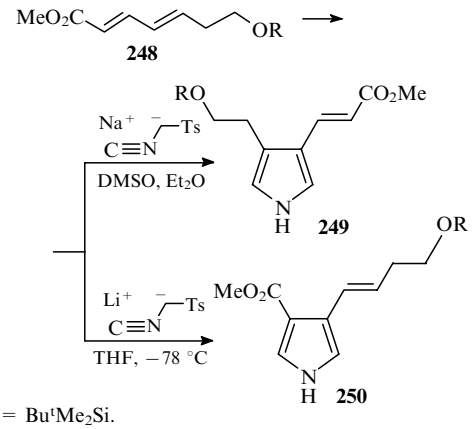


n = 1 (**a**), 2 (**b**); R^1 = H, Me; R^2 = Me, Ph; R^1–R^2 = $(CH_2)_4$.

The synthesis with the use of ethyl hexa-2,4-dienoate **245** as the Michael acceptor afforded isomeric pyrroles **246** and **247**. The direction of the reaction depends on its conditions. Thus the use of a more polar solvent in combination with a more dissociated ionic pair facilitates the addition of the anion derived from the isocyanide **228** to the δ position of the ester **245** bearing the highest positive charge. For example, the reaction of the sodium derivative of the isocyanide **228** with the ester **245** in a DMSO – Et_2O mixture afforded pyrrole **246**, whereas the reaction of the lithium derivative of the isocyanide **228** in tetrahydrofuran gave rise to 1,2-adduct **247**.[113]

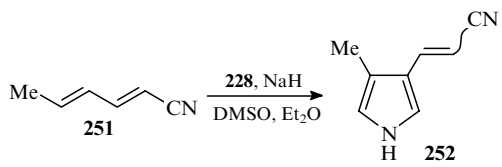


Condensation of ester **248** with the sodium derivative of the isocyanide **228** in the DMSO – Et_2O system produced a mixture of regioisomers **249** and **250** in a ratio of 7 : 1 in 55% yield. The use of the lithium derivative in THF at −78 °C afforded only pyrrole **250** with an impurity of the starting isocyanide **228**. The compound **250** was isolated as the *N*-benzyl derivative after treatment with benzyl bromide (NaH, DMF).[113]



R = Bu^tMe_2Si.

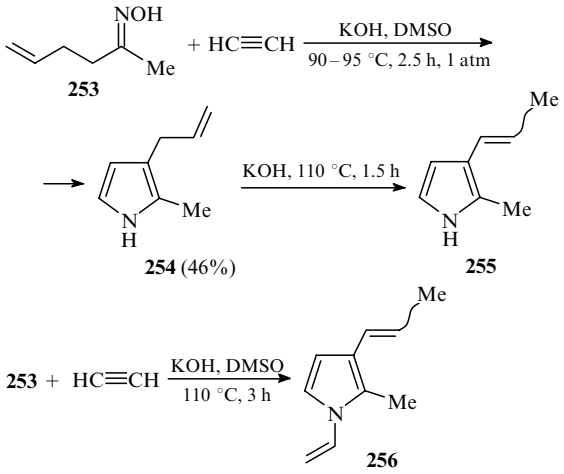
The reaction of nitrile **251** with the isocyanide **228** in the presence of sodium hydride in the DMSO – Et_2O system produced a mixture of (*E*)- and (*Z*)-3-(2-cyanovinyl)pyrroles **252**.[61]



2. Synthesis from unsaturated ketone oximes and acetylene

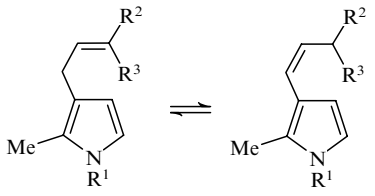
Heterocyclisation of unsaturated ketone oximes with acetylene in the superbasic KOH – DMSO system (Trofimov's reaction) is a promising procedure for the synthesis of *C*-vinylpyrroles.[114, 115] This procedure enables one to carry out a two-step transformation of readily available ketones to pyrroles and their 1-vinyl derivatives (in the presence of an excess of acetylene).

For example, 2-methyl-3-(prop-2-enyl)pyrrole (**254**) was prepared from hex-5-en-2-one oxime **253** and acetylene.[114] Heating of compound **254** with calcined KOH under an atmosphere of nitrogen led to prototropic isomerisation to form an equilibrium mixture of the *E* and *Z* isomers (in a ratio of 7 : 3) of 2-methyl-3-(prop-1-enyl)pyrrole (**255**) in a total yield of 93%.



The reaction with an excess of acetylene afforded only 2-methyl-3-(prop-1-enyl)-1-vinylpyrrole (**256**) (the yield was 80%, a mixture of the *E* and *Z* isomers in a ratio of 7 : 3).[115] Hence, the prop-1-enyl substituents are thermodynamically more favourable for these compounds due, apparently, to conjugation of the double bond with the pyrrole ring.

Isomerisation of 3-allylpyrroles **257a**,**b** in the KOH – DMSO (120 °C, 1 h, the molar ratio KOH : pyrrole **257** = 1 : 1) or Bu^tOK – DMSO system (60 – 65 °C, 1 h) afforded an equilibrium mixture of the pyrroles **257a**,**b** and (*E*)- and (*Z*)-3-(prop-1-enyl)pyrroles **258a**,**b**.[115]



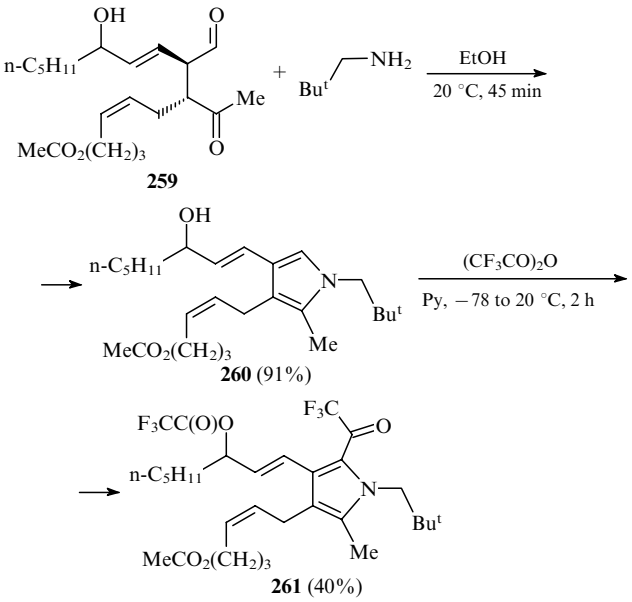
R^1 = H, CH=CH_2; R^2 = R^3 = Me (**a**), R^2–R^3 = $(CH_2)_5$ (**b**).

The allyl substituents in the 1-vinylpyrroles **257a**,**b** are isomerised into the corresponding prop-1-enyl substituents by 75% – 100%. For the corresponding 1*H*-pyrroles, the conversion was at most 30%. The higher conversion in the case of 1-vinylpyrroles results from conjugation between the 3-(alk-1-enyl) and 1-vinyl fragments through the double bonds and the nitrogen atom of the pyrrole ring.[115]

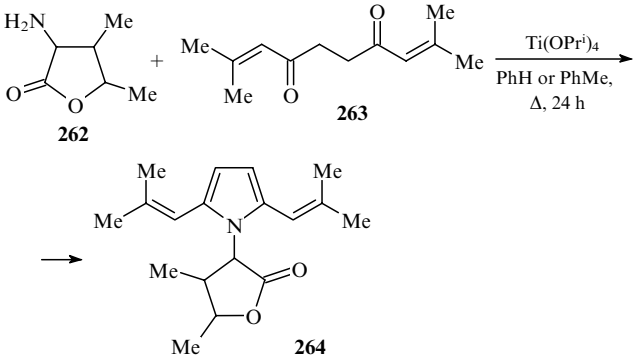
3. Synthesis from 1,4-dicarbonyl compounds

One of the most commonly used procedures for the preparation of pyrroles involves the transformation of 1,4-dicarbonyl compounds into pyrroles under the action of ammonia or amines (Paal – Knorr synthesis). In some cases, this procedure is applicable also to the synthesis of *C*-vinylpyrroles. These reactions performed with the use of unsaturated γ-ketoaldehydes, such as an analogue of levuglandin **259**, as the dicarbonyl component and

neopentylamine as the amino component, afforded pyrrole **260**.[116] Condensation was performed in dry degassed ethanol at 20 °C. However, the pyrrole **260** is unstable and completely decomposes in one day even under an atmosphere of argon. Stable functionalised β-*C*-vinylpyrrole **261** was prepared from the pyrrole **260** under the action of trifluoroacetic anhydride under an atmosphere of argon.[116]

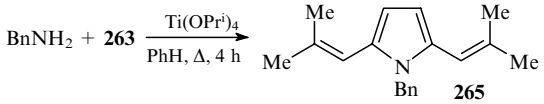


Refluxing of aminolactone **262** with 2,9-dimethyldeca-2,8-diene-4,7-dione (**263**) in benzene or toluene in the presence of titanium isopropoxide for 24 h afforded 2,5-diisobutenylpyrrole **264** in 53% yield.[117, 118]



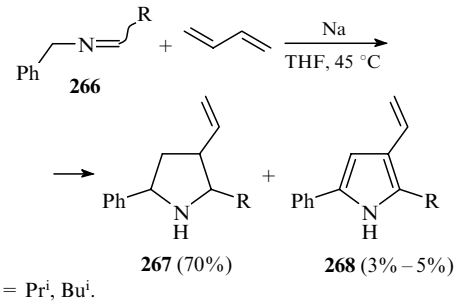
It should be noted that $TiCl_4$, which is widely used as a catalyst in the Paal–Knorr synthesis, is inefficient in this reaction. Thus, the pyrrole **264** was obtained only in trace amounts.

Under analogous conditions, the reaction of the diketone **263** with benzylamine gave rise to 1-benzyl-2,5-diisobutenylpyrrole (**265**) in 63% yield.[118]



4. Synthesis from imines and butadiene

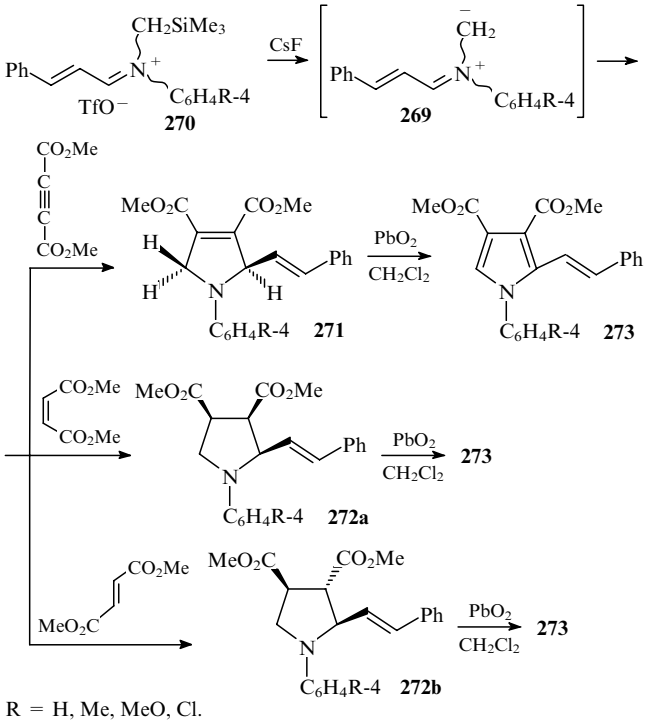
Condensation of alkylidenebenzylamines **266** with butadiene in the presence of catalytic amounts of sodium metal proceeded as the [3 + 2]-cycloaddition accompanied by imine–imine isomerisation to give a complex mixture of products containing alkyl(vinyl)phenylpyrrolidines **267** as the major component and pyrroles **268** (in small amounts).[119–121]



R = Pr^i, Bu^i.

The pyrroles **268** can also be prepared by catalytic dehydrogenation of the pyrrolidines **267** in the presence of Pd/C (250 °C, 5 h, the yield was 52%).[119]

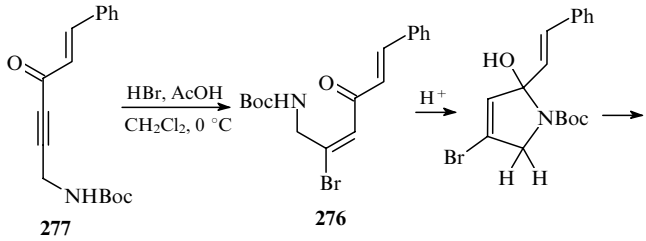
Ylide **269**, which was generated upon desilylation of a mixture of the *E*,*Z* and *E*,*E* isomers of salt **270**, reacted with different dipolarophiles, such as dimethyl acetylenedicarboxylate, dimethyl maleate or dimethyl fumarate, to form dihydropyrroles **271** or stereoisomeric pyrrolidine derivatives (**272a**,**b**).[122] Oxidation of the dihydropyrroles **271** and pyrrolidines **272a**,**b** gave rise to 2-styrylpyrroles **273**.[122]

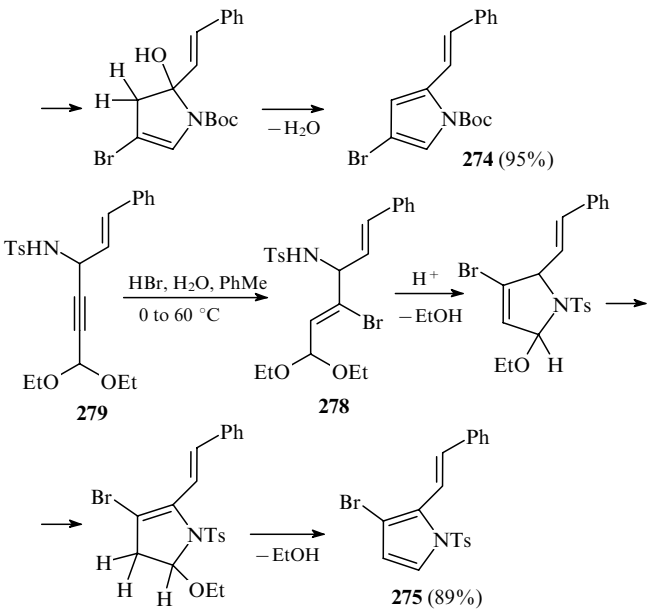


R = H, Me, MeO, Cl.

5. Synthesis from vinylacetylenic amides

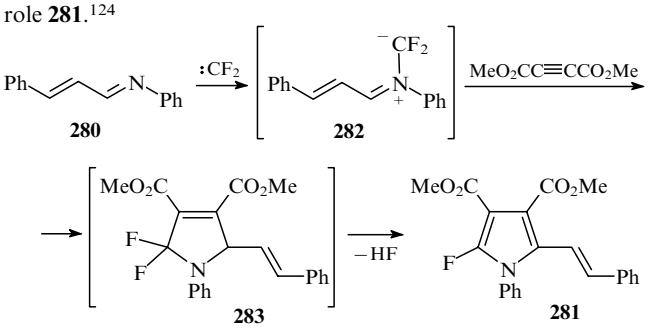
Nitrogen-protected β-bromo-α-styrylpyrroles **274** and **275** were synthesised by cyclisation of diene amidoketones **276** (generated from vinylacetylenic amidoketones **277**) or aminoacetals **278** (prepared from vinylacetylenic aminoacetals **279**) in the presence of HBr.[123]





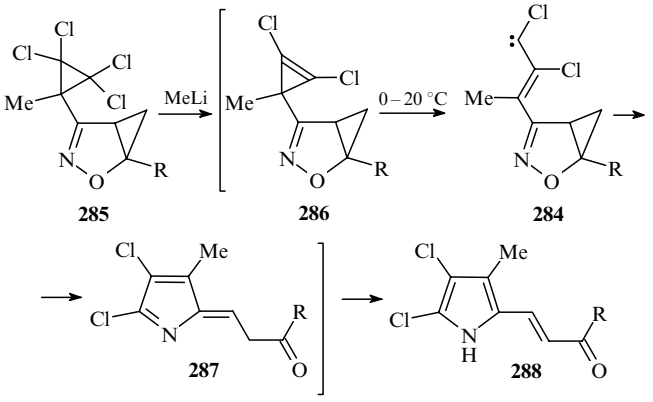
6. Synthesis involving carbenes

Imine **280** reacted with difluorocarbene in the presence of dimethyl acetylenedicarboxylate to give 5-fluoro-2-(*E*)-styrylpyrrole **281**.[124]



Apparently, difluorocarbene attacks the lone electron pair of the nitrogen atom to form azomethine ylide **282**, which adds as the 1,3-dipole to acetylenedicarboxylic ester to form dihydropyrrole **283**. Its subsequent dehydrofluorination affords the pyrrole **281**.[124]

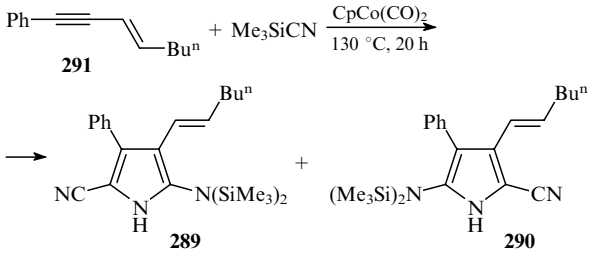
Vinylcarbenes **284** were prepared from 1-(2,2,3,3-tetrachloro-1-methylcyclopropyl)isoxazolines **285** by treatment with methyllithium followed by isomerisation of the resulting 1,2-dichlorocyclopropenes **286**. The attack of the carbene centre on the isoxazoline substituent was accompanied by rearrangement to give methylene-2*H*-pyrroles **287**, which underwent aromatisation under the reaction conditions to give 2-(2-acylvinyl)pyrroles **288**.[125]



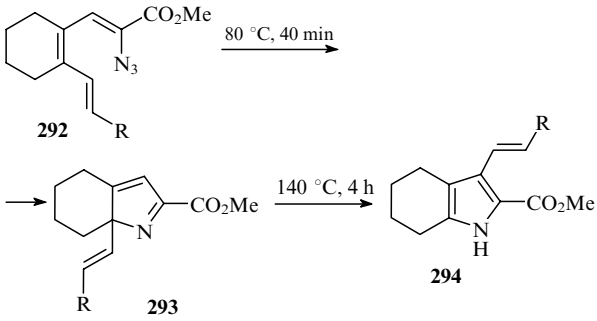
R = Et (82%), Bu^n (85%).

7. Other procedures for the synthesis

A mixture of isomeric pyrrole-2-carbonitriles **289** and **290** (in a ratio of 1 : 4) containing a hex-1-enyl substituent at the β position was prepared in a total yield of 53% from 1-phenyloct-3-en-1-yne (**291**) and trimethylsilyl cyanide in the presence of the cobalt cyclopentadienyl complex.[126]

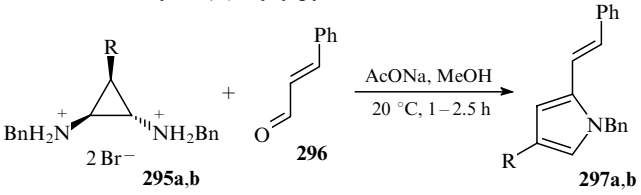


Thermolysis of β-cyclohexenyl α-azidoacrylates **292** in a solution of xylene, cyclohexane or DMF proceeded quantitatively to give substituted tetrahydrobenzo-2*H*-pyrroles **293** stable up to 130 °C.[127] Upon refluxing in xylene, the latter compounds were slowly rearranged through, apparently, the double 1,5-shift of the vinyl group to give 4,5,6,7-tetrahydro-2-methoxycarbonyl-3-vinylindoles **294**.[127]



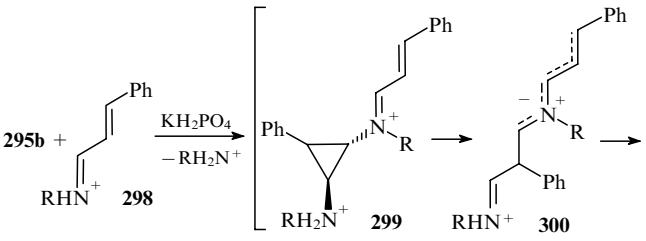
R = H, Ph, CH=CHPh.

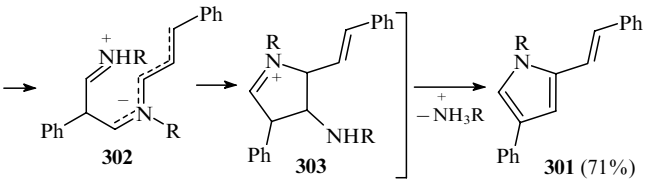
Treatment of *trans*-1,2-di(*N*-benzylammonio)cyclopropane dibromides **295a**,**b** with cinnamaldehyde (**296**) in an acetate buffer afforded 1-benzyl-2-(*E*)-styrylpyrroles **297a**,**b**.[128, 129]



R = H (**a**, 54%), Ph (**b**, 71%).

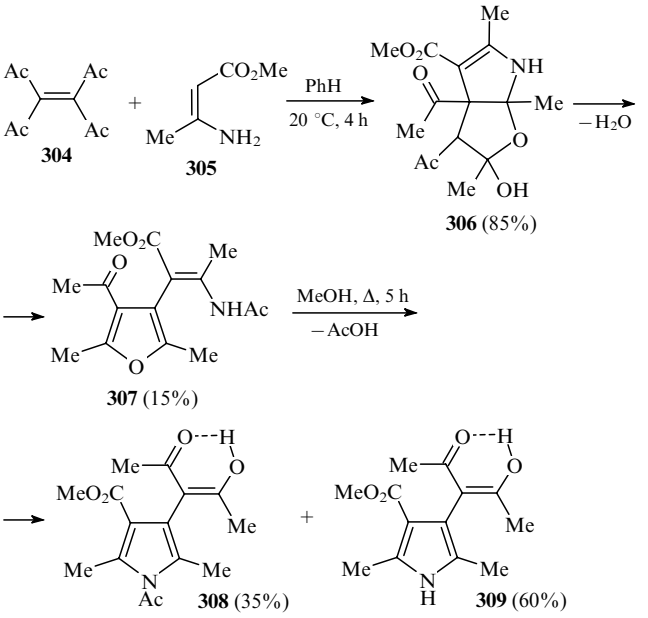
The reactions of K_2HPO_4 with salts of 3-phenylcyclopropane-1,2-diamines **295b** (R = Me, Bn) proceeded with the opening of the three-carbon ring to produce imminium ions **298**. The latter reacted with the salts **295** to give cyclopropane intermediates **299**. The ring opening in these intermediates afforded bipolar ions **300**. 2-Styrylpyrroles **301** were generated by cyclisation of intermediates **302** followed by aromatisation of 3,4-dihydro-2*H*-pyrroles **303**. The styrylpyrroles **301** were also derived from two molecules of the salt **295b** upon treatment with an aqueous solution of K_2HPO_4 (the yield was 59%) or AcONa (the yield was 60%).[129]



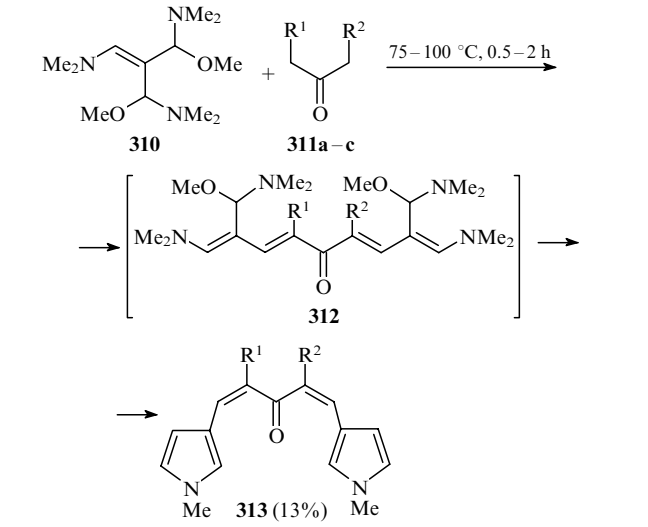


R = Me, Bn.

Tetraacetylethylene (**304**) reacted with methyl 3-aminobut-2-enoate (**305**) under mild conditions to give a mixture of dihydropyrrole **306** and tetrasubstituted furan **307**.[130] Upon refluxing in methanol, the latter underwent recyclisation to produce a mixture of *N*-acyl- (**308**) and NH-pyrroles (**309**).[130]

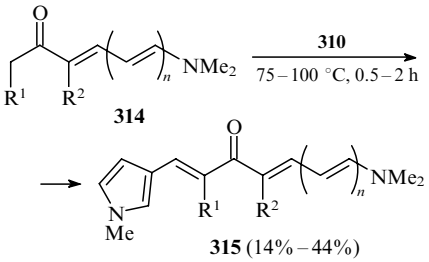


Condensation of 1,3-bis(dimethylamino)-2-[dimethylamino(methoxy)methyl]-1-methoxyprop-2-ene (**310**) with ketones **311a–c** did not furnish the expected polyenic bis(dimethylamino) ketones **312** containing the *N*,*O*-acetal groups at the γ,γ′ positions; instead, products of their intramolecular cyclisations, *viz*., di[β-(*N*-methylpyrrol-3-yl)vinyl] ketones **313**, were isolated.[131–133]



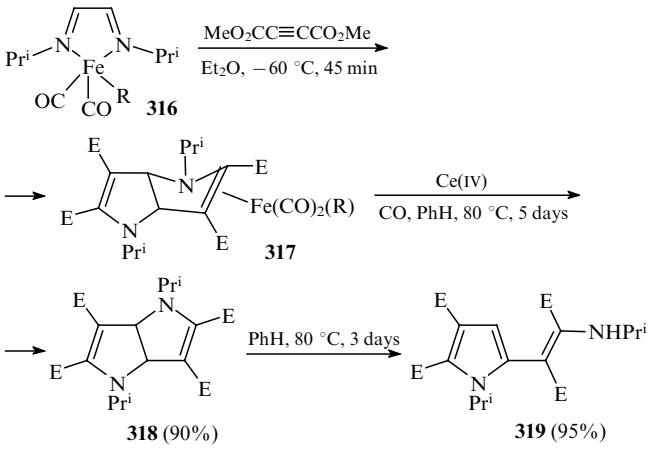
$R^1 = R^2 = H$ (**a**), $R^1–R^2 = (CH_2)_2$ (**b**), $(CH_2)_3$ (**c**).

The reactions of conjugated dimethylamino ketones **314** with the compound **310** taken in an equimolar ratio proceeded analogously to give unsaturated amino ketones **315** containing the pyrrole ring in one of the β positions.[131–133]



$R^1 = R^2 = H$; $R^1 =$ , $R^2 = H$; $R^1–R^2 = (CH_2)_2$, $(CH_2)_3$; $n = 0–2$.

The reactions of complexes **316** with dimethyl acetylenedicarboxylate proceeded as the 1,3-dipolar cycloaddition to the Fe–N=C fragment to form the 1,4,3*a*,6*a*-dihydropyrrolo[3,2-*b*]-pyrrole complexes **317** in good yields. Treatment of the latter with Ce(IV) led to liberation of dihydropyrrolo[3,2-*b*]pyrrole **318**.[134] Heating of the compound **318** in benzene caused the ring opening to give vinylpyrrole **319**.

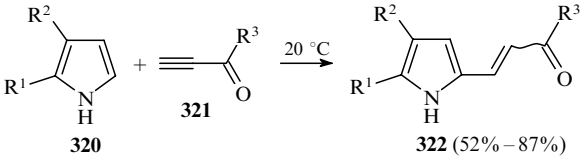


E = CO_2Me; R = CO, $CNBu^t$, $CNBu^i$, CNBn, CNC_6H_{11}-cyclo, CNC_6H_4Me-2, $CNC_6H_3Me_2$-2,6.

IV. Addition of pyrroles to acetylenes

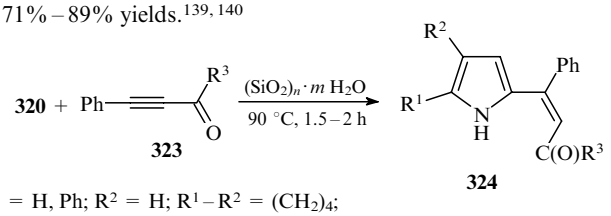
The direction of the reaction of pyrroles with activated acetylenes depends on the reaction conditions and the structures of the starting reagents. For example, diene condensation as well as C- or N-nucleophilic attack on the triple bond can occur.[16, 28, 29] In recent years, the addition of pyrroles as C-nucleophiles to the electron-deficient triple bond has been extensively studied because this reaction provides the most direct approach to functionally substituted *C*-vinylpyrroles.

Thus, the non-catalytic reactions of pyrroles **320** with terminal acylacetylenes **321** proceeded under mild conditions both without a solvent and in protic (methanol or ethanol) or aprotic (diethyl ether, benzene, hexane or acetonitrile) solvents to give 2-(2-acylvinyl)pyrroles **322** (predominantly, the *Z* isomers).[135–139] In the course of isolation and purification and even upon storage, the *Z* isomers are readily transformed into the *E* isomers.[135–139]



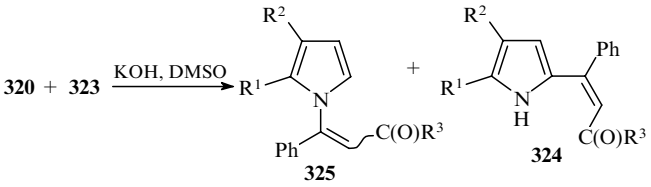
R^1 = H, Pr^n, Ph; R^2 = H, Me, n-C_7H_{15}; $R^1–R^2 = (CH_2)_4$; R^3 = Ph, 2-thienyl.

Unlike the alkynes **321**, 1-acyl-2-phenylacetylenes **323** are less reactive and do not react with pyrroles at 20 °C. The latter reaction was performed upon heating of equimolar amounts of the reagents in the presence of a 5–10-fold excess of silica gel. The *Z* isomers of 2-(2-acyl-1-phenylvinyl)pyrroles **324** were obtained in 71%–89% yields.[139, 140]



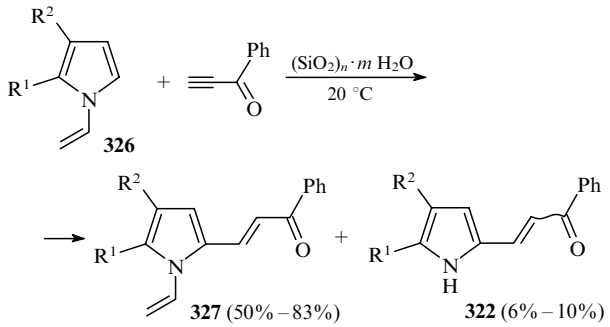
R^1 = H, Ph; R^2 = H; R^1–R^2 = $(CH_2)_4$;
R^3 = Ph, 2-thienyl, 2-furyl, CCl_3.

The reactions of the pyrroles **320** with ethynyl ketones **323** (R^3 = Ph, 2-furyl) in the superbasic KOH–DMSO system afforded a mixture of N- (**325**, *E* and *Z* isomers) and C-adducts (**324**, *Z* isomers) (in a total yield of 60%–80%), the ratio of the products being dependent on the structure of the starting pyrrole.[141]



R^1 = H, Ph; R^2 = H; R^1–R^2 = $(CH_2)_4$; R^3 = Ph, 2-furyl.

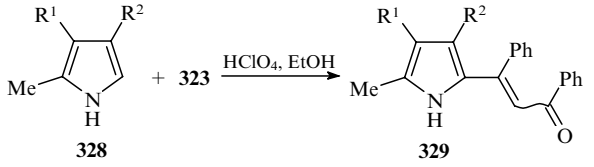
Regio- and stereospecific *C*-vinylation of 1-vinylpyrroles **326** with benzoylacetylene proceeded at 20 °C on the surface of silica gel under the conditions of mechanochemical activation to form *E* isomers of 1,2-divinylpyrroles **327**.[142]



R^1 = H, Me, Bu^n, 2,5-$Me_2C_6H_3$, Ph; R^2 = H, Me, Et, Pr^n.

The reactions of the pyrroles **326** (R^1 = Me and R^2 = Pr^n or R^1 = Ph and R^2 = Et) afforded compounds **327** along with the adducts **322**, which do not contain the vinyl substituent at the nitrogen atom. The formation of the latter compounds is associated with hydrolysis of the *N*-vinyl group both in the starting pyrroles **326** and in the reaction products **327** that occurs on SiO_2.[142]

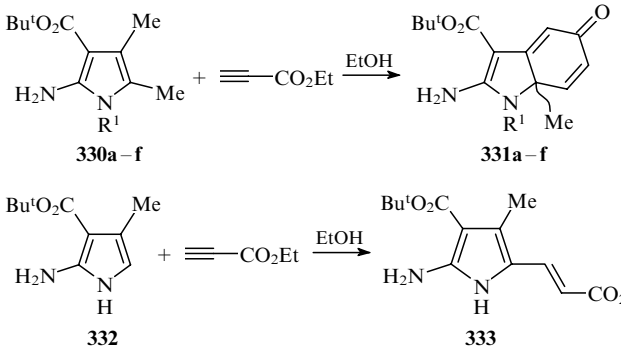
Trisubstituted pyrroles **328** reacted with phenylbenzoylacetylene (**323**, R^3 = Ph) in ethanol in the presence of $HClO_4$ to give vinylpyrroles **329** (mixtures of the *E* and *Z* isomers).[143]



R^1 = COMe, CO_2Me, CO_2Et; R^2 = Me, $(CH_2)_2CO_2H$.

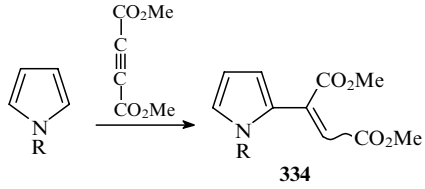
The yields of the vinylpyrroles **329** and the ratio of the *E* and *Z* isomers depend substantially on the structures of the starting compounds **328**. At R^1 = CO_2Me and R^2 = Me, the yield of the corresponding adduct **329** was 75% (the ratio *E*:*Z* = 7:1), whereas the adducts were obtained in yields of only 56% (*E*:*Z* = 2:1) and 12% (*E*:*Z* = 9:1) at R^1 = CO_2Me, R^2 = $(CH_2)_2CO_2H$ and R^1 = COMe, R^2 = $(CH_2)_2CO_2H$, respectively.[143]

The reactions of substituted 2-amino-4,5-dimethylpyrroles **330a**–**f** with ethyl propiolate proceeded predominantly as the cycloaddition resulting in functionalised dihydroindoles **331a**–**f**. Under the analogous conditions, the reaction of pyrrole **332**, which contains no substituents at positions 1 and 2, gave rise to (*E*)-2-vinylpyrrole **333** in 68% yield.[144]



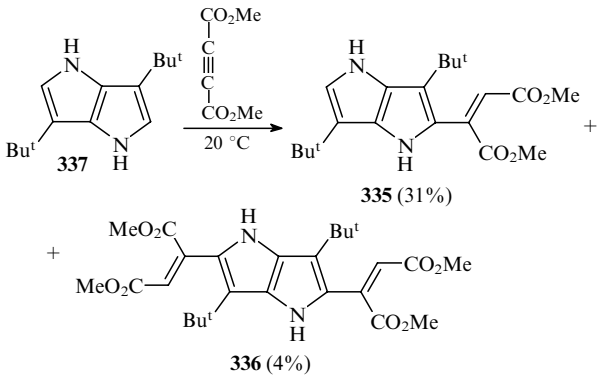
R^1 = Pr^n (**a**), $(CH_2)_2OMe$ (**b**), $(CH_2)_2Ph$ (**c**), Bn (**d**), 2-pyridylmethyl (**e**), 3-pyridylmethyl (**f**).

N-Substituted pyrroles add to dimethyl acetylenedicarboxylate to form mixtures of the *E* and *Z* isomers of 2-vinylpyrroles **334**. The reactions proceed upon stirring of the reagents at 20 °C or upon ultrasonic irradiation. In the latter case, the pyrroles are produced in substantially higher yields.[145]

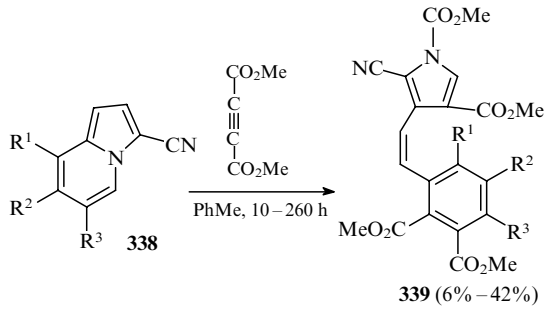


R = Me, $(CH_2)_2CN$, Ph.

A mixture of 2-vinyl- (**335**) and *E*,*Z*-2,5-divinylpyrrolo[3,2-*b*]-pyrroles **336** was obtained in the reaction of pyrrolopyrrole **337** with an excess of dimethyl acetylenedicarboxylate at 20 °C.[146] A mixture of the *E* and *Z* isomers of the divinylpyrrole **336** (in 24% and 47% yields, respectively) can also be prepared by the addition of the monoadduct **335** to dimethyl acetylenedicarboxylate under the same conditions.[146]

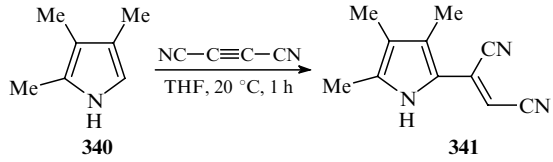


Recyclisation of indolizine-3-carbonitriles **338** under the action of dimethyl acetylenedicarboxylate selectively afforded the *Z* isomers of functionally substituted 3-styrylpyrroles **339**.[147]

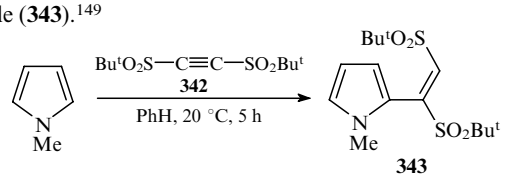


R^1 = H, Me; R^2 = H, Me, CN, Bn; R^3 = H, Me.

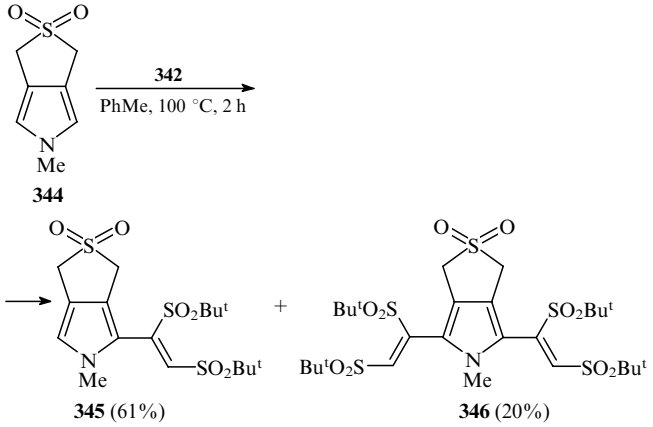
The reaction of 2,3,4-trimethylpyrrole (**340**) with dicyanoacetylene produced (*E*)-2-(1,2-dicyanovinyl)pyrrole **341** as the major product (in 63% yield), whereas the yield of the *Z* isomer was only 9%.[148]



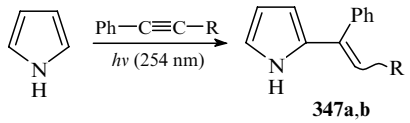
1-Methylpyrrole reacted with di(*tert*-butylsulfonyl)acetylene (**342**) to give (*E*)-2-[1,2-di(*tert*-butylsulfonyl)vinyl]-1-methylpyrrole (**343**).[149]



Heating of pyrrolosulfolene **344** with the acetylene **342** produced a mixture of *E* isomers of 2-vinyl- (**345**) and 2,5-divinylpyrroles (**346**).[150]



The photochemical reactions of pyrrole with phenyl- and diphenylacetylenes afforded 2-(1-phenylvinyl)- (**347a**) and 2-(1,2-diphenylvinyl)pyrroles **347b** (a mixture of the *E* and *Z* isomers in approximately equal amounts) in yields of only 7% and 9%, respectively.[151]



R = H (**a**), Ph (**b**).

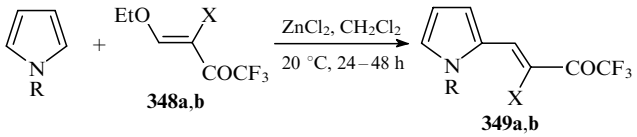
The low yields of the adducts were accounted[151] for by photoinduced dimerisation of arylacetylenes and the instability of the adduct **347a** in air.

V. Substitution reactions at the double bond

1. Substitution of functional groups in electron-deficient alkenes

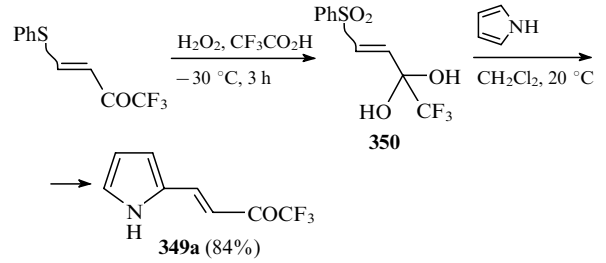
In recent years, the substitution of functional groups at the electrophilic double bond or the catalytic replacement of the hydrogen atom of the alkene fragment by halogenopyrroles (Heck and Stille reactions) have found wide use in the synthesis of *C*-vinylpyrroles.

The reactions of 1*H*- and 1-methylpyrroles with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**348a**) and 3-(ethoxymethylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione (**348b**), which are products of mono- and bistrifluoroacetylation of ethyl vinyl ether, respectively, led to the substitution of the ethoxy group and the formation of 2-(2-trifluoroacetyl)vinylpyrroles **349a**,**b**. The reactions proceeded under mild conditions in the presence of 25 mol.% $ZnCl_2$. In the presence of other Lewis acids, the reactions are accompanied by substantial resinification. The reaction of the ketone **348a** proceeded stereospecifically to produce the *E* isomer.[152–154]

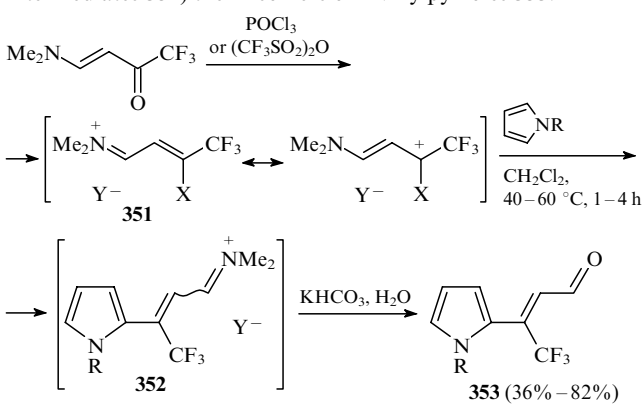


R = H, Me; X = H (**a**, 53%), $COCF_3$ (**b**, 88%).

The pyrrole **349a** (R = H) was also synthesised from 1*H*-pyrrole and 1,1,1-trifluoro-4-(phenylsulfonyl)but-3-ene-2,2-diol (**350**), which was prepared by oxidation of the trifluoroacetylation product of vinyl sulfide. The reaction proceeded under mild conditions as addition–elimination.[154, 155]

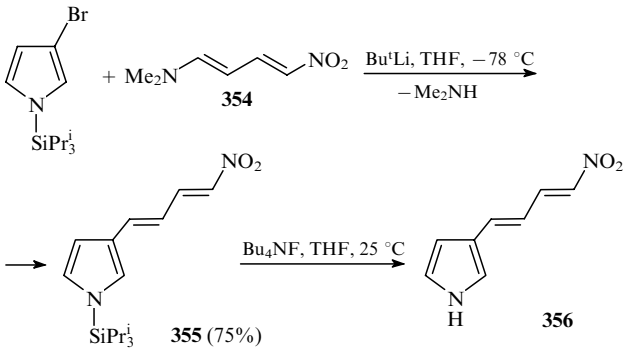


The reactions of iminium complex **351**, which was generated in the reaction of 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one with $POCl_3$ or trifluormethanesulfonic anhydride, with pyrroles proceeded stereospecifically to give finally (after hydrolysis of intermediates **352**) the *E* isomers of 2-vinylpyrroles **353**.[154, 156]

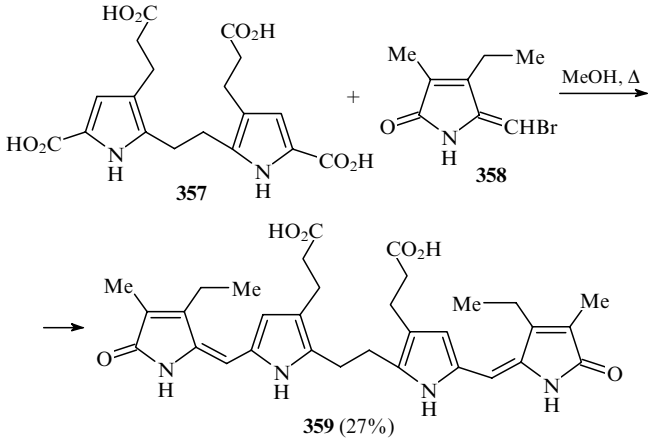


R = H, Me, Ph; X = $OP(O)Cl_2$, CF_3SO_2O; Y = Cl, $POCl_2$, CF_3SO_2O.

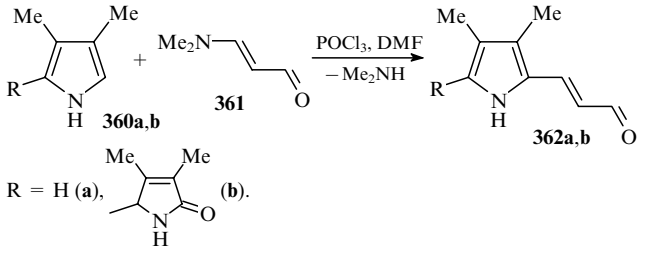
Condensation of 3-bromo-1-(triisopropylsilyl)pyrrole with nitrodieneamine **354** led to the replacement of the dimethylamino group to form 3-(4-nitrobuta-1,3-dienyl)-1-(triisopropylsilyl)pyrrole (**355**). Desilylation of the latter afforded pyrrole **356**.[157]



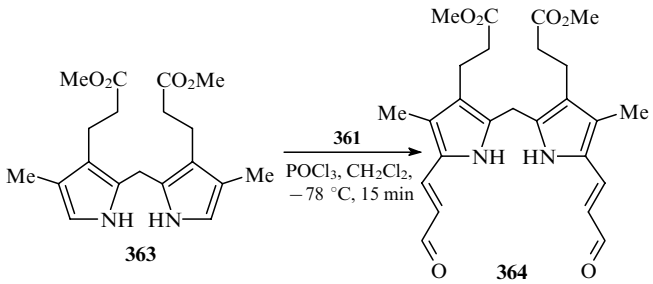
Refluxing of bispyrrole **357** with bromomethylidene-2,5-dihydropyrrol-2-one **358** in methanol produced homorubin **359**.[90] Initially, the compound **357** underwent α-decarboxylation and then the α-unsubstituted pyrrole reacted with the compound **358**.[90]



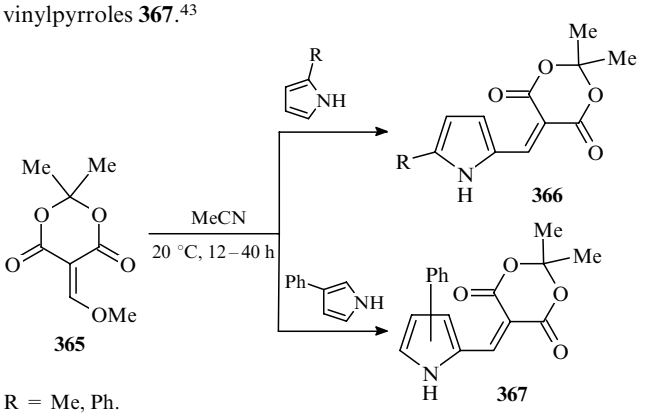
Vilsmeier double formylation of 3,4-dimethylpyrrole **360a**[158, 159] and dipyrrinone **360b**[159] with 3-(dimethylamino)-acrolein (**361**) afforded 2-vinylpyrroles **362a**,**b**.



Bispyrrole **363** was formylated with the acrolein **361** at both α positions to give bis[(formylvinyl)pyrrol-2-yl]methane **364**.[160]

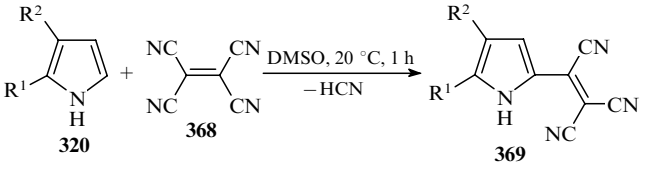


The reactions of 2-methyl- and 2-phenylpyrroles with the methoxymethylidene derivatives of Meldrum's acid **365** proceeded regioselectively under mild conditions to give 2-vinylpyrroles **366** in 60% and 70% yields, respectively.[43] Under analogous conditions, the reaction of 3-phenylpyrrole with the compound **365** produced a mixture (~1 : 1) of 3- and 4-phenyl-2-vinylpyrroles **367**.[43]



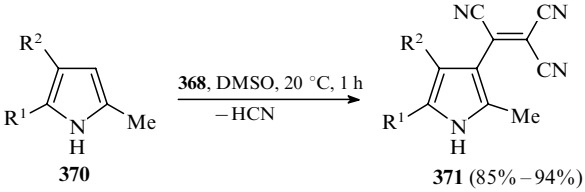
R = Me, Ph.

In the reactions of the pyrroles **320** with tetracyanoethylene (**368**), one of the nitrile groups in the latter compound was replaced to form 2-(tricyanovinyl)pyrroles **369** in quantitative yields.[161]



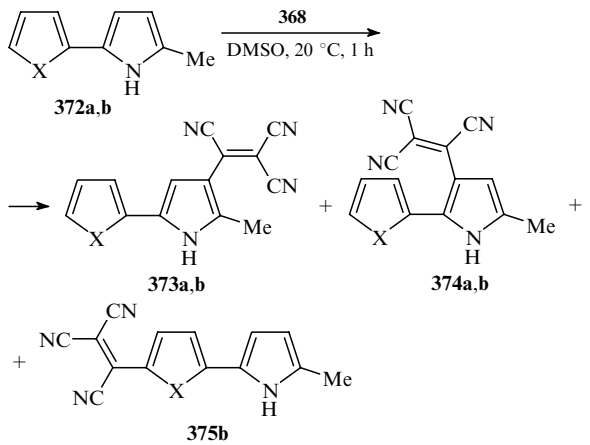
R^1 = H, Ph, R^2 = H; R^1–R^2 = (CH$_2$)$_4$.

The pyrroles **370** containing substituents at both α positions reacted with tetracyanoethylene (**368**) under the same conditions to give 3-tricyanovinylpyrroles **371**.[162, 163]



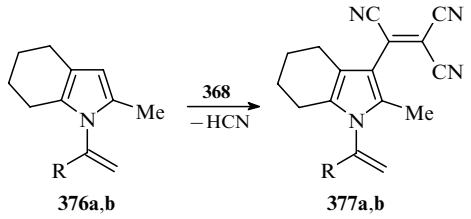
R^1 = Me, Ph, R^2 = H; R^1–R^2 = (CH$_2$)$_4$.

5-Methyl-2-(2-thienyl)pyrrole (**372a**) reacted with tetracyanoethylene (**368**) to yield 3-tricyanovinyl isomer **374a** along with 4-tricyanovinyl derivative **373a**.[162, 163] Under these conditions, 2-(2-furyl)-5-methylpyrrole (**372b**) behaved differently, *viz*., the major direction of the reaction with tetracyanoethylene involves the attack on the α position of the furan ring giving rise to product **375b**.



X	Yield (%)		
	373	**374**	**375**
S (**a**)	75	15	–
O (**b**)	18	9	67

The reactions of 1-vinyl- and 1-prop-2-enyl-substituted pyrroles **376a**,**b** with tetracyanoethylene (**368**) taken in equimolar amounts in DMSO afforded 3-tricyanovinyl-1-vinyl- (**377a**) and 1-(prop-2-enyl)-3-tricyanovinyl-susbtituted (**377b**) derivatives, respectively, as the only products.[162,163]



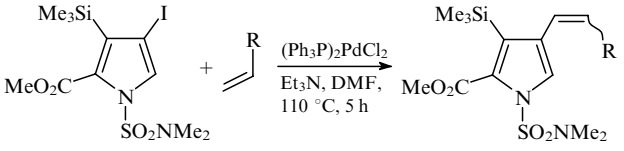
376a,**b** **377a**,**b**

R = H (**a**, 92%), Me (**b**, 91%).

Hence, the *N*-alkenyl substituent in the pyrroles **376a**,**b** does not react with tetracyanoethylene according to the [2 + 2]-cycloaddition mechanism typical of other 1-vinyl-substituted heterocyclic compounds.[164]

2. Catalytic vinylation of halogenopyrroles

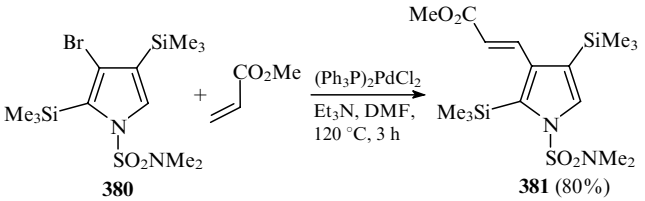
The Heck reaction of 4-iodopyrrole **378** with acrylonitrile in the presence of bis(triphenylphosphine)palladium chloride afforded a mixture of (*E*)- and (*Z*)-4-vinylpyrroles **379a** in 45% and 17% yields, respectively. The corresponding reactions involving methyl acrylate or methyl vinyl ketone proceeded stereoselectively to give pyrroles *Z*-**379b** or *E*-**379c**, respectively.[165]



378 **379a**–**c**

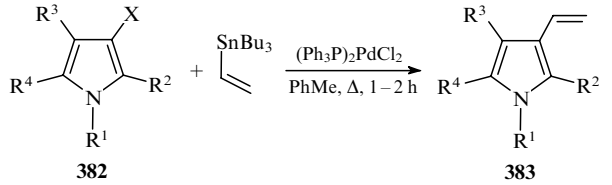
R = CN (**a**), CO_2Me (**b**), COMe (**c**).

Under analogous conditions, the reaction of 3-bromopyrrole **380** with methyl acrylate also proceeded selectively to form the *E* isomer of pyrrole **381**.[165]



380 **381** (80%)

The reactions of 4-halogenopyrroles **382** with vinyltributyltin (Stille reaction) were examined. 4-Iodopyrroles produced 4-vinylpyrroles **383** in 80%–92% yields. The reactions proceeded upon refluxing of the reagents in toluene in the presence of bis(triphenylphosphine)palladium chloride. Under analogous conditions, 4-bromopyrrole gave the corresponding 4-vinylpyrroles in low yields (10%–15%), whereas the reaction of 4-chloropyrrole with vinyltributyltin did not proceed at all.[166]

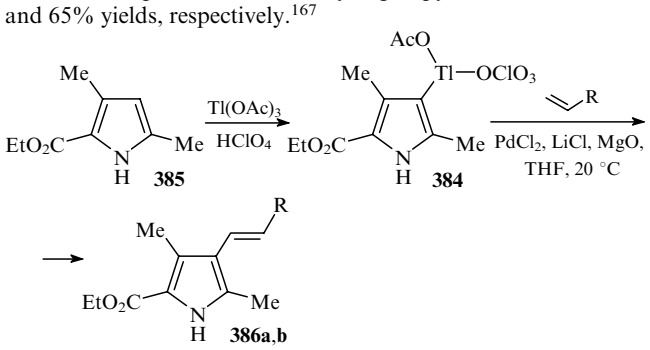


382 **383**

R^1 = H, Me, COPh, Ts; R^2 = H, Me; R^3 = H, Me;
R^4 = CHO, CO_2Et; X = Cl, Br, I.

Alkenyl derivatives of heteroaromatic compounds can also be prepared by Tl(III)–Pd(II) transmetallation. This reaction does not require thorough drying of the reagents and solvents and the use of an inert atmosphere and proceeds under mild conditions (often regio- and stereospecifically), Pd(II) complexes being used in catalytic amounts.

Thus hydrogen was readily replaced in methyl acrylate and styrene under the action of ethyl 4-[(acetoxyperchloryl)thallio]-3,5-dimethylpyrrole-2-carboxylate (**384**), which was synthesised from ethyl 3,5-dimethylpyrrole-2-carboxylate (**385**) and $Tl(OAc)_3$.[167] Olefination was carried out in the presence of $PdCl_2$, MgO or LiCl with the molar ratio pyrrole : alkene : ($PdCl_2$ – LiCl) = 1 : (5–10) : 0.1. It is necessary to add a base (generally, magnesium oxide or potassium carbonate) with the aim of preventing side reactions of pyrroles, which proceed in the presence of strong acids generated in the course of alkenylation. The reactions proceeded selectively to give pyrroles **386a**,**b** in 43% and 65% yields, respectively.[167]



386a,**b**

R = CO_2Me (**a**), Ph (**b**).

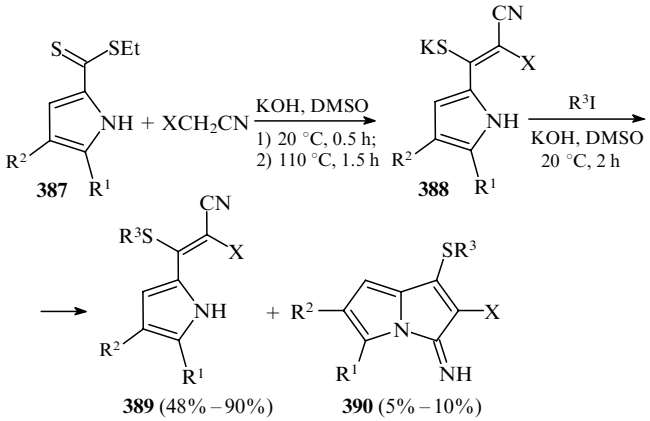
VI. Other procedures for the introduction of the vinyl group into the pyrrole ring

1. Synthesis from pyrrolecarbodithioates

Once a convenient and versatile procedure has been developed for the synthesis of pyrrole-2- and -3-carbodithioates by the direct reactions of pyrroles with carbon disulfide in the KOH–DMSO system,[168–178] these compounds found wide use in the synthesis of functionalised *C*-vinylpyrroles.[178–181]

The reactions of pyrrole-2-carbodithioates **387** with CH-acids (malononitrile, cyanoacetamide and ethyl cyanoacetate) in the KOH–DMSO system followed by alkylation of intermediate thiolates **388** with alkyl halides produced 2-vinylpyrroles **389**.[179–181] All three steps of the reactions were carried out in one pot.

The reactions of the pyrrole-2-carbodithioates **387** with malononitrile and cyanoacetamide afforded 2-vinylpyrroles **389** along with small amounts of products of their intramolecular cyclisation, *viz*., 3-imino-3*H*-pyrrolizines **390**. The reactions of the pyrrole-2-carbodithioates **387** with ethyl cyanoacetate gave rise to pyrrolizin-3-ones **391** as the major condensation products.



387 **388**

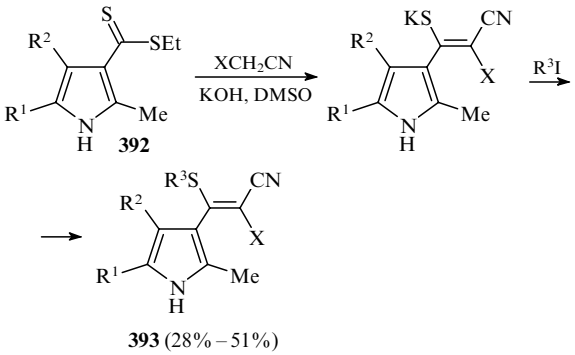
389 (48%–90%) **390** (5%–10%)

X = CN, $CONH_2$.



R^1 = Me, Pr^n, Bu^n, Ph; R^2 = H, Me, Et, Pr^n; R^1-R^2 = $(CH_2)_4$;
R^3 = Me, Et, Bu^n, All; X = CN, $CONH_2$, CO_2Et.

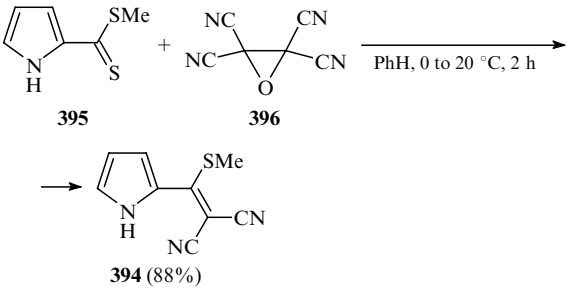
Under analogous conditions, pyrrole-3-carbodithioates **392** selectively reacted with nitriles containing the activated methylene group to form 3-vinylpyrroles **393**.[178]



R^1 = Me, Ph; R^2 = H, Me; R^1-R^2 = $(CH_2)_4$;
R^3 = Me, Et; X = CN, $CONH_2$, CO_2Et.

3-Vinylpyrroles **393** were obtained in low yields due to instability of the pyrrole-3-carbodithioates **392**, which partially (by 10%–20%) decomposed to 3-unsubstituted pyrroles under the reaction conditions.

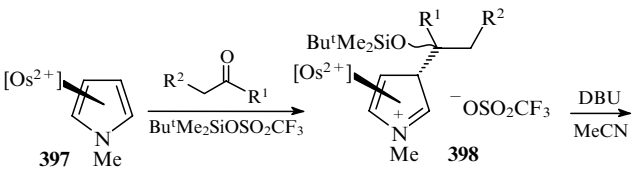
(2,2-Dicyano-1-methylthiovinyl)pyrrole (**394**) was synthesised from methyl pyrrole-2-carbodithioate **395** and epoxide **396**.[182]

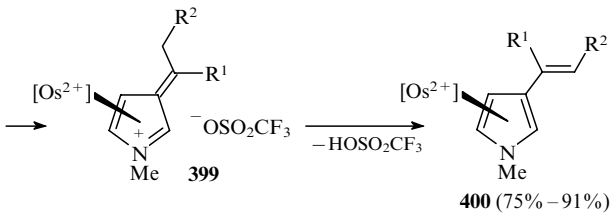


2. Vinylation of osmium complexes of pyrroles

In the pentaammineosmium complex of 1-methylpyrrole **397**, which was prepared from 1-methylpyrrole and $Os(NH_3)_5(OTf)_3$ in quantitative yield, the electrophilic activity of the C(3) atom is much higher than that of the C(3) atom in free pyrrole. This complex can be readily transformed into the 3-vinylpyrrole complexes according to several procedures.[183–186]

One procedure involves the reaction of complex **397** with a twofold excess of ketone in the presence of 1 equiv. of *tert*-butyldimethylsilyl triflate to form silylated aldol adducts **398**. Diazabicycloundecene-catalysed elimination of silanol $HOSiMe_2Bu^t$ followed by deprotonation of azafulvenium intermediates **399** afforded 3-vinylpyrrole complexes **400**.[183, 185]

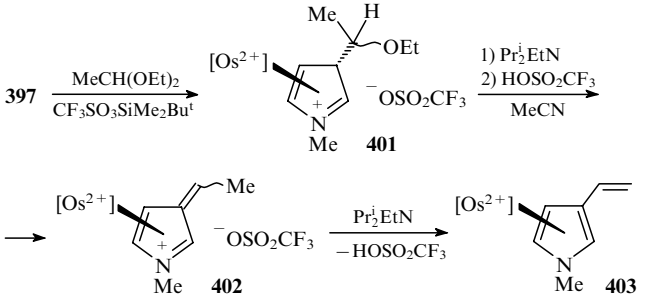




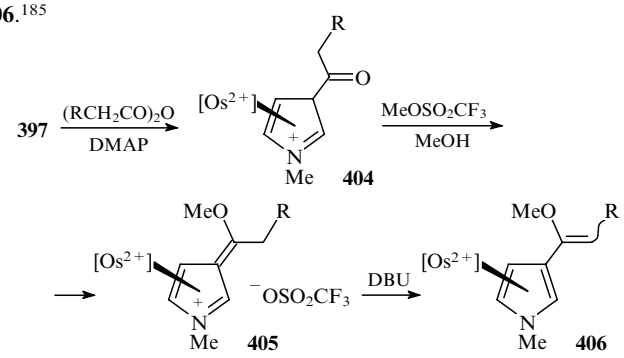
Hereinafter, $[Os^{2+}] = [Os^{II}(NH_3)_5]^{2+}$; R^1 = Me, Et, Pr^i, Ph;
R^2 = H, Me; R^1-R^2 = $(CH_2)_4$.

Another procedure involves the reaction of the complex **397** with acetaldehyde diethyl acetal in the presence of *tert*-butyldimethylsilyl triflate. In this case, 3*H*-pyrrole adduct **401** is generated. After deprotonation and elimination of ethanol catalysed by trifluoromethanesulfonic acid, compound **401** gives azafulvenium complex **402** in 93% yield (a mixture of stereoisomers in a ratio of 3 : 2).

Deprotonation of the complex **402** afforded unstable complex **403**, which was isolated as a product of the reaction with *N*-phenylmaleimide.[185]

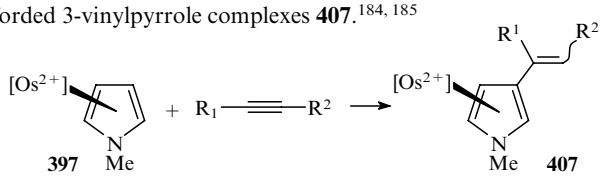


Yet another approach to 3-vinylpyrrole complexes of osmium is based on acylation of the pyrrole **397** with acid anhydrides in the presence of 4-dimethylaminopyridine (DMAP). Due to the nucleophilic properties, the oxygen atom of the carbonyl group in complex **404** can be methylated with methyl trifluoromethanesulfonate to give 2-azafulvenium complex **405**. The addition of diazabicycloundecene to the complex **405** led to deprotonation and the formation of methoxy-substituted 3-vinylpyrrole complex **406**.[185]



R = H, Me.

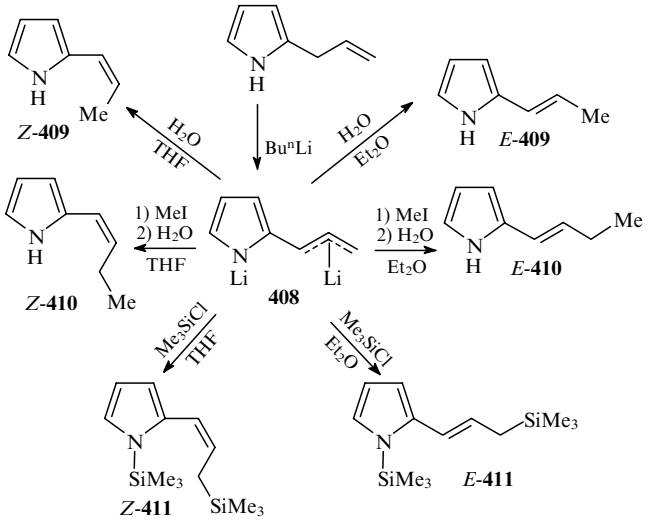
The addition of the complex **397** to activated acetylenes also afforded 3-vinylpyrrole complexes **407**.[184, 185]



R^1 = H, CO_2Me, Ph; R^2 = COMe, CO_2Me.

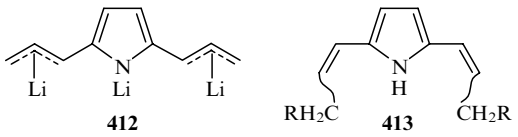
3. Synthesis from allyl derivatives

2-Allylpyrrole was transformed into *N*,*C*-dilithium derivative **408** in high yield under the action of 2 equiv. of Bu^nLi in the hexane–diethyl ether system. The compound **408** selectively reacts with various electrophilic agents (H_2O, MeI, Me_3SiCl) to form 2-(alk-1-enyl)pyrroles **409**–**411**.[187]



The reactions in Et_2O at 0 °C gave rise to the *E* isomers, whereas the reactions in THF afforded the *Z* isomers of compounds **409**–**411**.

The reactions of the *N*,*C*,*C*-trilithium derivative of 2,5-diallylpyrrole **412** with electrophiles (H_2O, D_2O, MeI, Me_3SiCl and Me_3SnCl) in THF proceed selectively to produce the *Z* isomers, whereas these reactions in the hexane–diethyl ether system give rise to mixtures of the *E* and *Z* isomers of 2,5-di(alk-1-enyl)pyrroles **413**.[188]

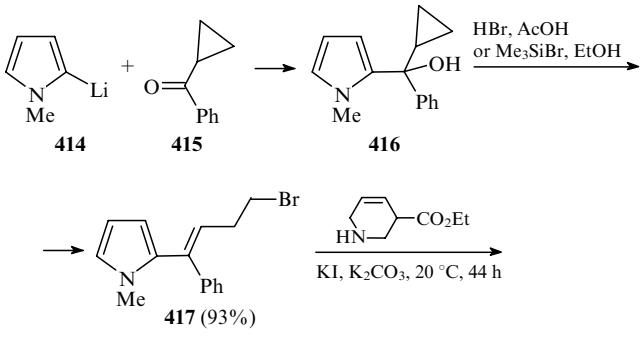


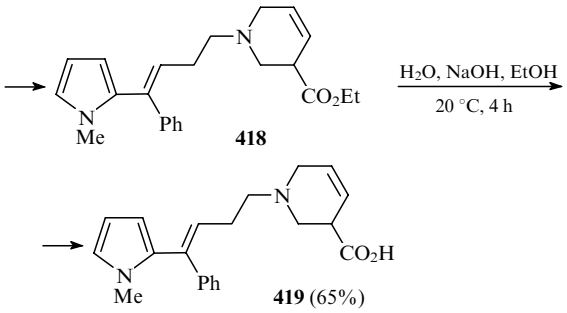
412 **413**

R = H, Me, $SiMe_3$, $SnMe_3$.

4. Condensation with carbonyl compounds and their synthetic equivalents

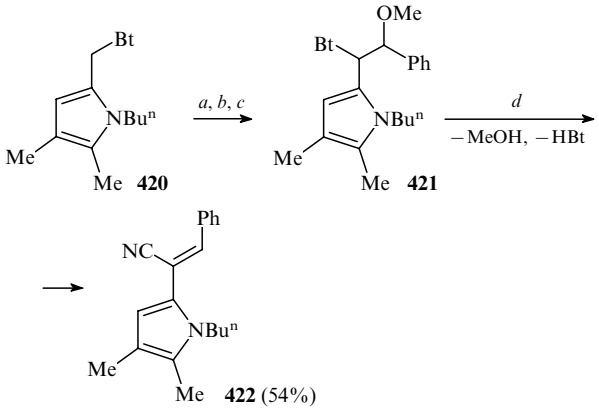
2-Lithio-1-methylpyrrole (**414**) reacted with cyclopropyl phenyl ketone (**415**) to form alcohol **416** whose three-carbon ring was opened under the action of either HBr in AcOH or Me_3SiBr in EtOH to give (*E*)-4-bromo-1-(1-methylpyrrol-2-yl)-1-phenylbut-1-ene (**417**).[189]

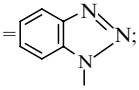




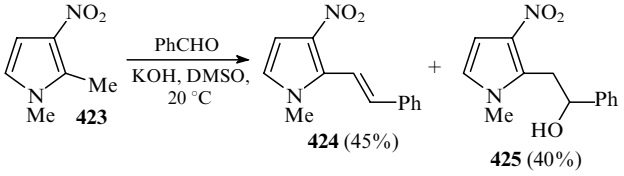
Alkylation of ethyl 1,2,3,6-tetrahydropyridine-3-carboxylate with the bromine-containing derivative **417** followed by hydrolysis of ester **418** produced acid **419**.[189]

Successive treatment of pyrrole **420** with Bu^nLi, benzaldehyde and methyl iodide in hexamethylphosphoramide (HMPA) afforded pyrrole **421**. The nucleophilic replacement of the benzotriazole group in the latter compound by the nitrile group followed by elimination of methanol gave 2-vinylpyrrole **422**.[190]



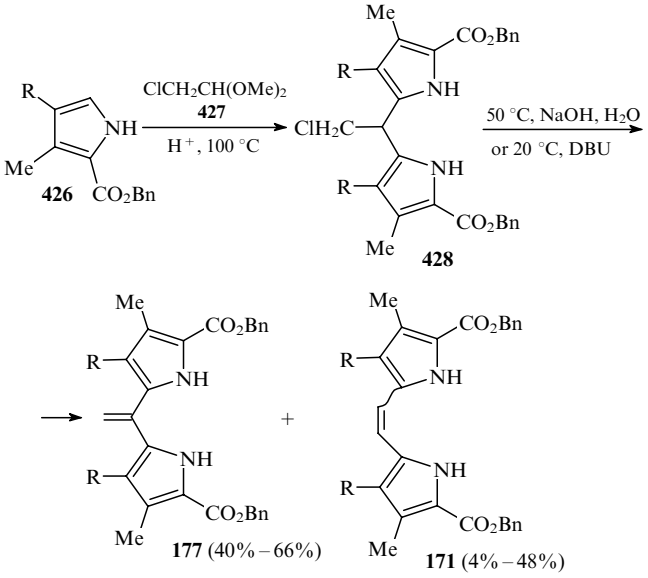
Bt = ; (*a*) Bu^nLi, THF, −78 °C; (*b*) PhCHO, THF, −78 °C; (*c*) MeI, HMPA, −78 to 20 °C; (*d*) NaCN, DMF, Δ, 12 h.

Base-catalysed condensation of 1,2-dimethyl-3-nitropyrrole (**423**) with benzaldehyde in the KOH–DMSO system afforded a mixture of 2-vinylpyrrole **424** and alcohol **425**.[191]



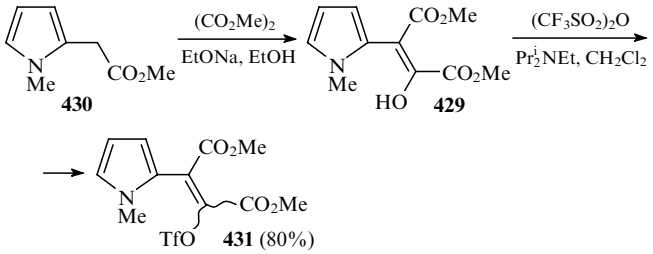
Condensation of pyrrole **426** with chloroacetaldehyde dimethyl acetal **427** proceeded upon heating in the presence of *p*-toluenesulfonic acid to form (chloromethyl)di(pyrrol-5-yl)methanes **428** in 75%–91% yields. The use of montmorillonite K-10 as an acid catalyst makes it possible to perform this process at 20 °C with retention of high yields of dipyrrolylmethanes **428**.[91]

Elimination of HCl from (chloromethyl)dipyrrolylmethanes **428** afforded 1,2-di(pyrrol-5-yl)ethenes **171** (a mixture of the *E* and *Z* isomers) along with 1,1-di(pyrrol-5-yl)ethenes **177**. This pathway allows one to prepare the 1,1-di(pyrrol-5-yl)ethenes **177** in higher yields compared to those obtained by acylation of the 3,4-dimethylpyrrolecarboxylic esters **176** (see Section II.4).[91,94]



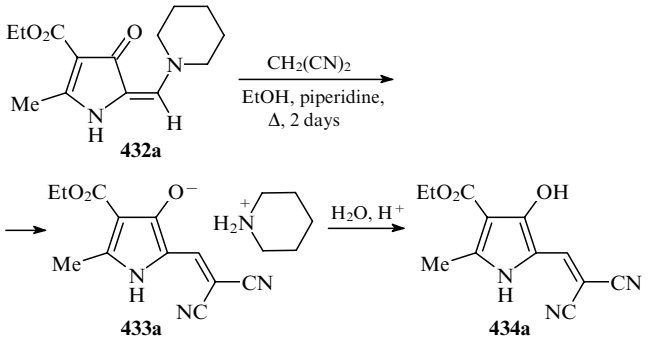
R = Me, Et.

Treatment of substituted 2-vinylpyrrole **429**, which was synthesised from 2-(methoxycarbonylmethyl)-1-methylpyrrole **430** and dimethyl oxalate, with trifluoromethanesulfonic anhydride afforded a mixture of *E*- and *Z*-triflates **431** in a ratio of 5 : 1.[192]

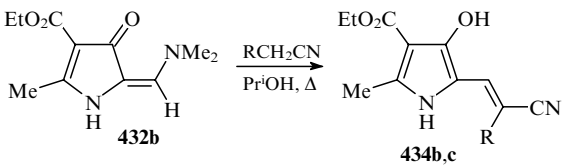


5. Synthesis from enaminoketones of the pyrrole series

Enaminoketone **432a** reacted with malononitrile to form salt **433a** whose acidification gave rise to 5-(2,2-dicyanovinyl)-3-ethoxycarbonyl-4-hydroxy-2-methylpyrrole **434a**.[34, 37]

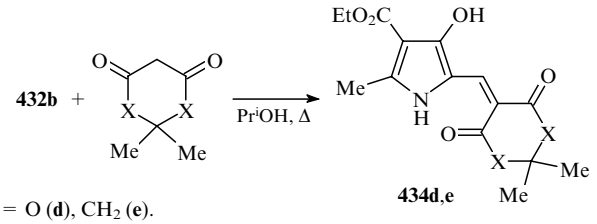


Vinylpyrroles **434b**,**c** were synthesised from enaminoketone **432b** and derivatives of cyanoacetic acid upon refluxing in isopropyl alcohol.[34]



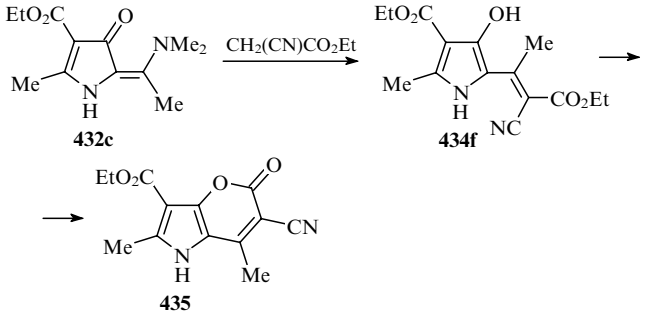
R = C(O)NH2 (**b**), CO2Et (**c**).

Under the same conditions, the enaminoketone **432b** reacted with Meldrum's acid and dimedone to give vinylpyrrole derivatives **434d**,**e**.[34]

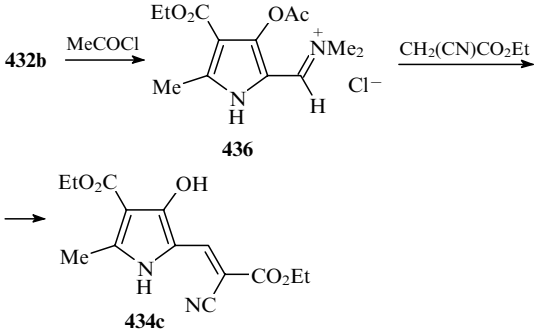


X = O (**d**), CH_2 (**e**).

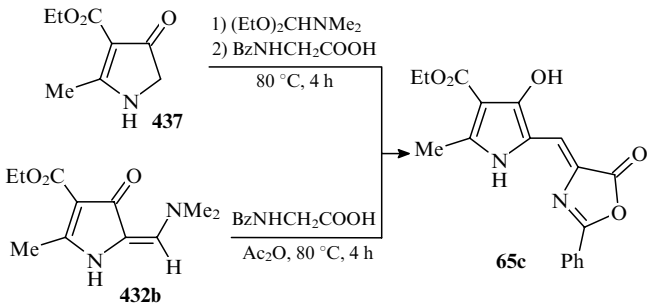
Condensation of the enaminoketone **432c** with ethyl cyanoacetate was accompanied by further cyclisation of pyrrole **434f** to 6-cyano-3-ethoxycarbonyl-2,7-dimethyl-5-oxopyrano[3,2-*b*]pyrrole (**435**).[34]



Vinylpyrrole **434c** can be prepared from immonium salt **436**, which was generated upon treatment of the enaminoketone **432b** with acetyl chloride.[36]



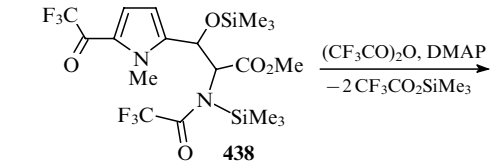
The pyrrole **65c** containing the azlactone substituent at the vinyl group was synthesised according to two procedures, *viz*., by aminomethylenation of ketone **437** with dimethylformamide diethyl acetal followed by the reaction of hippuric acid and by the reaction of the enaminoketone **432b** with hippuric acid in acetic anhydride.[48]

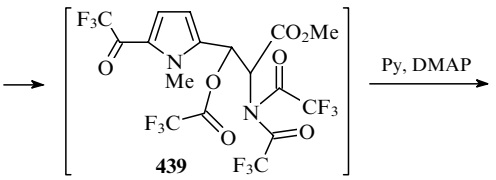


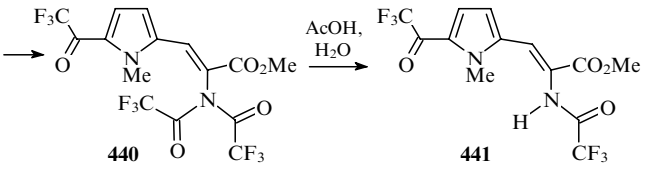
6. Other reactions

Elimination of trimethylsilyl trifluoroacetate [$(CF_3CO)_2O$, DMAP, dichloroethane] from compound **438** afforded intermediate **439**, which produced functionalised 2-vinylpyrrole **440** in the

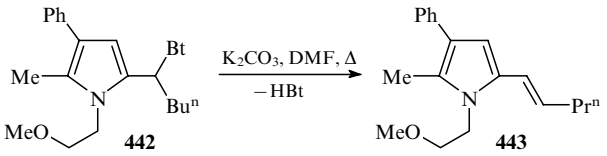
presence of pyridine and DMAP.[193] The compound **440** is unstable due to its high sensitivity to hydrolysis and is transformed into vinylpyrrole **441** after treatment with dilute acetic acid.[193]



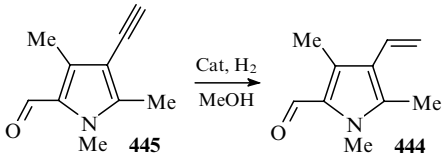




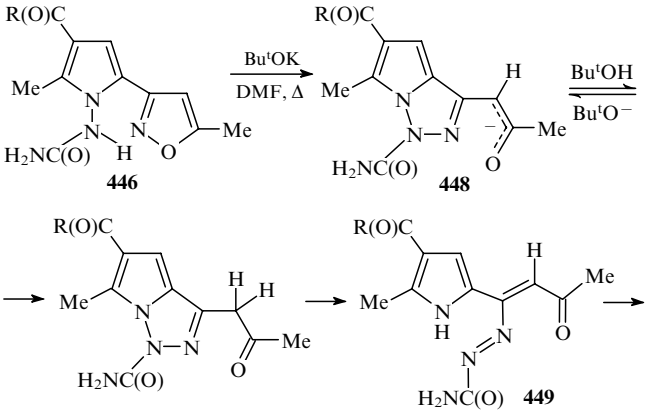
Refluxing of substituted pyrrole **442** in DMF in the presence of potassium carbonate led to elimination of benzotriazole to give 2-(pent-1-enyl)pyrrole **443** in 57% yield ($E:Z = 3:1$).[190]

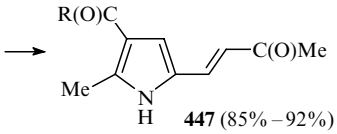


4-Vinylpyrrole **444** was prepared in 65% yield by selective hydrogenation of 4-ethynylpyrrole **445** in the presence of the Lindlar catalyst partially deactivated with 3,6-dithiaoctane-1,8-diol.[98]



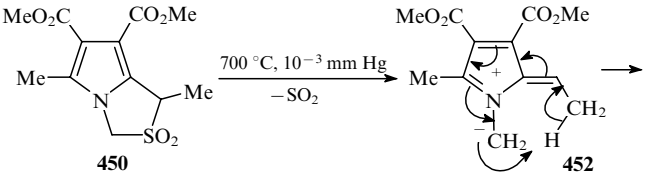
Substituted *N*-ureidopyrroles **446** were transformed into 5-vinylpyrroles **447** with the *E* configuration upon refluxing in DMF in the presence of Bu^{t}OK.[194] Their formation was attributed to the intramolecular nucleophilic attack of the deprotonated ureido group on the isoxazole nitrogen atom followed by isomerisation of intermediate **448** to azocarbonyl compound **449**, which gave the pyrroles **447** under the reaction conditions.

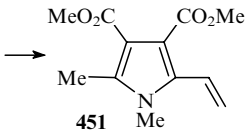




R = Me, OEt.

Vacuum pyrolysis of dihydrothienopyrrole *S*,*S*-dioxide **450** led to elimination of SO_2 to give 2-vinylpyrrole **451** whose formation proceeded, apparently, through the [1,8-*H*]-shift in the 1,7-bipolar system **452**.[195]





VII. Conclusion

The data surveyed in the present review demonstrate considerable advances in the synthesis of functionalised *C*-vinylpyrroles achieved in the last decade. Known procedures for the synthesis, which are based on reactions of acylpyrroles with CH-acids and the Wittig and Wittig – Horner reagents, are being improved and new preparative reactions, which could enable one to prepare *C*-vinylpyrroles from more readily accessible starting compounds, are being searched for. In particular, the reactions of alkenyl ketone oximes with acetylene in the KOH – DMSO system and base-catalysed condensation of pyrrolecarbodithioates, which have recently become available, with CH-acids are being extensively developed. These reactions provide simple approaches to groups of *C*-vinylpyrroles, which have previously been not easily accessible or unknown, starting from available compounds.

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