SYNTHESIS OF PYRAZOLES AND INDAZOLES FROM ALIPHATIC DIAZO COMPOUNDS (REVIEW)

I. K. Korobitsyna, V. V. Bulusheva,
and L. L. Rodina

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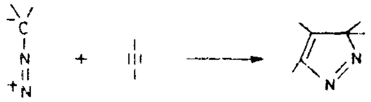
The literature data on the synthesis of indazoles and pyrazoles from aliphatic diazo compounds and compounds containing a carbon–carbon triple bond are reviewed. The dependence of the direction of the reaction and the yields of the final products on the structures of the reagents is discussed. The rearrangements that accompany cycloaddition are examined. Modern views of the mechanisms of the reactions discussed in the review are presented.

Of the numerous methods for the synthesis of heterocyclic compounds, cycloaddition reactions are undoubtedly among the most prominent. In particular, 1,3-dipolar cycloaddition is a method for the preparation of five-membered nitrogen-containing heterocycles with various structures. Of the 1,3 dipoles used in this reaction, most study has been devoted to diazoalkanes, the reaction of which with compounds that contain carbon–carbon double and triple bonds is widely used for the synthesis of pyrazolines, pyrazoles, indazolines, and indazoles.

In the present review we have attempted to summarize the available rather comprehensive data on the synthesis of pyrazoles and indazoles from aliphatic diazo compounds and compounds that contain triple bonds.

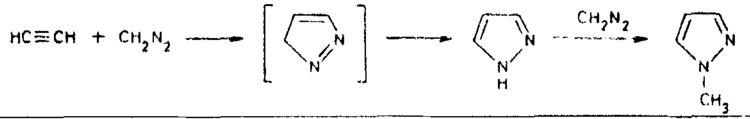


Some general information regarding these reactions has been presented in [1-9], but there has not yet been a special review of this topic. The necessity for this sort of correlation is due to the fact that, on the one hand, the simplest and most convenient method for the construction of five-membered heterocyclic systems with two adjacent nitrogen atoms is the addition of aliphatic diazo compounds to alkynes and arynes, whereas, on the other, the structures of the resulting compounds do not always follow unambiguously from the structures of the starting components, since cycloaddition is frequently accompanied by rearrangements, the principles of which we have attempted to describe.

1H-Pyrazoles and 1H-Indazoles from Monosubstituted Diazoalkanes and Compounds Containing a C≡C Bond

In 1889 Buchner established [10] that methyl diazoacetate in ether solution adds (with cooling) to dimethyl acetylenedicarboxylate to give a 1:1 adduct in 80% yield. He also demonstrated [11] that methyl diazoacetate reacts with methyl phenylpropiolate to give a compound that undergoes saponification to give 4-phenylpyrazole-3,5-dicarboxylic acid.

The reaction of the first members of the diazoalkane and acetylene series was investigated somewhat later by Pechmann [12]. He obtained pyrazole (50%) when he passed acetylene into an ether solution of diazomethane. When this reaction was carried out under pressure [13], pyrazole was formed in almost quantitative yield; the formation of 1-methylpyrazole was observed in the case of excess diazomethane [14]:



A. A. Zhdanov Leningrad State University, Leningrad 199004. Translated from Khimiya Geterotsilicheskikh Soedinenii, No. 5, pp. 579-597, May, 1978. Original article submitted May 26, 1977.

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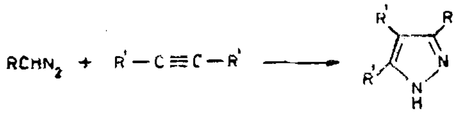
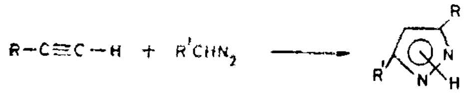
An important principle was established in [10-14]: The reaction of diazomethane and monosubstituted diazomethanes with alkynes always leads to the formation of 1H-pyrazoles:



Despite the fact that the reaction under consideration has been known for more than 90 yr, researchers' interest in it is not waning. On the contrary, after the development of Huisgen's concept of 1,3-dipolar cycloaddition, the number of studies devoted to the reaction of alkynes with diazo compounds increased sharply.

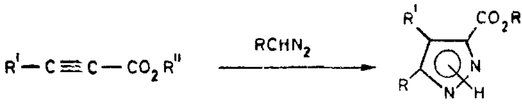
An extremely large number of compounds have been investigated. Both diverse monosubstitued diazoalkanes themselves — diazomethane, alkyl- and aryldiazomethanes, perfluoroalkyldiazomethanes, α-diazo ketones, and α-diazo esters — and various compounds containing a carbon-carbon triple bond — acetylene, alkyl- and arylacetylenes, acetylenic compounds with functional groups, compounds with several multiple bonds (enynes and diynes), and compounds with triple bonds in the ring — have been used.

An important problem in the examination of the reactions of diazoalkanes with unsymmetrically substituted unsaturated compounds is the mutual orientation of the components (regioselectivity). In many cases it corresponds to polarization of the multiple bond [4] and is subject to the Auwers rule [15, 16]: The carbon atom bearing the diazo group forms a σ bond with the most electrophilic alkyne atom, and this leads to a pyrazole with an electron-acceptor substituent in the 3(5) position of the ring. Thus, for example, it is known that acetylenes that contain electron-acceptor groups (aryl, carbonyl, carboxyl, carbalkoxy, trifluoromethyl, etc.) attached to the triple bond react with diazomethane and monosubstituted diazomethanes to give 3(5)-substituted pyrazoles in good yields [17-23]:



$R = p\text{-}NO_2C_6H_4, COCH_3, COC_6H_5, CN, CONH_2, CHO$;
$R' = H, CH_3, CH_2CO_2CH_3$

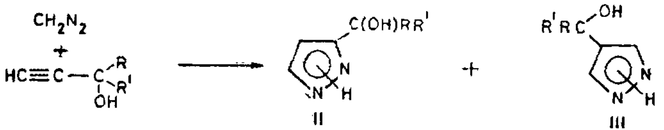
However, the addition of diazoalkanes does not by any means always proceed so unambiguously, and a mixture of isomeric 1H-pyrazoles is often formed [4, 16, 18, 24-44]. Thus, for example, esters of alkyl-substituted acetylenecarboxylic acids react with diazomethane, diazoethane, and aryldiazomethanes to give 3(5)-carbalkoxy-1H-pyrazoles (I) [4, 16, 32]:



I

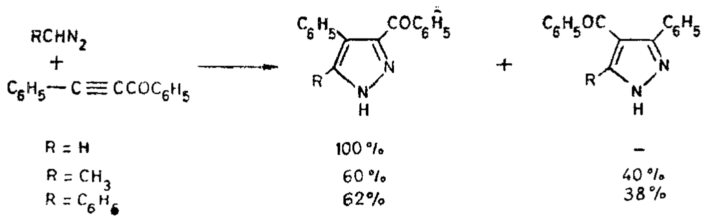
Both 3(5)- and 4-carbalkoxy-1H-pyrazoles are obtained from esters of aryl-substituted acetylenecarboxylic acids (R' = Ph, $p\text{-}NO_2C_6H_4$, and $p\text{-}CH_3OC_6H_4$) [4, 16, 18, 25-31].

An increase in the volume of the substituents attached to the triple bond affects the isomer ratio: Propargyl alcohol reacts with diazomethane to give mainly 3(5)-hydroxymethylpyrazole (II), whereas the yields of 4-substituted pyrazoles III increase when phenyl(ethynyl)carbinol and dimethyl(ethynyl)carbinol are used [24, 32].

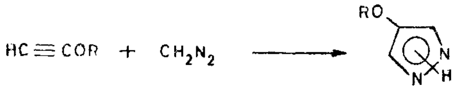


	II	III
$R = R' = H$	75%, 94%	25%, 6%
$R = R' = CH_3$	65%	35%
$R—R' = —(CH_2)_5—$	54%	46%
$R = H, R' = C_6H_5$	40%	60%

In the case of phenylbenzoylacetylene it was shown that an increase in the volume of the substituent in the diazoalkane also leads to an increase in the amounts of 4-benzoylpyrazoles [25, 30]:



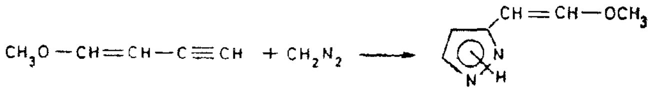
The addition of diazoalkanes to dipolarophiles containing electron-donor groupings proceeds in a different manner. Thus, for example, diazomethane adds to alkoxyacetylenes to give exclusively 4-alkoxypyrazoles [33, 34]:



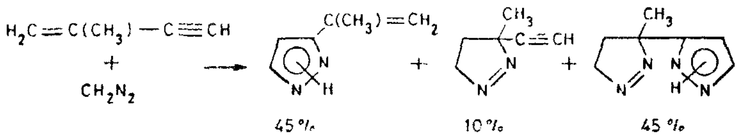
The above examples show that one should take into account both electronic and steric factors in the formation of pyrazoles [1, 45-47]. In the opinion of Huisgen [9], the change in the direction of addition of diazoalkanes to unsymmetrically substituted acetylenes is impressive evidence in favor of the ambident nucleophilicity of diazoalkanes. However, it is far from possible to correctly predict the isomeric composition of the resulting pyrazoles in all cases.

A convenient method for the synthesis of pyrazoles containing unsaturated groupings is the reaction of diazo compounds with enynes and diynes. In the simplest enyne — vinylacetylene — the double bond is more reactive [48-50].

When the triple bond in the enyne is unsubstituted and the carbon atom of the double bond bears substituents, the reaction most often takes place at the triple bond regardless of the nature of the substituents (electron-acceptor or electron-donor) [4, 49, 51-54]:

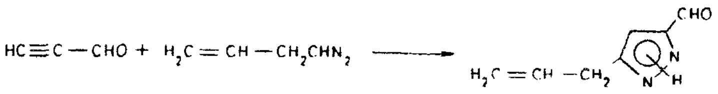


However, in addition to the products of addition to the triple bond, diadducts and, in small yields, products of addition to the double bond were sometimes isolated in the case under consideration [4, 51-56].

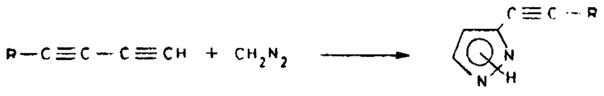


In the case of enynes with substituents attached to the carbon atom of the triple bond diazoalkanes add to the double bond regardless of whether it is substituted or not [53, 55, 57].

3(5)-Alkenylpyrazoles can also be obtained from acetylenes and diazoalkenes. Thus Manecke and Schenck in a study of the cycloaddition of vinyldiazomethane to activated acetylenes obtained a series of 3(5)-vinylpyrazoles [17, 58] in high yields. 3-Allyl-5-formylpyrazole (62%) is similarly formed from allyldiazomethane and propiolaldehyde [58]:

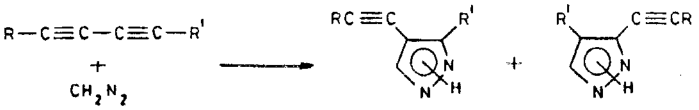


Diacetylenes (diynes) as a rule react readily with diazoalkanes to give both monoadducts (alkynylpyrazoles) and diadducts (dipyrazolyls). Monoadducts are usually obtained in the case of unsymmetrically substituted diacetylenes. Monoalkyldiacetylenes give mainly 3(5)-alkynylpyrazoles in this case [59]:



$R = CH_3, C_2H_5$

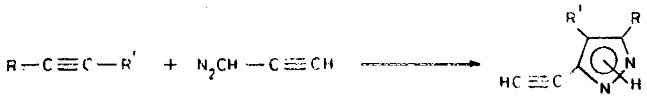
Diacetylenes containing acetyl or carbalkoxy groupings attached to the triple bond give primarily 4-alkynyl-3(5)-acyl(carbalkoxy)pyrazoles (IV), and the isomeric pyrazoles V are obtained in amounts that do not exceed 5-10% [40, 41].



IV V

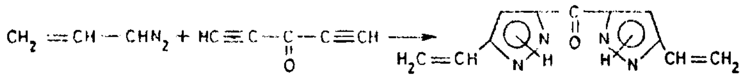
$R = C_6H_5$, p-ClC_6H_4, p-$NO_2C_6H_4$; $R' = CO_2CH_3$, COC_6H_5, $COCH_3$

Reimlinger also obtained 3(5)-alkynylpyrazoles by the addition of diazopropyne to acetylenes — methyl propiolate and dimethyl acetylenedicarboxylate [60]:



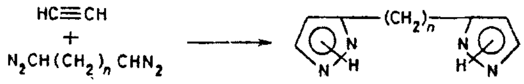
R, R'(yield ,%) : H, H(17) ; CO_2CH_3, H(62) ; CO_2CH_3, CO_2CH_3

On reaction with diazoalkanes symmetrically substituted diacetylenes may give both mono- and diadducts. Precisely the same result was obtained in the reaction of diazomethane and diazoethane with diacetylene [37, 38]. In a number of cases the reaction of diazo compounds with diacetylenes leads to the formation of only diaddition products. The preparation of dipyrazolyl ketone VI from vinyldiazomethane and pentadiynone may serve as an example of this [17]:



VI

Reimlinger proposed a different and more convenient method for the synthesis of dipyrazolylalkanes from bisdiazoalkanes and acetylene [13]; the yields are higher in this case (75-90%):

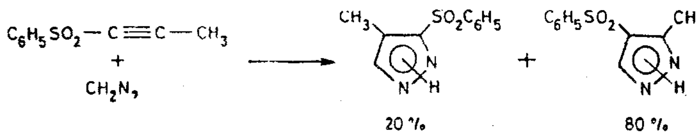


$n = 1-4, 8$

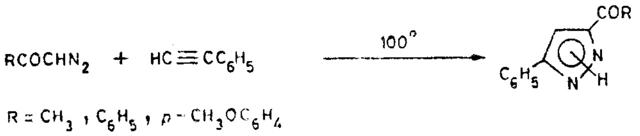
Papers devoted to the synthesis of 1H-pyrazoles with heteroorganic substituents from diazo compounds and acetylenes containing heteroorganic fragments were recently published [4, 33, 34, 61-65]; as a rule, the dominant direction of addition is that in which the nitrogen atom of the diazomethane adds to the carbon atom of the triple bond that bears the heteroatom [65]:

$R = H, C_6H_5$; $X = (C_6H_5)_3Sn$, $(C_6H_5)_2P$, $(C_6H_5)_2As$, $(CH_3)_3Si$, $(C_6H_5)_3Ge$, $(CH_3)_3Si$

Examples of the addition of diazomethane to acetylenic sulfones constitute an exception to this observation [65]:

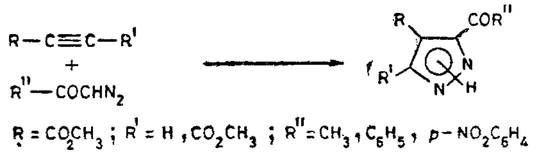


The reaction of alkynes with diazo compounds that have less pronounced nucleophilic properties as compared with diazomethane (for example, diazoacetic ester and α-diazo ketones) takes place more sluggishly: The temperature conditions are frequently more severe, and the yields of adducts are somewhat lower as a rule. Thus Ried and Omran obtained 3(5)-acylpyrazoles in 30-60% yields by the addition of a series of α-diazo ketones to phenylacetylene [66]:

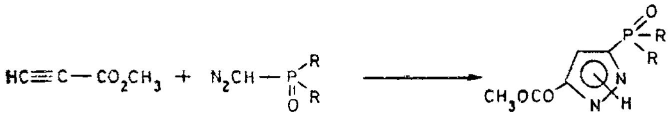


Only 3(5)-acyl-5(3)-hydroxyalkylpyrazoles were also isolated in the reactions of α-diazo ketones with alkynylcarbinols; however, the yields of the former decreased sharply (from 50 to 16%) as the molecular weight of the carbinol increased [66].

At the same time, the use of acetylenic compounds containing electron-acceptor substituents as the dipolarophiles makes it possible to synthesize pyrazoles in high yields under relatively mild conditions. Thus the corresponding pyrazoles were obtained in 70-85% yields from propiolic or acetylenedicarboxylic acid esters, which are most often used for the synthesis of pyrazoles and have been studied most thoroughly, and aryl- and alkyldiazo ketones or diazo carbohydrates [68]; the reaction was carried out either by prolonged (3-4 days) reaction of the reagents in ether solution or by heating in toluene for several hours:

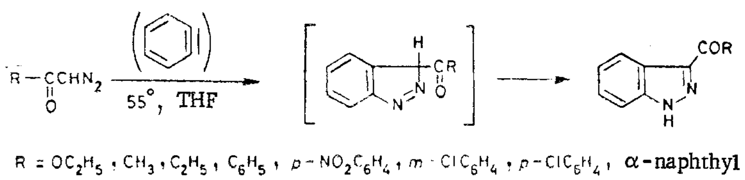


Propiolic acid esters also react quite readily with phosphoryl diazo compounds [69] in ether solution at room temperature. This reaction is used successfully for the synthesis of 3(5)-phosphorylpyrazoles (in higher than 80% yields).



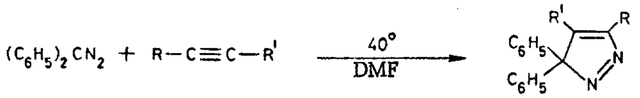
Dehydrobenzene, which is frequently used for the synthesis of various indazoles, displays the highest reactivity of all of the compounds with a C≡C bond in 1,3-cycloaddition reactions. The reaction with α-diazo carbonyl compounds is realized in most cases in solution in tetrahydrofuran (THF) at 50-60°C; the dehydrobenzene is generated from benzenediazonium-2-carboxylate. Thus ethyl indazole-3-carboxylate is obtained in high yield in the addition of ethyl diazoacetate to dehydrobenzene [70].

The reaction of dehydrobenzene with α-diazo ketones with various structures (aliphatic and aromatic α-diazo ketones, bisdiazo ketones, and diazo ketones of the carbohydrate series) is a convenient method for the synthesis of 3-acyl-1H-indazoles (in 75-95% yields) [68, 70-72]:



Thus diazomethane and its homologs react most readily with acetylenes activated by electron-acceptor substituents in the α position relative to the triple bond and with arynes, which contain a triple bond in the six-membered ring.

Unsubstituted acetylenes and alkyl-substituted acetylenes in which conjugation between the triple bond and the substituents is absent display low reactivities [13, 17, 23, 29, 49, 60, 73-77], and cycloaddition with their participation can be realized only at high temperatures (and sometimes also under pressure [74, 77]). Electron-acceptor substituents raise the reactivities of carbon–carbon multiple bonds; this is indicated convincingly by the rates of addition of diphenyldiazomethane to substituted acetylenes [78]:



$$\underset{1}{C_6H_5C\equiv CH}\ ;\quad \underset{900}{CH_3-C\equiv C-CO_2CH_3}\ ;\quad \underset{8200}{C_2H_5OCO-C\equiv C-CO_2C_2H_5}$$

On the basis of kinetic studies, Huisgen [78] estimated the abilities of various groups to activate the carbon–carbon multiple bonds as follows:

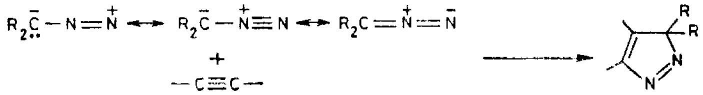
$$-COOC_6H_5 > -COOC_2H_5 > -C\equiv N > -COCH_3 > -C_6H_4NO_2\text{-}p > -C_6H_5$$

The reactivities of diazo compounds in the reactions under consideration increase when electron-donor substituents are present and decrease sharply in the order [47, 79]

$$CH_3CHN_2 > CH_2N_2 > (C_6H_5)_2CN_2 > N_2CHCO_2C_2H_5 > -COCN_2- > -COCN_2CO-$$

The mechanism of the reactions of diazo compounds with alkynes has been discussed in detail by a large number of researchers. There are presently two* principal concepts with respect to this problem: the concerted 1,3-dipolar cycloaddition of Huisgen, and the diradical mechanism proposed by Firestone.

After the studies by Huisgen [1, 9, 45-47, 83] commencing in 1963, the reaction of diazoalkanes with compounds containing a carbon–carbon triple bond has been treated in most cases as a process involving 1,3-dipolar cycloaddition (which is a special case of the cycloaddition reactions known since the end of the last century [84]) in which the diazo compound acts as a 1,3 dipole and the acetylene compound is a dipolarophile:



The mechanism of 1,3-dipolar cycloaddition consists in concerted four-center addition of the 1,3 dipole to the multiple bond of the dipolarophile accompanied by transfer of electrons within the cyclic transition state, neutralization of the formal charges in the starting compounds, and the formation of two new σ bonds [1, 45, 47]. The mechanism proposed by Huisgen satisfactorily explains the experimental facts: the stereospecificity (strict cis addition), the activation parameters of the reactions under consideration, and the absence of an appreciable effect of the solvent on the rate and stereochemistry of the reactions. The Huisgen concept is in good agreement with an examination of the orbital symmetry, which provides impressive theoretical evidence in favor of a concerted mechanism of 1,3-dipolar cycloaddition. According to the selection rules for the intermolecular formation of rings [85, 86], 1,3-dipolar cycloaddition in which the (4 + 2)π electrons participate is permitted as a concerted process in the case of thermal control if it is assumed that the reaction of the dipole with the dipolarophile is realized supra–supra relative to the surface, for it is precisely in this case that the steric interactions in the transition state are considerably smaller than in the use of antara–antara or supra-antara reactions. Studies by Houk and coworkers on the cycloaddition of diazoalkanes to compounds with unsaturated carbon–carbon bonds with the application of perturbation theory showed that the concerted mechanism does not contradict the phenomenon of regioselectivity [87-89].

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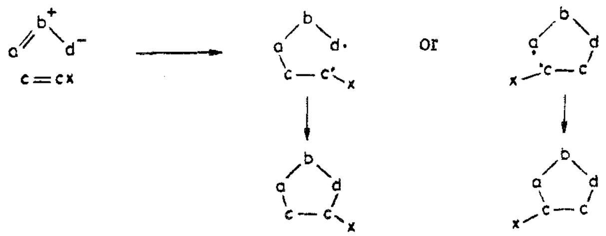
*The untenable character of the two-step mechanism proposed by Eistert [80-82] has been demonstrated convincingly by Huisgen [45, 47].

The two-step mechanism of Firestone [90, 91] includes the formation of a spin-paired diradical in the first and slowest step:



From Firestone's point of view, the phenomenon of regioselectivity in the case of cycloaddition of diazoalkanes to compounds with carbon–carbon triple bond is explainable only on the basis of this mechanism. The chief drawback of the Firestone mechanism is the fact that it cannot sufficiently convincingly explain the stereospecificity of the addition of diazoalkanes to unsaturated compounds.*

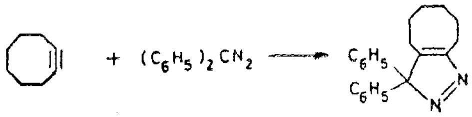
Thus the available literature data do not as yet make it possible to make an unambiguous choice in favor of any of the proposed mechanisms for the cycloaddition of diazoalkanes to unsaturated bonds. However, the views of Huisgen, who has classified the indicated reactions as typical multicenter concerted processes, have been argued more persuasively.

3H-Pyrazoles and 3H-Indazoles from Disubstituted Diazomethanes and Compounds with a Carbon–Carbon Triple Bond

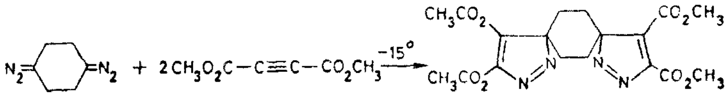
3H-Pyrazoles (pyrazolenines) and 3H-indazoles are formed in the addition of disubstituted diazomethanes to acetylenes and cycloalkynes, i.e., in cases in which there is no hydrogen atom attached to the carbon atom connected to the nitrogen atom in the aliphatic diazo compound:

The same principles as those observed in the reaction of acetylenic compounds with diazomethane and its monosubstituted homologs are characteristic for these reactions: Acetylenic compounds that are activated by electron-acceptor groupings react better than acetylene itself and alkyl- or arylacetylenes [34, 49, 51, 55, 78, 93-106]. Dimethyldiazomethane, diphenyldiazomethane, and various diaryldiazomethanes have been used most frequently as the diazo component [20, 26, 27, 76, 107-112].

The reaction of diazoalkanes with cycloalkynes has also been described. Thus in 1970 Witting and co-workers showed that diphenyldiazomethane adds quantitatively to cyclooctyne [113]:



The synthesis of 3H-spiropyrazoles from bisdiazocycloalkanes is of undoubted interest, although the yields in this case are low [77, 114, 115]:



Diazocyclopentadienes react considerably better with activated acetylenes. Dürr and Schrader have investigated this reaction for a significant number of examples and have shown that the corresponding spiropyrazoles are formed in 70-85% yields in the reaction of diazotetraphenylcyclopentadiene with the dinitrile or dimethyl ester of acetylenedicarboxylic acid [115]:

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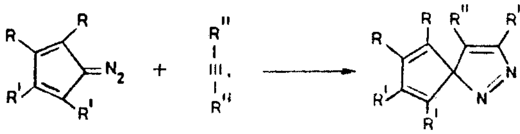
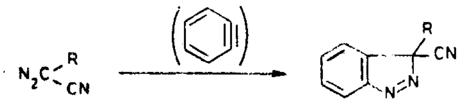
*We will now examine the cycloaddition mechanism in detail, since a number of papers [9, 85-89, 92] have been devoted to this problem.



$R = C_6H_5$, o-phenylene; $R' = C_6H_5$, o-phenylene, $R'' = CO_2CH_3, CN$

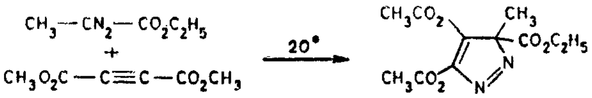
Reimlinger has synthesized 3H-spiropyrazoles on the basis of the reaction of diazofluorene with acetylene and esters of propiolic and acetylenedicarboxylic acids [77].

3,3-Disubstituted indazoles were isolated in the case of cycloaddition of diazo nitriles to dehydrobenzene [116, 117]:

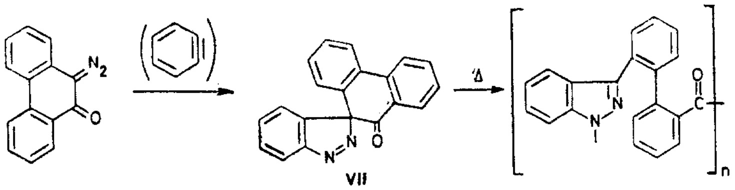


$R = C_6H_5$, $p\text{-}ClC_6H_4$, $CH_2C_6H_5$

Several examples of the synthesis of 3-carbalkoxy-3H-pyrazoles and 3-acyl-3H-indazoles from α-diazo carbonyl compounds and alkynes are known. Frank-Neumann and Buchecker, who studied the addition of ethyl 2-diazopropionate to dimethyl acetylenedicarboxylate, obtained 3-methyl-4,5-dicarbomethoxy-3-carbethoxy-3H-pyrazole in 80% yield [118]:



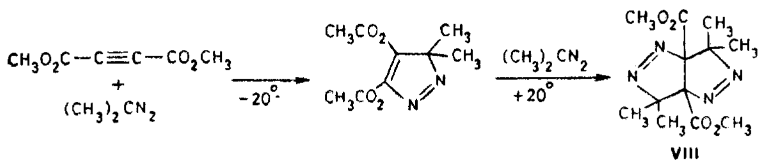
In the addition of 9-diazo-10-oxophenanthrene to dehydrobenzene Yamazaki and Shechter isolated 3-acyl-3H-indazole VII, which underwent rearrangement and polymerization during thermolysis in refluxing cumene [119]:



Information regarding 3H-pyrazoles and indazoles obtained from diazo carbonyl compounds that do not contain a hydrogen atom attached to the carbon atom bearing the diazo group is virtually exhausted by these two examples. In all of the remaining cases products of subsequent transformations, which are examined in greater detail in the next section, rather than the primary cyclization products were isolated.

The processes involving the formation of pyrazoles and indazoles may also be complicated by some side reactions. For example, the formation of cyclopropenes and nitrogen evolution are sometimes observed in the reaction of diazoalkanes with acetylenes [104-106, 120]. This side reaction becomes particularly appreciable if the preparation of the pyrazoles or indazoles is carried out at high temperatures.*

A possible side process in the reaction of an acetylenic component with excess diazoalkane is the addition of 2 moles of diazoalkane to give adduct VIII [93]:



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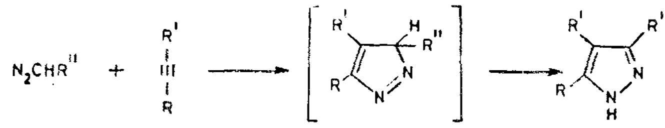
*It is known that the thermolysis and photolysis of 3H-pyrazoles and indazoles (with nitrogen evolution) are methods for the synthesis of cyclopropenes.

Rearrangements of 3H-Pyrazoles and 3H-Indazoles

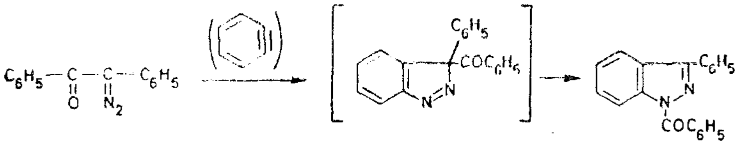
The 3H-pyrazoles and 3H-indazoles formed as the primary products of the reactions of diazo compounds with acetylenes, cycloalkynes, and arynes cannot always by any means be isolated from the reaction mixtures. This is due to the fact that some of them are capable of further transformations (primarily rearrangements) under very mild conditions (often even under the reaction conditions).

First of all one should note the well-known rearrangement of 3H-pyrazoles to 1H-pyrazoles, which always occurs if the diazo compound contains a hydrogen atom attached to the carbon atom that bears the diazo group (see the first section):



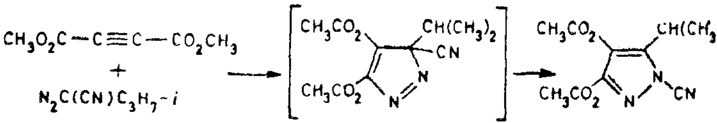
3H-Pyrazoles with a hydrogen atom attached to $C_{(3)}$ have never been isolated; in all cases in which one might have expected their formation the energically more favorable aromatic 1H-pyrazole system is obtained.

The 3H-pyrazoles and 3H-indazoles formed from alkynes and disubstituted diazo compounds containing electron-acceptor substituents (α-diazo-substituted ketones, esters, nitriles, phosphonate esters, and phosphine oxides) in most cases also cannot be isolated from the reaction medium, since they undergo rearrangement with migration of the substituent from $C_{(3)}$ to the nitrogen atom leading to 1H-pyrazoles. This sort of migration of the substituent was first observed in 1966 by Baum [121]: In the case of the cycloaddition of phenylbenzoyldiazomethane to dehydrobenzene he isolated 1-benzoyl-3-phenylindazole (X) from the reaction mixture instead of the expected 3-benzoyl-3-phenylindazole (IX).



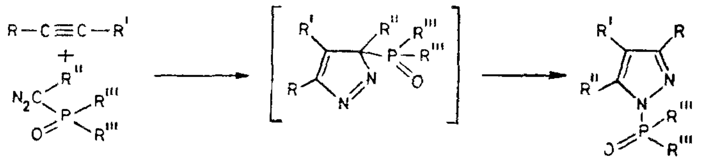
IX X

Later, in 1972, Frank-Neumann and Buchecker [118] observed a similar spontaneous migration of the electron-acceptor groups in the pyrazole series. In a study of the reaction of isopropylcyanodiazomethane with dimethyl acetylenedicarboxylate [118], instead of the expected 3H-pyrazole XI they obtained 1H-pyrazole XII, which arises as a result of migration of the nitrile group from the 3(5) to the 2 position (1,2 migration):



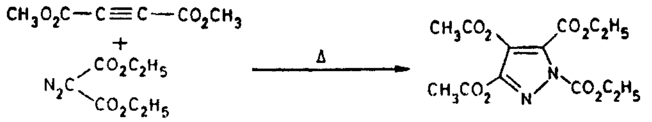
XI XII

Similar transformations have been noted by Regitz and co-workers [69, 122, 123] in the reaction of α-diazophosphonic acid esters and α-diazophosphine oxides with activated acetylenes — esters and nitriles of propiolic, phenylpropiolic, and acetylenedicarboxylic acids:



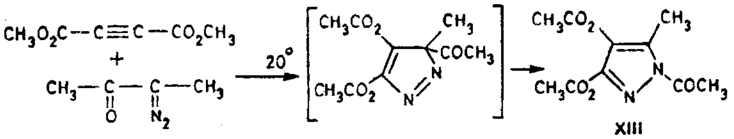
$R = H, CO_2CH_3, CN$; $R' = CO_2CH_3, CN, C_6H_5$; $R'' = H, CH_3, C_6H_5$; $R''' = C_6H_5, OCH_3$

A communication by Bramley and co-workers in 1973 [124] reported that a 1H-pyrazole — the product of migration of a carbethoxy group from the 3 position to the nitrogen atom — is obtained in low yield by prolonged refluxing in benzene of diazomalonic ester with dimethyl acetylenedicarboxylate:

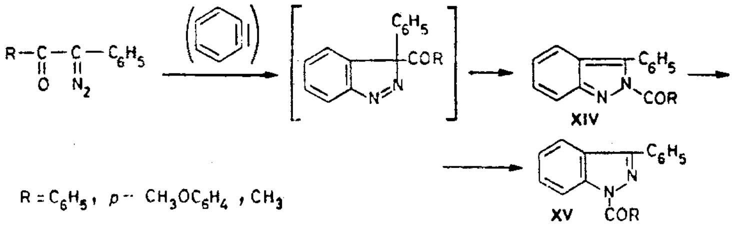


Acyl groups have extremely high migration capacities in the rearrangements under consideration, and 3,3-disubstituted 3-acyl-3H-diazoles therefore cannot be isolated [118, 119, 121, 125-133]. The only positive example is 3-acyl-3H-indazole VII (see above). In some cases [68, 71, 134, 135] erroneous data on the synthesis of 3,3-disubstituted 3-acyl-3H-pyrazoles and indazoles have been presented in the literature. Later studies showed that N-acylpyrazoles and indazoles [118, 121, 126, 128, 133], which are, as a rule, products of 1,2 migration of the acyl groups, are obtained in the reactions under consideration.

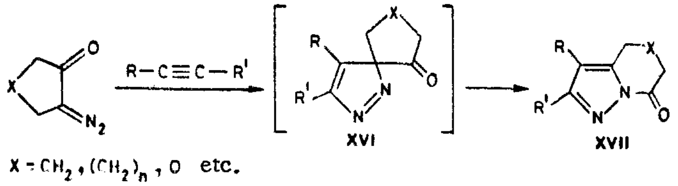
It has been demonstrated for a large number of examples of the reaction of acyclic, alicyclic, and heterocyclic α-diazo ketones with alkynes that migration of the acyl groups to the nitrogen atom, which leads to N-acylpyrazoles and N-acylindazoles, occurs most frequently. Thus 2-diazobutanone reacts with dimethyl acetylenediacarboxylate to give N-acylpyrazole XIII [118, 119]:


XIII

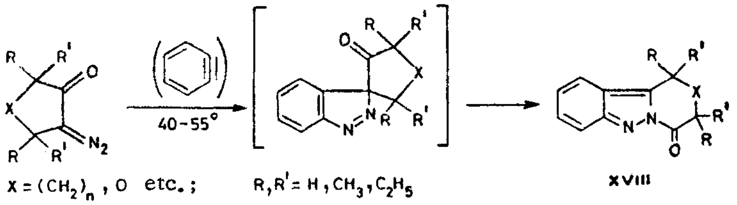
The cycloaddition of acyclic α-diazo ketones to dehydrobenzene leads to the formation of 2-acylindazoles XIV, which undergo rearrangement to 1-acylindazoles XV under the reaction conditions (25-41°C) or when the mixtures are heated to higher temperatures [121, 127]:



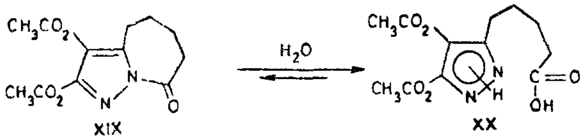
Alicyclic and heterocyclic α-diazo ketones react with phenylacetylene and dimethyl acetylenedicarboxylate to give the corresponding N-acylpyrazoles XVII with a lactam structure in good yields instead of the expected 3H-spiropyrazoles XVI [119, 125-131]:



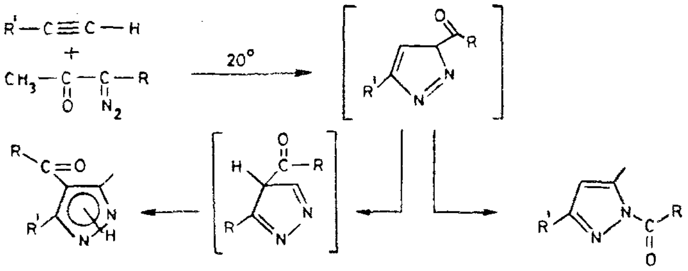
The reaction of alicyclic and heterocyclic α-diazo ketones with dehydrobenzene proceeds similarly — three-ring XVIII systems containing lactam and indazole rings are formed [119, 128, 133]:



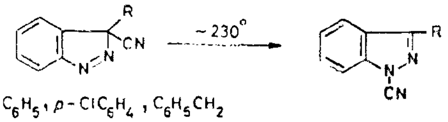
It is interesting to note that the two- and three-ring compounds under consideration are hydrolyzed extremely readily at the lactam bond; this leads to the synthesis of carboxylic acids containing 3-indazole or substituted 3-pyrazole rings in the γ and δ positions in good yields [133]. In the case of the reaction with α-diazocyclohexanone lactam structure XIX was erroneously assigned [129] to acid XX, which is formed in the hydrolysis of lactam XIX [131]:



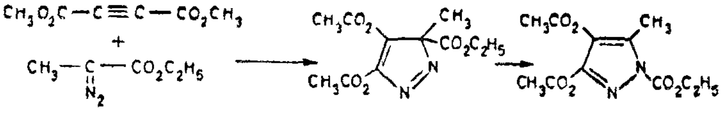
It is remarkable that when Frank-Neumann and Buchecker subjected 2-diazobutanone, some 2-diazocycloalkanones, and methyl diazopropionate to reaction with monosubstituted acetylenes containing electron-acceptor groups ($COCH_3$, CO_2CH_3, and CN), they observed spontaneous competitive 1,2 migrations of acyl and carbalkoxy groups from the 3 position of 3H-pyrazoles to, on the one hand, the nitrogen atom and, on the other, to the carbon atom in the 4 position even at room temperature. The latter was the dominant reaction pathway. 3H-Pyrazoles were not isolated.



Direct proof that the formation of 1H-pyrazoles and 1H-indazoles from disubstituted diazo compounds and alkynes proceeds through intermediate 3H-pyrazoles and 3H-indazoles is provided by the isolation in some cases under mild conditions of 3H-pyrazoles and 3H-indazoles, which are converted to 1H-pyrazoles and 1H-indazoles at high temperatures. Thus the 3,3-disubstituted indazoles obtained by 1,3-dipolar cycloaddition of diazonitriles to dehydrobenzene [116, 117] upon thermolysis undergo rearrangement with migration of the nitrile group to the nitrogen atom in the 1 position:



3-Methyl-3,4,5-tricarbalkoxypyrazole, which was isolated by Frank-Neumann and Buchecker [118] in the reaction of ethyl 2-diazopropionate with dimethyl acetylenedicarboxylate, undergoes slow rearrangement at room temperature (at 20°C for 2 h; 80% yield) and more rapid rearrangement at higher temperatures (at 80°C for 10 h; 100% yield) to a 1H-pyrazole:



The examined transformations of 3H-pyrazoles to 1H-pyrazoles, which take place spontaneously under the reaction conditions, are extremely similar to the rearrangements of 3,3-disubstituted pyrazoles. These rearrangements, which were discovered by Van Alphen [110] and were studied in detail by other researchers [8, 113, 125, 136, 137], are observed during thermolysis or in the case of the catalytic action of acids and bases.

The rearrangements of 3,3-disubstituted 3H-pyrazoles can be classified as follows: a) migration of a substituent from the 3(5) position to the nitrogen atom to give 1-substituted pyrazoles XXI (this sort of migration is particularly characteristic for electron-acceptor groupings);


XXI

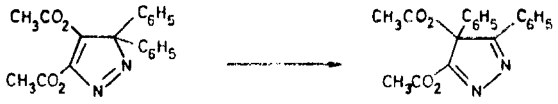
b) migration of substituents from the 3(5) position to $C_{(4)}$


XXII

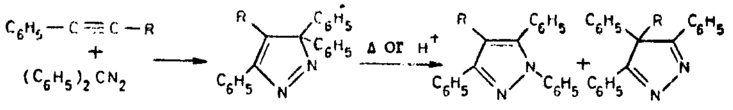
Several variants are possible in this case: Either the resulting 4H-pyrazoles (isopyrazoles XXII) are stable and are isolated from the reaction sphere or the R' group migrates to the nitrogen atom to give 1H-pyrazoles XXIII:


XXIII

In the opinion of Baums and co-workers [138], 4H-pyrazoles are stable when the substituents bonded to the sp^3-hybridized carbon atom are alkyl or aryl groups. Thus 3,4-diphenyl-4,5-dicarbomethoxy-4H-pyrazole is formed when 3,3-diphenyl-4,5-dicarbalkoxymethyl-3H-pyrazole is refluxed in acetic acid:

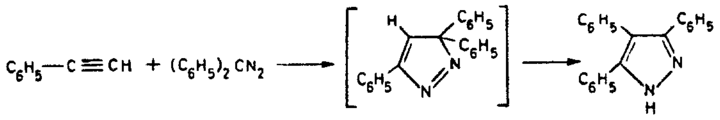


Komendantov and Bekmukhametov have shown [105, 136] that the thermal and acid-catalyzed isomerization of 3,3,5-triphenyl-3H-pyrazole-4-carboxylic acid derivatives (XXIV) leads to the formation of, in addition to 1,3,5-triphenylpyrazole-4-carboxylic acid derivatives (XXV), the corresponding 4H-pyrazoles XXVI, to which pyrazole-1-carboxylic acid structures were previously erroneously assigned [26, 27, 100, 110, 137]:

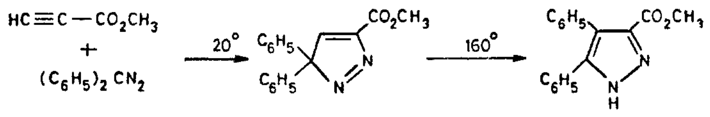

R = CN, CO_2CH_3, $CO_2C_2H_5$ XXIV XXV XXVI

The formation of 1H-pyrazoles from 3,3-disubstituted pyrazoles through a step involving the formation of 4H-pyrazoles takes place if there is a hydrogen atom attached to $C_{(4)}$, i.e., if acetylene or a monosubstituted acetylene and a disubstituted diazoalkane are subjected to the reaction.

Thus, for example, the preparation of 3,4,5-triphenylpyrazole from phenylacetylene and diphenyldiazomethane (at 20°C; 83% yield) can be interpreted as isomerization of the intermediately formed 3,3,5-triphenyl-3H-pyrazole [139]:

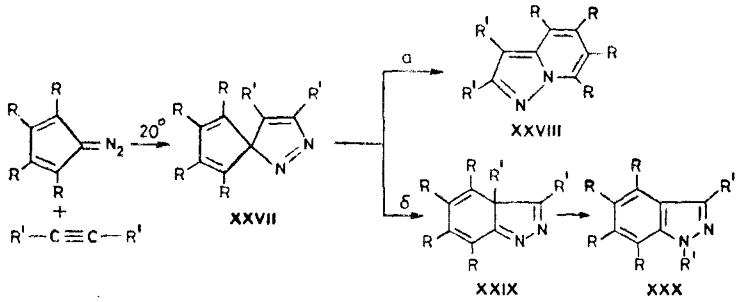


The reaction of diphenyldiazomethane with methyl propiolate proceeds similarly [27]:



Examples of the thermal rearrangements of pyrazoles with the migration of hydrogen atoms and alkyl and phenyl groups have also been presented in [106, 132, 140, 141].

Migration takes place particularly readily in the case of 3H-spiropyrazoles. Thus a thorough investigation of the rearrangements of the products of cycloaddition of substituted diazocyclopentadienes to mono- and disubstituted alkynes by Dürr and co-workers [120, 142, 143] showed that spiropyrazoles XXVII obtained from tetraphenyldiazocyclopentadienes and disubstituted alkynes [dimethyl acetylenedicarboxylate or bis(trifluoromethyl)acetylene] undergo rearrangement to pyrazolopyridines XXVIII spontaneously under the reaction conditions.

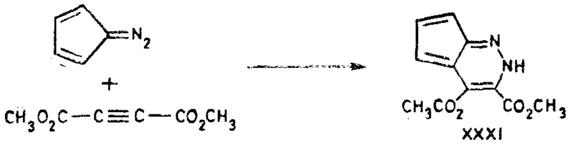


XXVII XXVIII XXIX XXX

$R = H, C_6H_5, Cl$, o-phenylene $R' = H, C_6H_5, CN, CF_3, CO_2CH_3, CO_2C_2H_5$

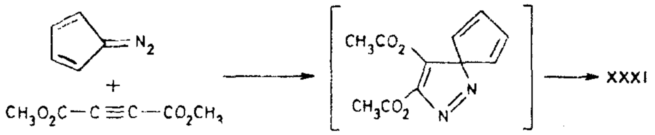
Migration of the substituents may proceed in two directions (a and b) in 3H-spiropyrazoles XXVII formed from monosubstituted alkynes (ethyl propiolate and phenylacetylene) and diazocyclopentadienes; not only spiropyrazoles XXVII but pyrazolopyridines XXVIII and indazoles XXX were isolated as the products of these reactions. The latter are the products of rearrangement of isoindazoles XXIX.

However, it is interesting to note that unsubstituted diazocyclopentadiene adds to dimethyl acetylenedicarboxylate in a different way than that observed for substituted diazocyclopentadienes: In this case the product is 2H-cyclopenta[*a*]pyridazine XXXI, and Houk and Luskus interpret this reaction as a thermally allowed [$\pi8_s + \pi2_s$] process [144]:



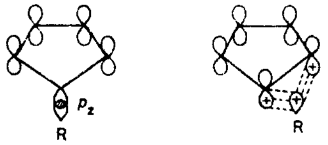
XXXI

However, in this case also one might assume the initial formation of the usual 1,3-cycloaddition adduct and its subsequent sigmatropic rearrangements, analogous to the rearrangement examined above:



The thermal rearrangements of 3H-pyrazoles and 3H-indazoles with the participation of phenyl, nitrile, carbalkoxy, and acyl groups are currently interpreted as the well-known class of sigmatropic rearrangements in which one of the σ bonds migrates along the polyene chain with retention of the total number of σ and π bonds in the system — in this case as [1,5]-sigmatropic shifts [126-133]. In accordance with the selection rules, on the basis of the theory of the retention of orbital symmetry this migration for the migrating groups in the systems under consideration (the number of electrons participating in the process is six) is allowed in the ground state as a supra-surface migration with retention of the configuration of the migrating group [85, 92].

The upper occupied molecular orbital (UOMO) of the pentadiene system participates in transformations that include 1,2 migration of the substituents. This MO has wave functions with identical signs on the $C_{(1)}$ and $C_{(5)}$ atoms, and a [1,5]-sigmatropic shift should consequently take place in a supra-surface manner; since this orbital is an upper occupied orbital in the ground state of the pentadienyl system, the process is allowed during thermolysis (i.e., in the ground state of the compounds under consideration).



The aromatization of the pyrazoles and indazoles by means of a prototropic shift that is described in the first section can also, in our opinion, be interpreted in terms of a [1,5]-sigmatropic or two successive [1,5]-sigmatropic shifts, which for the examined systems with six participating electrons are allowed in their ground state (during thermolysis) as supra-surface shifts [85, 92].

The extremely high migration capacity displayed by the hydrogen atom during [1,5]-sigmatropic shifts (as compared, for example, with phenyl or methyl groups) is explained by a number of researchers [92, 145] by the fact that the bonding capacity of the s orbital of the hydrogen atom in the cyclic transition state (when it is overlapped with the orbitals of the terminal carbon atoms) is greater than that of the hybrid phenyl or methyl orbitals. Acyl and phosphoryl groups migrate readily, whereas carbalkoxy, nitrile, phenyl, and alkyl groups migrate less readily. The driving force of the [1,5]-sigmatropic rearrangements is evidently the formation of energically more favorable (than the direct products of cycloaddition — 3H-pyrazoles and 3H-indazoles) 1H-pyrazoles and 1H- and 2H-indazoles.

LITERATURE CITED

1. R. Huisgen, Angew. Chem., 75, 604 (1963).
2. B. Eistert, G. Regitz, and H. Schwall, in: Houben-Weyl, Methoden der Organischen Chemie, Vol. 10/4, Georg Thieme Verlag, Stuttgart (1968), p. 482.
3. T. V. Jacobs, in: Heterocyclic Compounds (ed. by R. Elderfield), Vol. 5, Wiley (1961), Chap. 2.
4. J. Bastide, J. Hamelin, F. Texier, V. Vo-Quang, Bull. Soc. Chim. France, Nos. 7-8, 2555 (1973).
5. I. K. Korobizina and L. L. Rodina, in: Methodicum Chimicum, Vol. 6, Georg Thieme Verlag, Stuttgart, Academic Press, New York (1974), p. 260.
6. A. N. Kost and I. I. Grandberg, Advances in Heterocyclic Chemistry, Vol. 6 (1966), p. 381.
7. H. Wiehe (editor), The Chemistry of Acetylene Compounds [Russian translation], Khimiya, Moscow (1973), p. 232.
8. R. R. Bekmukhametov, in: Modern Problems in Organic Chemistry [in Russian], No. 5, LGU, Leningrad (1976), p. 105.
9. R. Huisgen, J. Org. Chem., 41, 403 (1976).
10. E. Buchner, Ber., 22, 842 (1889).
11. E. Buchner and M. Fritsch, Ber., 26, 256 (1893).
12. H. Pechmann, Ber., 31, 2950 (1898).
13. H. Reimlinger, Ber., 92, 970 (1959).
14. W. Hückel, J. Datow, and E. Simmersbach, Z. Phys. Chem., 186A, 129 (1940).
15. K. Auwers and E. Cauer, Ann., 470, 284 (1929).
16. K. Auwers and O. Ungemach, Ber., 66, 1205 (1933).
17. G. Manecke and H. U. Schenck, Tetrahedron Lett., No. 8, 617 (1969).
18. P. B. Terent'ev, T. P. Moskvina, L. V. Moshentseva, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 4, 498 (1970).
19. R. Hüttel, Ber., 74, 1680 (1941).
20. R. Hüttel and A. Gebhardt, Ann., 558, 34 (1948).
21. K. Bowden and E. R. H. Jones, J. Chem. Soc., 953 (1946).
22. S. Hauptmann and K. Kirschberg, J. Prakt. Chem., 35, 105 (1967).
23. T. Sasaki and K. Kanematsu, J. Chem. Soc., C, No. 11, 2147 (1971).
24. J. Bastide, J. Lematre, and J. Soulier, Compt. Rend., C, 269, 358 (1969).
25. J. Bastide, O. Henri-Rousseau, and L. Aspart-Pascot, Tetrahedron, 30, 3355 (1974).
26. L. Aspart-Pascot and J. C. Bastide, Compt. Rend., C, 273, 1772 (1971).
27. R. Hüttel, J. Riedl, H. Martin, and K. Franke, Chem. Ber., 93, 1425 (1960).
28. E. Mungaini and P. Grunanger, Att. Acad. Naz. Lincei, 14, 95 (1953).
29. J. Bastide and J. Lematre, Compt. Rend., C, 268, 532 (1969).
30. J. Bastide and J. Lematre, Bull. Soc. Chim. France, No. 10, 3543 (1970).
31. C. Bischoff and K. H. Platz, J. Prakt. Chem., 312, 2 (1970).

32. C. Sabate-Alduy and J. Bastide, Bull. Soc. Chim. France, No. 7, 2764 (1972).
33. S. N. Groen and J. F. Arens, Rec. Trav. Chim., 80, 879 (1961).
34. P. Grunanger and P. Vita-Finzi, Att. Acad. Naz. Lincei, 31, 128 (1961).
35. E. Stephan, L. Vo-Quang, and Y. Vo-Quang, Bull. Soc. Chim. France, Nos. 9-10, 2795 (1973).
36. R. G. Jones, J. Am. Chem. Soc., 71, 3994 (1949).
37. R. Kuhn and K. Henkel, Ann., 549, 279 (1941).
38. H. Reimlinger, J. J. M. Vanderwalle, and A. V. Overstraeten, Ann., 720, 124 (1968).
39. F. W. Hoover and D. D. Coffman, J. Org. Chem., 29, 3657 (1964).
40. E. Stephan, L. Vo-Quang, and Y. Vo-Quang, Compt. Rend., C, 272, 1731 (1971).
41. E. Stephan, L. Vo-Quang, and Y. Vo-Quang, Bull. Soc. Chim. France, No. 12, 4781 (1972).
42. H. Reimlinger, Chem. Ber., 93, 1859 (1960).
43. K. Henkel and F. Weygand, Ber., 76, 812 (1943).
44. F. De Las Heras, S. Tam, R. Klein, and J. Fox, J. Org. Chem., 41, 84 (1976).
45. R. Huisgen, Angew. Chem., 75, 742 (1963).
46. R. Huisgen, J. Org. Chem., 33, 2291 (1968).
47. R. Huisgen, R. Grashey, and G. Sawyer, in: The Chemistry of Alkenes (ed. by S. Patai), Interscience (1964).
48. A. T. Troshchenko and A. A. Petrov, Dokl. Akad. Nauk SSSR, 119, 292 (1958).
49. G. Bettinetti, G. Desimoni, and P. Grunanger, Gazz. Chim. Ital., 94, 91 (1964).
50. G. S. Nikol'skaya and A. T. Troshchenko, Zh. Org. Khim., 3, 498 (1967).
51. M. Noel, Y. Vo-Quang, and L. Vo-Quang, Compt. Rend., C, 270, 80 (1970).
52. L. Vo-Quang, Compt. Rend., C, 266, 642 (1968).
53. L. Vo-Quang and Y. Vo-Quang, Bull. Soc. Chim. France, No. 11, 2575 (1974).
54. L. Vo-Quang and Y. C. Vo-Quang, Compt. Rend. C, 279, 915 (1974).
55. J. Bastide, J. Lematre, and J. Soulier, Compt. Rend., C, 266, 1393 (1968).
56. H. Reimlinger and C. H. Moussenbois, Chem. Ber., 98, 1805 (1965).
57. G. Casnati, J. Castells, and J. C. Pascual, Ann. Real. Soc., 55B, 739 (1959).
58. G. Manecke and H. U. Schenck, Tetrahedron Lett., No. 17, 2061 (1968).
59. L. B. Sokolov, Ya. L. Porfir'eva, and A. A. Petrov, Zh. Org. Khim., 1, 610 (1965).
60. H. Reimlinger, Ann., 713, 113 (1968).
61. G. Guillerm and M. Lequan, Compt. Rend., C, 269, 853 (1969).
62. E. Ott and W. Bossaller, Ber., 76, 88 (1943).
63. A. N. Pudovik, N. G. Khusainova, T. V. Timoshina, and O. E. Raevskaya, Zh. Obshch. Khim., 41, 1476 (1971).
64. A. N. Pudovik, N. G. Khusainova, and T. V. Timoshina, Zh. Obshch. Khim., 44, 272 (1974).
65. G. Guillerm, A. L. Honore, L. Veniard, G. Pourcelot, and J. Benaim, Bull. Soc. Chim. France, Nos. 9-10, 2739 (1973).
66. W. Ried and J. Omran, Ann., 666, 144 (1963).
67. M. Sprinzl and J. Farkaš, Coll. Czech. Chem. Commun., 32, 3787 (1967).
68. L. L. Rodina, V. V. Bulusheva, and I. K. Korobitsyna, Zh. Org. Khim., 8, 1108 (1972).
69. A. Hartmann and M. Regitz, Phosphorus, Vol. 5 (1974), p. 21.
70. H. Huisgen and R. Knorr, Naturwissenschaften, 48, 716 (1961).
71. W. Ried and M. Schön, Ann., 689, 141 (1965).
72. E. Garcia-Abbad, J. Heterocycl. Chem., 13, 1241 (1976).
73. R. Huisgen, W. Scheer, and H. Mader, Angew. Chem., Int. Ed., 8, 602 (1969).
74. G. Able, Chem. Rev., 69, 345 (1969).
75. H. Reimlinger, Chem. Ber., 92, 970 (1959).
76. C. Dumont, J. Naire, M. Vidal, and P. Arnaud, Compt. Rend., C, 268, 348 (1969).
77. H. Reimlinger, Chem. Ber., 100, 3097 (1967).
78. R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, Angew. Chem., 73, 170 (1961).
79. G. Cowell and A. Ledwith, Quart. Rev., 24, 119 (1970).
80. B. Eistert, Angew. Chem., 54, 124 (1941).
81. G. Young, L. Andrews, S. Lindenbaum, and S. Cristal, J. Am. Chem. Soc., 66, 810 (1944).
82. D. Hammik and D. Voaden, Chem. Ind., No. 28, 739 (1956).
83. R. Huisgen, Angew. Chem., 80, 329 (1968).
84. L. Smith, Chem. Rev., 23, 193 (1938).
85. R. B. Woodward and R. Hoffmann, Conservation of Orbital Symmetry, Academic Press.
86. R. B. Woodward and R. Hoffmann, J. Am. Chem. Soc., 87, 395, 2046 (1965).
87. K. Houk, J. Sims, C. Watts, and L. Luskus, J. Am. Chem. Soc., 95, 7301 (1973).
88. K. Houk, J. Sims, C. Watts, and L. Luskus, J. Am. Chem. Soc., 95, 7287 (1973).

89. K. Houk, J. Am. Chem. Soc., 94, 8953 (1972).
90. R. Firestone, J. Org. Chem., 33, 2285, 2291 (1968).
91. R. Firestone, J. Org. Chem., 37, 2181 (1972).
92. T. L. Gilchrist and R. C. Storr, Organic Reactions and Orbital Symmetry, Cambridge Univ. Press (1972).
93. M. Frank-Neumann, Angew. Chem., 79, 98 (1967).
94. M. Frank-Neumann, Thesis à la Faculté de Sciences de l'Université de Strasbourg (1968).
95. A. C. Day and M. C. Whiting, Chem. Commun., No. 13, 292 (1965).
96. A. C. Day and M. C. Whiting, Proc. Chem. Soc., No. 11, 368 (1964).
97. G.P. Bettinetti, G. Desimoni, and P. Grunanger, Gazz. Chim. Ital., 93, 150 (1963).
98. G. P. Bettinetti and G. Desimoni, Gazz. Chim. Ital., 93, 658 (1963).
99. G. P. Bettinetti, G. Desimoni, and P. Grunanger, Gazz. Chim. Ital., 94, 91 (1964).
100. J. Van Alphen, Rec. Trav. Chim., 62, 491 (1943).
101. R. Grüning and J. Lorlerth, J. Organomet. Chem., 69, 213 (1974).
102. D. M. Gale, W. J. Middleton, and C. G. Krespan, J. Am. Chem. Soc., 88, 3617 (1966).
103. M. Jones, M. E. Hendrick, and W. J. Baron, J. Am. Chem. Soc., 93, 1554 (1971).
104. W. R. Cullen and M. C. Waldman, Can. J. Chem., 48, 1885 (1970).
105. M. I. Komendantov and R. R. Bekmukhametov, Khim. Geterotsikl. Soedin., No. 1, 79 (1975).
106. J. Moritani, T. Hosokowa, and N. Obata, J. Org. Chem., 34, 670 (1969).
107. M. Frank-Neumann and C. Buchecker, Tetrahedron Lett., No. 1, 15 (1969).
108. A. C. Day and R. N. Inwood, J. Chem. Soc., C, No. 7, 1065 (1969).
109. G. Snatzke and H. Langen, Chem. Ber., 102, 1865 (1969).
110. J. Van Alphen, Rec. Trav. Chim., 62, 485 (1943).
111. M. Frank-Neumann and C. Buchecker, Angew. Chem., 82, 549 (1970).
112. A. Day and M. Whitting, J. Chem. Soc., C, No. 19, 1719 (1966).
113. G. Wittig and J. J. Hatchison, Ann., 741, 89 (1970).
114. K. Heyns and A. Heins, Angew. Chem., 73, 64 (1961).
115. H. Dürr and L. Schrader, Z. Naturforsch., 24b, 536 (1969).
116. R. Bernard, Diss. Abstr., B, 28, 4925 (1968).
117. R. Bernard and H. Shechter, Tetrahedron Lett., No. 44, 4529 (1972).
118. M. Frank-Neumann and C. Buchecker, Tetrahedron Lett., No. 10, 937 (1972).
119. T. Yamazaki and H. Shechter, Tetrahedron Lett., No. 16, 1417 (1973).
120. H. Dürr and R. Sergio, Tetrahedron Lett., No. 33, 3479 (1972).
121. G. Baum, Dissertation Abstracts, B, 27, 97 (1966); Chem. Abstr., 65, 20071d (1966).
122. U. Felcht and M. Regitz, Chem. Ber., 109, 3675 (1976).
123. U. Felcht and M. Regitz, Angew. Chem., 88, 377 (1976).
124. R. Bramley, R. Grigg, G. Guilford, and P. Milner, Tetrahedron, 29, 4159 (1973).
125. M. Martin and M. Regitz, Ann., 1702 (1974).
126. A. Katner, J. Org. Chem., 38, 825 (1972).
127. T. Yamazaki, G. Baum, and H. Shechter, Tetrahedron Lett., Nos. 49-50, 4421 (1974).
128. T. Yamazaki and H. Shechter, Tetrahedron Lett., No. 44, 4533 (1972).
129. M. Frank-Neumann and C. Buchecker, Angew. Chem., 85, 259 (1975).
130. L. L. Rodina, V. V. Bulusheva, T. G. Ekimova, and I. K. Korobitsyna, Zh. Org. Khim., 10, 55 (1974).
131. L. L. Rodina, V. V. Bulusheva, and I. K. Korobitsyna, Zh. Org. Khim., 10, 1937 (1974).
132. M. Frank-Neumann and C. Buchecker, Tetrahedron Lett., No. 24, 2069 (1976).
133. V. V. Bulusheva, Master's Dissertation, Leningrad State Univ., Leningrad (1975).
134. O. Diels and H. König, Ber., 71, 1179 (1938).
135. O. Tsuge, J. Shinkai, and M. Koga, J. Org. Chem., 36, 745 (1971).
136. M. I. Komendantov and R. R. Bekmukhametov, in: Fifth All-Union Conference on the Chemistry of Acetylene [in Russian], Tbilisi (1975), p. 374.
137. R. Hüttel, K. Franke, H. Martin, and J. Riedl, Chem. Ber., 93, 1433 (1960).
138. R. Baums, J. Elguero, R. Jacquier, and G. Tárrago, Tetrahedron Lett., No. 39, 3781 (1973).
139. W. Kirmse and L. Horner, Ann., 614, 1 (1958).
140. T. Sato and S. Watanabe, Bull. Chem. Soc. Jpn., 41, 3017 (1968).
141. I. I. Grandberg, A. P. Krasnoshchek, A. N. Kost, and G. K. Faizova, Zh. Obshch. Khim., 33, 2586 (1963).
142. H. Dürr and R. Sergio, Chem. Ber., 107, 2027 (1974).
143. H. Dürr and W. Schmidt, Ann., No. 6, 1140 (1974).
144. K. Houk and L. Luskus, Tetrahedron Lett., No. 46, 4029 (1970).
145. L. Miller, R. Greisinger, and R. Boyer, J. Am. Chem. Soc., 91, 1578 (1969).