Translated from *Uspekhi Khimii* **34** 275–302 (1989) U.D.C. 547.741

Synthesis of pyrroles from aliphatic compounds

L N Sobenina, A I Mikhaleva, B A Trofimov
Irkutsk Institute of Organic Chemistry, Siberian Branch, USSR Academy of Sciences

ABSTRACT. The most recent information about the methods for constructing a pyrrole ring from functional aliphatic compounds has been classified and correlated.
The bibliography includes 196 references.

Contents

I. Introduction 163
II. $C_2 + C_2$ reactions 163
III. $C_3 + C_1$ reactions 171
IV. $C_4 + N$ (C_4-N) reactions 173

I. Introduction

The pyrrole ring forms part of the molecular structure of many natural and biologically active compounds. Hence the constant interest in the chemistry of pyrroles is understandable. Since the last monographs[1–3] and reviews[4–7] appeared, covering different questions concerning the structure, reactivity, and synthesis of pyrroles, a large number of new studies in this field which require classification and correlation have been published in the literature.

The many methods for synthesising pyrroles can be divided into three main groups: cyclisation of functional aliphatic compounds, conversion of five-membered heterocyclic compounds containing one nitrogen atom in the ring, and conversions of other heterocycles.

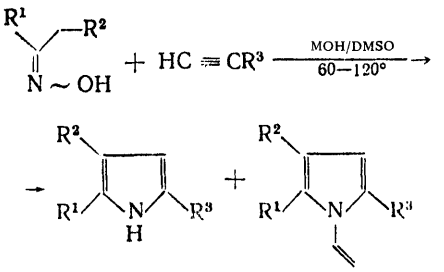
The methods for synthesising pyrroles by cyclisation of aliphatic compounds are usually classified[1,2] according to the number of carbon atoms provided to the pyrrole ring by the initial reagents: $C_2 + C_2$, $C_3 + C_1$, and $C_4 + N$ (C_4-N).

The methods for synthesising pyrroles from aliphatic compounds have undergone considerable development in recent years. They are the subject of the present review, which covers publications from 1980 to 1987 that have, as a rule, not yet appeared in monographs or reviews.

II. $C_2 + C_2$ reactions

1. Pyrroles from ketoximes and acetylene

In recent years there has been the most rapid development of a new general method for constructing a pyrrole ring which is based on the reaction, which was discovered at the beginning of the 1970s, between ketoximes and acetylenes in the system alkali metal hydroxide–DMSO [3,6] (it was suggested[8,9] that this synthesis should be called the Trofimov reaction)

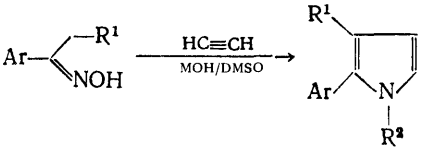


R^1, R^2 = Alk, Ar, etc.; R^3 = H, Ph; M = K, Na, Li.

The yields of pyrroles and *N*-vinylpyrroles (the latter are readily formed with excess acetylene) depend on the structure of the initial compounds and, as a rule, amount to 50–70%, while in favourable cases they reach 90%. A necessary condition for this reaction to take place is the presence of an α-CH_2 group in the ketoxime. Aldoximes do not form pyrroles but are converted to nitriles, amides, or salts of carboxylic acids.[3,6,10]

This simple and effective synthesis has made it possible to convert ketones in two stages to pyrroles with the widest range of substituents—alkyl,[3] alkenyl,[11] aryl,[3,12,13] hetaryl [3,14]—as well as to annelated pyrrole systems.[3,6] For the first time the simplest alkyl- and aryl-substituted pyrroles not containing functional groups became accessible, the majority of known methods for obtaining them being not very suitable. It is not surprising that the discovery of this reaction acted as a powerful stimulus for the development of pyrrole chemistry. Within a short time more than 120 studies were published in this field. The majority of them have already been covered in a review[6] and monograph.[3] We have therefore restricted ourselves here to examining the most recent information that has not appeared in these review publications.

In one study[15] the synthesis of the previously unknown 2-arylpyrroles and their 1-vinyl derivatives is reported.



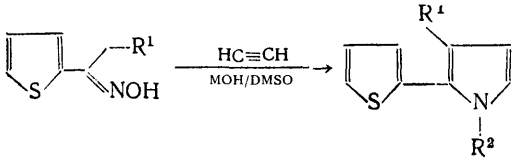
Ar = Ph, 4-RC_6H_4 (R = Me, Et, MeO, Cl, Br, iso-Pr, t-Bu), Bz;

R^1 = H, Me, C_6H_{13}, C_7H_{15}, C_8H_{17}, Ph; R^2 = H, CH = CH_2;

MOH = LiOH, KOH.

Pyrroles that are not substituted on the nitrogen atom are obtained in LiOH–DMSO (100 °C, 3 h) and their 1-vinyl derivatives are obtained in KOH–DMSO. By using an equimolar quantity of KOH relative to ketoxime and a tenfold excess of DMSO (from the total weight of the reagents) it is possible to reduce the reaction temperature considerably (to 50–60 °C) and obtain 3-alkyl-2-arylpyrroles and their 1-vinyl derivatives with total yields of up to 90%.[16]

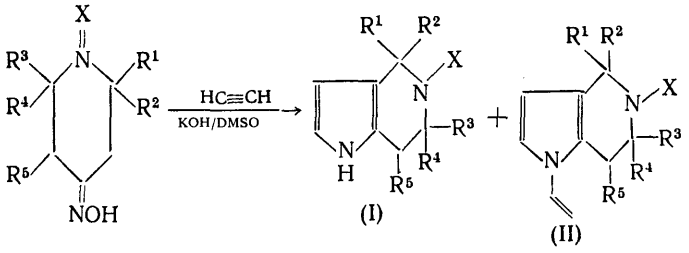
Oximes of a thiophene series and acetylene underwent the Trofimov reaction to give thienylpyrroles and the previously unknown 1-vinylthienylpyrroles in 50–70% yield.[17]



R^1 = H, Me, Et, Pr, Bu, C_6H_{13}; R^2 = H, CH = CH_2.

The reaction takes place smoothly at 100–130 °C and can be effected both at elevated pressure (1.0–1.6 MPa) and atmospheric pressure of acetylene. The ratio of pyrroles to their 1-vinyl derivatives formed in this synthesis is governed by the reaction conditions—its duration, the temperature system, concentration of acetylene, addition of water, and change in cation from the hydroxide.

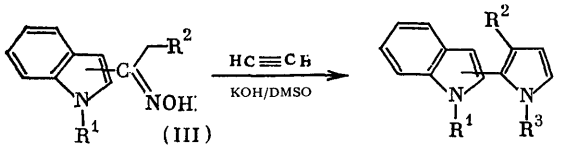
The heterocyclisation (50–100 °C, 4–5 h) of acetylene with piperidine oximes,[18–21] their *N*-hydroxy derivatives, and nitroxyl radicals[18,19] has been carried out.



X = H, Me, OH, O·; $R^1 = R^3$ = H, Me, Ph; $R^2 = R^4 = R^5$ = H, Me.

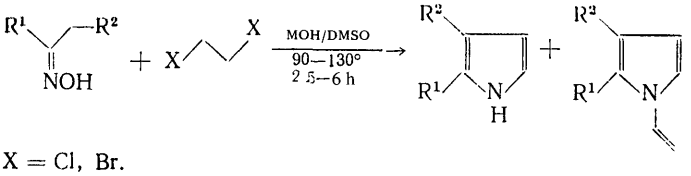
Tetrahydro-5-azaindoles (I) and (II), including those with a free valency (X = O) have been obtained in this way. A special feature of the reaction when X = OH is that it mainly gives tetrahydroazaindoles with a nitroxyl free-radical centre (compounds with a vinyloxy group at the 5-position are formed in very small quantities in the process).[18,19]

Reaction between acetylene and oximes of 2- and 3-acylindoles (III) gives 2- and 3-(pyrrolyl)indoles with yields of 30–45%.[22,23] The optimum conditions for synthesis are: temperature 100–105 °C (30 min to 2 h), ratio of ketoxime to KOH = 1:1.2.



R^1=H, Me; R^2=H, Me, Pr, Ph; R^3=H, CH=CH_2.

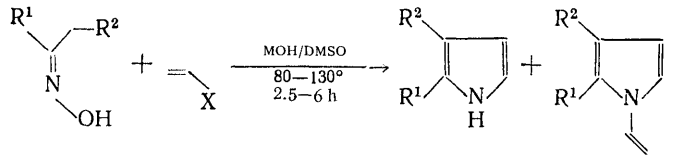
A variant of the reaction under discussion is the interaction between ketoximes and haloethanes, which gives pyrroles and their 1-vinyl derivatives with a total yield of 50–60%.[3,24,25]



X = Cl, Br.

Trofimov and Mikhaleva[3] achieved 94–95% selectivity with respect to the main product—a pyrrole—at the cost of a reduction in yield to 30%. As in the reaction with acetylene,[3,6] this was mainly achieved by adding small quantities of water (10–20%) to the reaction mixture.

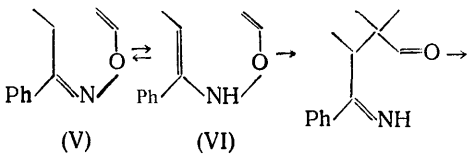
The reaction between ketoximes and vinyl halides occurs in a similar manner.[26,27]

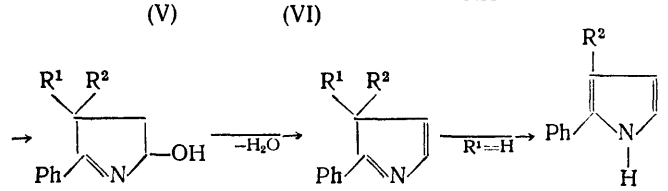


By varying the ratio of reagents and the conditions it is possible to carry out the reaction with a sufficient degree of selectivity to obtain either mainly pyrroles in about 40% yield or their 1-vinyl derivatives (yields up to 35%).

These variants of the Trofimov reaction, despite the lower yields of pyrroles, can in some cases prove to be more suitable for laboratory experiments, since they exclude the use of free acetylene.

One of the possible methods for forming pyrroles from ketoximes and acetylene in the superbasic catalytic system KOH–DMSO is a heteroatomic variant of the Claisen rearrangement of the intermediate *O*-vinyloxime (V), which undergoes isomerisation by proton transfer to give the *O*,*N*-divinylhydroxylamine (VI).[3]

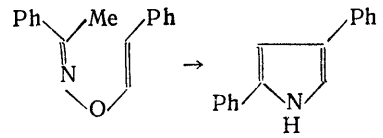




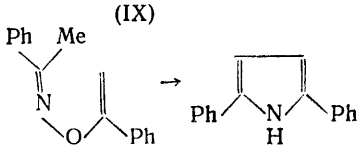
R^1 = Me; R^2 = Me; R^1 = H, R^1 = H, R^2 = iso-Pr.

It was shown[28] that *O*-vinylarylketoximes (V), which can be obtained in 50% yield from ketoximes and acetylene, on heating (100 °C) in KOH–DMSO are completely converted to the corresponding pyrroles even after 1.5 h. When isopropyl- and isobutyl-phenylketoximes were reacted with acetylene in the same system the reaction was stopped at the stage where 4*H*-2-hydroxy-2,3-dihydropyrroles (VII) were formed,[29] and on heating (70 °C, 5 h) compound (VII) (R^1 = R^2 = Me) with acetylene, the 3*H*-pyrrole (VIII) was isolated.[30]

Confirmation of this mechanism was also obtained[31] by rearrangement of the isomeric *O*-(phenylvinyl) acetophenone oximes (IX) and (X) in KOH–DMSO to give the corresponding pyrroles.

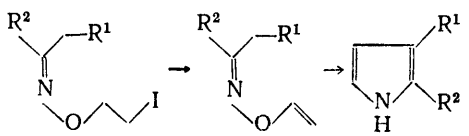


(IX)



(X)

O-(2-Iodoethyl)ketoximes (XI), obtained in two stages from ketones, on heating in the presence of t-BuOK and t-BuOH are converted to pyrroles (yields 65–74%).[32]

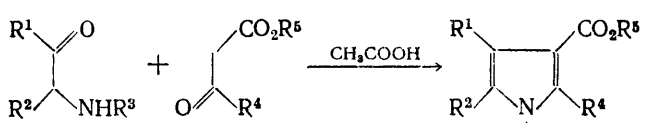


(XI) (XII)

It was possible to stop the reaction at the stage where the *O*-vinyloxime (XII) was formed, R^1 = H, R^2 = Ph (yield 41%), by lowering the concentration of t-BuOK and reducing the time of reaction. The pyrrole was obtained in 89% yield by thermolysis of oxime (XII).

2. Condensation of aminoketones with ketones

In recent years there has been further development of one of the most widely used methods for synthesising pyrroles—the Knorr synthesis, which in its original form is regarded as the condensation of α-aminoketones with carbonyl compounds that have active methylene groups adjacent to the carbonyl group such as in β-ketoesters and β-diketones.



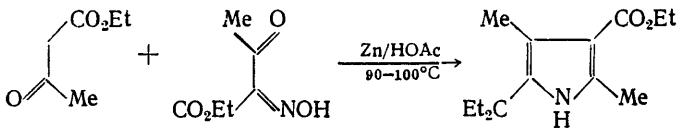
(XIII)

When phenylacylamines are reacted with methyl and ethyl acetoacetates, pyrroles (XIII) are obtained: (R^1 = Ar; R^2 = H; R^3 = H, Ar; R^4 = Me; R^5 = H, Me, Et),[33] (R^1 and R^3 = Me; R^2 = 4-ClC_6H_4O; R^4 = CH_2CO_2Et; R^5 = Et).[34]

The reaction of amino derivatives of sugars with dimethyl diacetylenedicarboxylate (DMADC) may be regarded as a unique version of the Knorr synthesis; this gives pyrroles with carbalkoxy substituents (XIII) (R^1 = H; R^2 = $(CHOH)_nCH_2OH$, *n* = 2, 3; R^3 = Alk, Ar; R^4 = Co_2Me; R^5 = Me).[35,36]

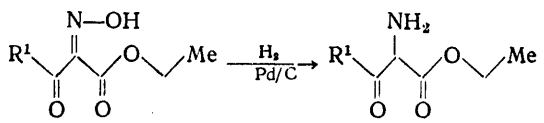
The aminoketone component of the reaction is most frequently obtained by reduction *in situ* of the corresponding monooxime, which in turn is formed by nitrosation of a ketone or β-dicarbonyl compound.[37–43]

The reducing agent most frequently used is zinc in acetic acid.

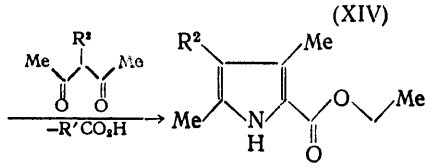


Although quite versatile, the Knorr synthesis does have some disadvantages. These are mainly the moderate yields of pyrroles (40–60%). The reaction efficiency is substantially reduced in the case of asymmetric β-dicarbonyl compounds, which usually form mixtures of different pyrroles.

The higher yields of pyrrole-2-carboxylates (60–70% for the main product synthesised from an asymmetric ketone and 75–90% from a symmetric ketone) in comparison with the method described by Kleinspen[5] (reduction *in situ* of diethyl oximinomalonate with zinc) were achieved by reaction of 1,3-diketones with diethyl aminomalonate (XIV), which was prepared in advance in boiling glacial acetic acid.[44] Reduction of oximinomalonate is carried out in ethanol solution in the presence of Pd/C.[44]

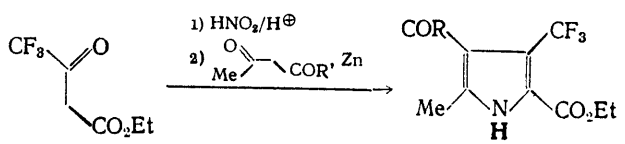


(XIV)



R′ = Me, EtO; R^2 = H, Me, Et, Pr.

The usual conditions for the Knorr synthesis are not very suitable for the synthesis of β-trifluoromethylpyrroles (yield 5%). The yield of these compounds can be increased by using a strong acid medium during nitrosation. In neutral solution ethyl trifluoroacetoacetate is enolised to a considerable extent. A strong acid medium shifts the tautomeric equilibrium towards the keto tautomer, which results in a greater yield of pyrroles (41–47%). A mixture of acetic and trifluoroacetic acids saturated with HCl is used as the solvent.[38]

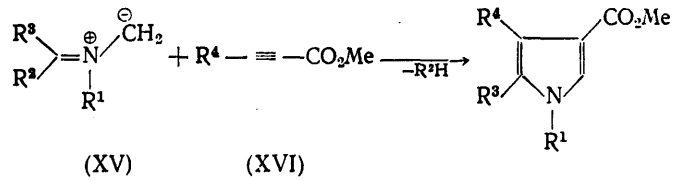


R = Alk, AlkO.

3. 1,3-Dipolar cycloaddition

Dipolar cycloaddition[45] has formed the basis for the development of many methods for synthesising pyrroles in recent years. 1,3-Dipolar cycloaddition of nitrile or azomethine ylides to dipolarophiles gives pyrroles either directly or via pyrroline derivatives. For this purpose it is possible to use mesoionic compounds which formally contain a system of azomethine ylide bonds. Thus, the azomethine ylide (XV), which is generated by reaction of α-cyanoaminosilanes [46] or α-(phenylthio)aminosilanes [47] with silver fluoride and also by alkylation of imidates with trimethylsilylmethyltriflate (DMF, 25 °C,

3 h) followed by desilylation of the resulting salts with caesium fluoride,[48] reacts with methyl propiolate or DMADC to form pyrroles.[46–48]



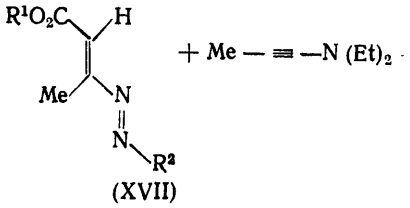
(XV) (XVI)

R^1 = Me, $PhCH_2$; R^2 = H, EtO, Me; R^3 = H, Me, Ph; R^4 = H, CO_2Me.

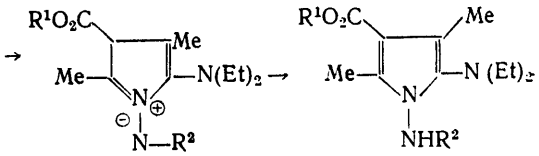
The reaction between compounds (XV) and (XVI) in the presence of silver fluoride takes place when there is a small excess of the latter in acetonitrile at 25 °C over a period of 10 h in the dark. The residue (pyrroline) formed after removal of solvent is oxidised by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone to give the corresponding pyrroles in 62–65% yield.[46,47] The reaction takes place under similar conditions in the presence of anhydrous CsF, with a yield of pyrroles of up to 75%.[48]

N-Protonated azomethine ylides (XV) (R^1 = H, R^3 = Et, Bu, Ph; R^2 = NPh, $NC_6H_{11}S$) readily add on to electron-deficient acetylene compounds (dry acetonitrile, 20–25 °C, 16 h) forming the corresponding pyrroles (yield 44–96%).[49,50]

One of the most unusual examples of 1,3-cycloaddition of hetero-1,3-dienes to alkynes has been reported in one study;[51] 1,2-diaminopyrroles (XVIII) are obtained in 46–59% yield by reaction of diazabutadienes (XVII) with 1-propynyldiethylamine.



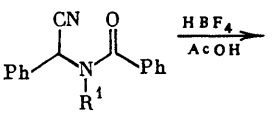
(XVII)



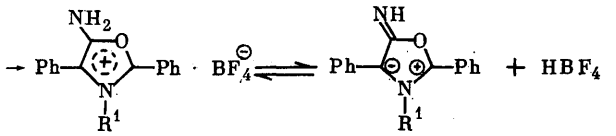
(XVIII)

R^1 = Me, Et; R^2 = Ts, $CO_2CMe_2CCl_3$.

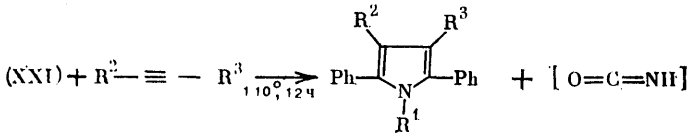
Acyclic analogues (XIX) of Reissert compounds have been used for the synthesis of pyrroles under both acidic and alkaline conditions.[52] Thus, the mesoionic compounds (XXI), which are formed by dissociation of hydrophobic salts of Reissert compounds (XX), undergo 1,3-dipolar cycloaddition to alkynes to give the corresponding pyrroles.



(XIX)

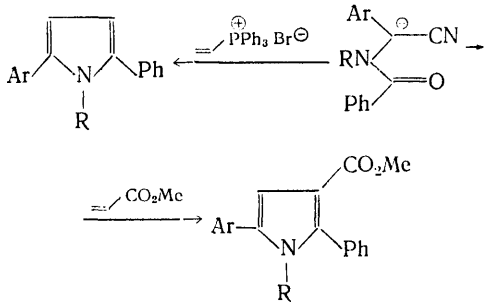


(XX) (XXI)



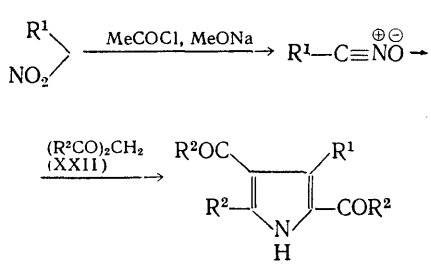
R^1 = Ph, Bz; R^2 = R^3 = H, CO_2Me.

Similar pyrroles are formed by reaction between methyl acrylate [52] or vinyltriphenylphosphonium cation[53,54] and anions which are products of the reactions of superbases (BuLi/THF, NaH/DMSO or DMF/NaH) with Reissert compounds. In the first case the reaction occurs at room temperature, in the second case heating is required (110 °C) for 24 h.



R = Ph, 3-$MeOC_6H_4$, 4-ClC_6H_4, C_6H_{13}, cyclo-C_6H_{11}; Ar = Ph, 4-ClC_6H_4, 3, 4-$Me_2C_6H_3$.

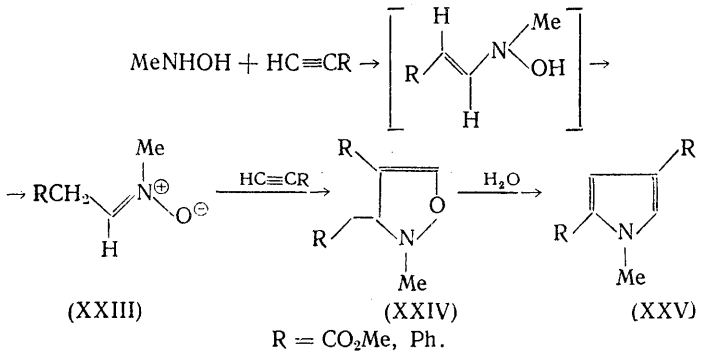
A 1,3-dipolar cycloaddition route is followed in the reaction of aliphatic nitro compounds, 1,3-diketones, and acetyl chloride (MeONa/MeOH, *N*,*N*-dimethylacetamide, 0–20 °C, 12 h), which gives diacylpyrrole derivatives in 35–85% yield.[55]



R^1, R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4.

It is suggested[55] that the first stage of the reaction is formation of nitrile oxide, which as a result of 1,3-dipolar cycloaddition to 1,3-diketone (XXII) forms a pyrrole.

1,3-Dipolar cycloaddition of nitrones (XXIII), which are formed from methylhydroxylamine and methyl propiolate or phenylacetylene (80 °C, 12 h) gives the pyrrole (XXV).[56] When the reaction is carried out at 25 °C (24 h) it is possible to stop it at the stage involving formation of the intermediate isoxazoline (XXIV), which at 80 °C over a period of 12 h rearranges to pyrrole (XXV).



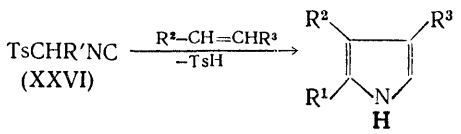
(XXIII) (XXIV) (XXV)

R = CO_2Me, Ph.

With alkyl-substituted acetylenes this reaction does not occur even with prolonged heating.[56]

4. Pyrroles from isonitriles

An effective method of obtaining pyrrole derivatives which are unsubstituted at the 1- and 5-positions is the base-catalysed addition of tosylmethylisocyanide (XXVI) to activated alkenes.[57,58]



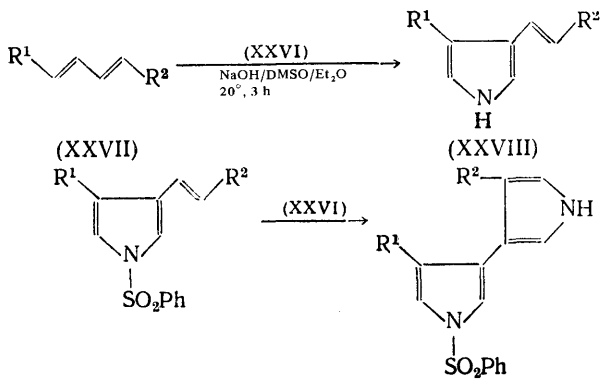
(XXVI)

R^1 = Me, CH_2=CH—CH_2, Bz; R^2 = Me, Ph;

R^3 = CO_2Me, Bz, C≡N.

The reaction can be carried out in superbasic systems—NaH in a DMSO—Et_2O mixture or in dimethoxyethane. The yields of pyrroles are 70–90%.

When 1,3-diene esters (XXVII) are used as the Michael acceptor, the addition to them of two molecules of isonitrile (XXVI) to give a bipyrrolyl is to be expected. However, under the given conditions only the 3,4-substituted pyrrole (XXVIII) is obtained in 80% yield.[59–61] The addition of the second isonitrile molecule does not occur apparently because of the reduction in electrophilicity of the α,β-unsaturated ester (XXVIII). A 3,3′-bipyrrolyl can only be obtained after addition of a $PhSO_2$ group to the nitrogen atom.

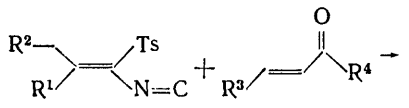


(XXVII) (XXVIII)

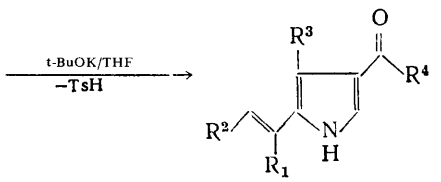
R^1 = Me, Et; R^2 = CO_2Me, CO_2Et.

If the reaction of isonitrile (XXVI) and the 1,3-diene ester is carried out in the presence of BuLi in THF (−70° to 0 °C, 2 h), the other isomer of pyrrole (XXVIII) (R^1 = CO_2Me, R^2 = Me) is obtained in 34% yield.[61]

Pyrroles (XXX), which have an alkenyl group at the α-position, are synthesised in high yield (83–96%) by the base-catalysed addition of 1-tosylalk-1-enylisocyanides (XXIX), readily formed by reaction of tosylmethylisocyanide with carbonyl compounds, to Michael acceptors.[62]



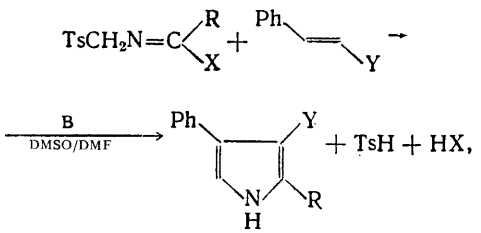
(XXIX)



(XXX)

R^1 = Me, Ph; R^2 = H; R^1R^2 = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;
R^3 = H, Me, Ph; 2-furyl, 2-thienyl, MeCH = CH, PhCH = CH;
R^4 = Me, MeO, EtO, Ph, 2-furyl, 2-thienyl

Methyl isocyanoacetates (RO_2CCH_2NC) are quite frequently used for the synthesis of pyrrole-2-carboxylates.[63–65] The reaction takes place under the same conditions as for isonitriles (XXVI). *N*-(Tosylmethyl)imino derivatives[66] react in a similar manner with Michael acceptors.



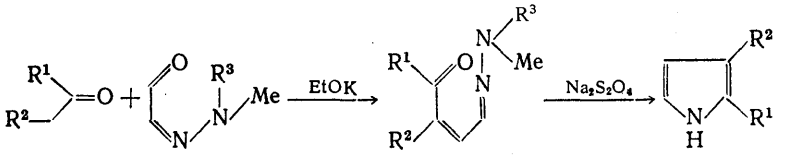
B = NaH, t-BuOK

R = Me, Ph, SMe, OMe; X = SMe, OMe; Y = COPh, CO_2Me, CN.

It appears that in this case the first stage involves removal of a proton from the activated methylene group, generating a 2-azaallyl anion $Ts\overline{C}-N=CRX$, which subsequently reacts with the unsaturated substrate either according to a 1,3-dipolar addition mechanism (after elimination of Ts^- or X^-) or according to a 1,3-anionic cycloaddition mechanism.

5. Reactions involving hydrazones and azoalkenes

Carbonyl compounds containing an active methylene group when reacted with glyoxal monohydrazones form hydrazones (XXXI),[67,68] which on treatment with sodium dithionite give pyrroles in 21–48% yield.[68]

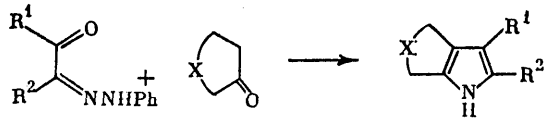


(XXXI)

R^1 = H, Alk, AlkO, Ar; R^2 = H; Alk, AlkO, CN, CO_2Alk; R^3 = Alk, Ar.

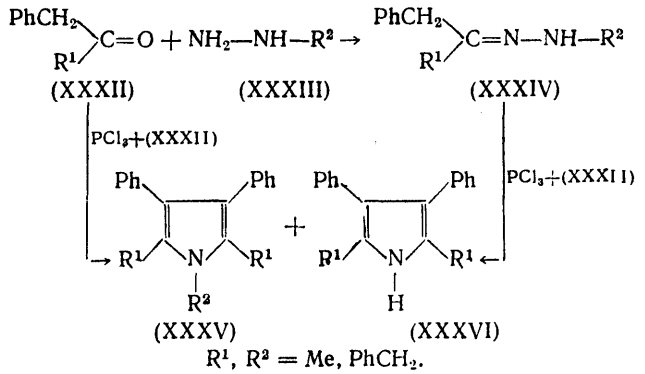
Compounds (XXXI) when treated with sodium borohydride are converted to alcohols, which on heating or in the presence of acids eliminate water to form *N*-aminopyrroles, and subsequently on hydrogenation give pyrroles unsubstituted on the nitrogen atom.[67]

Reductive condensation of phenylhydrazones with cyclic ketones in the presence of zinc and sodium acetate in acetic acid gives pyrrolocycloalkanes in 19–25% yield.[69]



R^1=Me, Et; R^2=CO_2Me, CO_2Et; X=$(CH_2)_3$, $(CH_2)_4$.

The reaction of enolisable ketones (XXXII) with their hydrazones (XXXIV) in the presence of two equivalents of PCl_3 (CH_2Cl_2, 20 °C or C_6H_6, 80 °C) results in the formation of a mixture of symmetrically substituted pyrroles (XXXV) and (XXXVI).[70] The yield (28–46%) and ratio of products depend on the structure of the reagents and the reaction conditions.



R^1, R^2 = Me, $PhCH_2$.

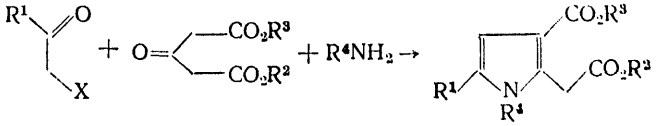
A mixture of pyrroles (XXXV) and (XXXVI) (1 : 1) is also obtained by direct reaction of the initial ketones (2 equivalents), hydrazine (XXXIII) (1 equivalent) and PCl_3 (3 equivalents).

Azoalkenes react with 1,3-dicarbonyl compounds.[71–88]

The reaction occurs via intermediate 1,4-adducts (XXXVII), which subsequently cyclise to a pyrrole by elimination of water. In a number of cases these intermediates have been isolated. The synthesis proceeds smoothly at room temperature and is complete after several hours. The process can be speeded up by heating the reaction mixture or by using a catalyst ($CuCl_2$,[71–80] Na_2CO_3 [81]). Aminocarbonyl-,[73,74] aryl-,[75–77] aroyl-,[72] arylsulphonyl-,[78,79] alkoxycarbonyl-,[71,80] and β-chloro-azoalkenes [81] have been used as the first reaction component. 1,3-Diketones,[71,73,75,77,79,81] β-ketoesters,[71,73,75,77,79,81] and 3-oxoalkanamides [72,74,76,78,80] have been used as the second components.

6. Reactions involving haloketones

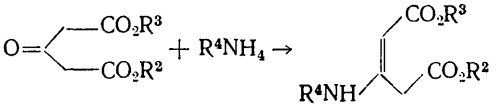
A series of studies have recently appeared which are devoted to extending the Hantzsch method,[82–95] which is based on the reaction of α-haloketones or α-haloaldehydes with β-ketoesters and amines.



R^1, R^4 = H, Alk; R^2, R^3 = Alk, Ar; X = Cl, Br.

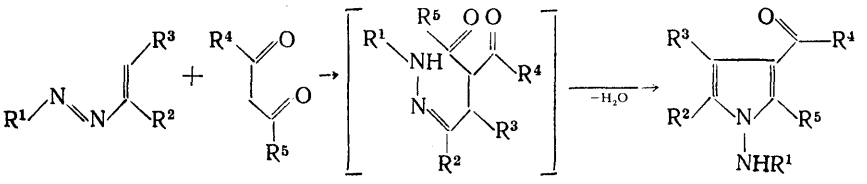
The reaction is carried out in the same water–dioxan or water–alcohol solution, in a two-phase system, or without any solvent at room temperature (prolonged standing of the mixture) as well as with heating for several hours. In some cases[95] the reaction is catalysed by carboxylic acids.

The probable reaction route[5] assumes the formation of aminocrotonate (XXXVIII) at the first stage.

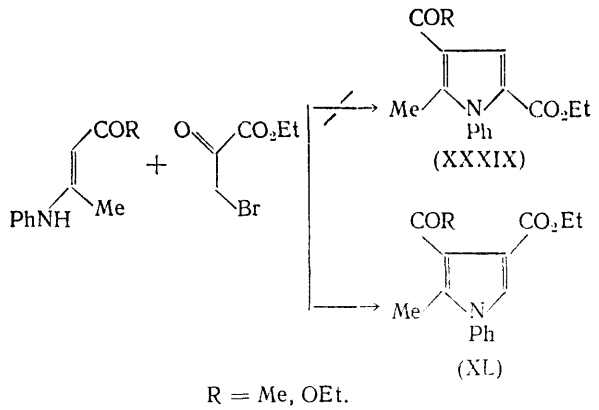


(XXXVIII)

In fact, such aminocrotonates have successfully been used as initial compounds for the synthesis of pyrroles.[96]



(XXXVII)

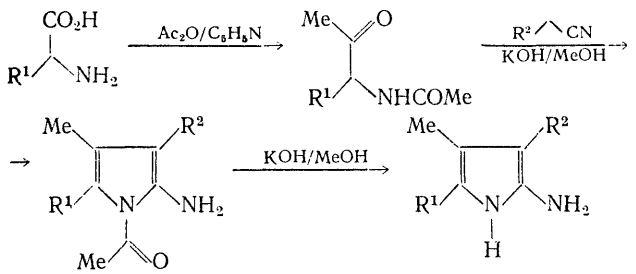


R = Me, OEt.

An unexpected result of this study was that instead of pyrrole (XXXIX) its isomer (XL) was formed in 72% yield. The reaction took place when the reagents were refluxed in ethanol for 30 min.

7. Reactions involving amino and nitrile groups

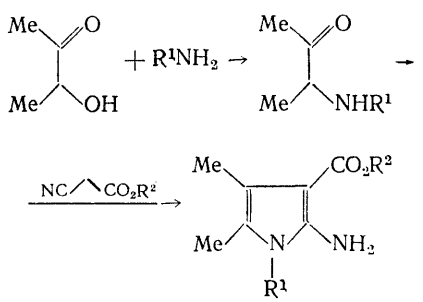
N-Acetyl-α-aminoketones, obtained from *L*- or *DL*-amino acids, when condensed with nitriles form substituted 2-amino-3-cyano-4-methylpyrroles (120 °C, 3–4 h).[97]



R^1 = Me, Pr, iso-Pr, Ph, Bz; R^2 = CN, SO_2R.

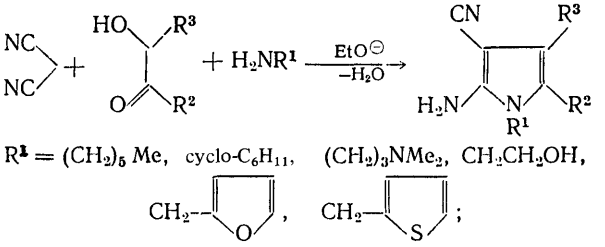
The pH of the medium must be kept within the range 9–10 and the temperature at 55–60 °C when decarbonylation takes place.

Condensation of 3-hydroxy-2-butanone with primary aryl- and alkyl-amines in boiling cyclohexane gives aminoketones, which react with cyanoacetates to give various 2-amino-3-carbalkoxy-4,5-dimethylpyrroles in 36–87% yield.[98]



R^1 = Alk, Ar; R^2 = Me, t-Bu.

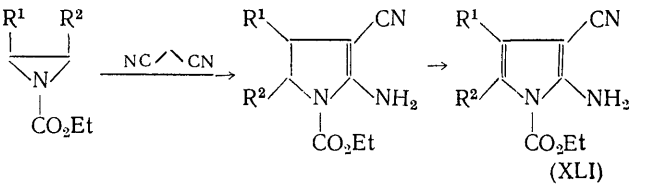
The reaction of hydroxyketones with amines and malononitrile, giving 2-amino-3-cyanopyrroles in yields up to 96%, also takes place via the intermediate formation of an aminoketone. The reaction is carried out in ethanol in the presence of sodium ethoxide.[99]



R^1 = $(CH_2)_5$Me, cyclo-C_6H_{11}, $(CH_2)_3NMe_2$, CH_2CH_2OH, CH_2–(O), CH_2–(S);

$R^1 = R^3$ = Me, Ph; $R^2R^3 = (CH_2)_4$, $(NH_2)_5$.

The reaction of malononitrile with 1-carbethoxyaziridines in the presence of sodium hydride (THF, 100 °C, 4 h) gives 2-amino-3-cyano-1-carbethoxy-4,5-dihydropyrroles (yield 45–50%), which are aromatised (chloranil, benzene, 80 °C, 3 h) to the corresponding pyrroles (XLI) in 30–90% yield.[100]

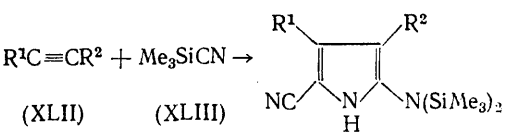


(XLI)

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

Pyrroles (XLI) (R^1 = Me, Ph; R^2 = H) were also obtained by counter-synthesis from malononitrile and *N*-phenacyl- or *N*-acetonyl-carbamates $R^1COCH_2NHCO_2Et$ on boiling the reagents in benzene in the presence of acetic acid and ammonium acetate or piperidine.

When trimethylsilylcyanide (XLIII) is reacted with alkynes (XLII) (N_2, 20 h) in the presence of palladium or nickel catalysts, 5-aminopyrrole-2-carbonitriles are obtained in high yield.[101]



(XLII) (XLIII)

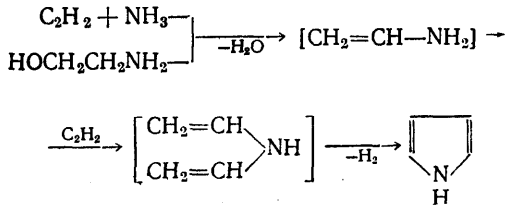
R^1 = H, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-thienyl, 2-$MeOC_6H_4$;
R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-thienyl.

There has been a study of the reaction of nitrile (XLIII) with silylacetylenes (XLII) (R^1 = $Me_3SiC{\equiv}C$, $CH_3(CH_2)_5$, Ph, Me_3Si; R^2 = $SiMe_3$),[102] (120–160 °C, 9–12 h) in the presence of palladium catalysts to give 2-amino-5-cyanosilylpyrroles (yield 49–84%).

8. Reactions involving enamines and imines

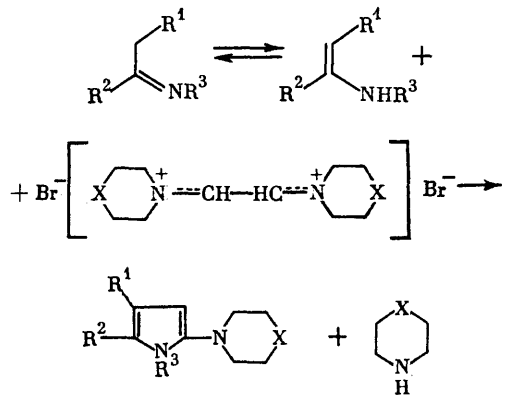
The Chichibabin reaction—the catalytic interaction of acetylene with ammonia—remains one of the most promising methods for obtaining unsubstituted pyrrole.[2] In recent years definite progress has been made in this direction. By varying the catalysts and reaction conditions it has been possible to increase the yield of pyrrole to 10.4% (cadmium calcium phosphate catalyst).[103] The same catalyst has been used for the condensation of acetylene with aniline (410–430 °C),[104] with a 15–17% yield of 2-phenylpyrrole.

It has been proposed[103] that at the first stage of the reaction between acetylene and ammonia, vinylamine is generated, which then reacts with acetylene to give divinylamine, which cyclises to pyrrole.



Such a scheme is consistent with the synthesis of pyrrole from mono- and di-ethanolamines, which presumably involves the intermediate formation of mono- and di-vinylamines.[105,106] The reaction takes place at a high temperature on a complex catalyst: Al_2O_3 (95%), ZnO (2%), Cr_2O_3 (3%). The yield of pyrrole is 10% from monoethanolamine and 18.5% from diethanolamine.

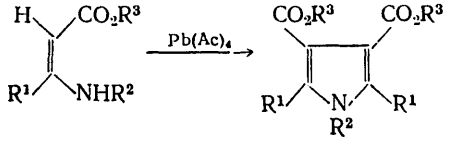
Enamines react under mild conditions (CH_2Cl_2, 20 °C, 2 h) with certain *bis*-iminium salts, forming aminopyrroles in good yield.[107]



$R^1 = CO_2Et, CO_2CMe_3, Ph$; $R^2 = Me, Ph$; $R^3 = H, Alk$; $X = O, NMe$.

The formation of pyrroles in this reaction is due to double electrophilic attack by the dication on the nitrogen atom and β-carbon atom of the enamine. The 2,3-dihydropyrroles thus obtained eliminate an amine during the synthesis and are converted to α-aminopyrroles. When $R^1 = H$, pyrroles are not formed. This supports the conclusion[107] that α-aminopyrroles containing a hydrogen at C(4) are unstable compounds.

Oxidation of enaminoesters (XLIV) with an equivalent quantity of lead tetra-acetate (CH_2Cl_2, 20 °C, 3–7 h) results in the formation of symmetrically substituted pyrroles (XLV).[108–110]



(XLIV) (XLV)

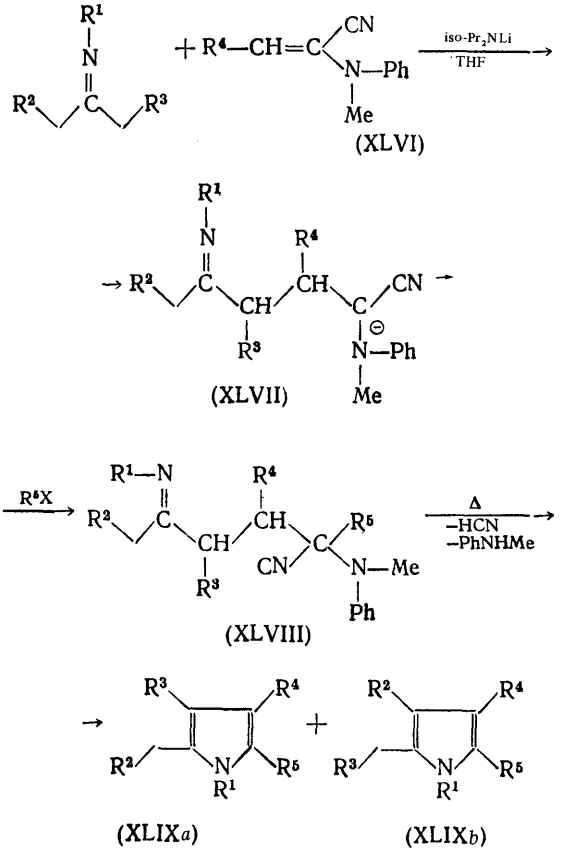
$R^1 = CO_2Me$, Me, Ph; $R^2 = Me$, Pr, Bu, $PhCH_2$, 4-ClC_6H_4, $R^3 = Me$, Et.

In the opinion of Vernon and co-workers,[108] the new C–C bond is formed by two-electron oxidation of enamine (XLIV).

The yields of the pyrroles synthesised from β-aminocrotonates amount to 20–40%. The oxidation of β-aminocinnamates is less effective (yields of pyrroles 10–20%) and only takes place in an atmosphere of nitrogen.

The reaction of 2-(*N*-methylanilino)-2-alkenonitriles (XLVI) with ketimine anions followed by alkylation or protonation of the intermediate carbanion (XLVII) and culminating in the pyrolysis of adduct (XLVIII) gives pyrroles.[111]

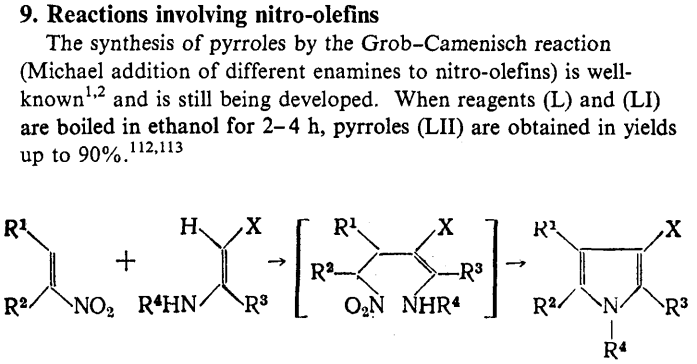
Asymmetrically substituted ketimines (R^2 = n-Pr, R^3 = H) form a mixture of pyrroles (XLIXa, b) in the ratio 85:15. It is possible to obtain pyrroles (XLIXa) selectively by deprotonation at −78 °C.



R^1 = Me, cyclo-C_6H_{11}, iso-Pr, $PhCH_2$;
R^2 = H, Me, Pr; R^3 = H, Me, Pr; $R^2R^3 = (CH_2)_3$, $(CH_2)_4$;
R^4 = H, Et; R^5 = H, Me, Et, Pr; X = OH, I, Br.

9. Reactions involving nitro-olefins

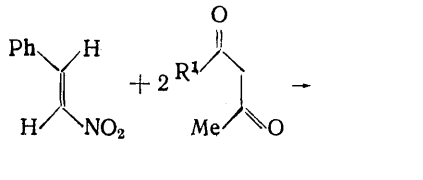
The synthesis of pyrroles by the Grob–Camenisch reaction (Michael addition of different enamines to nitro-olefins) is well-known[1,2] and is still being developed. When reagents (L) and (LI) are boiled in ethanol for 2–4 h, pyrroles (LII) are obtained in yields up to 90%.[112,113]

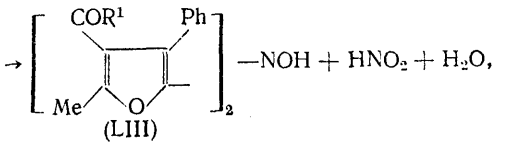


(L) (LI) (LII)

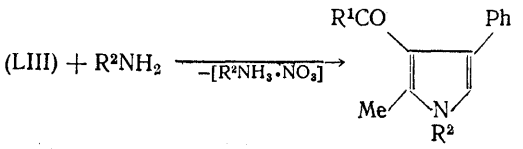
X-acceptor: COMe, CO_2Me, CO_2Et; R^1 = Me, Ph; R^2 = H, Me; R^3 = H, Me, Ph; R^4 = Me, Bu, Ph, $PhCH_2$, 4-$AlkOC_6H_4$.

1,3-Dicarbonyl compounds are being used for the reaction with nitro-olefins with increasing frequency.[114,115] Thus, the reaction of ethyl acetoacetate and pentane-2,4-dione with β-nitrostyrene in a solution of MeONa/MeOH gives the *bis*-dihydrofuran intermediate (LIII). Treatment of the latter with ammonia or amines in methanol gives 3-acylpyrroles in high yield.



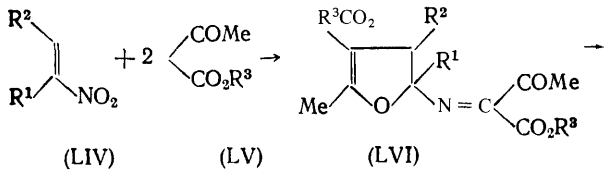


(LIII)

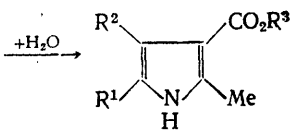


R^1 = Me, OEt; R^2 = H, Alk, Ar.

Acylpyrroles (LVII) are obtained by two methods—by hydrolysis of polyfunctional dihydrofurans (LVI) formed by reaction of nitro-olefins (LIV) with twice the amount of acetoacetates (LV) [116]

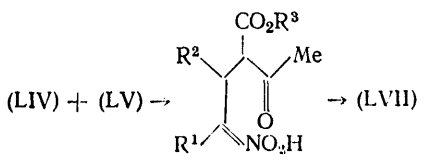


(LIV) (LV) (LVI)



(LVII)

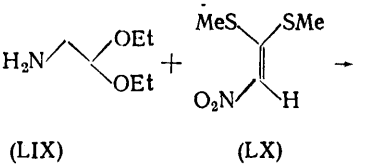
and by reduction of the nitronic acid (LVIII), which is an adduct of compounds (LIV) and (LV), with different reducing agents (Zn/HCl, $Zn/ZnCl_2$/HCl, 2-phenylethanethiol/benzene).[116]



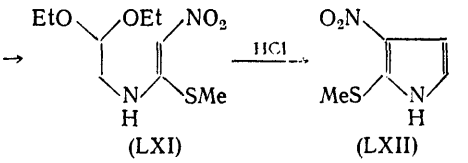
(LVIII)

R^1, R^3 = Alk; R^2 = Ar

The 3-nitropyrrole (LXII) was obtained in 58% yield by reaction of aminoacetaldehyde acetal (LIX) with 1,1-di(methylthio)-2-nitroethene (LX).[117] In this case the acyclic intermediate (LXI) is first formed and in the presence of HCl it cyclises to the pyrrole.

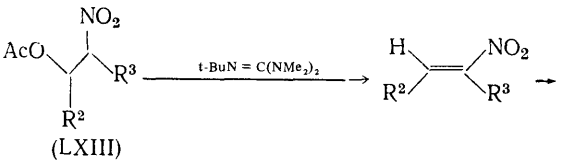


(LIX) (LX)

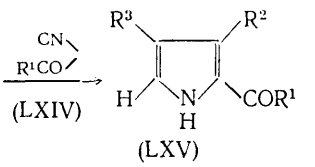


(LXI) (LXII)

The base-catalysed reaction between α-isocyanoacetates (LXIV) and nitroalkenes or their precursors—β-acetoxynitro compounds (LXIII)—gives pyrroles (LXV) in 55–95% yield.[118]



(LXIII)



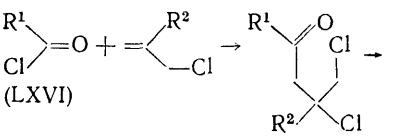
(LXIV) (LXV)

R^1 = EtO, t-BuO, Me_2N; R^2 = H, Me, Et, 4-$MeOC_6H_4$, 4-$PhCH_2OC_6H_4$; R^3 = Me, $CH_2CH_2CO_2Me$

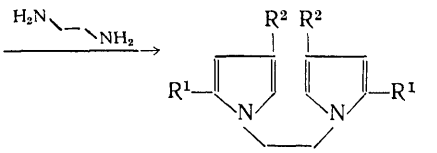
III. C_3 + C_1 reactions

1. Pyrroles from β,γ-dihaloethanes and amines

In a refinement of the Kost–Ibragimov–Mamedov method,[119–122] the intermediate products (LXVII) from the electrophilic addition of carboxylic acid chlorides (LXVI) to allyl and methallyl chlorides ($AlCl_3$, dichloroethane, −20° to 25 °C) when treated with diamines (aqueous NaOH, 70–80 °C, 6 h) form *bis*-pyrrole compounds.[123]



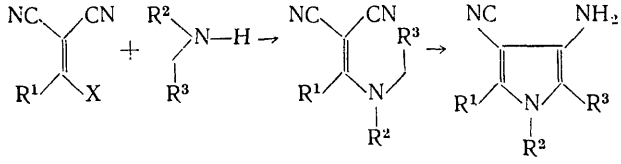
(LXVI) (LXVII)



R^1 = cyclo-C_6H_{11}, cyclo-$C_6H_{10}NH_2$; R^2 = H, Me

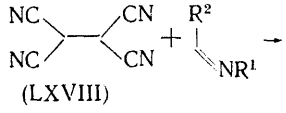
2. Reactions involving a cyano group

β-Aminopyrroles that have a CN group at the β′-position are obtained by reaction of α,β-unsaturated dinitriles with secondary amines containing functional groups; the intermediates are either isolated or not isolated.[124]

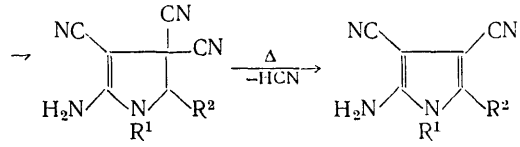


X = Cl, AlkO; R^1 = H, Alk, Ar; R^2=H, Alk, Ar; R^3 = CN, CO_2H, CO_2Alk.

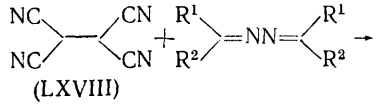
A convenient and simple method for the synthesis of pyrroles that contain amino and cyano groups is based on the reaction between tetracyanoethane (LXVIII) and azomethines or azines.[125–127] The reaction occurs in water–alcohol and alcohol media or in DMSO, giving 3-cyanodihydropyrroles, which on gentle heating in DMF eliminate a molecule of hydrocyanic acid and are converted to the corresponding pyrroles in high yield.



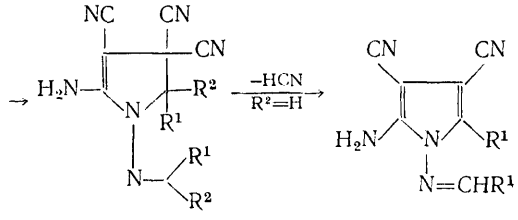
(LXVIII)



R^1 = Ph, 4-HOC_6H_4; R^2 = Ph, 2-furyl, 2-HOC_6H_4.



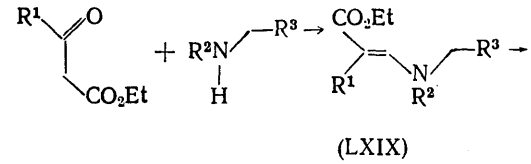
(LXVIII)



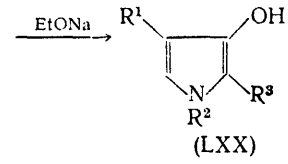
R^1 = Pr, iso-Pr, Ph, 2-furyl, 3-pyridyl, R^2 = H

3. Reactions of amino acids and their derivatives with 1,3-dicarbonyl compounds

Hydroxypyrroles (LXX) [128–130] are synthesised by Dieckmann cyclisation (NaOEt/EtOH, boiling for 3 h) of enaminodicarboxylates (LXIX), which are formed by reaction of amino acid amides and esters with β-ketoesters [128] or with diethyl ethoxymethylenemalonate.[129,130]



(LXIX)



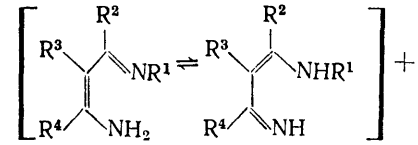
(LXX)

R^1=H, Ph, CO_2Et; R^2=H,Me,Ph,Bz; R^3=$CONH_2$, CONHMe, CO_2Et, CO_2CMe_3, CH_2CO_2Et

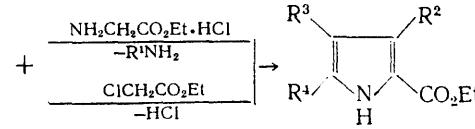
A number of pyrroles have been obtained from amino acids and 1,3-diketones [131–132] and also from α-(aminomethylene)cyclohexanone.[133] Cyclisation of the intermediates often occurs simply by heating.[133]

4. Reactions of azabutadienes

Azabutadienes (LXXI) react with glycine ethyl ester hydrochloride (80 °C, 4 h) or ethyl chloroacetate (100 °C, 6 h) in pyridine, giving in both cases pyrrole-2-carboxylates (LXXIII).[134] The regiospecificity of the reaction suggests that only one of the tautomeric diimine forms, namely (LXXII), participates in it.



(LXXI) (LXXII)



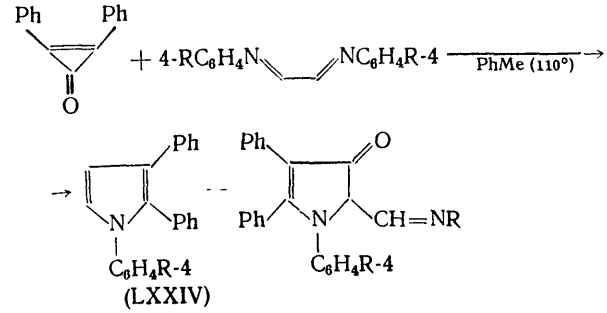
(LXXIII)

R^2 = Ph, 4-ClC_6H_4; R^3 = H, Me;

R^4 = Pr, Ph, 4-MeC_6H_4, cyclo-C_6H_{11}.

In the first case heterocyclisation probably takes place by transamination of diimine (LXXII) with the amino group of glycine.

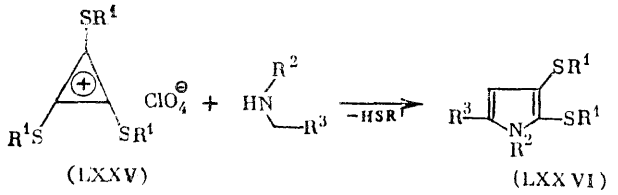
1,4-Diazabutadienes form the pyrrole (LXXIV) as a by-product (5–17%) by reaction with 2,3-diphenylcyclopropen-1-one. The main route in this case is formation of pyrroline-4-ones.[135]



(LXXIV)

5. Reactions involving cyclopropanes

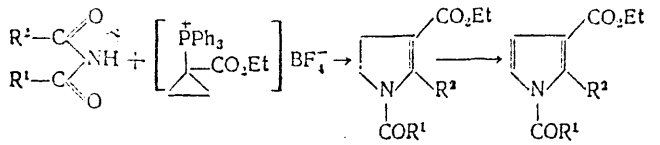
Condensation of *tris*-(t-butylthio)cyclopropenyl salts (LXXV) with secondary amines in the presence of the superbasic system t-BuOK – DMSO at 20–25 °C gives pyrroles (LXXVI) in 40–80% yield.[136–138]



(LXXV) (LXXVI)

R^1 = t-Bu; R^2 = Me, Et; R^3 = Me, CN, Ph, CO_2Me; R^2R^3 = $(CH_2)_3$, $(CH_2)_4$.

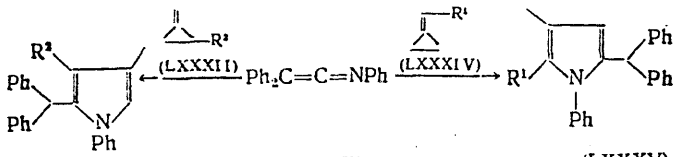
Anions of acyclic imides (LXXVII) (NaH, xylene, 20 °C) and cyclopropylphosphonium salts (LXXVIII) give Δ^2-pyrrolines, which are dehydrogenated with 2,3-dichloro-5,6-*p*-benzoquinone to the corresponding pyrroles (LXXX).[139]



(LXXVII) (LXXVIII) (LXXIX) (LXXX)

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

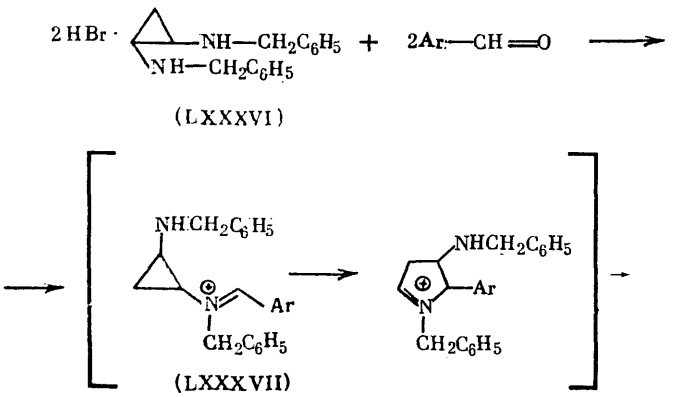
The [3 + 2]-cycloaddition of methylenecyclopropanes (LXXXII) and (LXXXIV) to the ketenimine (LXXXIII) (125 °C, 22–30 h), catalysed by $(PhP)_4Pd$, gives pyrroles (LXXXI) and (LXXXV) in 77–96% yield.[140]



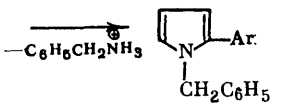
(LXXXI) (LXXXIII) (LXXXV)

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

Reaction of hydrobromide salts of 1,2-cyclopropanediamine (LXXXVI) with a twofold excess of aromatic aldehydes (MeOH or EtOH, NaOAc, 20–25 °C, 15 h) goes to completion with the formation of 2-arylpyrroles (LXXXVIII).[141]



(LXXXVI) (LXXXVII)



(LXXXVIII)

Ar = Ph; 4-$NO_2C_6H_4$; 4-$(Me)_2NC_6H_4$; 2,4,6-$(Me)_3C_6H_2$; 2-pyridyl.

The benzylidenammonium ions (LXXXVII) formed at the first stage of the reaction are converted to pyrrolinium ions, which are aromatised with elimination of benzylamine.

IV. C_4 + N(C_4–N) reactions

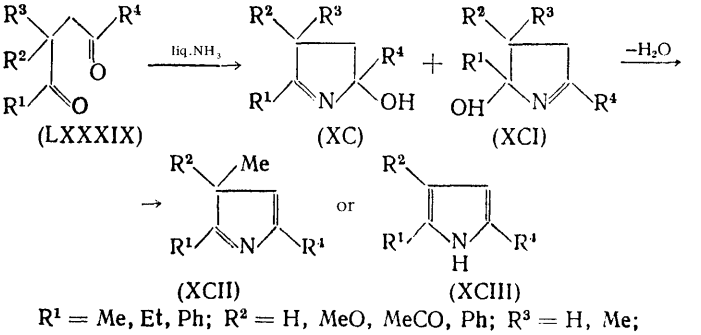
1. Reactions of 1,4-dicarbonyl compounds

The formation of pyrroles from 1,4-dicarbonyl compounds by treatment with ammonia or amines (the Paal–Knorr synthesis) is one of the most common methods for obtaining substituted pyrroles. Interest in it continues unabated. In recent years it has been developed further in several studies.[142–161] In particular, a large number of pyrroles have been obtained from hexane-2,5-dione.[143,144,148,149,156,161] Apart from simple alkyl- and aryl-amines, aminoalcohols,[144,146,147] aminoacetals,[144] amino acids and their derivatives,[146,147,156,157] sulphamoylbenzoic acid derivatives,[143] and amides[150–152] have been used in the condensation.

Reaction of 1,4-diketones with hydroxylamine and hydrazines gives 1-hydroxy- and 1-amino-pyrroles respectively.[5]

As a rule, cyclisation is carried out by boiling the reagents in an acidic medium. Acetic acid is used the most frequently for this purpose.[141,142,145,149,150–152] The method has virtually no limitations. In a number of cases it is possible to obtain (dioxan, 100 °C, 3 h) pyrroles with bulky substituents[145,149] which are difficult to prepare by another method because of steric hindrance.

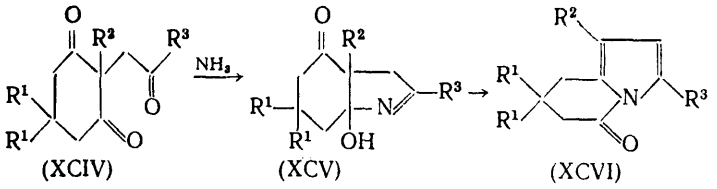
In some cases the Paal–Knorr reaction can be stopped at intermediate stages. Thus, the reaction of diketone (LXXXIX) (R^2 = R^3 = Me) with liquid ammonia results in the formation of a mixture of 2-hydroxy-3,4-dihydro-2*H*-pyrroles (XC) and (XCI), which are readily dehydrated (boiling in methylene chloride, basic Al_2O_3, 8 h) to the 3*H*-pyrrole (XCII). Less substituted diketones (LXXXIX) (R^2 = Me, R^3 = H) give the analogous hydroxypyrrolines (XC) and (XCI) (R^2 = Me, R^3 = H), which are dehydrated to the 1*H*-pyrrole (XCIII) on standing for several days.[162]



(LXXXIX) (XC) (XCI) (XCII) (XCIII)

R^1 = Me, Et, Ph; R^2 = H, MeO, MeCO, Ph; R^3 = H, Me; R^4 = Me, Ph.

The hydroxypyrroline intermediates (XCV) have also been isolated in the reaction of cyclic 2-(acylmethyl)1,3-diketones (XCIV) with liquid ammonia.[163]

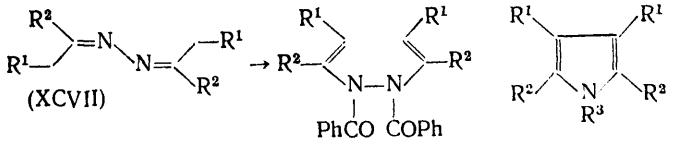


(XCIV) (XCV) (XCVI)

On heating in acetic acid in the presence of ammonium acetate or without a solvent up to the melting point, hydroxypyrrolines (XCV) rearrange to pyrroles (XCVI) in high yield. This rearrangement may occur either by dehydration to a 3*H*-pyrrole with two successive 1,5-acyl shifts or by transannular interaction between the amide nitrogen atom and the carbonyl group.

2. Pyrroles from azines

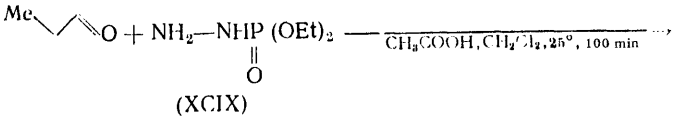
There is a continuous development of methods for the synthesis of pyrroles based on the Piloty reaction. When this reaction is used in its original form, the yields of pyrroles are usually low since strong acid media are used, and it is not possible to convert aldazines to pyrroles. Therefore, in one study[164] azines (XCVII) of enolisable aldehydes and ketones were first converted to *N,N'*-dibenzoyl-*N,N'-bis*(enyl)hydrazines (XCVIII) (by reaction with benzoyl chloride and pyridine in benzene), which on boiling in xylene gave *N*-benzoylpyrroles. Hydrazinolysis of the latter in isopropyl alcohol (80 °C, 1–3 days) yielded *N*-unsubstituted pyrroles.[164]



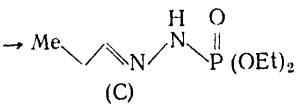
(XCVII) (XCVIII)

R^1 = H, Me, Et; R^2 = Me, Et; R^1R^2 = $(CH_2)_5$; R^3 = COPh, H

Reaction of propanal with diethyl phosphorohydrizidate (XCIX) gives the hydrazone (C).

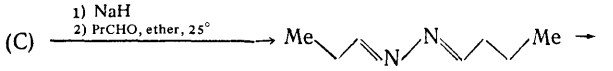


(XCIX)

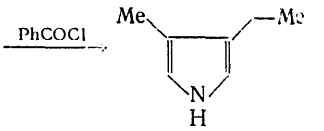


(C)

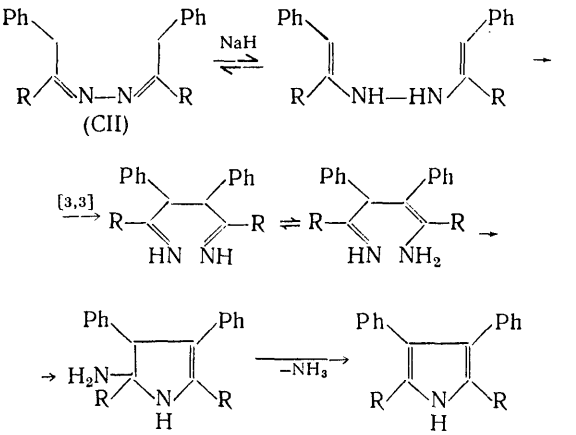
The sodium salt of (C) reacts with butanal to form the asymmetric azine (CI), which after reaction with benzoyl chloride cyclises to a pyrrole.[164]



(CI)



Azines (CII) of carbonyl compounds that contain a readily enolisable benzyl group can undergo thermolysis by catalysis with sodium hydride to give pyrroles.[165,166]

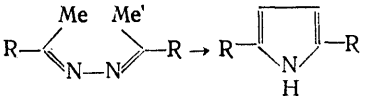


(CII)

R = Me, Et, Pr, iso-Pr, Ph

At the first stage of the cyclisation azine (CII) is converted to a dienehydrazine. An alkaline catalyst, not displacing the equilibrium itself, considerably increases the rate of the tautomeric conversion. At the next stage a [3,3]-sigmatropic shift occurs and after that (via several stages accompanied by elimination of ammonia) the pyrrole is formed. The probability that the stage involving C–C bond formation occurs as a [3,3]-sigmatropic shift is borne out by the fact that pyrrole formation takes place by thermolysis without a catalyst.

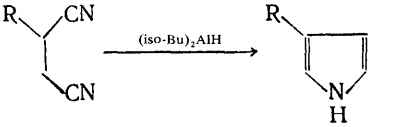
The thermal (150–170 °C) uncatalysed rearrangement of methylarylketazines to 2,5-diarylpyrroles [167] has also been reported.[167]



R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, α-naphthyl

3. Reactions involving a nitrile group

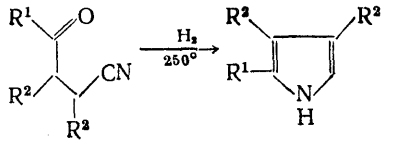
Succinonitriles (CIII) when treated with diisobutylaluminium hydride followed by hydrolysis (NaH_2PO_4, 100 °C, 0.5 h) are converted to pyrroles (CIV) in 34–57% yield.[168]



(CIII) (CIV)

R = iso-Pr, Bu, Ph, 2-ClC_6H_4

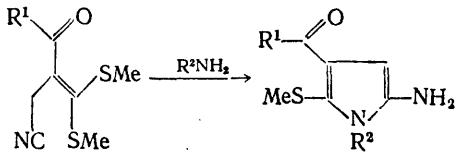
Alkylpyrroles (CVI) are obtained by gas-phase reductive cyclisation of ketonitriles (CV) in the presence of Group VIII metals (Rh, Pd, Pt, Ni).[169]



(CV) (CVI)

R^1 = Alk; R^2 = H, Alk

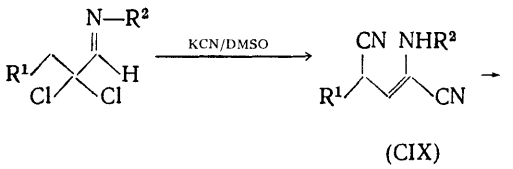
Cyclisation of α-acylketene *S*,*S*-acetals (CVII) with amines (EtOH, 75 °C, 1–1.5 h) gives pyrroles (CVIII) in 41–61% yield.[170]



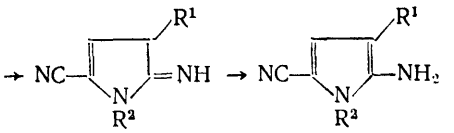
(CVII) (CVIII)

R^1 = Ph, 4-ClC_6H_4, 4-$HO_2CC_6H_4$; R^2 = Me, Et, Bz

Cyclisation of 1,3-dicyanoenamines (CIX), obtained from α,α-dichloroaldimines by treatment with KCN–DMSO (120 °C, 2 h) gives 2-amino-5-cyanopyrroles (CXI) (43–71% yield).[171] Pyrrole formation occurs as a result of intramolecular attack by the amine nitrogen on the CN group and prototropic rearrangement of the intermediate 2-iminopyrroline (CX).



(CIX)

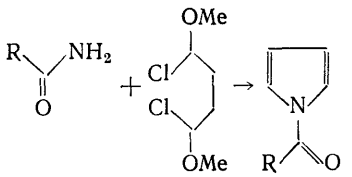


(CX) (CXI)

R^1 = Me, Et; R^2 = iso-Pr, t-Bu

4. Reactions of halogen-containing compounds

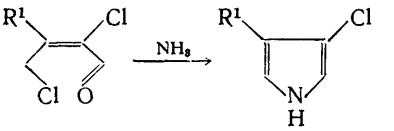
Some primary amides are converted to *N*-acylpyrroles (yield 55–85%) by reaction with 1,4-dichloro-1,4-dimethoxybutane (CXII) in the presence of an ion-exchange resin (MeCN, 45–60 °C, 12 h).[172]



(CXII)

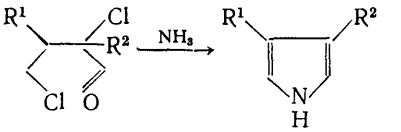
R = Me, Pr, $C_{17}H_{35}$, Ph.

The condensation of chloroaldehydes (CXIV) and (CXV) with ammonia in diglyme gives pyrroles (CXIII).[173–175]



(CXIV) (CXIII)

R^1 = H, Cl

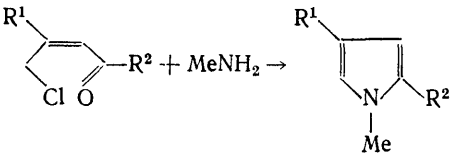


(CXV) (CXIII)

R^1 = HCl; R^2 = Ar

If 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is used as the catalyst it is possible to carry out the reaction at room temperature.[176]

2,4-Substituted pyrroles (CXVII) are obtained by reaction of chloropropenyl ketones (CXVI) with primary amines.[177]

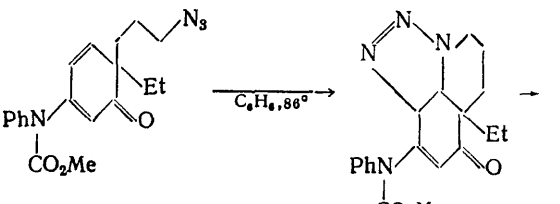


(CXVI) (CXVII)

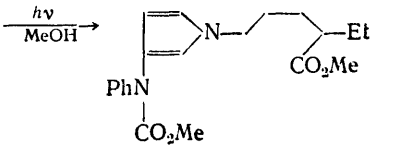
When secondary amines are used, only replacement of the chlorine atom by an amino group occurs.[177]

5. Pyrroles from azides

Irradiation of the triazoline (CXIX), which was derived by intramolecular conversion of azide (CXVIII), in methanol solution gave the pyrrole (CXX) in 75% yield.[178]

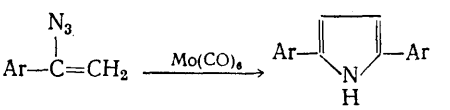


(CXVIII) (CXIX)



(CXX)

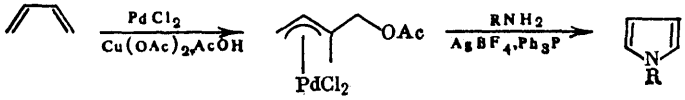
Reaction of the vinylazide (CXXI) with molybdenum hexacarbonyl in protic and aprotic solvents occurs with the formation of 2,5-diarylpyrrole.[179]



(CXXI)

6. Other reactions

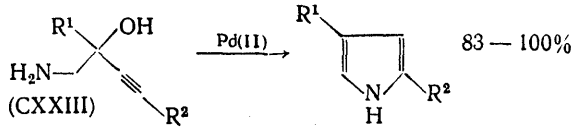
The reaction of dienes with $PdCl_2$ and $Cu(OAc)_2$ in acetic acid gives stable palladium π-allyl complexes (CXXII), which on treatment with primary amines in the presence of 1 equivalent of $AgBF_4$ and 0.1 equivalent of triphenylphosphine form pyrroles in 13–54% yield.[180]



(CXXII)

R= Et, Bz.

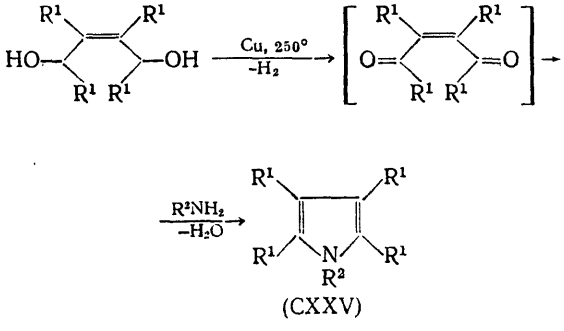
Cyclisation of the acetylenic aminoalcohols (CXXIII) to pyrroles (CXXIV) has been successfully carried out in the presence of palladium [$PdCl_2$ or $Pd(OAc)_2$].[181] A $Pd(Ph_3P)_4$ complex is less effective.



(CXXIV)

$R^1 = C_6H_{13}$, Ph; R^2 = H, Et, iso-Pr

N-Substituted pyrroles (CXXV) are obtained in good yield by gas-phase cyclocondensation (250 °C) of 2-butene-1,4-diols with primary amines, catalysed by transition metals, in particular, by Cu.[182] At the first stage of the reaction the butenediol is probably dehydrated to a dialdehyde or diketone, which then reacts with the amine.

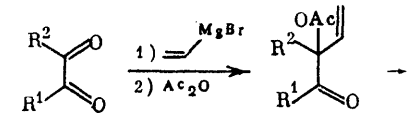


(CXXV)

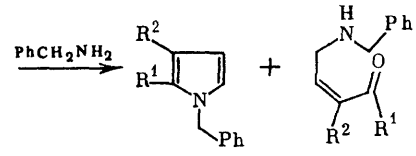
R^1, R^2 = H, Alk, Ar

The possibility of using a reduced fused iron catalyst for the gas-phase synthesis of pyrrole and its derivatives from butanediol, ammonia, and hydrogen has been investigated.[183] At 250–310 °C a mixture consisting of pyrrolidine, *N*-butylpyrrolidine, n-butylamine, n-butanol, 4-(1-pyrrolidyl)-butanol, 1,4-dipyrrolidinebutane, di-n-butylamine, pyrrole, and *N*-butylpyrrole was formed with a total yield of 10–15%. It has been suggested[183] that at lower values of the partial pressure of hydrogen, pyrrole and its derivatives could become the main reaction products.

α-Acetoxy-α-vinylalkanones (CXXVI) (products derived from the reaction of α-dicarbonyl compounds with vinylmagnesium bromide and acetic anhydride) react with benzylamine in the presence of $Pd(PPh_3)_4$



(CXXVI)

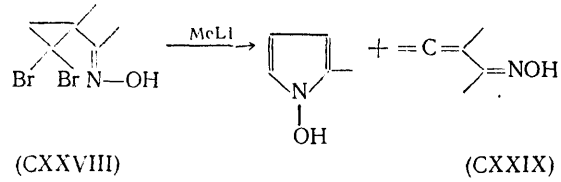


(CXXVII)

R^1 = H, Me, Ph; R^2 = H, Me, Ph; R^1R^2 = $(CH_2)_4$.

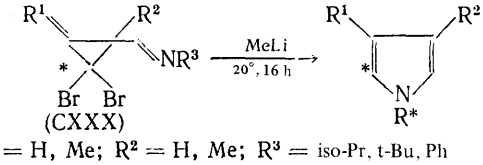
(xylene, THF) to give *N*-benzylpyrroles in 43–65% yield.[184] In addition to pyrroles, aminoketones (CXXVII) are also formed; however, they are not a source of pyrrole.

From oximes of alkyl dibromocyclopropyl ketones (CXXIII) and MeLi were isolated *N*-hydroxypyrroles and allenes (CXXIX),[185] which Santelli considered to be intermediates.



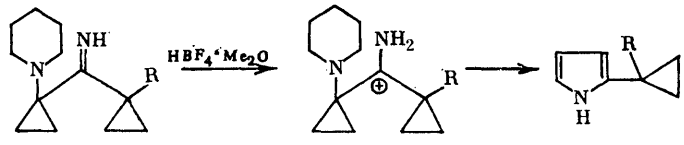
(CXXVIII) (CXXIX)

It was shown subsequently[186,187] using dibromocyclopropanimines (CXXX) that pyrroles are formed in similar reactions as a result of a carbene-carbene rearrangement. Imines with a labelled carbon atom were used to demonstrate the mechanism.



R^1 = H, Me; R^2 = H, Me; R^3 = iso-Pr, t-Bu, Ph

On heating dicyclopropylketimines (CXXXI) in xylene in the presence of a dimethyl ether—fluoroboric acid complex, pyrroles (CXXXIII) are formed with yields of 32 and 42%.[188]

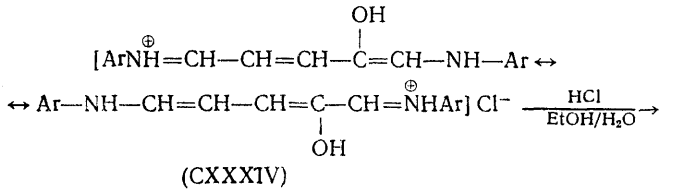


(CXXXI) (CXXXII) (CXXXIII)

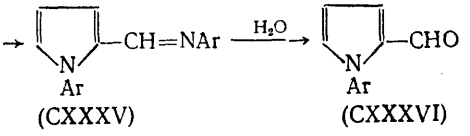
R= H, SPh.

The reaction starts with formation of the carbocation (CXXXII).

N-Arylpyrrole-2-carbaldehydes (CXXXVI) were obtained by acid hydrolysis of salts (CXXXIV).[189]



(CXXXIV)



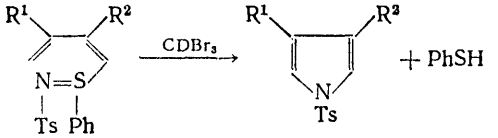
(CXXXV) (CXXXVI)

Ar = Ph, 3-$O_2NC_6H_4$; 4-$O_2NC_6H_4$;

4-Me-3-$O_2NC_6H_3$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

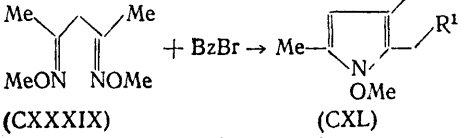
When an ethanol solution of the salts was heated without acid, the intermediate anils (CXXXV) were isolated, readily hydrolysing to aldehydes (CXXXVI) in the presence of acids.

A 1 : 1 mixture of the *N*-tosylpyrrole (CXXXVIII) and thiophenol is obtained from *S*-butadienylsulphimines (CXXXVII) (130 °C, 0.5 h, $CDCl_3$).[190] The reaction takes place with preparative yields in different solvents, but the best results are obtained in phenylisocyanate, which combines with thiophenol.



(CXXXVII) (CXXXVIII)

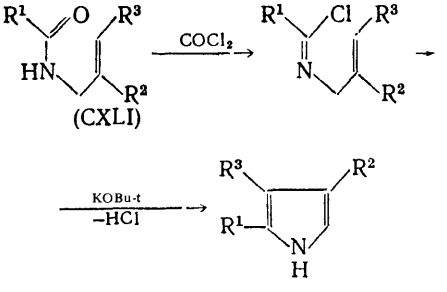
Condensation of benzyl bromide with the diketoxime dimethyl ether (CXXXIX) (HCl, H_2O, CH_2Cl_2, 30 °C, 12 h) gives pyrroles (CXL).[191]



(CXXXIX) (CXL)

$R^1 = H$, $R^2 = Bz$, $R^1 = Bz$, $R^2 = H$

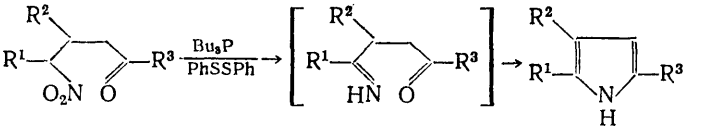
Pyrroles with various substituents are obtained by reaction of *N*-allylamides (CXLI) with $COCl_2$ and then with t-BuOK.[192,193]



(CXLI)

R^1 = Ph, 2-furyl, 2-thienyl, 2-HOC_6H_4, t-Bu; R^2 = H, Me; R^3 = H, Me.

The intramolecular cyclisation of iminoketones (CXLIII), which are formed by reduction of nitroalkanones (CXLII) with tributylphosphine and diphenyl sulphide (THF, 20 °C) gives pyrroles (CXLIV) in high yield.[194,195]



(CXLII) (CXLIII) (CXLIV)

R^1 = Me, CO_2Et; R^2 = Me, Ph; R^3 = Ph, Me

Thus, the methods for constructing a pyrrole ring from aliphatic compounds continue to undergo rapid development. Along with an improvement of the known synthetic methods based on the classical reactions of Knorr, Paal–Knorr, Hantzsch, Chichibabin, and Piloty, there is a constant search for new preparative reactions which can form a pyrrole ring from the most accessible starting materials and under the mildest possible conditions. A particularly rapid development is taking place at present for the recently discovered formation of pyrroles from ketoximes when treated with acetylene or its equivalents (vinyl halides, dihaloethanes) in the presence of superbasic systems of the type KOH–DMSO. This reaction has opened up a simple route to groups of pyrroles that were previously difficult to obtain, including *N*-vinylpyrroles, which are now being synthesised rapidly and studied in detail.

In the present-day synthesis of pyrroles from aliphatic compounds the following trends prevail: 1) there is a wider use of acetylenic compounds or their equivalents (especially acetylenes with strong acceptor substituents and conjugated diacetylenes) as starting materials; 2) different ketone derivatives (oximes, imines, hydrazones, β-nitro derivatives, etc.) are involved in synthesis; 3) there is a change to reagents and catalysts having superbasicity,[196] such as KOH–DMSO, t-BuOK–DMSO, dimsyl sodium, NaH–THF, $NaNH_2$–NH_3, lithium diisopropylamide, etc.; this achieves a substantial increase in the yield of pyrroles, an acceleration of different base-catalysed processes, and in a number of cases gives rise to new reactions.

References

1. A Gossauer *Die Chemie der Pyrrole*, Springer Verlag, Berlin–Heidelberg–New York, 1974, p. 433
2. R A Jones, G P Bean *The Chemistry of Pyrroles*, Acad. Press, London–New York–San Franciso, 1977, p. 525
3. B A Trofimov, A I Mikhaleva *N-Vinilpirroly* (*N*-Vinylpyrroles), Izd. Nauka, Novosibirsk, 1984, p. 262
4. R J Sundberg *Comprehensive Heterocyclic Chemistry*, Vol. 4 (Edited by A R Katritzky et al.), Pergamon Press, Oxford–New York, 1984, p. 313
5. A H Jackson *General Organic Chemistry* (Translated into Russian), Vol. 8, Izd. Khimiya, Moscow, 1985, p. 332
6. B A Trofimov, A I Mikhaleva *Khim. Geterotsikl. Soed.*, 1980, 1299
7. J M Patterson *Synthesis*, 1976, 281
8. Ya P Stradyn' *Khim. Geterotsikl. Soed.*, 1979, 1567
9. Ya P Stradyn' *Khim. Geterotsikl. Soed.*, 1981, 1412

10. B A Trofimov *Geteroatomnye Proizvodnye Atsetilena. Novye Polifunktsional'nye Monomery, Reagenty i Poluprodukty* (Heteroatomic Derivatives of Acetylene, New Polyfunctional Monomers, Reagents, and Intermediates), Izd. Nauka, Moscow, 1981, p. 319
11. A I Mikhaleva, M V Sigalov, G A Kalabin *Tetrahedron Lett.*, 1982, **23** 5063
12. L N Sobenina, Candidate's Thesis in Chemical Sciences, Irkutsk Institute of Organic Chemistry, Siberian Branch, USSR Academy of Sciences, Irkutsk, 1983, p. 216
13. S E Korostova, A I Mikhaleva *Zhur. Org. Khim.*, 1982, **18** 2620
14. B A Trofimov, A I Mikhaleva, R I Polovnikova, et al. *Khim. Geterotsikl. Soed.*, 1981, 1058
15. S E Korostova, L N Sobenina, R N Nesterenko, et al. *Zhur. Org. Khim.*, 1984, **20** 1960
16. S E Korostova, A I Mikhaleva, L N Sobenina, et al. *Khim. Geterotsikl. Soed.*, 1985, 1501
17. S E Korostova, A I Mikhaleva, R N Nesterenko, et al. *Zhur. Org. Khim.*, 1985, **21** 406
18. B A Trofimov, A I Mihaleva, R N Nesterenko, et al. *Tezisy Dokladov VII Vsesoyuznoi Konferentsii po Khimii Atsetilena* (Abstracts of Reports at the VIIth All-Union Conference on Acetylene Chemistry), Erevan, 1984, p. 110
19. B A Trofimov, A B Shapiro, R N Nesterenko, et al. *Khim. Geterotsikl. Soed.*, 1988, 350
20. T N Borisov, A V Varlamov, N S Prostakov *Tezisy Dokladov I Vsesoyuvnoi Konferentsii po Khimii, Biokhimii i Farmakologii Proizvodnykh Indola* (Abstracts of Reports at the Ist All-Union Conference on the Chemistry, Biochemistry, and Pharmacology of Indole Derivatives), Tbilisi, 1986, p. 39
21. T N Borisov, Candidate's Thesis in Chemical Sciences, P Lumumba People's Friendship University, 1987, 152
22. M A Yarovskaya, V V Druzhinina, E V Snetkova, and Yu G Bundel' *Khim. Geterotsikl. Soed.*, 1983, 356
23. V V Druzhinina, Candidate's Thesis in Chemical Sciences, Izd. MGU, Moscow, 1983, p. 161
24. S E Korostova, A I Mikhaleva, L N Sobenina, et al. *Zhur. Org. Khim.*, 1986, **27** 492
25. B A Trofimov, A I Mikhaleva, A N Vasil'ev, et al. *Khim. Geterotsikl. Soed.*, 1985, 59
26. I A Aliev, D G Almamedova, B R Gasanov, A I Mikhaleva *Khim. Geterotsikl. Soed.*, 1984, 1359
27. I A Aliev, A I Mikhaleva, M V Sigalov *Sulfur Lett.*, 1984, **2**(2) 55
28. B A Trofimov, S E Korostova, A I Mikhaleva, et al. *Khim. Geterotsikl. Soed.*, 1983, 273
29. B A Trofimov, S E Korostova, A I Mikhaleva, et al. *Khim. Geterotsikl. Soed.*, 1983, 276
30. B A Trofimov, S G Shevchenko, S E Korostova, et al. *Khim. Geterotsikl. Soed.*, 1985, 1573
31. M A Yurovskaya, A Z Afanas'ev, Yu G Bundel', et al. *Khim. Geterotsikl. Soed.*, 1984, 1077
32. D Dhanak, C B Reese, S Romana, G Zappia *Chem. Commun.*, 1986, 903
33. G Filacchioni, L Cecci, G C Porreta, et al. *Farmaco. Ed. Sci.*, 1983, **38** 619
34. P Rubio Zurita, Spanish P. 502 650; *Chem. Abs.*, 1982, **97** 162 811
35. E Pando, M C Garcia Bala, C Martin Madero *Afinidad*, 1983, **40**(387) 445
36. E Pando, C Martin Madero, C Vergara *An. Quim., Ser. C*, 1980, **76**(1) 53
37. Central Glass Co., Japanese P. 59 167 568; *Chem. Abs.*, 1985, **102** 78 719
38. H Ogoshi, M Homma, K Yokota, et al. *Tetrahedron Lett.*, 1983, **24** 929
39. J V Cooney, E J Beal, R N Hazlett *Org. Prep. Proceed. Int.*, 1983, **15** 292
40. P S Clezy, M W Duncan, B N Ravi, L. van Thuc *Austral. J. Chem.*, 1986, **39** 399
41. M F Chen, S F MacDonald *Can. J. Chem.*, 1974, **52** 1760
42. Laboratoires Pharmedical SA, BRD P. 3 242 203; *Chem. Abs.*, 1983, **99** 122 290
43. J B Paine, D Dolphin *J. Heterocycl. Chem.*, 1975, **12** 1317
44. J B Paine, D Dolphin *J. Org. Chem.*, 1985, **50** 5598
45. A Padwa *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984, p. 1521
46. A Padwa, Y-Y Chen, W Dent, H Nimmesgern *J. Org. Chem.*, 1985, **50** 4006
47. A Padwa, W Dent, H Nimmesgern, et al. *Chem. Ber.*, 1986, **119** 813
48. A Padwa, G Haffmanns, M Tomas *Tetrahedron Lett.*, 1983, **24** 4303
49. O Tsuge, S Kanemasa, K Matsuda *Chem. Lett.*, 1985, 1411
50. O Tsuge, S Kanemasa, K Matsuda *J. Org. Chem.*, 1986, **51** 1997
51. K Burger, S Rottegger *Tetrahedron Lett.*, 1984, **25** 4091
52. W E McEwen, A V Grossi, R J MacDonald, A P Stamegna *J. Org. Chem.*, 1980, **45** 1301
53. J V Cooney, W E McEwen *J. Org. Chem.*, 1981, **46** 2570
54. J V Cooney, B D Bearer, W E McEwen *J. Heterocycl. Chem.*, 1985, **22** 635
55. S Zen, K Harada *Chem. Pharm. Bull.*, 1982, **30** 366
56. A Padwa, G S K Wong *J. Org. Chem.*, 1986, **51** 3125
57. G Holland, US P. 4 282 242; Chem. Abs., 1981, **95** 187 068
58. G Genda, H Muro, S Nakayama, et al., Japanese P. 6 130 571; Chem. Abs., 1986, **105** 60 520
59. P Magnus, Y S Or *Chem. Commun.*, 1983, 26
60. P Magnus, T Gallagher *Chem. Commun.*, 1984, 389
61. S P J Van Nispen, O Mensink, A M van Leusen *Tetrahedron Lett.*, 1980, **21** 3723
62. J Moskal, A M van Leusen *J. Org. Chem.*, 1986, **51** 4131
63. K Sakai, M Suzuki, K Nunami, N. Yoneda *Chem. Pharm. Bull.*, 1980, **28** 2384
64. Nippon Soda Co., Japanese P. 59 212 468; *Chem. Abs.*, 1985, **102** 149 104
65. Nippon Soda Co., Japanese P. 5 885 861; *Chem. Abs.*, 1983, **99** 122 293
66. H A Houwing, A M van Leusen *J. Heterocycl. Chem.*, 1981, **18** 1127
67. L A Mayring, T Severin *Chem. Ber.*, 1981, **114** 3863
68. Du Pont de Nemours Co., Israel P. 61 768; *Chem. Abs.*, 1985, **102** 95 535
69. T O Lash, K A Bladel, M C Johnson *Tetrahedron Lett.*, 1987, **28** 1135
70. G Baccolini, C Sandali *Chem. Commun.*, 1987, 788
71. O Attanasi, P Filippone, A Mei, F Zerra-Zanetti *Synth. Commun.*, 1986, **16** 343
72. O Attanasi, M Grossi, F Zerra-Zannetti *Org. Prep. Proced. Int.*, 1986, **18** 1
73. O Attanasi, P. Filippone, A Mei, et al. *Synthesis*, 1985, 157

74. O Attanasi, P Filippone, A Mei, S Santeusanio *Synthesis*, 1984, 671
75. O Attanasi, P Bonifazi, E Foresti, G Pradella *J. Org. Chem.*, 1982, **47** 684
76. O Attanasi, S Santeusanio *Synthesis*, 1983, 742
77. O Attanasi, P Bonifazi, F Buiani *J. Heterocycl. Chem.*, 1983, **20** 1077
78. O Attanasi, F R Perrulli *Synthesis*, 1984, 874
79. O Attanasi, F R Perrulli, F Zerra-Zanetti *Heterocycles*, 1985, **23** 867
80. O Attanasi, P Filippone, A Mei, S Santeusanio *Synthesis*, 1984, 873
81. T L Gilchrist, B Parton, J A Stevens *Tetrahedron Lett.*, 1981, **22** 1059
82. D A Robinson, J Chen Chen, BRD P. 2942140; *Chem. Abs.*, 1980, **93** 150113
83. M J Dagani, US P. 4565876; *Chem. Abs.*, 1985, **105** 42636
84. M J Dagani, US P. 4388468; *Chem. Abs.*, 1983, **99** 105120
85. Y Cai, W Dong *Yiyao Gongye* 1983, (5) 3; *Chem. Abs.*, 1983, **99** 139683
86. J T F Kao, E M Marlett, US P. 4383117; *Chem. Abs.*, 1983, **99** 38359
87. G Bottaccio, S Campolmi, V Carletti, A Marchi, Europ. P. 92487; *Chem. Abs.*, 1984, **100** 174654
88. M J Dagani, Europ. P. 72441; *Chem. Abs.*, 1983, **99** 22312
89. J T F Kao, Canadian P. 1146564; *Chem. Abs.*, 1983, **99** 139758
90. J T F Kao, R E Farritor, US P. 4374255; *Chem. Abs.*, 1983, **98** 160584
91. R Albert, S A Willemsen, G van der Veken, US P. 4363918; *Chem. Abs.*, 1983, **98** 143271
92. Ethyl Corp., Japanese P. 58177964; *Chem. Abs.*, 1984, **100** 68165
93. G Bottaccio, S Campolmi, V Carletti, M Marchi, Europ. P. 105664; *Chem. Abs.*, 1984, **101** 54915
94. M J Dagani, J T F Kao, Europ. P. 89393; *Chem. Abs.*, 1984, **100** 51446
95. E M Marlett, US P. 4455433; *Chem. Abs.*, 1984, **101** 110727
96. C G Kazembe Takawiva, D A Taylor *Tetrahedron*, 1980, **36** 2125
97. R J Mattson, L C Wang, J W Sowell *J. Heterocycl. Chem.*, 1980, **17** 1793
98. J A S Lacks, J R Ross, S M Bayomi, J W Sowell *Synthesis*, 1985, 291
99. H Pichler, G Folkers, H J Roth, K Eger *Liebigs Ann. Chem.*, 1985, 1485
100. M Sonoda, N Kuriyama, Y Tomioka, M Yamazaki *Chem. Pharm. Bull.*, 1982, **30** 2357
101. N Chatani, T Hanafusa *Tetrahedron Lett.*, 1986, **27** 4201
102. T Kusumoto, T Hiyama, K Ogata *Tetrahedron Lett.*, 1986, **27** 4197
103. D Yusipov, Abstract of Doctorate Thesis in Chemical Sciences, M V Lomonosov Moscow Institute of Technology and Chemical Technology, 1987, p. 40.
104. A K Kulimov, D Yusipov, K M Akhmerov, A B Kuchkarov *Dokl. Akad. Nauk UzSSR*, 1984, (5) 40
105. K M Akhmerov, D Yusipov, A B Kuchkarov, K Akhmedov, USSR P. 514820; *Byul. Izobret.*, 1976, (19) 54
106. K M Akhmerov, D Yusipov, A B Kuchkarov, K Akhmedov *Khim. Geterotsikl. Soed.*, 1974, **428**
107. S Baroni, R Straid, M L Saccarello *J. Heterocyclic Chem.*, 1980, **17** 1221
108. J M Vernon, R M Carr, M A Sukari *J. Chem. Res. S*, 1982, 115
109. R M Carr, R O C Norman, J M Vernon *J. Chem. Soc., Perkin Trans. I*, 1980, 156
110. M A Sukari, J M Vernon *Tetrahedron*, 1983, **39** 793
111. H Ahlbrecht, A von Daacke *Synthesis*, 1984, 610
112. A Gomes-Sanchez, M Mancerai, F J Caballero, J Bellanato *An. Quim. Ser. C*, 1983, **79**(2) 175
113. H Meyer *Liebigs Ann. Chim.*, 1981, 1534
114. A Gomes-Sanchez, B M Stiefel, R Fernandez-Fernandez, et al. *J. Chem. Soc., Perkin Trans. I*, 1982, 441
115. A Gomes-Sanchez, B M Stiefel, R Fernandez-Fernandez, Spanish P. 500331; *Chem. Abs.*, 1982, **97** 92129
116. F Boberg, K H Garburg, K J Gorlich, et al. *Liebigs Ann. Chem.*, 1985, 239
117. M L Roantree, R C Young, Europ. P. 5985; *Chem. Abs.*, 1980, **93**, 46411
118. D H R Barton, S Z Zard *Chem. Commun.*, 1985, 1098
119. A G Ismailov, E I Mamedov, USSR P. 498295; *Byul. Izobret.*, 1976, (1) 82
120. A G Ismailov, E I Mamedov *Uchenye Zapiski. Min. Vysshego i Srednego Spetsial'nogo Obrazovaniya AzSSR, Ser. Khim. Nauk*, 1975, (2) 54
121. A G Ismailov, R D Goyushov *Uchenye Zapiski. Min. Vysshego i Srednego Spetsial'nogo Obrazovaniya AzSSR, Ser. Khim. Nauk*, 1975, (1) 30
122. I I Ibragimov, A N Kost, M M Guseinov, et al. *Khim. Geterotsikl. Soed.*, 1976, 790
123. E I Mamedov, A G Ismailov, V G Ibragimov, R D Goyushov *Khim. Geterotsikl. Soed.*, 1983, 1561
124. K Gewald, H Schaefer, E Schindler, GDR P. 138976; *Chem. Abs.*, 1980, **93** 71547
125. O E Nasakin, V V Alekseev, V K Promonenkov, et al. *Khim. Geterotsikl. Soed.*, 1981, 402
126. O E Nasakin, V V Alekseev, P B Teren'tev, et al. *Khim. Geterotsikl. Soed.*, 1983, 1062
127. O E Nasakin, V V Alekseev, P B Terent'ev, et al. *Khim. Geterotsikl. Soed.*, 1983, 1067
128. G Kresze, A Bizhiv *Dokl. Bolg. Akad. Nauk*, 1982, **35** 1387
129. J B Doherty, M N Chang, C P Dorn, US P. 443175; *Chem. Abs.*, 1984, **100** 191732
130. J B Doherty, M N Chang, C P Dorn, Europ. P. 72013; *Chem. Abs.*, 1983, **99** 22311
131. S Mataka, K Takahashi, Y Tsuda, M Tashiro *Synthesis*, 1982, 157
132. Du Pont de Nemours Co., Israel P. 56243; *Chem. Abs.*, 1983, **99**, 70557
133. N J Bach, E C Kornfeld, US P. 4235776; *Chem. Abs.*, 1981, **94** 121320
134. J Barluenga, V Rubio, V Gotor *J. Org. Chem.*, 1982, **47** 1696
135. M Takahashi, T Funaki, H Honda, et al. *Heterocycles*, 1982, **19** 1921
136. Nippon Soda Co., Japanese P. 8051065; *Chem. Abs.*, 1981, **94** 30559
137. S Yoneda, H Hirai, Z Yoshida *Heterocycles*, 1981, **15** 865
138. Z Yoshida, Japanese P. 7944669; *Chem. Abs.*, 1980, **98** 6404
139. W Flitsch, K Pandl, P Russkamp *Liebigs Ann. Chem.*, 1983, 529
140. H J Weintz, P Binger *Tetrahedron Lett.*, 1985, **26** 4075

141. H Quast, W Saal, J Stawitz *Angew. Chem.*, 1981, **93** 619
142. G Zoller, R Beyerle, U Schindler, et al., Europ. P. 124067; *Chem. Abs.*, 1985, **102** 131904
143. D Lenke, C D Mueller, K H Geiss, J U Bliesgher, BRD P. 2914615; *Chem. Abs.*, 1981, **94** 83939
144. W J Thompson C A Buhr *J. Org. Chem.*, 1983, **48** 2769
145. W Hua, M Zhu *Xuaxue Tongbao*, 1982, (5) 281; *Chem. Abs.*, 1982, **97** 182142
146. W Hua, L Chen, X Peng, et al. *Beijing Daxue Xuebao, Ziran Kexueban*, 1984, (2) 35; *Chem. Abs.*, 1985, **102** 6097
147. M Salmon, O Villarino, A Jimenez, R Zawadski *Rev. Soc. Quim. Mex.*, 1980, **24**(1) 32
148. Dainippon Pharmaceutical Co., Japanese P. 8270864; *Chem. Abs.*, 1982, **97** 162808
149. T Sato, M Uchida, F Tafusa, K Nakagawa, Japanese P. 7979271; *Chem. Abs.*, 1980, **92** 41752
150. C Bernhart, J P Gagnol, P Gautier, US P. 4329343; *Chem. Abs.*, 1982, **97** 72250
151. H Damarne, C Bernhart, M Serre, French P. 2492374; *Chem. Abs.*, 1982, **97** 127492
152. Japanese P. 57139063; *Chem. Abs.*, 1983, **98** 107153
153. C Bernhart, J P Gagnol, P Gautier, S. African ZA 81004880; *Chem. Abs.*, 1982, **97** 92131
154. N Filipovic-Marinic, G Nalic *Liebigs Ann. Chem.*, 1984, 199
155. W T Hua *Hua Wsuch Tung Pao*, 1980, 662; *Chem. Abs.*, 1981, **94** 174785
156. T Tanaka, T Wakabayashi, A Otsu, S Kurozumi, Europ. P. 2392; *Chem. Abs.*, 1980, **92** 76277
157. Nippon Soda Co., Japanese P. 80118458; *Chem. Abs.*, 1981, **95** 7047
158. B Li, S Zhang *Gaedeng Xuexiao Xuebao*, 1985, **6** 513; *Chem. Abs.*, 1986, **104** 129728
159. B Li, S Zhang *Gaedeng Xuexiao Xuebao*, 1985, **6** 341; *Chem. Abs.*, 1986, **104** 129729
160. B Li, S Zhang *Gaedeng Xuexiao Xuebao*, 1985, **6** 917; *Chem. Abs.*, 1986, **105** 152868
161. US P. 4551540; *Chem. Abs.*, 1986, **105** 114895
162. P K Chiu, K H Lui, P N Maini, M P Sammes *Chem. Commun.*, 1987, 109
163. M P Sammes, P N Maini, A R Katritzky *Chem. Commun.*, 1984, 354
164. J E Baldwin, J C Bottaro *Chem. Commun.*, 1982, 624
165. I I Grandberg, O Yu Kutsenko, USSR P. 1101441; *Byul. Izobret.*, 1984, (25) 57
166. I I Grandberg *Zhur. Org. Khim.*, 1983, **19** 2439
167. Yu V Shurukhin, N A Klyuev, I I Grandberg *Zhur. Org. Khim.*, 1985, **21** 2057
168. J H Babler, K P Spina *Tetrahedron Lett.*, 1984, **25** 1659
169. Europ. P. 66346; *Chem. Abs.*, 1983, **98** 125866
170. S Apparao, H Ila, H Junjappa *Synthesis*, 1981, 65
171. R Verhe, N De Kimpe, L De Buyck, et al. *Tetrahedron*, 1980, **36** 131
172. S D Lee, M A Brook, T H Chan *Tetrahedron Lett.*, 1983, **24** 1569
173. A Heda, H Nagasaki, J Takakura, S Kojima, Europ. P. 92890; *Chem. Abs.*, 1984, **100** 103170
174. A Heda, H Nagasaki, J Takakura, S Kojima, International P. 8401773; *Chem. Abs.*, 1984, **101** 171082
175. Nippon Soda Co., Japanese P. 59130864; *Chem. Abs.*, 1984, **101** 191685
176. Nippon Soda Co., Japanese P. 5978160; *Chem. Abs.*, 1984, **101** 171083
177. G M Bairamov, S P Godzhaev, R D Goyushev *Azerb. Zhur. Khim.*, 1985, (2) 79
178. A G Schulz, C K Sha *J. Org. Chem.*, 1980, 2041
179. T Kobayashi, M Nitta *Nippon Kagaku Kaishi*, 1985, 451
180. J E Backväll, J E Nyström *Chem. Comm.*, 1981, 59
181. K Utimoto, H Miwa, H Nozaki *Tetrahedron Lett.*, 1981, **22** 4277
182. H Mening, M Fisher, K Baer, BRD P. 3309355; *Chem. Abs.*, 1985, **102** 45769
183. G A Kliger, O A Lesik, E V Marchevskaya, et al. *Khim. Geterotsikl. Soed.*, 1987, 195
184. B M Trost, E Keinan *J. Org. Chem.*, 1980, **45** 2741
185. C Santelli *Tetrahedron Lett.*, 1980, 2893
186. J Arct, L Skatteebøl *Tetrahedron Lett.*, 1982, **45** 2741
187. Y H Brinker, M Boxberger *J. Chem. Res. Synop.*, 1983, (4) 100
188. H H Wasserman, R P Dion *Tetrahedron Lett.*, 1983, **24** 3409
189. B R D'Arcy, K G Lewis, C E Mulquiney *Austral. J. Chem.*, 1985, **36** 953
190. Y Gaoni *Tetrahedron Lett.*, 1982, **23** 2051
191. S Shatzmiller, R Lidor *Synthesis*, 1983, 590
192. S Cherkofsky, US P. 4267190; *Chem. Abs.*, 1982, **96** 68810
193. H Koenig, A Franke, F F Friekel, BRD P. 2835439; *Chem. Abs.*, 1980, **93** 132363
194. D H R Barton, W B Motherwell, S Z Zard *Tetrahedron Lett.*, 1984, **25** 3707
195. D H R Barton, W B Motherwell, E S Simon, S Z Zard *J. Chem. Soc., Perkin Trans. I*, 1986, 224
196. B A Trofimov *Zhur. Org. Khim.*, 1986, **22** 1991