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SYNTHESIS OF COMPOUNDS WITH TWO OR MORE PYRAZOLE RINGS LINKED TO EACH OTHER (REVIEW)

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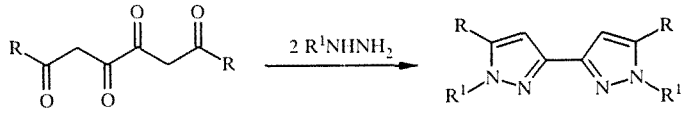
Data on the synthesis of compounds containing two or more directly linked pyrazoline rings are summarized.

In the present review published data on the synthesis of bi- and polypyrazoles containing C—C, C—N, and N—N bonds between the rings and also pyrazolopyrazoles, i.e., compounds containing two or more pyrazole rings directly fused to each other, which gives these systems specific characteristics differing from other types of pyrazoles, are summarized.* Such compounds have a wide spectrum of biological activity [1-6]. Methods for their preparation are often specific and in a whole series of important cases differ from the standard methods for the synthesis of monopyrazoles. Data on the synthesis of certain pyrazolopyrazoles were partly summarized in the reviews [7-8]. Papers on the production of bi- and polypyrazoles are reviewed for the first time.

1. Production of C—C-Bonded Bi-, Ter-, and Quaterpyrazoles

The classical method for the synthesis of pyrazoles, which has also been used for the production of bipyrazoles, involves the reaction of hydrazine and monosubstituted hydrazines with 1,3-dicarbonyl compounds or their derivatives. Mixtures of isomeric pyrazoles can be formed from unsymmetrical dicarbonyl compounds or monosubstituted hydrazines. Such mixtures have sometimes been taken as individual compounds.

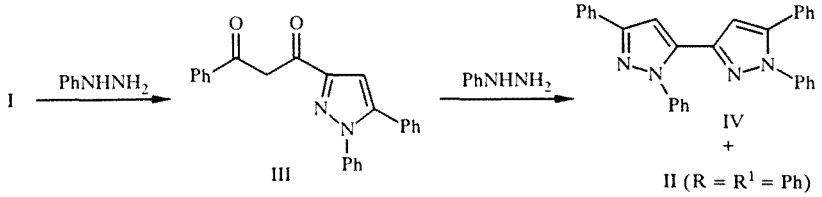
Thus, one of the early methods for the production of bipyrazoles (II) is the treatment of tetraketones (I) with phenylhydrazine [9] or methylhydrazine [10].



I II

R = R¹ = Ph; R = Me, R¹ = Ph; R = Ph, R¹ = Me

More recent investigations have shown that the 1,6-diphenyl-1,3,4,6-hexanetetraone (I) (R = Ph) reacts with one mole of phenylhydrazine to form the diketone (III), while the further action of another mole of phenylhydrazine leads to the isomeric 1,1′,5,5′-tetraphenyl-3,3′-bipyrazole (II) (R = R¹ = Ph) and 1,1′,3′,5-tetraphenyl-3,5′-bipyrazole (IV). The production of two isomers even when two moles of phenylhydrazine are used at once shows that the reaction in this case takes place through the formation of the ketone (III) [11].



*In certain cases the synthesis of pyrazolones, pyrazolines, etc., from which the pyrazoles can be obtained by known simple methods, is described.

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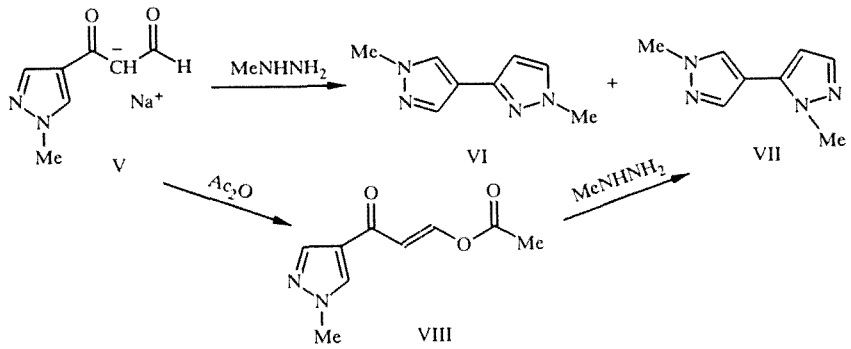
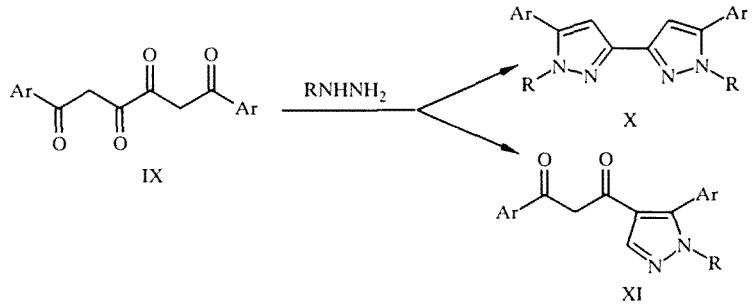
Similarly, the 1-(1-methyl-4-pyrazolyl)-1,3-propanedione sodium salt (V) reacts with methylhydrazine to form 3,4′- and 4,5′-bipyrazoles (VI) and (VII) [(VI):(VII) = 1:9]. The overall yield amounts to 33% and is increased to 66% with the same product ratio if the sodium salt (V) is first converted into the ester (VIII) by the action of acetic anhydride [12].

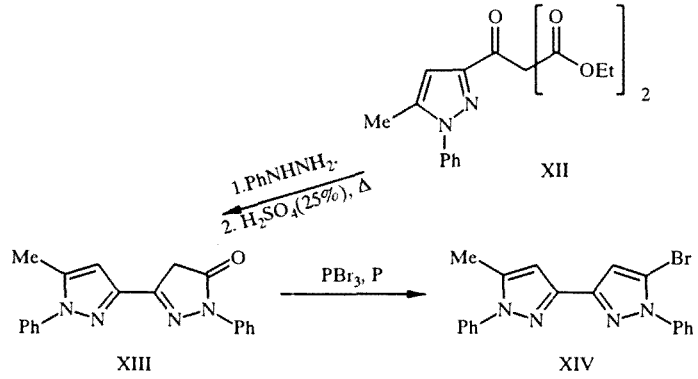


The selectivity of the formation of one or the other isomer is affected by a whole series of structural and experimental factors. For example, the reaction of hydrazines with the tetraketone (IX), which has electron-donating substituents in the phenyl ring, leads to the formation of the 3,3′-bipyrazoles (X), while only the monopyrazoles (XI) are formed in other cases [13].

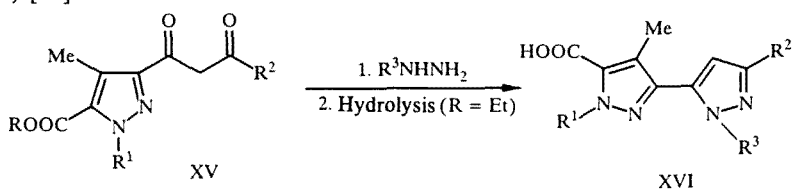


Ar, R, yield (%) : C_6H_4OH-4, H, 53 or Ph, 42; $C_6H_4OCONHMe$-4, H, 48 or Ph, 49

The reaction of substituted malonic ester (XII) with phenylhydrazine followed by heating with sulfuric acid gives the pyrazolylpyrazolone (XIII). The latter is converted by the action of red phosphorus and phosphorus tribromide into 3,3′-bipyrazole (XIV), the yield of which amounts to 33% [14].

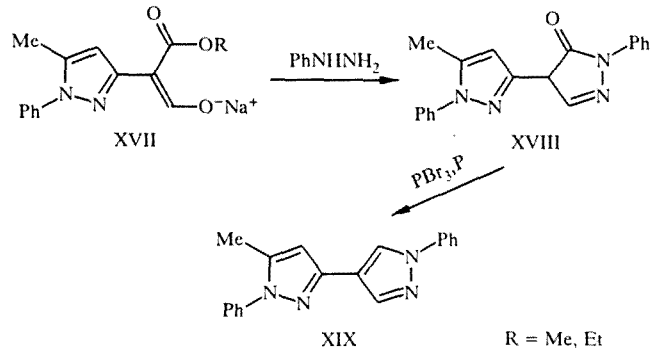


The treatment of α-pyrazolyl-1,3-diketones containing substituents in the pyrazole ring (XV) with hydrazines only gives the 3,5′-bipyrazoles (XVI) [15].



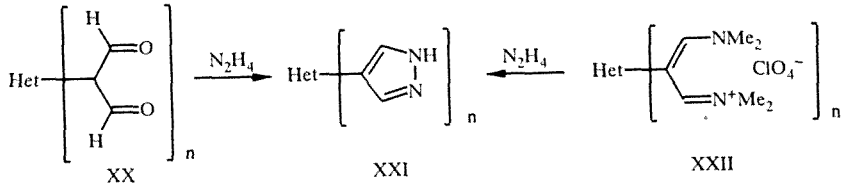
R = R³ = H, R¹ = R² = Me; R = H, R¹ = R² = Me, R³ = Ph; R = Et, R¹ = H, R² = Me, R³ = Ph; R = Et, R¹ = Me, R² = R³ = Ph

The use of the salt (XVII) in the reaction with phenylhydrazine leads to the pyrazolylpyrazolone (XVIII), which can be converted into the 3,4′-bipyrazole (XIX) [14].

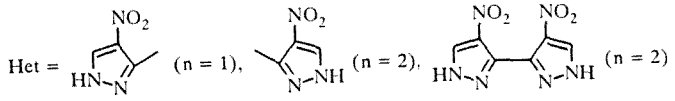


XVII XVIII XIX R = Me, Et

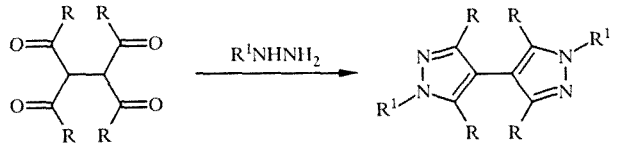
Recently it was shown that 3(5),5′(3′)-bonded bi-, ter-, and quaterpyrazoles (XXI) can be obtained successfully from the easily synthesized C-(diformylmethyl)-substituted nitropyrazoles (XX) and also from the precursors of the latter, i.e., the trimethinium salts (XXII) [16].



XX XXI XXII



The 4,4′-bipyrazoles (XXIV) are obtained from the β,β′-1,3-tetraketones (XXIII) [12,17-19].

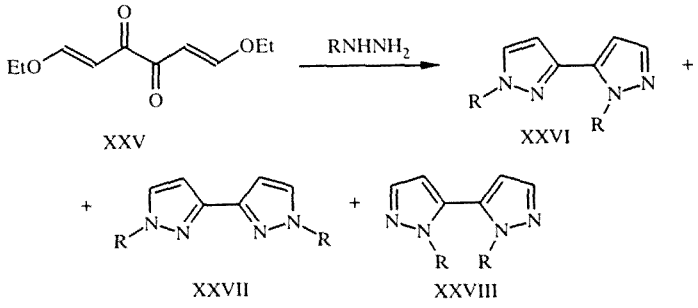


XXIII XXIV

R, R^1, yield (%) : H, H, 95; Me, Ph, 99; H, Me, 54; Me, H, 82

If the initial compound also contains an activated multiple bond in addition to the carbonyl groups, there is competition between two processes, i.e., the formation of a hydrazone and the addition of the hydrazine at the C=C bond, and this leads to a mixture of isomers.

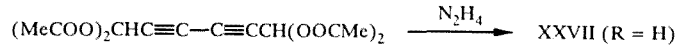
Thus, the direct condensation of compound (XXV) with methylhydrazine by Effenberger's method [20] leads to the three isomeric products (XXVI-XXVIII) (R = Me) in a (XXVI):(XXVII):(XXVIII) ratio of 2:1:2 with an overall yield of 25-30% [12].



XXV XXVI XXVII XXVIII

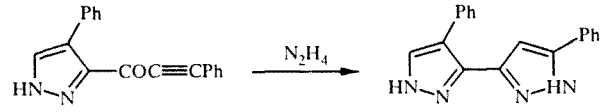
It is difficult to predict the preferred direction of synthesis; it depends on the nature of the reagent, the solvent, and the temperature. In a number of cases it is possible to obtain only one isomer by varying the reaction conditions. Thus, the reaction of the above-mentioned diketone (XXV) with phenylhydrazine in m-cresol only leads to 1,1′-diphenyl-3,3′-bipyrazole (XXVII) (R = Ph) with an 85% yield [21].

Effenberger synthesized the unsubstituted 3,3′-bipyrazole (XXVII) (R = H) by a similar method [20]. This compound is also formed with a yield of 34% when the diacylal (XXIX) is treated with hydrazine [22].



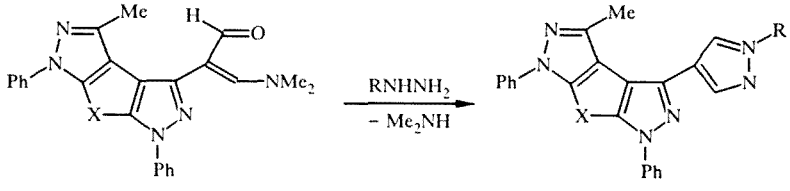
XXIX

Derivatives of 3,3′-bipyrazole can also be obtained from ethynyl ketones of the (XXX) type, and the product yield in the case of the latter amounted to 93%. However, this method is rarely used on account of the poor availability of the initial ketones [23].

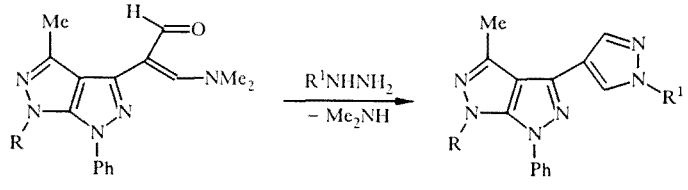


XXX

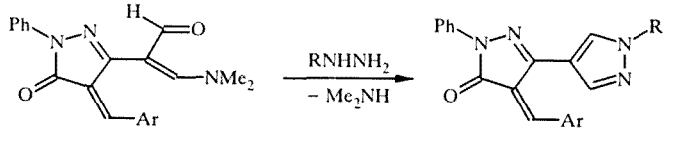
It should be noted that the reaction of pyrazole-containing enamines (XXXI-XXXIII) with hydrazine or phenylhydrazine leads after removal of the amino group to derivatives of 3,4′-bipyrazoles (XXXIV-XXXVI) [2,3,24,25].



XXXI X = O, S; R = H, Ph XXXIV

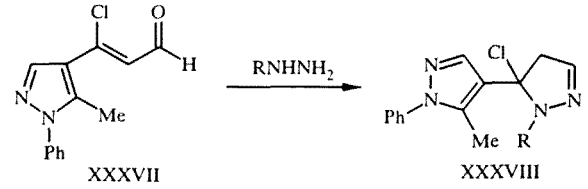


XXXII R = R1 = H, Ph XXXV



XXXI Ar, R = Ph, H; C6H4Cl-4, Ph XXXVI

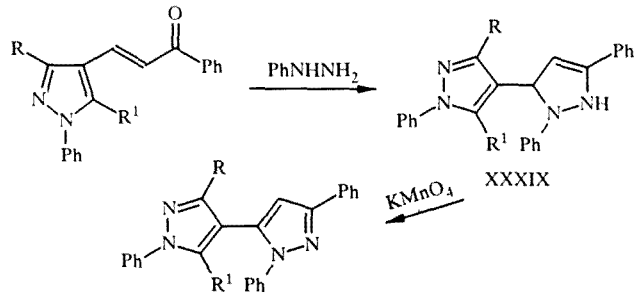
The 4,3′-bonded pyrazolinylpyrazoles (XXXVIII) are formed in the reaction of the unsaturated β-chloroaldehyde (XXXVII) with substituted hydrazines [26].



XXXVII XXXVIII

R = Ph, $C_6H_3(NO_2)_2$-2, 4

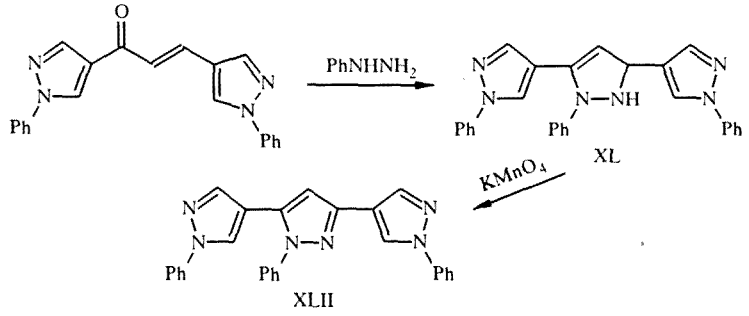
The pyrazolines (XXXIX, XL), synthesized similarly from vinyl ketones, were easily oxidized by a standard procedure (potassium permanganate in pyridine) to the corresponding bi- and terpyrazoles (XLI, XLII). The yields amounted to 50-98% [27-29].



XXXIX

XLI

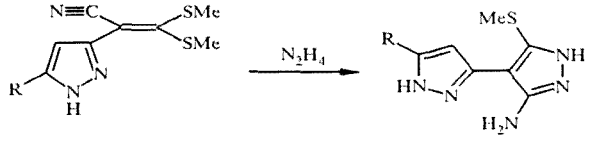
R = H, Me, Ph; R^1 = H, Me, Ph; R = H, R^1 = Cl



XL

XLII

The 3,4′-bipyrazoles (XLIV) were obtained from the dithioacetals of pyrazole-substituted ketenes (XLIII) [30].



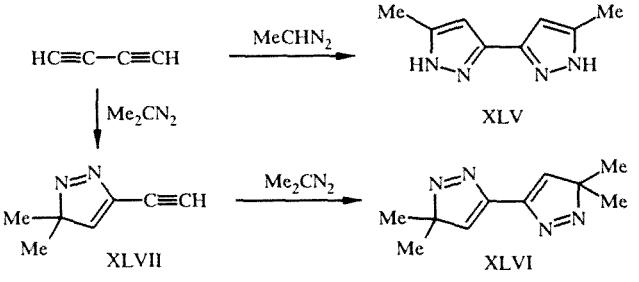
XLIII

XLIV

R = C_6H_4F-4, C_6H_4Cl-4

1,3-Cycloaddition at multiple carbon—carbon bonds has been widely used for the construction of directly linked pyrazole rings. Diazoalkanes are the most widely studied of the 1,3-dipoles used in this reaction.

Unsubstituted diacetylene reacts with diazomethane to form unsubstituted 3,3′-bipyrazole (yield 3%). In the case of 1,4-diphenylbutadiyne nitrogen is released, and polymethylene is precipitated [23]. 3,3′-Bipyrazoles (XLV, XLVI) are formed from substituted diazomethanes [31,32].



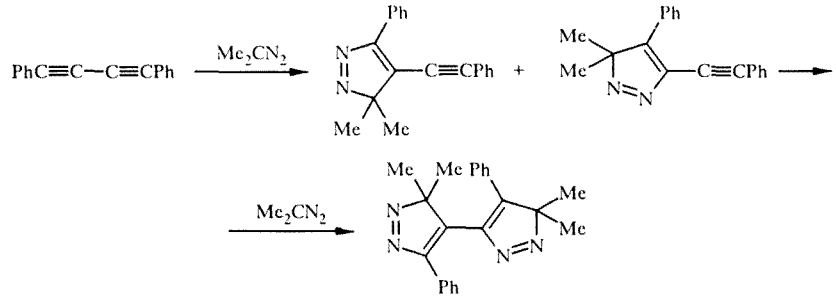
XLV

XLVII

XLVI

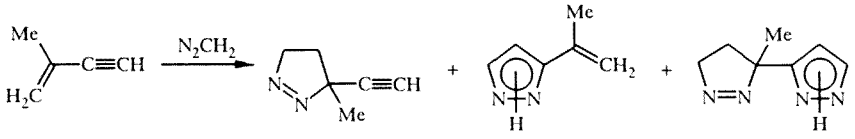
The reaction probably takes place in steps, since the intermediate isopyrazole (XLVII) was isolated when dimethyldiazomethane was used [33]. The yield of the final product (XLVI) amounted to 60%.

The reaction of dimethyldiazomethane with 1,4-diphenylbutadiyne takes place similarly, and only one isomer, i.e., the 3,4′-isopyrazole (XLVIII), is formed with a 58% yield [34,35].



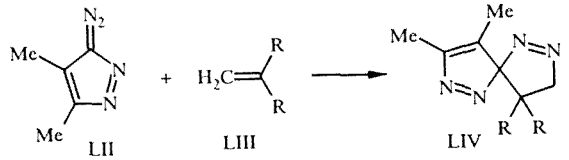
XLVIII

The structure and the yields of the products from the reaction of diazomethane with 3-methylvinylacetylene [10% of (XLIX), 45% of (L), and 40% of (LI)] also confirm the stepwise nature of addition and indicate that it is directed preferentially at the triple bond [36-38%].



XLIX L LI

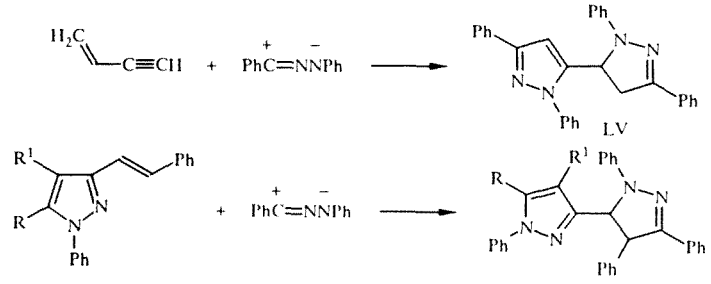
Diazopyrazole (LII) reacts with electron-excessive olefins of type (LIII) by a [3 + 2]-cycloaddition mechanism. In the case of compound (LIII) (R = OMe) the spiroisopyrazolinylpyrazole (LIV) is formed with a high yield [39].



LII LIII LIV

R = OMe

Pyrazole structures are also formed by nitrile imines during 1,3-cycloaddition to unsaturated compounds. Thus, 5-pyrazolinyl-5-pyrazole (LV) was obtained from diphenylnitrile imine [40]. The reaction of the same diphenylnitrile imine with β-phenylvinylpyrazoles (LVI) gave the substituted 3-pyrazolinyl-5-pyrazoles (LVII) [41].

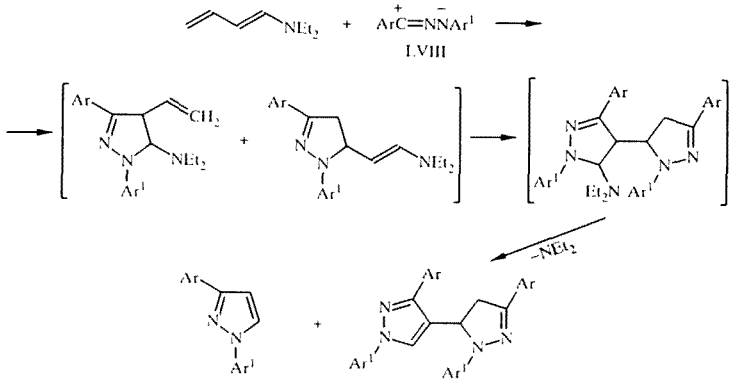


LV

LVI LVII

R = Me, R^1 = Ac, OC(O)Et; R = Ph, R^1 = OC(O)Et, CN, COPh; R = CN, R^1 = H, Ph

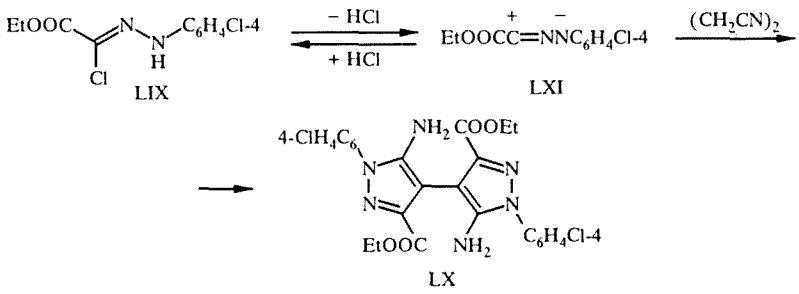
As supposed, the condensation of diarylnitrile imines (LVIII) with 1-diethylamino-1,3-butadiene takes place in stages according to the following scheme [42]:



LVIII

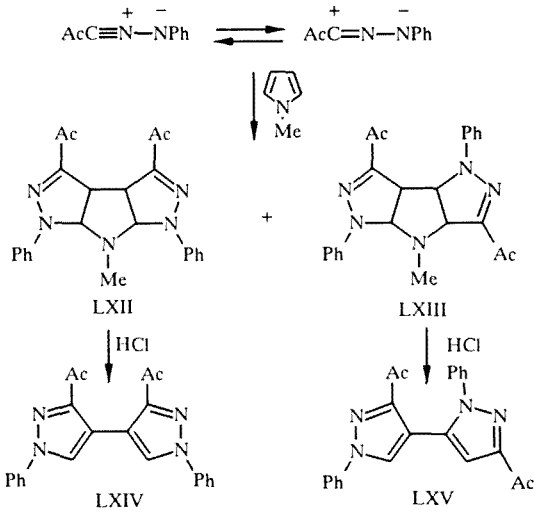
Ar = Ph, Ar^1 = Ph, $C_6H_4NO_2$-4, C_6H_4Cl-4; Ar = C_6H_4Cl-4, Ar^1 = Ph

The reaction of the hydrazonoyl chloride (LIX) with succinonitrile results in a 68% yield of the 4,4′-bonded bipyrazole (LX). It is considered that in this case too the reaction takes place as the 1,3-dipolar addition of the nitrile imine (LXI) that forms [43].



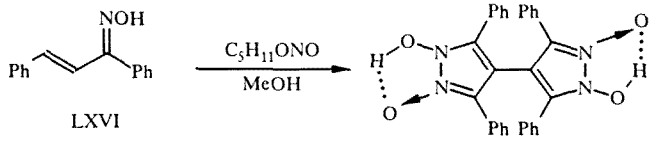
LIX LXI LX

A mixture (3:1) of compounds (LXII, LXIII) was obtained from C-acetyl-N-phenylnitrile imine and N-methylpyrrole. Their treatment with concentrated sulfuric acid led to quantitative yields of the corresponding 4,4′- and 4,5′-bonded bipyrazoles (LXIV, LXV) [44].



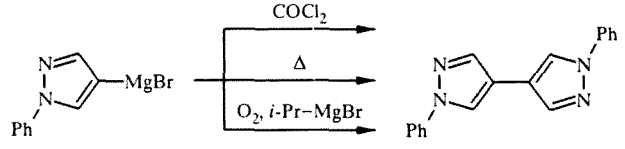
LXII LXIII LXIV LXV

N,N′-Dihydroxy-3,3′,5,5′-tetraphenyl-4,4′-bipyrazole N,N′-dioxide was synthesized by the nitrosation of chalcone oxime (LXVI) [45].



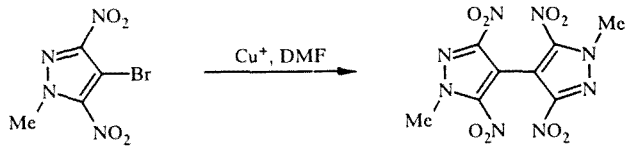
LXVI

The treatment of 1-phenyl-4-pyrazolylmagnesium bromide with dry cobalt chloride gave a 40% yield of 1,1′-diphenyl-4,4′-bipyrazole. A similar product was formed with yields of 59 and 14.3% respectively when the above-mentioned Grignard reagent was heated or was oxidized with oxygen in an excess of isopropylmagnesium bromide [46,47].



In these cases the reaction probably takes place by a radical mechanism.

It should be noted that 4-bromo-3,5-dinitro-1-methylpyrazole enters into the Ullman reaction and also forms the substituted 4,4′-bipyrazole (LXVII) with a yield of 34% [48].

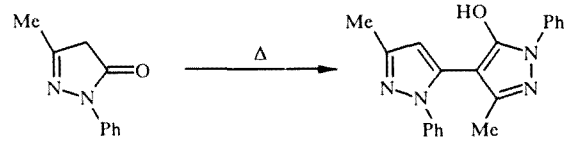


LXVII

The hydroxy derivatives of 4,4′-bipyrazole (LXIX) are obtained during the bromination of the pyrazolone (LXVIII) with N-bromosuccinimide or bromine in chloroform [49].

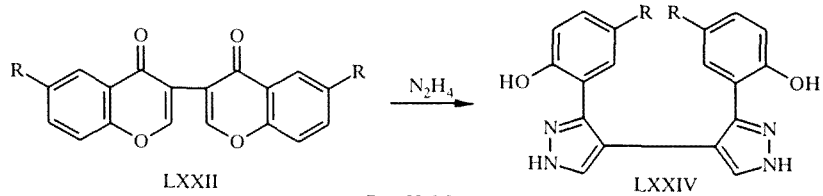
LXVIII R = Me, Ph LXIX

It is interesting to note that the thermal condensation of the pyrazolone (LXX) leads to the formation of the 4,5′-bipyrazole (LXXI) [50,51].

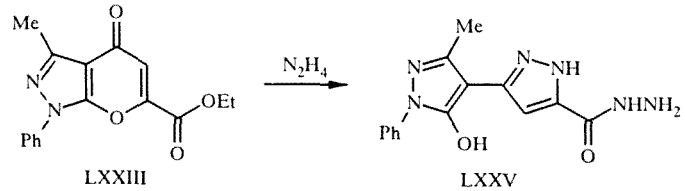


LXX LXXI

C—C-Bonded pyrazoles are often obtained from other heterocyclic compounds. Thus, γ-pyrone derivatives (LXXII, LXXIII) are the starting compounds in the synthesis of the bipyrazoles (LXXIV, LXXV) [52,53].

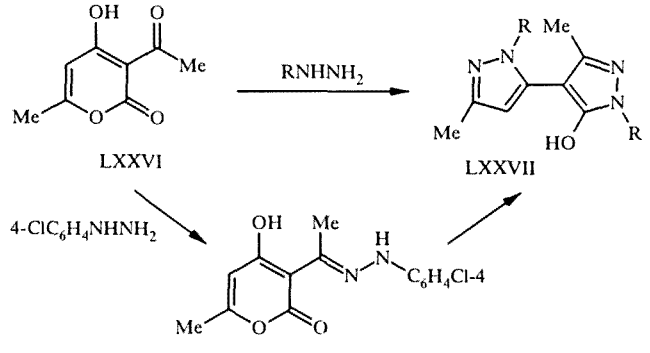


LXXII R = H, Me LXXIV



LXXIII LXXV

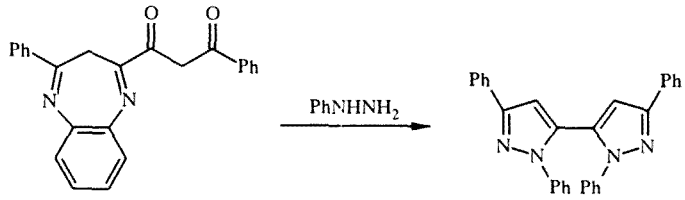
The treatment of dehydracetic acid (LXXVI) with hydrazines gave derivatives of 4,5′-bipyrazole (LXXVII), and in the case of the chlorophenyl-substituted hydrazine the intermediate hydrazone (LXXVIII) was isolated [54-56].



LXXVI LXXVII LXXVIII

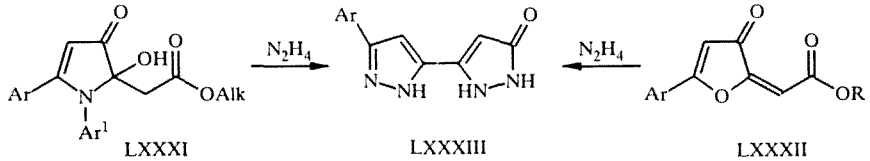
R, yield LXXVII (%) : Me, 33; C_6H_4Cl-4, 17; −CH=CHOH, 38

The reaction of the benzodiazepine (LXXIX) with phenylhydrazine in acetic acid leads to the tetraphenyl-substituted 5,5′-bipyrazole (LXXX) [57].



LXXIX LXXX

Derivatives of 5,5′-bipyrazole (LXXXIII) were also obtained by treating the pyrrolinones (LXXXI) and furanones (LXXXII) with aqueous hydrazine [58,59].

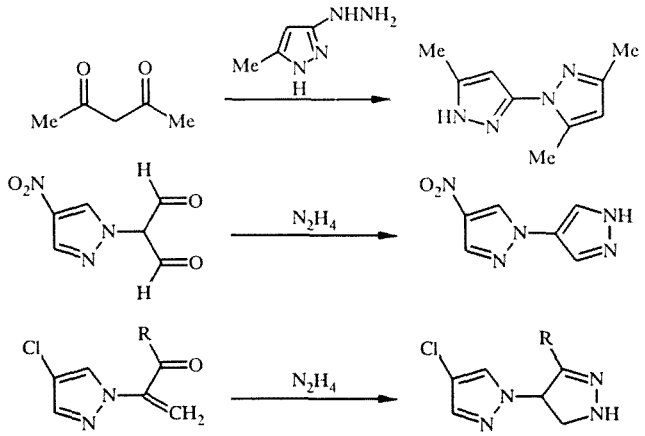


LXXXI LXXXIII LXXXII

LXXXII R = Me, Ar = Ph, C_6H_4Me-4; R = Et, Ar = C_6H_4OMe-4

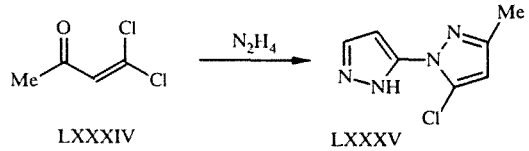
2. Production of C—N-Bonded Bi- and Terpyrazoles

Like their C—C-bonded isomers, bipyrazoles with a C—N bond between the rings are usually obtained by the general method from hydrazines and various bifunctional compounds that as a rule have one pyrazole ring [5,60-66].



R = C_6H_4Cl-4, C_6H_4F-4

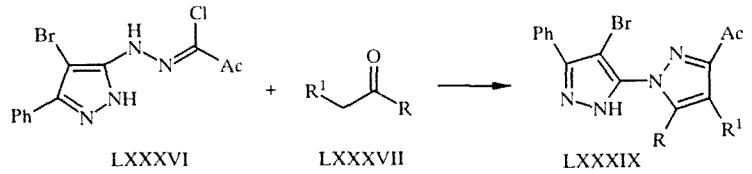
It is interesting to note that the treatment of β,β-dichlorovinyl methyl ketone (LXXXIV) with hydrazine leads to the bipyrazole (LXXXV) [67]. 3-Methyl-5-chloropyrazole is probably formed at the first stage of the reaction, and two molecules of this compound react with each other (nucleophilic substitution of the chlorine atom), resulting in the formation of the product (LXXXV) with a yield of 40%.



LXXXIV LXXXV

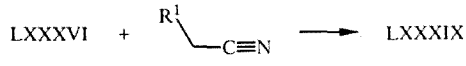
At the same time the reaction of the ketone (LXXXIV) with the less basic 2,4-dinitrophenyl- and phenylhydrazines leads to the usual hydrazones [67].

Hydrazonoyl halides (LXXXVI) react with compounds containing an activated methylene unit (LXXXVII, LXXXVIII) with the formation of 1,5′-bonded bipyrazoles (LXXXIX). The methylene component (LXXXVII) is usually acetoacetic ester or acetylacetone [68-70].



LXXXVI LXXXVII LXXXIX

R = Me, R^1 = COMe, CO_2Et; R = Ph, R^1 = CN

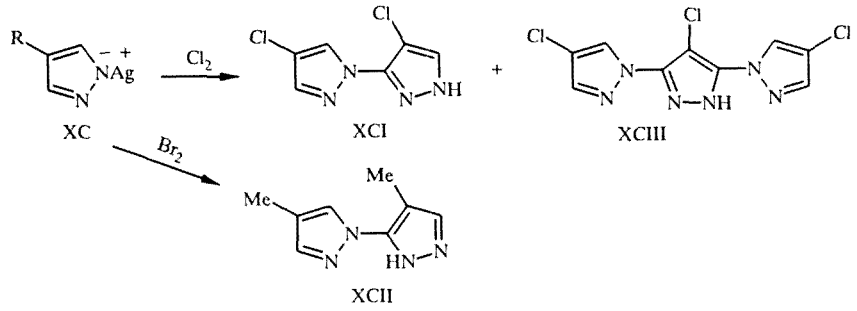


LXXXVI LXXXVIII LXXXIX

R = NH_2, R^1 = CO_2Et

The reaction mechanism probably includes alkylation of the active methylene unit of compounds (LXXXVII) and (LXXXVIII) by the halide (LXXXVI) with the formation of an acyclic hydrazone and cyclization of the latter to pyrazole. In the case of unsymmetrical β-diketones the formation of two different products is basically possible at the second stage, but usually only one isomer is obtained.

During the chlorination or bromination of the silver salts of pyrazoles (XC) the C—N-bonded bipyrazoles (XCI, XCII) or terpyrazoles (XCIII) are formed as side products [71-73].

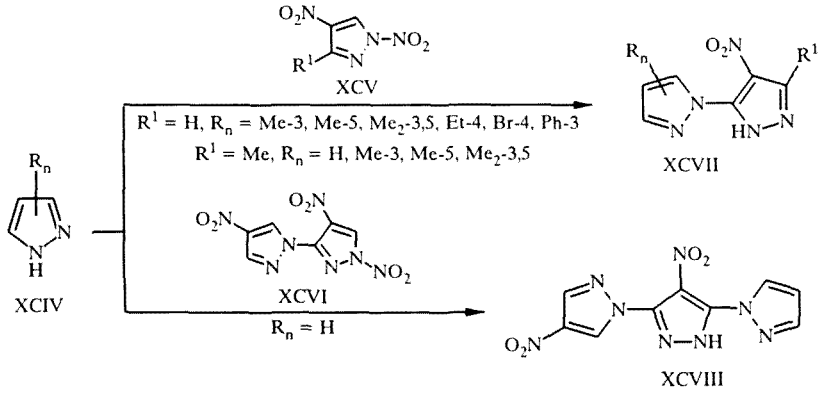


XC XCI XCIII XCII

R, product, yield (%) : H, XCI, 25; Cl, XCI, 30 and XCIII, 1; Me, XCII, 10

It should be noted that in certain cases the bipyrazole (XCII) was also formed during the direct bromination of 4-methylpyrazole [74].

Cine substitution is observed in the reaction of N-unsubstituted pyrazoles (XCIV) with 1,4-dinitropyrazoles (XCV, XCVI), and this leads to the formation of 1,5′-bipyrazoles (XCVII) and terpyrazoles (XCVIII) [75,76].



XCV

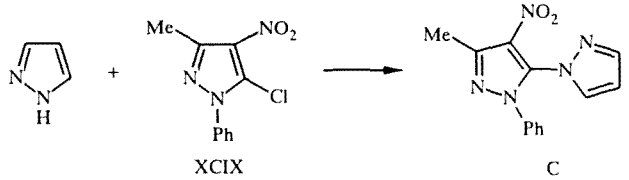
R^1 = H, R_n = Me-3, Me-5, Me_2-3,5, Et-4, Br-4, Ph-3

R^1 = Me, R_n = H, Me-3, Me-5, Me_2-3,5

XCIV XCVI XCVII

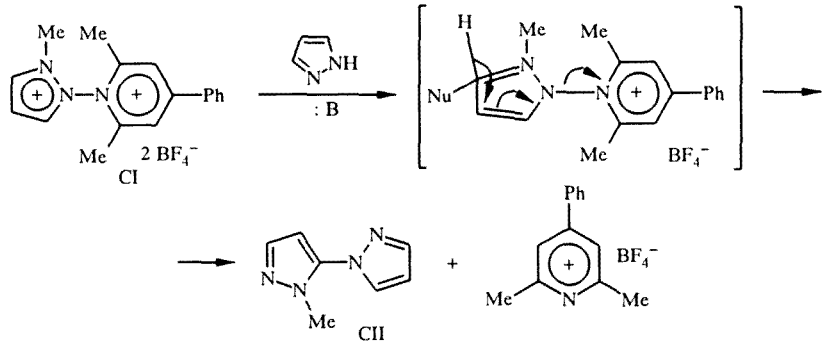
R_n = H XCVIII

In the case of N-substituted 5-chloropyrazoles in the absence of activating groups substitution takes place under very drastic conditions. In the presence of an electron-withdrawing group at position 4 [see compound (XCIX)], however, it can even take place at room temperature with the formation of 77% of 1,5′-bipyrazole (C) [77].

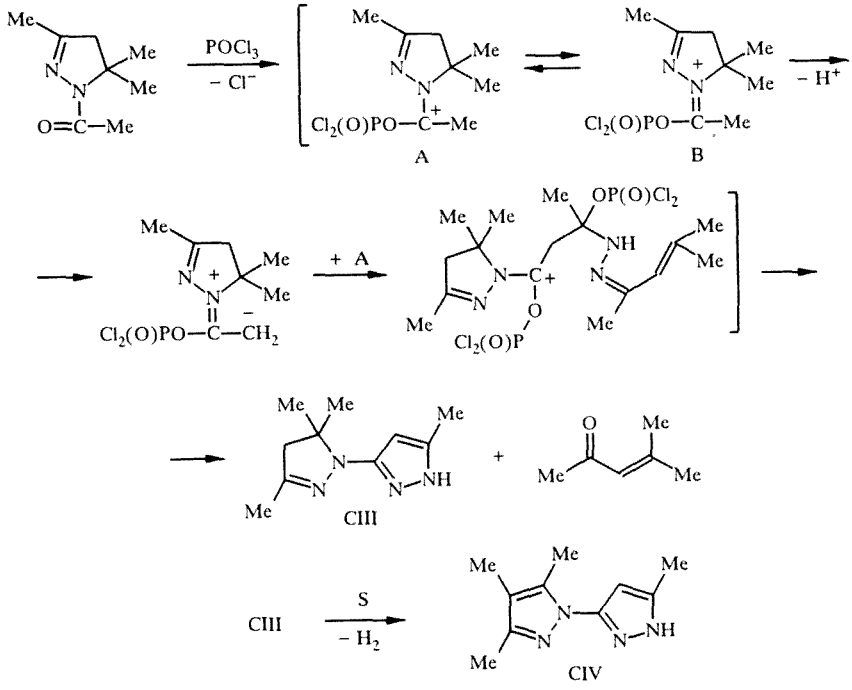


XCIX C

Regioselective nucleophilic substitution at position 5 also takes place in the case of the activated 1-aminopyrazolium cation (CI). The corresponding 1,5′-bipyrazole (CII) is formed with a yield of 73% [64].



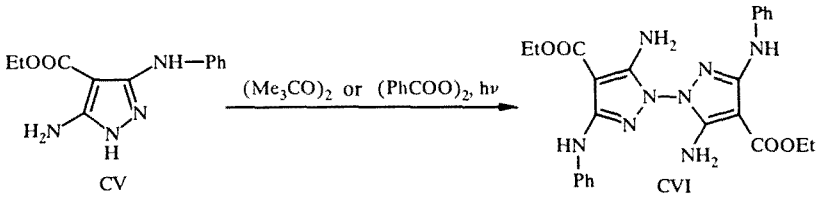
The action of phosphorus oxychloride on 1-acetyl-3,5,5-trimethylpyrazoline gives 1,3′-pyrazolinylpyrazole (CIII), which is easily dehydrogenated to the corresponding 1,3′-bipyrazole (CIV) [78].



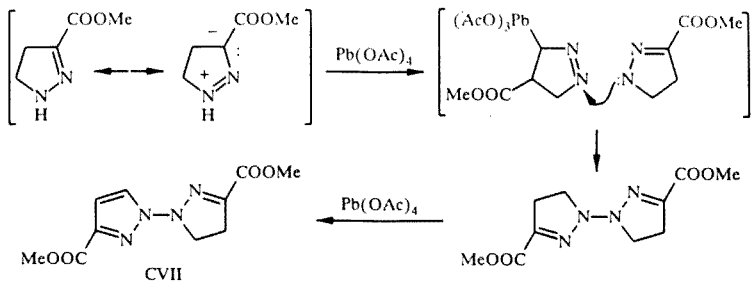
3. Production of N,N-Bonded Bipyrazoles

N—N-bonded pyrazoles are encountered rarely, and only a few cases of their synthesis have been described in the literature.

The radical dimerization of the pyrazole (CV) in the presence of dibenzoyl peroxide or di-tert-butyl peroxide leads to the N,N′-bipyrazole (CVI) with yields of 20 and 40% respectively [79].

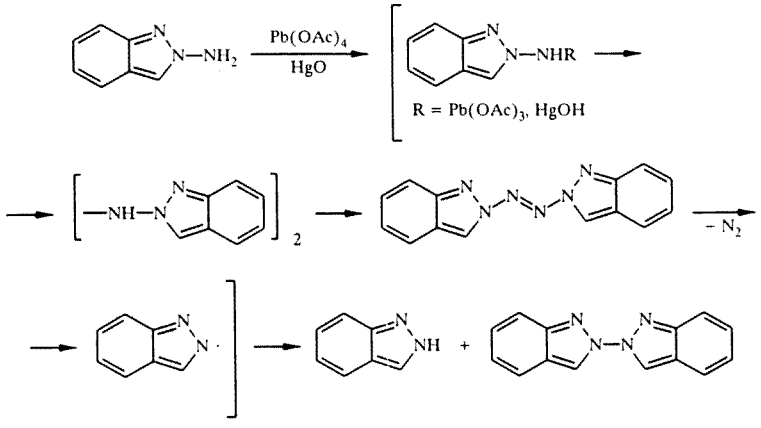


During the treatment of 3-methoxycarbonyl-2-pyrazoline with lead tetraacetate the N—N-bonded pyrazolinylpyrazole (CVII) was isolated as one of the products with a yield of 16% [80,81].

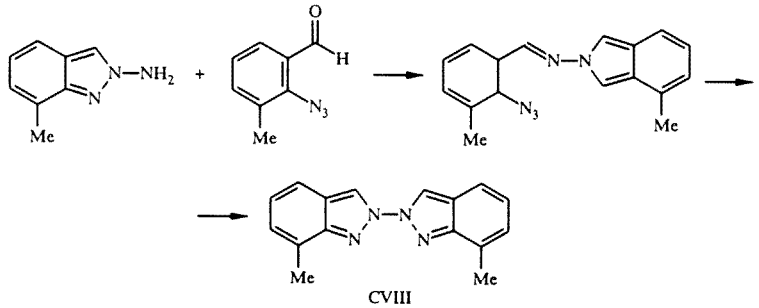


CVII

In the presence of lead tetraacetate (or mercuric oxide) N-aminoindazole forms N—N′-bisindazole. It is considered that the reaction takes place by a radical mechanism [82].

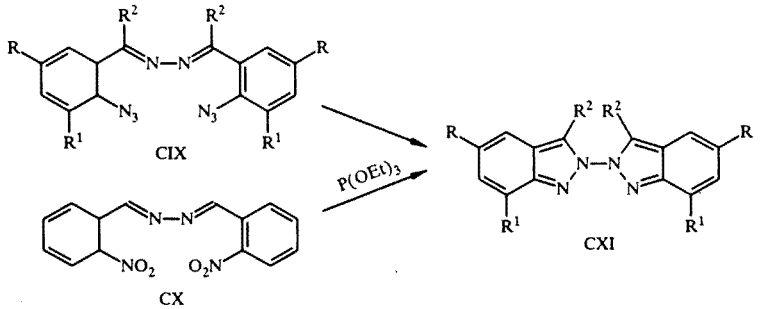


The dimethyl-substituted N—N′-bisindazole (CVIII) was synthesized from 2-amino-7-methylindazole and 2-azido-3-methylbenzaldehyde [83].



CVIII

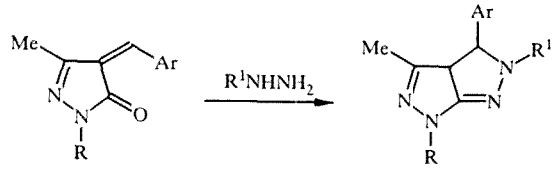
During the thermal rearrangement of bis(o-azidophenylazomethines) (CIX) or the action of triethyl phosphite on bis(o-nitrophenylazomethine) (CX) other bisindazoles (CXI) of the series were obtained. In the first case the yield of the products (CXI) amounted to 80-90% [83].



R = H, R¹, R²: NO_2, H; NO_2, Me; H, Me; Me, H; R = Me, R¹ = R² = H

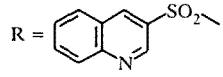
4. Production of Annellated Bicyclic Pyrazoles (Pyrazolopyrazoles)

4.1. Production of Pyrazolo[3,4-c]pyrazoles. The classical method for the synthesis of pyrazoles from hydrazines and various functional compounds has also been used for the production of annellated pyrazoles. Here pyrazole derivatives are usually employed as bifunctional compounds. For example, the corresponding dihydropyrazolopyrazoles (CXII) are formed during the reaction of 4-arylidene-3-methyl-1-aryl-5-pyrazolones with hydrazines [4,84].

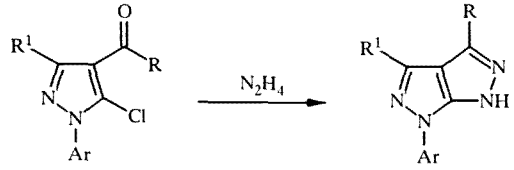


CXII

R = H, $C_6H_3(NO_2)_2$-2,4, R^1 = Ph, Ar = Ph, C_6H_4Me-4; R = $CONH_2$, R^1 = H, Ar = C_6H_4Me-4

R =  , R^1 = H, Ar = Ph, C_6H_4Me-4, $C_6H_4NO_2$-4, C_6H_4Cl-4

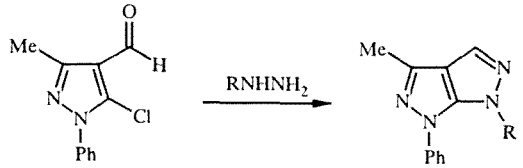
The pyrazolo[3,4-c]pyrazoles (CXIII) are obtained by the treatment of 4-acyl-5-chloro-1-arylpyrazoles with hydrazine [85,86].



CXIII

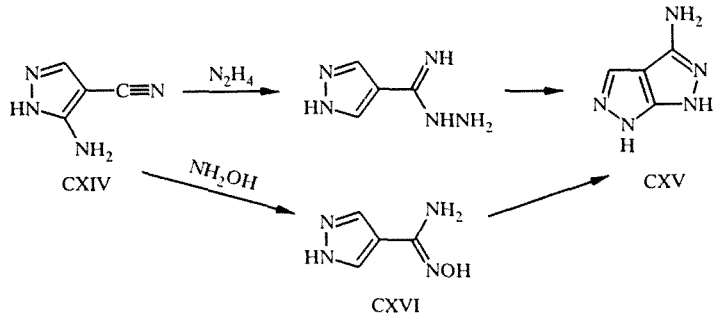
R, R^1, Ar : C_6H_4Me-4, Ph, Me; Ph, Ph, Ph; Ph, Me, Me

The cyclocondensation of 3-methyl-1-phenyl-4-formyl-5-chloropyrazole with hydrazines takes place similarly [87].



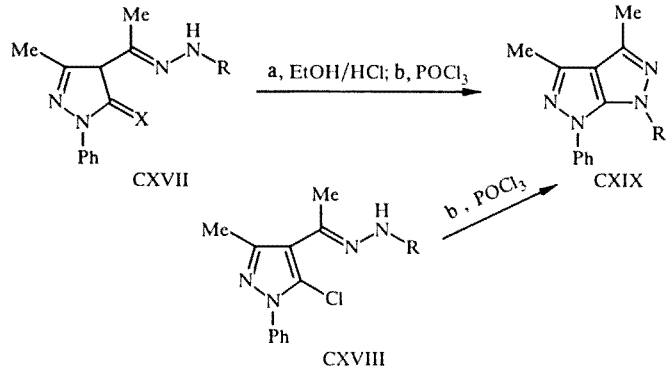
R = H, Ph

The reaction of 3-amino-4-cyanopyrazole (CXIV) with hydrazine hydrate leads to 1H,6H-3-aminopyrazolo[3,4-c]pyrazole (CXV) with a yield of 50%. In this case the process probably takes place through the initial addition of hydrazine to the cyano group, accompanied by nucleophilic cyclization [88]. It should be noted that the same product (CXV) is formed with a 15% yield when the pyrazole (CXIV) is boiled with hydroxylamine, possibly, through the corresponding imidoxime (CXVI) [89].



CXIV CXV CXVI

The cyclization of the hydrazones (CXVII, CXVIII) leads to the pyrazolopyrazoles (CXIX) [7,25,90].

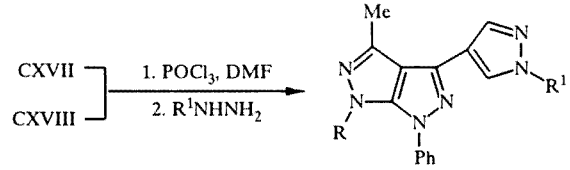


CXVII CXIX

CXVIII

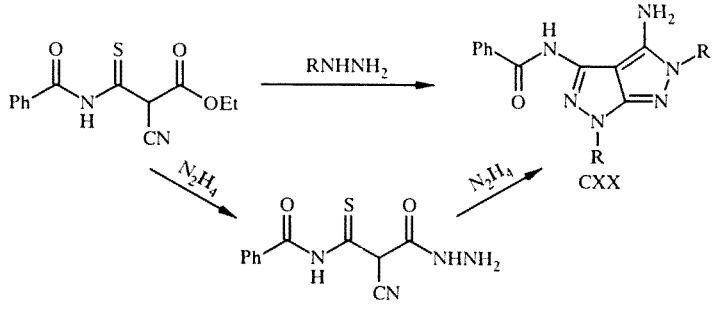
a X = O, R = Ph; b X = O, S; R = H, Ph

During the cyclization of the above-mentioned compounds (CXVII, CXVIII) with phosphorus oxychloride in dimethylformamide simultaneous formylation of the methyl group occurs with the formation of the enamines (XXXII). As mentioned above, these compounds can in turn be used for the synthesis of pyrazole derivatives of the (XXXV) type [25].



$R = R^1 = H, Ph$ XXXV

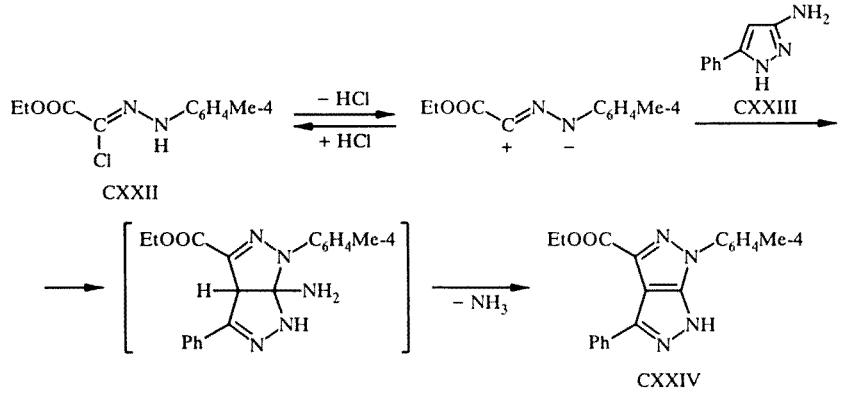
The respective pyrazolo[3,4-c]pyrazoles (CXX) were obtained with yields of 70-72% by heating ethyl β-benzoylamino-3-thio-2-cyanooxopropionate with hydrazine or phenylhydrazine. In the case of hydrazine the reaction was also realized at room temperature, and here it was possible to isolate the hydrazide (CXXI), from which in an excess of hydrazine the product (CXX) (R = H) was obtained [91].



CXXI

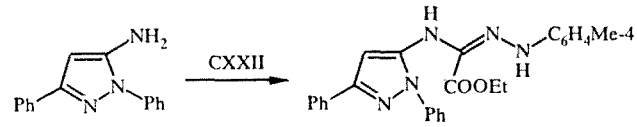
R = H, Ph

The nitrile imines formed from hydrazonoyl halides usually add to pyrazoles at the C=N bond, leading to pyrazolotriazoles (e.g., see [92]). In the recently published paper [93], however, it was reported that the nitrile imine (CXXII) adds at the C=C bond of the pyrazole (CXXIII) with formation of the pyrazolopyrazole (CXXIV). It is considered that the reaction may take place either by a mechanism of stepwise alkylation or as 1,3-dipolar addition. The last path seems much more likely.

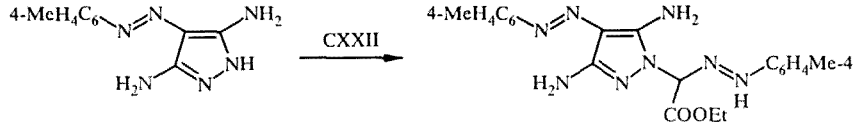


CXXII CXXIII CXXIV

If position 1 of the pyrazole (CXXIII) is occupied [see (CXXV)], alkylation takes place at its NH_2 group with the formation of the product (CXXVI). If there is a substituent at position 4 as, for example, in compound (CXXVII), alkylation takes place at the nitrogen atom of the ring, and the substituted pyrazole (CXXVIII) is formed. Subsequent cyclization of the latter with the formation of bipyrazoles was not observed [94].

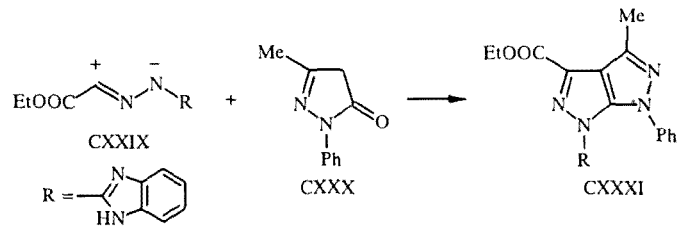


CXXV CXXVI



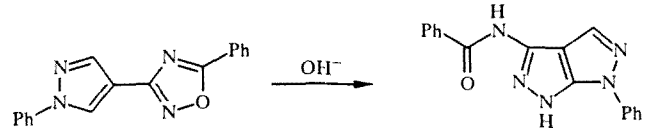
CXXVII CXXVIII

In [95] it was mentioned that the reaction of the nitrile imine (CXXIX) with the pyrazolone (CXXX) leads to the pyrazolopyrazole (CXXXI).



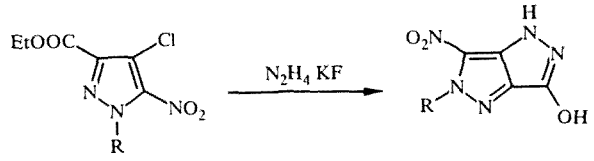
CXXIX CXXX CXXXI

The oxadiazole (CXXXII) readily isomerizes in the presence of alkali to the corresponding pyrazolopyrazole (CXXXIII) with an almost quantitative yield [96].



CXXXII CXXXIII

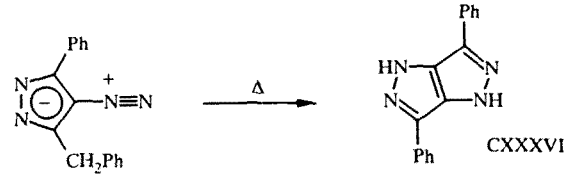
4.2. Production of Pyrazolo[4,3-c]pyrazoles. The reactions of hydrazine with bifunctional pyrazoles (CXXXIV), which lead to the formation of pyrazolo[4,3-c]pyrazoles (CXXXV) but with very small yields (1-2%), have been described in the literature [97].



CXXXIV CXXXV

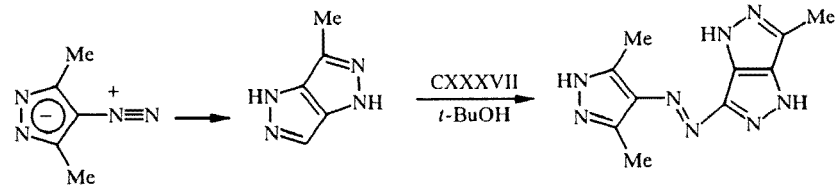
R = $C_6H_4NO_2$-4, $C_6H_2Br_3$-2,4,6

Pyrazolo[4,3-c]pyrazoles are much more often obtained from diazopyrazoles. Thus, the intramolecular cyclization of 3-benzyl-4-diazo-5-phenylpyrazole when heated leads to the annellated product (CXXXVI). The latter is obtained with a quantitative yield when a solution of diazopyrazole in acetic acid is heated. In this case a radical reaction mechanism has been proposed [98,99].

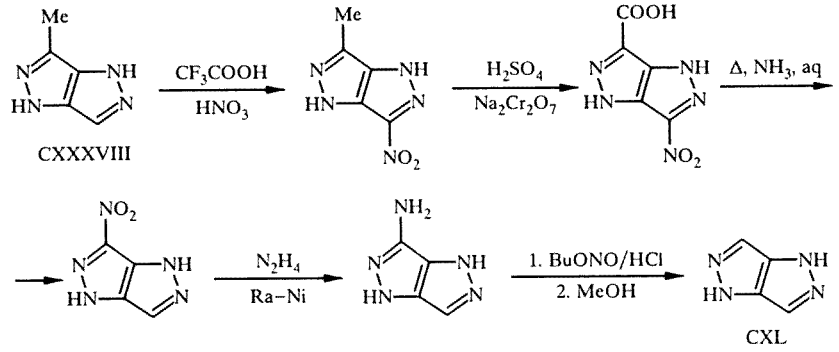


CXXXVI

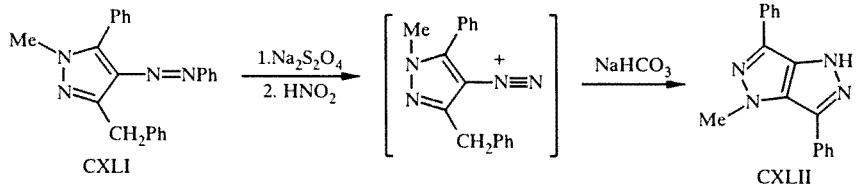
3,5-Dimethyldiazopyrazole (CXXXVII) also undergoes cyclization with the formation of the pyrazolopyrazole (CXXXVIII), the yield of which depends on the employed solvent: 25% with boiling in benzene, 70% in tert-butyl alcohol, 75-80% in ethyl acetate, and 80-95% in a mixture of ethyl acetate and acetic acid [99-101]. It should be noted that if tert-butyl alcohol is used the product (CXXXVIII) then reacts with the initial diazopyrazole. This leads to the azo derivative of pyrazolopyrazole (CXXXIX), the yield of which amounts to 40-45% [102].



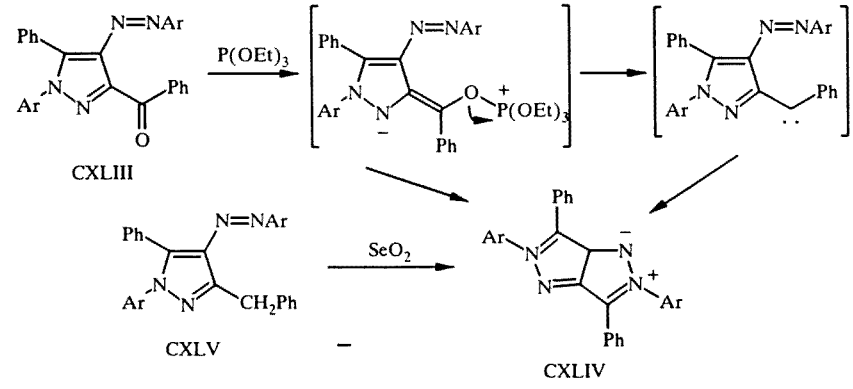
Recently the methyl-substituted pyrazolopyrazole (CXXXVIII) was converted into its unsubstituted analog (CXL) according to the scheme presented below [103].



Reduction of the azopyrazole (CXLI) and diazotization of the obtained amine followed by treatment with aqueous sodium bicarbonate leads to the bipyrazole (CXLII) with a yield of 34% [104].

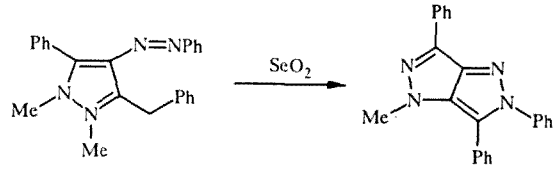


The N-aryl-substituted 3-benzoyl-4-arylazopyrazoles (CXLIII) undergo reduction with high yields (68-96%) under the influence of triethyl phosphite followed by cyclization to the pyrazolopyrazoles (CXLIV). Analogous products are obtained but with significantly lower yields (12-14%) during the oxidation of 3-benzyl-substituted 4-arylazopyrazoles (CXLV) with selenium oxide [105,106].



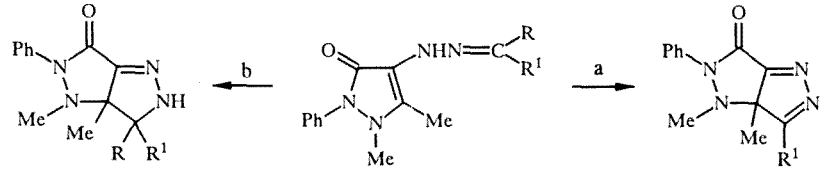
CXLIII Ar = C_6H_4Cl-4, C_6H_4Br-4, Ph; CXLV Ar = C_6H_4Cl-4, Ph

It should be noted that the yield of the corresponding product (CXLVII) during the oxidation of 5-benzyl-substituted phenylazopyrazole (CXLVI) under the same conditions amounted to 83% [105,106].



CXLVI CXLVII

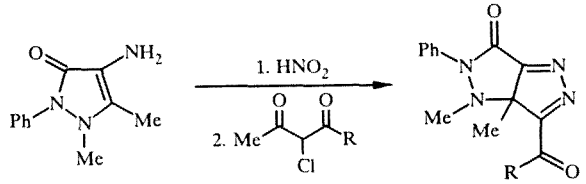
When treated with hydrochloric acid, the hydrazones (CXLVIII) undergo cyclization to the corresponding derivatives of pyrazolo[4,3-c]pyrazolones (CXLIX, CL) [107].



CL CXLVIII CXLIX

a R = CN, R^1 = CONHPh, $CONHC_6H_4NO_2$-4; R = Ac, R^1 = $CONHC_6H_4Cl$-4;
b R = COPh, R^1 = COOEt; R = Ac, R^1 = CONHPh

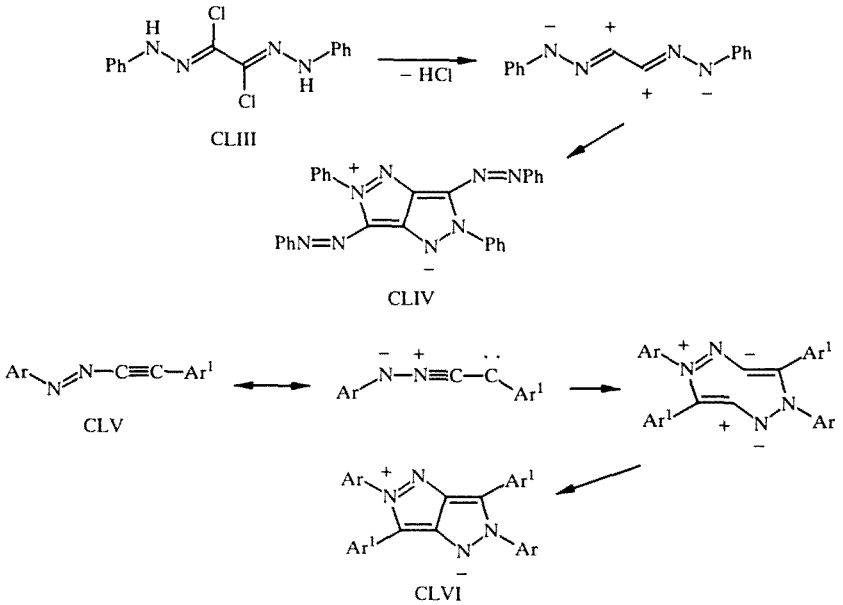
Analogous pyrazolo[4,3-c]pyrazolones (CLII) are obtained by the reaction of 3-chloro-2,4-pentanedione or ethyl 3-oxo-2-chlorobutyrate with diazotized aminopyrazole (CLI) [108].



CLI CLII

R, yield (%) : Me, 74; OEt, 53

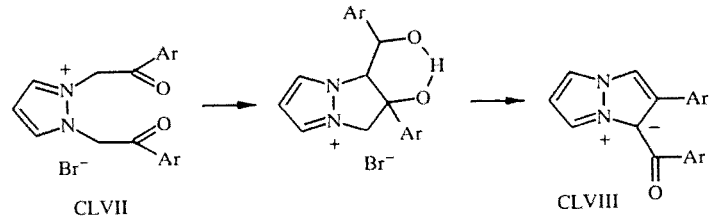
Derivatives of mesoionic 2H,5H-pyrazolo[4,3-c]pyrazoles (CLIV, CLVI) are formed by the cyclodimerization of the nitrile imines (CLIII, CLV). The yields of the products (CLVI) amount to 15-60% [109-112].



CLIII CLIV CLV CLVI

Ar = C_6H_4X-4, X = Cl, Br, NO_2; Ar^1 = C_6H_4X-4, X = H, Me, Br, NO_2

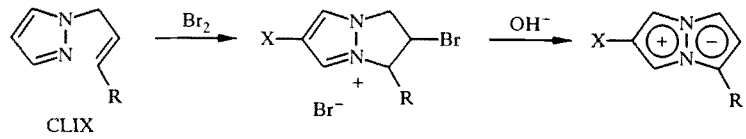
4.3. Production of Pyrazolo[1,2-a]pyrazoles. The intramolecular condensation of the pyrazole (CLVII) in the presence of sodium bicarbonate leads to derivatives of pyrazolo [1,2-*a*]pyrazole (CLVIII), the yields of which amount to 80-90% [113].



CLVII CLVIII

Ar = C_6H_4X; X = H, 4-Cl, 4-Br, 3-NO_2

Similar compounds were also obtained as a result of the bromination of 1-allylpyrazole (CLIX) followed by dehydrobromination in the presence of a base [114,115].

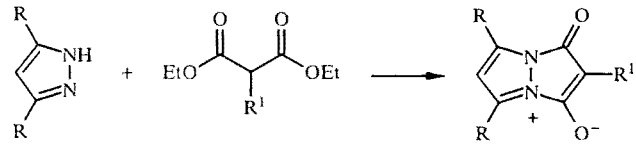


CLIX

X = H, R = Ph, H; X = Br, R = H

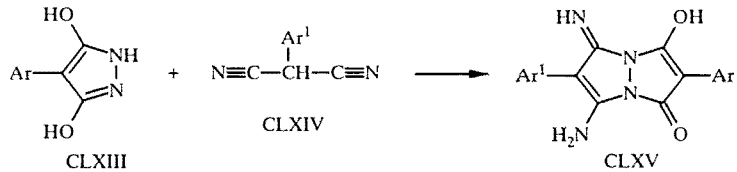
Pyrazolo[1,2-*a*]pyrazoles not containing an electron-withdrawing substituent at position 1 are decomposed extremely readily in the presence of even traces of air.

If the pyrazoles (CLX) are treated with β-dicarbonyl compounds (CLXI) and the pyrazoles (CLXIII) are treated with derivatives of malononitrile (CLXIV), the corresponding heterocyclic betaines (CLXII, CLXV) are formed [116-119].



CLX CLXI CLXII

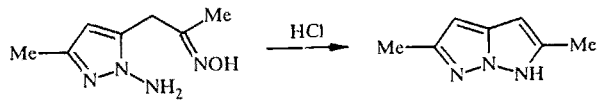
R = Me, R^1 = Ph, CN; R = H, R^1 = CH_2Ph; R = Ph, R^1 = Me



CLXIII CLXIV CLXV

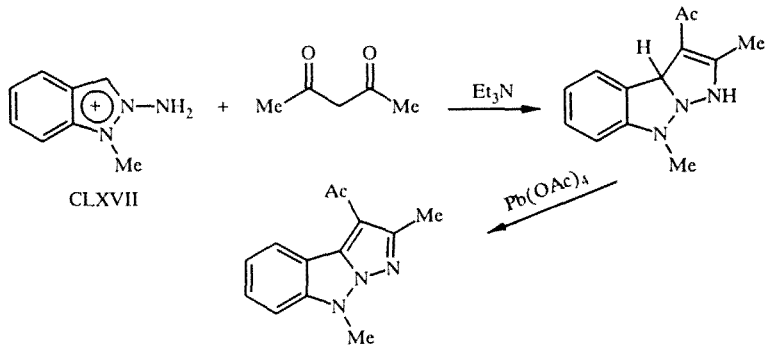
Ar, Ar^1 = C_6H_4X-4; Ar X = H, Cl, OMe, Ar^1 X = H, OMe

4.4. Production of Pyrazolo[1,5-b]pyrazoles. When boiled in a water—alcohol solution of hydrochloric acid, 1-amino-3-methyl-5-(2-oxoiminopropyl)pyrazole is converted into pyrazolo[1,5-b]pyrazole (CLXVI) (triazapentalene) [120].



CLXVI

Benzopyrazolopyrazole (CLXVIII) is formed with a low yield from the 2-aminoindazolium salt (CLXVII) as a result of a series of transformations [121].



CLXVII

CLXVIII

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