

SYNTHESIS OF HETEROCYCLES BY 1,3-DIPOLAR CYCLOADDITION REACTIONS
WITH THE PARTICIPATION OF NITROALKENES (REVIEW)

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The advances in the synthesis of five-membered nitrogen-containing heterocycles by reactions involving 1,3-dipolar cycloaddition of conjugated and unconjugated nitroalkenes to various 1,3-dipoles (diazocompounds, azides, nitrile N-oxides, etc.) are systematized.

The chemistry of unsaturated nitro compounds is a promising direction in modern organic chemistry that is undergoing intensive development; this is associated with the progress in methods used to obtain them and their high and specific reactivities. Among the numerous chemical transformations of conjugated and unconjugated nitroalkene reactions that lead to the formation of heterocyclic systems are known. Some information regarding these reactions has been set forth in monographs [1-3] and reviews [4-8]; however, this information is being replenished annually with new examples.

In recent years the 1,3-dipolar cycloaddition of nitroalkenes to various 1,3-dipoles, which makes it possible to obtain diverse five-membered nitrogen heterocycles, has occupied a special place among these reactions. Reactions of this type are of considerable interest for the methodology of specific organic synthesis, since in a number of cases 1,3-dipolar cycloaddition using nitroalkenes as the dipolarophiles is the only possibility for obtaining nitro derivatives of the heterocyclic series [3, 5, 9].

Despite the great interest of chemists in such reactions of nitroalkenes and the constantly increasing number of publications in this area some general information regarding reactions involving 1,3-dipolar cycloaddition with the participation of nitroalkenes as dipolarophiles has been examined briefly in only four publications [1, 3, 5, 9].

In the present review we have attempted to systematize and critically examine the most important, from our point of view, aspects of the [2 + 3]-cycloaddition of nitroalkenes: data on the regio- and stereochemistry of reactions, the reactivities of both nitroalkenes and 1,3-dipoles, etc.

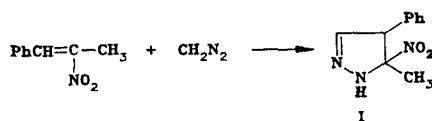
We arranged the material taking into account the character of the 1,3-dipole that participates in the cycloaddition process. This systematization gives a graphical representation of the synthetic possibilities of the method and may be useful in the selection of the direction of future research.

1. Reaction of Nitroalkenes with Diazo Compounds

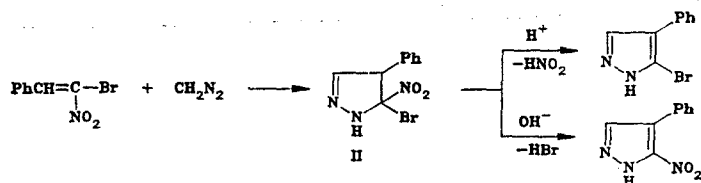
The condensation of aliphatic diazo compounds with compounds that contain activated double bonds leads to substituted pyrazolines, which can be converted to pyrazolines [10].

A mixture of products formed as a result of polymerization of β -nitrosytrene and its reaction with the pyrazoline was obtained in the reaction of β -nitrosytrene due to the activated methylidyne group bonded to the nitro group. The absence of polymerization products in the reaction of secondary nitroalkenes confirms this assumption. Thus an adduct, to which the 5-methyl-5-nitro-4-phenyl- Δ^2 -pyrazoline structure (I) was assigned, was obtained in quantitative yield in the condensation of 2-nitro-1-phenyl-1-propene with diazomethane.

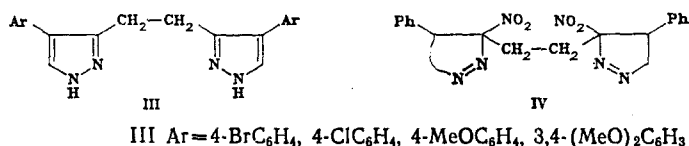
T. Kosciusko Polytechnical Institute, Krakow, Poland 31-155. I. M. Gubkina Institute of Petroleum and Gas, Moscow 117917. Translated from Khimiya Geterotsiklicheskih Soedinenii, No. 4, pp. 435-452, April, 1990. Original article submitted May 16, 1988; revision submitted August 18, 1989.



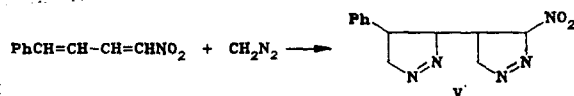
Parham and Bleasdale [12] also demonstrated that β -bromo- β -nitrostyrene reacts with diazomethane in ether to form 5-nitro- Δ^2 -pyrazoline II, treatment of which with concentrated hydrochloric acid or sodium bicarbonate solution gave, respectively, 5-bromo- or 5-nitro-4-phenylpyrazole.



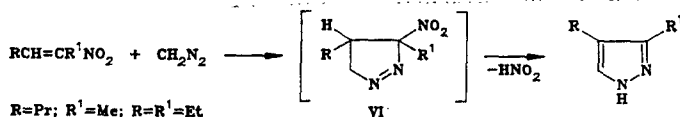
1,2-Bis(4-aryl-3-pyrazolyl)ethanes III were obtained in 47-82% yields in the reaction (ether, 6 h, 20°C) of 1,6-diaryl-2,5-dinitro-2,5-hexadienes with diazomethane. At the same time, 1,6-diphenyl-2,5-dinitro-2,5-hexadiene under similar conditions gave 1,2-bis(3-nitro-4-phenyl- Δ^1 -pyrazolin-3-yl)ethane (IV) in 80% yield [13].



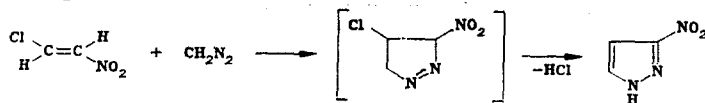
1-Nitro-4-phenylbutadiene also reacts with diazomethane to give 3-nitro-4-(4-phenyl- Δ^1 -pyrazolin-3-yl)- Δ^1 -pyrazoline (V) [14].



3,4-Dialkylpyrazoles, which are probably formed as a result of the elimination of the elements of nitrous acid from intermediate nitropyrazolines VI, were isolated in the reaction of 2-nitro-2-hexene and 3-nitro-3-hexene with diazomethane [11].

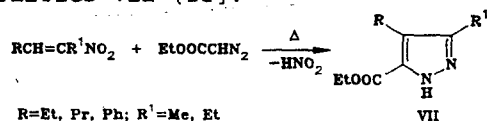


At the same time, the cycloaddition of diazomethane to trans-1-nitro-2-chloroethylene leads to the formation of 3-nitropyrazole in 65% yield [15]. In this case the elimination of a molecule of HCl from the intermediate 3-nitro-4-chloro- Δ^1 -pyrazoline is evidently more preferable than the splitting out of a molecule of HNO₂, since the chloride anion is a better leaving group than the NO₂⁻ anion [16].



This reaction is a convenient preparative method for the synthesis of difficult-to-obtain 3-nitropyrazoles, since the direct nitration of pyrazoles usually leads to 4-substituted derivatives [17].

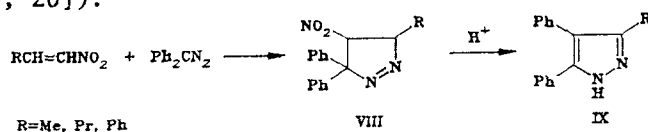
Ethyl diazoacetate reacts with conjugated nitroalkenes at 100-140°C to give 5-ethoxycarbonyl-3,4-disubstituted pyrazoles VII [11].



When β -nitrostyrene derivatives are used in this reaction, the yields of pyrazoles VII range from 68% to 92%; however, in the case of aliphatic nitroalkenes the yields of the corresponding pyrazoles do not exceed 25-46%.

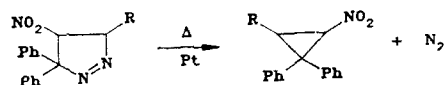
The reaction of trans-1-nitro-2-chloroethylene with ethyl diazoacetate proceeds at room temperature with splitting out of HCl leading to 3-nitro-5-ethoxycarbonylpyrazole in 43% yield [15]. At the same time, diazomalonate ester does not react with nitroalkenes even in the case of prolonged refluxing of the reagents in benzene [18].

The above-presented 1,3-dipolar cycloaddition reactions of diazomethane and ethyl diazoacetate with conjugated nitroalkenes proceed via the Auwers empirical rule [19-21], according to which the terminal nitrogen atom of the diazonium group adds to the carbon atom of the double bond that bears an activating grouping. However, the cycloaddition of diazo compounds to nitroalkenes does not always proceed to accordance with the Auwers rule [22-24]. For example, 1-nitro-1-propene, 1-nitro-1-butene, and β -nitrostyrene react with diphenyldiazomethane to give Δ^1 -pyrazolines VIII, which contain a nitro group in the 4 position. The latter on treatment with hydrochloric acid eliminate a molecule of HNO_2 to give pyrazoles IX; this elimination is accompanied by migration of a phenyl radical (the Van Alphen-Huttel rearrangement [25, 26]).

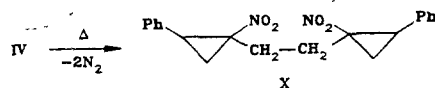


The fact that this reaction proceeds with the formation of 4-nitro- Δ^1 -pyrazolines VIII was confirmed by the introduction of 1-nitro-1-propene and 1-nitro-2-(4-benzyloxyphenyl)-ethylene with a labeled carbon atom in the 1 position into the reaction with diphenyldiazomethane and by a study of the isotope compositions of the final products of oxidation of the cycloadducts obtained [22, 23].

Some 4-nitro- Δ^1 -pyrazoline derivatives decompose to the corresponding nitrocyclopropanes at 145-165°C in the presence of catalytic amounts of platinum [27].

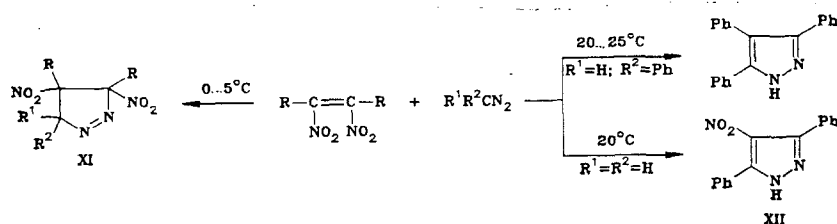


1,2-Bis(Δ^1 -pyrazolin-3-yl)ethane IV is converted to 1,2-bis(1-nitro-2-phenylcyclopropyl)ethane (X) in 80% yield on refluxing in chlorobenzene in the absence of a platinum catalyst [13].



Nitropyrazolines are sometimes exceptionally unstable compounds and decompose with the liberation of nitrogen under the reaction conditions. For example, nitrocyclopropane derivatives were obtained in high yields when substituted β -nitrostyrenes were refluxed with 9-diazofluorene in benzene for 8-10 h [28], as well as in the reaction of nitroethylene with diphenyldiazomethane and 9-diazofluorene in benzene at room temperature [18, 27, 29].

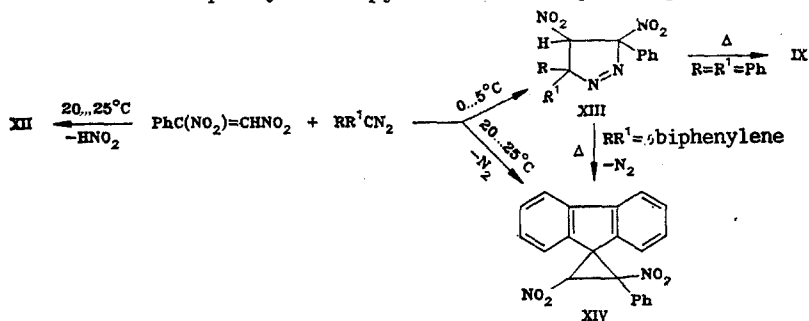
The cycloaddition of diazo compounds to vic-dinitro-alkenes proceeds in different directions, depending on the nature of the substituents in the starting compounds and the reaction conditions. For example, cis-2,3-dinitro-2-butene reacts with phenyldiazomethane, diphenyldiazomethane, and 9-diazofluorene at 0-5°C to give the corresponding 3,4-dinitro- Δ^1 -pyrazolines XI in rather high yields [30-33], while cis-dinitrostilbene reacts only with diazo- and phenyldiazomethane and does not react with diphenyldiazomethane and 9-diazofluorene.



R=Me, Ph; R¹=H, Ph; R²=H, Ph; R¹R²=biphenylene

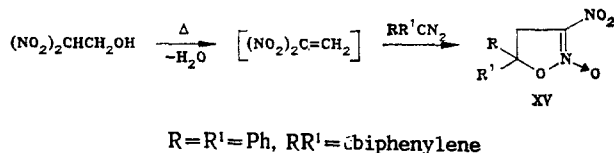
The reaction of *cis*- and *trans*-dinitrostilbene with phenyldiazomethane at 20-25°C proceeds with splitting out of both nitro groups and the formation of the same product, viz., 3,4,5-triphenylpyrazole [30-33]. The reaction of the same alkenes with diazomethane at 20-25°C is accompanied by splitting out of the elements of nitrous acid and migration of the phenyl group from the C₍₄₎ atom to the C₍₅₎ atom and leads to 4-nitro-3,5-diphenylpyrazole (XII) [31, 32]. It should be noted that *trans*-dinitrostilbene reacts with the above-indicated diazo compounds with considerably greater difficulty than the *cis* isomer.

1,2-Dinitro-1-phenylethylene reacts with diazo- and phenyldiazomethane at 20-25°C with the formation of 4-nitro-3-phenyl-5-R-pyrazoles XII [30-34].

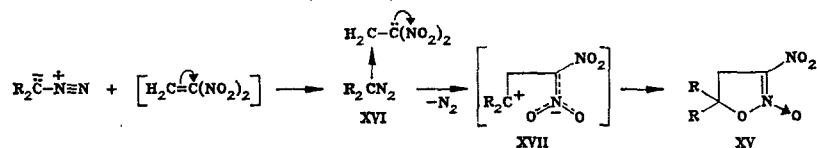


The cycloaddition of diphenyldiazomethane and 9-diazo-fluorene to this dinitroalkene at 0-5°C leads to 3,4-dinitro- Δ^1 -pyrazolines XIII in 74-84% yields. In the first case the cycloadduct on refluxing in ethanol is converted to pyrazole IX ($R = Ph$) as a consequence of splitting out of the nitro groups and migration of one phenyl group to the 4 position. In the second case brief heating of the cycloadduct in dioxane at 50-55°C leads to 1,2-dinitro-2-phenyl-3-diphenylcyclopropane (XIV) in quantitative yield. The same compound is formed as the only product in the reaction of 1,2-dinitro-1-phenylethylene with 9-diazofluorene at 20-25°C [34].

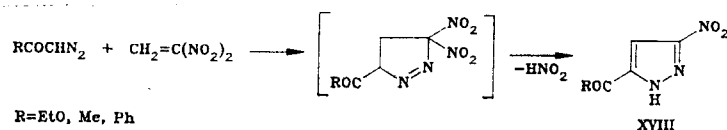
The reaction of disubstituted diazomethanes with *gem*-dinitroethylene led unexpectedly [32, 35-38] to 3-nitroisoxazoline N-oxide derivatives XV in high yields:



Diazomethane reacts similarly with biphenylenedinitroethylene to give 3-nitro-4-biphenyleneisoxazoline N-oxide [38]. Fridman and coworkers [38] note that 1,1-dinitro-2,2-diphenylethylene does not react with diazomethane; this is evidently due to shielding of the reaction center by bulky phenyl groups. The following mechanism for the formation of 3-nitroisoxazoline N-oxides is proposed:

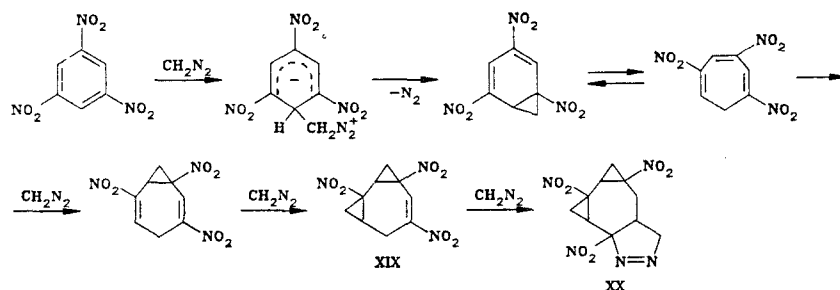


Ring formation evidently occurs after splitting out of nitrogen from intermediate adduct XVI. Such unusual behavior of *gem*-dinitroethylene can be explained by the fact that the negative charge that develops in bipolar form XVII on the carbon atom that bears the nitro groups is delocalized on the oxygen atoms of the nitro group. The intermediate development of dinitro-pyrazolines and their subsequent conversion to 3-nitroisoxazoline N-oxides XV are unlikely, since 3-nitro-5-substituted pyrazoles XVIII were isolated in 50-75% yields as a result of the reaction of *gem*-dinitroethylene with ethyl diazoacetate and diazo ketones [35,39]. Consequently, if dinitropyrazolines are formed in this reaction, they decompose primarily with the liberation of nitrous acid rather than nitrogen.



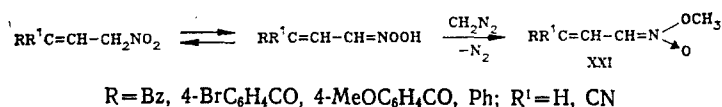
The reason for the different behavior of diazo compounds in the reaction of dinitroethylene evidently consists in the nature of the substituents in the diazo compounds. Due to the I - effect and the effect of p,π conjugation electron-acceptor groupings, viz., carboxy and carbonyl groups, promote delocalization of the negative charge of the carbon atom that bears the diazo group [40] and strengthening of the donor-acceptor C-N bond in the diazo fragment. An increase in the strength of this bond evidently leads to the following: the diazo group after the development of a new C-C bond in the reaction with the gem-dinitroethylene is not cleaved but rather is subsequently attached by the β-nitrogen atom to the nucleophilic carbon atom.

Cycloaddition using diazomethane and sym-trinitrobenzene is interesting [41-44]. The latter at -80°C adds successively three molecules of dinitromethane to give cyclic nitroalkene XIX, which reacts with a subsequent molecule of diazomethane to give the typical 1,3-cycloaddition product, viz., 3-nitro-Δ¹-pyrazoline XX.



Diazomethane evidently also reacts similarly with trinitrobenzene derivatives, viz., 2,4,6-trinitrotoluene, picryl chloride, picryl acetate, trinitroxylene, etc. [45].

Unconjugated nitroalkenes that contain hydrogen atoms in the α position react with excess diazomethane in THF to give the corresponding nitronic acid esters XXI in 28-35% yields [46, 47].

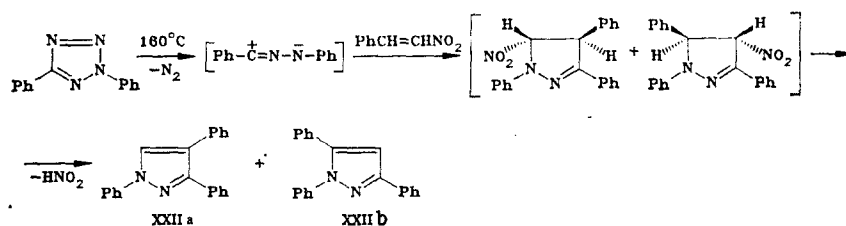


The above-presented reactions of unsaturated nitro compounds with diazo compounds are convenient preparative methods for obtaining various derivatives of pyrazoline, pyrazole, and cyclopropane. The reaction of conjugated nitroalkenes with diazo compounds proceeds in most cases via the synchronous multicenter mechanism that is characteristic for 1,3-dipolar cycloaddition [48]. The primary kinetic products of the reaction are probably Δ¹-pyrazolines, which undergo subsequent transformations. If a hydrogen atom and an aryl substituent are located in the 3 position of the pyrazoline ring, rearrangement to Δ²-pyrazolines - thermodynamically more stable compounds due to conjugation of the N(2) = C(3) bond with the phenyl ring - occurs [49]. In these cases one does not observe the formation of cyclopropane derivatives that is most characteristic for 3,3-disubstituted Δ¹-pyrazolines [50, 51]. The formation of pyrazoles due to the elimination of nitrous acid occurs if there is a hydrogen atom in the β position with respect to the nitro group of the intermediate Δ¹-pyrazolines.

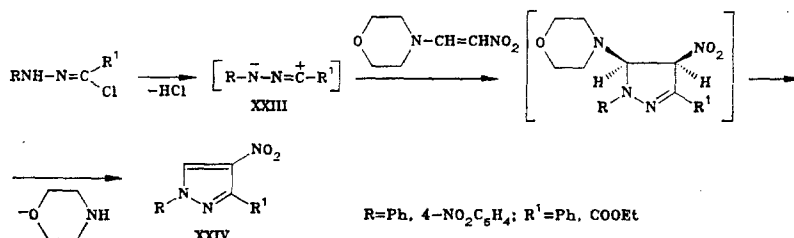
2. Reaction of Conjugated Nitroalkenes with Nitrileimines, Azomethineimines, and Azomethine Ylids

Nitrileimines undergo 1,3-dipolar cycloaddition with alkenes to give five-membered heterocyclic systems similar to those that are formed in reactions with diazo compounds [10, 48]. With the exception of isodiazomethane, nitrileimines are unstable, and cycloaddition with their participation is therefore usually carried out in situ.

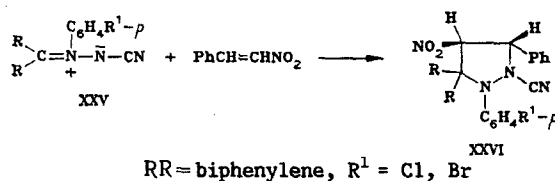
It has been shown that a mixture of regioisomeric triphenylpyrazoles XXIIa, b in a ratio of 1:2 is formed in high yield as a result of the reaction of β -nitrostyrene with 1,3-diphenylnitrileimine (obtained by thermolysis of 2,5-diphenyl-tetrazole) [52, 53]. 4-Nitro- and 5-nitro- Δ^2 -pyrazolines, which undergo dehydronitration to the corresponding pyrazoles, are evidently intermediates in this reaction.



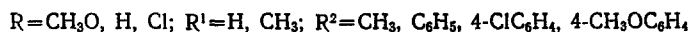
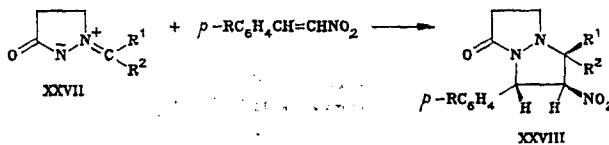
The reaction of 2-morpholino-1-nitroethylene with nitrileimines XXIII (generated by dehydrochlorination of the corresponding chlorohydrazones) occurs regioselectively with the formation of 4-nitro-1,3-disubstituted pyrazoles XXIV as a result of the elimination of morpholine from the intermediate 4-nitro-5-morpholino- Δ^2 -pyrazolines; however, the yields of the pyrazoles do not exceed 20% [54].



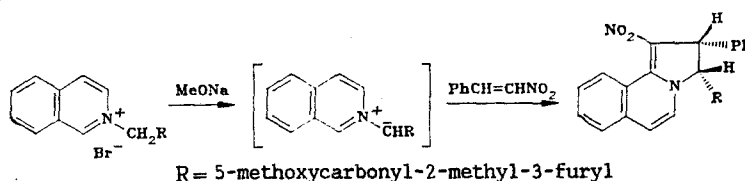
Azomethineimines are included among the most active of the known 1,3-dipoles [48]. 4-Nitropyrazolines XXVI were isolated in quantitative yields in the reaction (CH_2Cl_2 , 40°C, 130 h) of β -nitrostyrene with azomethineimines XXV [55].



Under similar conditions the cycloaddition of azomethineimines XXVII to β -nitrostyrene and its *p*-substituted derivatives leads to adducts XXVIII [55].



Let us note that products XXVI and XXVIII have structures that are predicted taking into account the electronic effects of the substituents; this means that the nucleophilic nitrogen atom of 1,3-dipoles XXV and XXVII is attached by the electrophilic β -carbon atom of the dipolarophile.

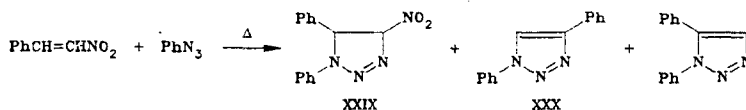


An azomethine ylid, which, as a 1,3-dipole, undergoes cycloaddition with β -nitrostyrene, is formed when a 1-R-substituted isoquinolinium bromide is treated with sodium methoxide [56]. As a result, 1-nitro-2-phenyl-3-R-2,3-dihydrobenzo[g]indolizine is obtained in 14% yield.

At present, this is the only example of the reaction of azomethine ylids with nitroalkenes.

3. Reaction of Nitroalkenes with Organic Azides

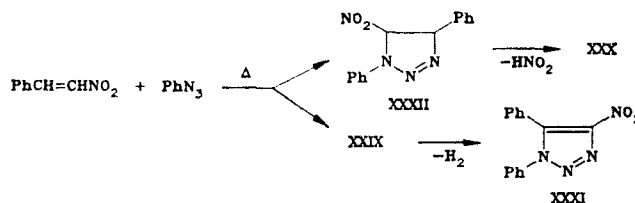
β -Nitrosytyrene reacts with phenyl azide at 20°C in the course of several weeks to give a cycloadduct (15% yield), to which the 4-nitro-1,5-diphenyl- Δ^2 -1,2,3-triazoline structure (XXIX) was assigned [57]. In addition to adduct XXIX (20% yield), 1,4-diphenyl-1,2,3-triazole (XXX) (40%) and a small amount of 1,5-diphenyl-1,2,3-triazole were obtained when β -nitrostyrene was refluxed (for 17 h) with phenyl azide in toluene.



However, there is some doubt regarding the formation of a significant amount of adduct XXIX under these conditions, since it is known [58-60] that nitro- Δ^2 -1,2,3-triazolines upon heating should readily undergo dehydronitration to give the corresponding 1,2,3-triazoles.

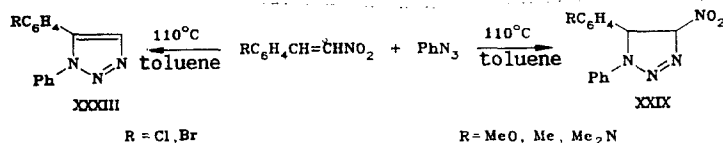
It has been reported [61] that in 1-propanol or DMF (100°C, 9 h) the indicated reaction proceeds regioselectively with the formation of only adduct XXIX; however, its yield did not exceed 9-11%.

The final products of the reaction of β -nitrostyrene with phenyl azide when they are refluxed in cyclohexane for 156 h are 1,2,3-triazole XXX and 4-nitro-1,5-diphenyl-1,2,3-triazole (XXXI) [59]. These compounds are formed from the primary cycloaddition products - 1,2,3-triazoline XXXII and Δ^2 -1,2,3-triazoline XXIX - as a result of dehydronitration and dehydrogenation, which are realized under the reaction conditions.

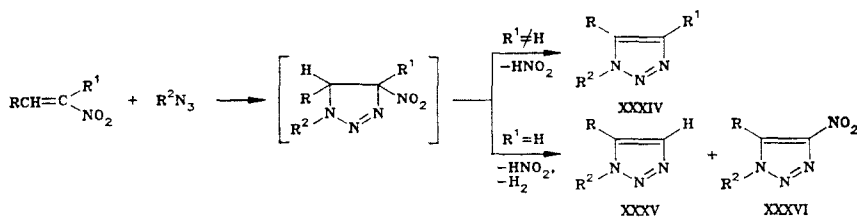


4-Nitro-1,2,3-triazole XXXI was obtained in 37% yield in the reaction of phenyl azide with β -bromo- β -nitrostyrene as a result of spontaneous elimination of HBr from the intermediate Δ^2 -1,2,3-triazoline [57].

According to the data in [57], the products of the reaction of R-substituted β -nitrostyrenes with phenyl azide are, depending on the nature of the substituent, either 1,5-diaryl-1,2,3-triazoles XXXIII (where R is an electron-acceptor substituent) or 4-nitro- Δ^2 -1,2,3-triazolines XXIX (where R is an electron-donor substituent).

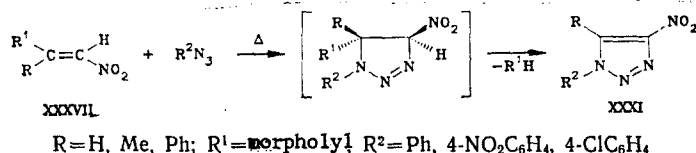


When α -substituted nitroalkenes are subjected to reaction with organic azides, cycloaddition proceeds regioselectively with the formation of only one regioisomer - 1,4,5-trisubstituted 1,2,3-triazole XXXIV [60]. The use of nitroalkenes that contain a hydrogen atom in the α position ($\text{R}^1 = \text{H}$) leads to 4-nitro-1,5-disubstituted 1,2,3-triazoles XXXV and 1,5-disubstituted 1,2,3-triazoles XXXVI.



R = H, alkyl, aryl; $\text{R}^1 = \text{H, alkyl, CN, COOEt}$; $\text{R}^2 = \text{aryl}$

Heating (60-100°C) β -morpholinonitroethylenes XXXVII with aromatic azides leads only to 4-nitro-1,2,3-triazoles XXXI in 30-47% yields, i.e., in this case the reaction proceeds strictly regioselectively with splitting out of a molecule of morpholine from the intermediate 4-nitro-5-morpholino-1,5-disubstituted Δ^2 -1,2,3-triazolines.



The reaction of aryl azides with β,β -diaminonitroethylenes XXXVII ($R = R_1 = \text{morpholyl}$, piperidyl, pyrrolidinyl) proceeds similarly [64].

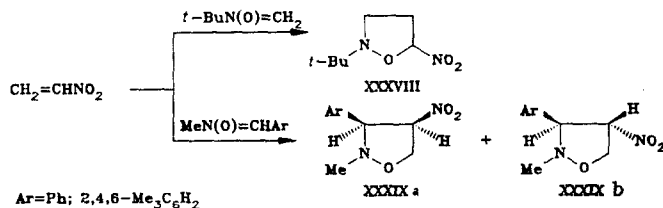
Maiorana and coworkers [62, 63] synthesized 4-nitro-5-substituted 1,2,3-triazoles in 13-56% yields by refluxing equimolar amounts of nitroalkenes XXXVII and p-tosyl azide in alcohol as a result of the elimination of morpholine p-tosylate.

It is recommended that the reaction of 3-nitro, 4-nitro, and 3,5-dinitrophenyl azides with nitroalkenes XXXVII ($R = H$) be carried out in the dark by refluxing in alcohol for 5-7 days [65]; the yields of triazoles XXXI ($R = H$) range from 56% to 75%.

The corresponding triazoles are also formed in the reaction of sodium azide with nitroalkenes [66-74]. However, these reactions should be regarded as two-step intramolecular cyclization [66, 67, 73] while the reactions of nitroalkenes with organic azides are typical examples of intermolecular 1,3-dipolar cycloaddition.

4. Reaction of Nitroalkenes with Nitrones and Nitronic Acid Esters

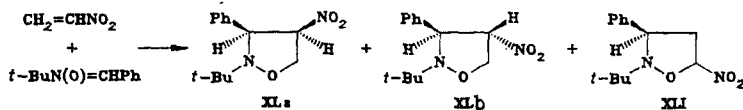
The 1,3-dipolar cycloaddition of nitroalkenes with nitrones leads to 4-nitro- and (or) 5-nitroisoxazolidines, which are regarded as promising synthones in the synthesis of penicillins and antibiotics of the cephalosporin group [75-77].



The unstable 5-nitro-2-tert-butylisoxazolidine (XXXVIII) is formed in the reaction of nitroethylene with N-tert-butyl-nitrone (25°C, CCl_4) [78, 79], while C-aryl-N-methylnitrones (60°C, CCl_4) give mixtures of stereoisomeric 2-methyl-3-aryl-4-nitroisoxazolidines XXXIXa, b in which cis isomer XXXIXa predominates.

The regiochemistry of these reactions is explained in [78, 79] from the position of the theory of boundary orbitals.

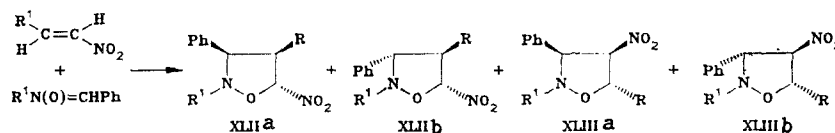
The cycloaddition of nitroethylene and C-phenyl-N-tert-butyl-nitrone leads to a mixture (2:1) of stereoisomeric 4-nitroisoxazolidines XLa, b, the yield of which is 50%; however, regioisomeric 5-nitroisoxazolidines XLI with an undetermined configuration are also formed in 24% yield [80].



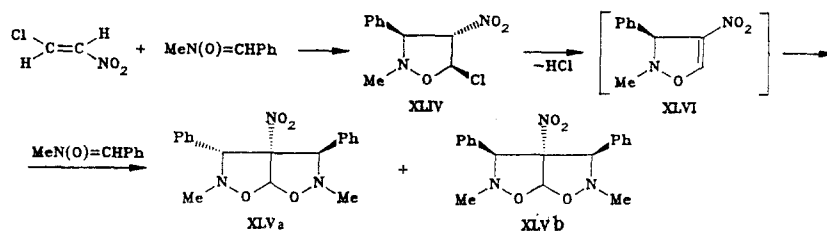
The regiochemistry and stereochemistry of the reactions of β -substituted trans-nitroethylenes with C-phenylnitrones have been investigated in rather great detail [76, 80]. It was established that mixtures of cis- (XLIa) and trans-3-phenyl- R^1 -5-nitroisoxazolidines (XLIb), as well as the regioisomeric cis- (XLIIa) and trans-3-phenyl-4-nitro-5- R^1 -nitroisoxazolidines (XLIIb), the compositions of which depend substantially on the structures of the starting reagents, are formed as a result of the reaction of trans- β -nitroacrylonitrile and methyl trans- β -nitroacrylate with C-phenyl-R-N-nitrones (Table 1).

TABLE 1. Compositions of the Products of the Reaction of trans- β -Nitroacrylic Acid Derivatives with C-Phenyl-N-R₁-nitrones [76, 80]

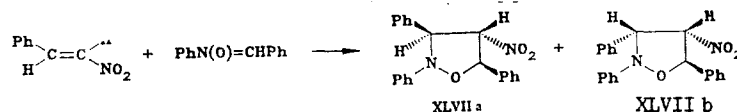
R	R ¹	Yields of adducts, %			
		XLIIa	XLIIb	XLIIIa	XLIIIb
CN	Me	56	17	27	—
CN	<i>t</i> -Bu	—	57	43	—
COOMe	Me	25	15	30	30
COOMe	<i>t</i> -Bu	13	13	45	5



The reaction of trans- β -chloronitroethylene with C-phenyl-N-methylnitron (benzene, 25°C, 18 h) proceeds peculiarly; in addition to the expected cycloaddition product, viz., trans-5-chloro-4-nitro-2-methyl-3-phenylisoxazolidine (XLIV) (41%), trans- (XLVa) (20%) and cis-4,6-diphenyl-3,7-dimethyl-5-nitro-3,7-diaza-2,8-dioxabicyclo[3.3.0]octane (XLVb) (15%) were also isolated [80]. The formation of diastereomeric bis-adducts XLVa, b evidently occurs as a result of cycloaddition of the starting nitron to the intermediate Δ^4 -isoxazoline XLVI — the product of dehydrochlorination of XLIV.

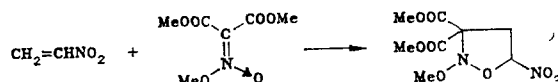


A mixture (6:1) of stereoisomeric 4-nitro-2,3,5-triphenylisoxazolidines XLVIIa, b is formed when equimolar amounts of β -nitrostyrene and C,N-diphenylnitron are refluxed in benzene [84]. Tartakovskii [84] notes that under similar conditions β -nitrostyrene reacts with C-benzoyl-N-phenylnitron to give only one cycloadduct — trans-3-benzoyl-4-nitro-2,5-diphenylisoxazolidine — in quantitative yield.

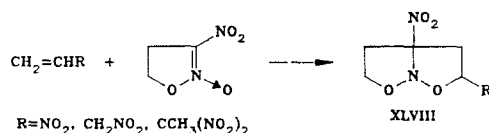


In the nineteen sixties Tartakovskii and Novikov discovered the 1,3-dipolar cycloaddition of nitronic acid esters to alkenes, which leads to the formation of isoxazoline or isoxazolidine derivatives [82-84]. Nitroalkenes can also be used as the dipolarophiles in reactions of this type [85, 86].

For example, 2-methoxy-3,3-dimethoxycarbonyl-5-nitro-isoxazolidine was synthesized in 22% yield in the reaction of dimethylnitromalonate O-methyl ester with excess nitroethylene [85].



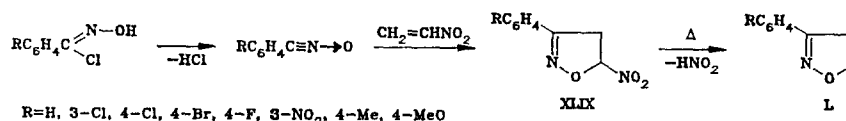
It has been shown [86] that the reaction of 3-nitroisoxazoline N-oxide (which is formally a cyclic O-alkyl ester of a nitronic acid) with excess conjugated or unconjugated nitroalkene proceeds regiospecifically with the formation of 3-substituted 5-nitro-1-aza-2,8-dioxabicyclo[3.3.0]octanes XLVIII, the yields of which range from 41% to 60%.



5. Reaction of Nitroalkenes with Nitrile N-Oxides

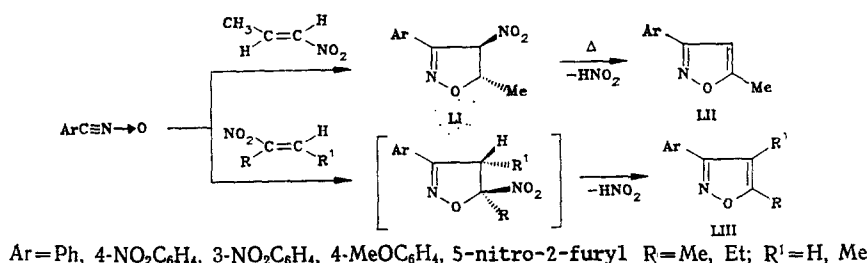
In these reactions primarily N-oxides of aromatic and heterocyclic nitriles have been used as 1,3-dipoles, and conjugated and unconjugated nitroalkenes have been used as dipolarophiles. An analysis of the available data on the cycloaddition of N-oxides of aromatic nitriles to conjugated nitroalkenes provides evidence that the structural specificity of the cycloaddition of the indicated reactions depends on the nature of the starting nitroalkene

The reaction of aromatic nitrile N-oxides *in situ* with excess nitroethylene in ether (20°C, 12 h) leads to 3-aryl-5-nitro- Δ^2 -isoxazolines XLIX (86-92% yields), which are readily converted to 3-arylisoxazoles L on refluxing in toluene [87-89].

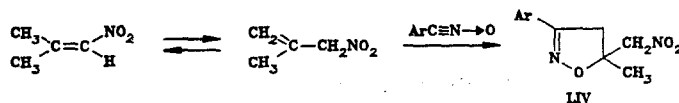


Quantum-chemical calculations and kinetic studies have shown that the reactivities of N-oxides in reactions with nitroethylene vary as a function of the nature of the substituent in the benzene ring in the following order: MeO > Me > H > F > Cl = Br > NO₂ [90].

trans-5-Methyl-4-nitro-3-aryl- Δ^2 -isoxazolines LI, which give the corresponding 5-methyl-3-arylisoxazoles LII on prolonged refluxing in xylene, are formed in 63-68% yields as a result of the reactions of aromatic nitrile N-oxides with trans-1-nitro-1-propene under similar conditions [88]. 5-Alkyl-4-R-3-arylisoxazoles LIII, which are formed as a result of spontaneous dehydronitration of the primary cycloaddition products – the corresponding 5-alkyl-5-nitro- Δ^2 -isoxazolines – were isolated in 30-67% yields in the reaction of N-oxides with 2-nitro-1-propene, 2-nitro-1-butene, and 2-nitro-2-butene [88,91].

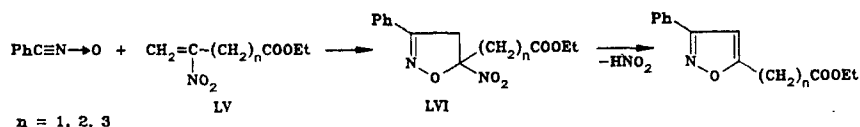


The reaction of nitrile N-oxides with 1-nitro-2-methyl-1-propene proceeds in an unusual way: instead of the expected cycloaddition products, viz., 5,5-dimethyl-4-nitro-3-aryl- Δ^2 -isoxazolines, 5-methyl-5-nitromethyl-3-aryl- Δ^3 -isoxazolines LIV were isolated in ~20% yield [88]. The starting alkene evidently undergoes isomerization during the reaction to 3-nitro-2-methyl-1-propene, in which the double bond is less shielded and which therefore reacts considerably more readily with nitrile N-oxides.

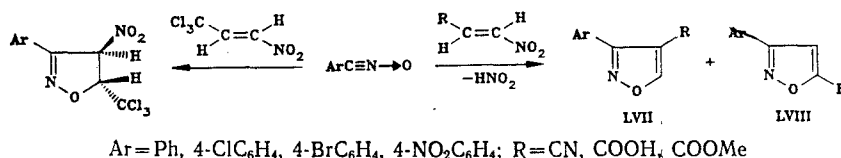


5-Nitro-3-phenylisoxazole was obtained in 44-48% yield as a result of the reaction of equimolar amounts of benzonitrile N-oxide with 1-chloro- or 1-bromo-1-nitroethylene in ether (20°C, 12 h) [91]; at the same time, mixtures of two regioisomers – 5-nitro-3-arylisoxazole and a 4-nitro-3-arylisoxazole – are formed in quantitative yields in the reaction of nitrile N-oxides with excess trans-2-chloro-1-nitroethylene [92]. However, in [15] it was noted that in the latter case only 5-nitro-3-phenylisoxazole was obtained in 55% yield. The formation of nitroisoxazoles in these reactions can be explained as follows: the primary cycloaddition products – halonitro- Δ^2 -isoxazolines – eliminate a molecule of hydrogen halide more readily than a molecule of HNO₂.

Benzonitrile N-oxide reacts with α -substituted nitroethylenes of the LV type at 0°C in ether to give cycloadducts LVI, which at temperatures above 20°C undergo spontaneous conversion to 3,5-disubstituted isoxazoles [93].

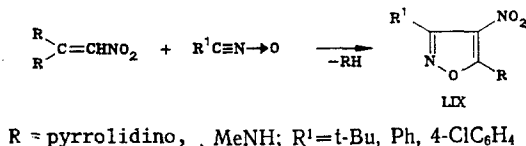


The regiochemistry and stereochemistry of the cycloaddition of aromatic nitrile N-oxides to some trans- β -substituted nitroethylenes, which are introduced into the reaction in a twofold excess, have been studied in detail [92, 94, 95]. It was established that trans-3,3,3-trichloro-1-nitro-1-propene gives only one stable regioisomer - trans-4-nitro-5-trichloromethyl-3-aryl- Δ^2 -isoxazoline - in 58-68% yield. Mixtures of regioisomeric isoxazoles, viz., LVII and LVIII, in which regioisomer LVII predominates, are formed as the principal products in 63-70% yields from trans- β -nitroacrylonitrile, trans- β -nitroacrylic acid, and methyl trans- β -nitroacrylate.

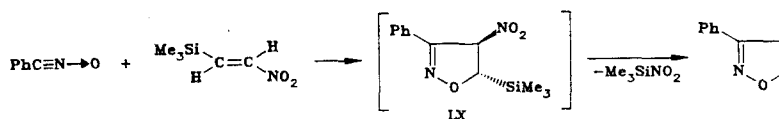


In addition to regioisomers LVII and LVIII, 5-methoxycarbonyl-4-nitro-3-arylisoxazoles, the yields of which range from 10% to 28%, are also formed in the reaction of equimolar amounts of the nitrile N-oxide and methyl trans- β -nitroacrylate in DMF, ether (20°C), or THF (5°C) [92, 95].

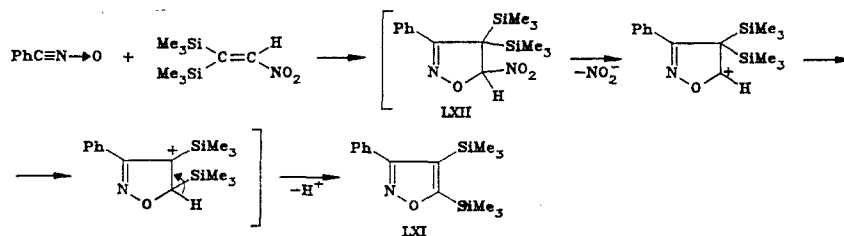
N-Substituted β,β -diaminonitroethylenes react with nitrile N-oxides to give 5-amino-4-nitro-3-R-isoxazoles LIX, the yields of which, however, do not exceed 12-25% [96].



The reaction of benzonitrile N-oxide with trans-2-(trimethylsilyl)-1-nitroethylene (CCl_4 , 0°C) gave 3-phenylisoxazole (27% yield), which is formed as a result of anti-elimination of trimethylnitrosilane from intermediate cycloadduct LX [97, 98].



At the same time β -bis(trimethylsilyl)nitroethylene under similar conditions gives 4,5-bis(trimethylsilyl)-3-phenylisoxazole (LXI) in 70% yield [97, 98]. Padwa and MacDonald [97, 98] explain the formation of LXI by elimination of the NO_2^- anion from primary cycloadduct LXII with subsequent 1,2 migration of the Me_3Si grouping and elimination of a proton.



3-Aryl-5-phenylisoxazoles, which are formed as a result of the elimination of HNO_2 from the intermediate 3-aryl-5-nitro-5-phenyl- Δ^2 -isoxazolines, were synthesized in 36-51% yields by the reaction of aromatic nitrile N-oxides with α -nitrostyrene in ether at 0-10°C [99].

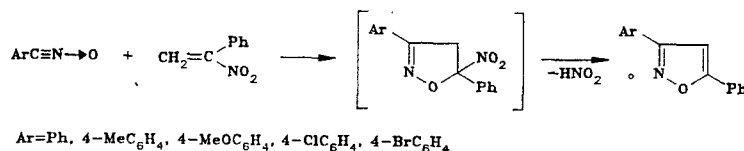


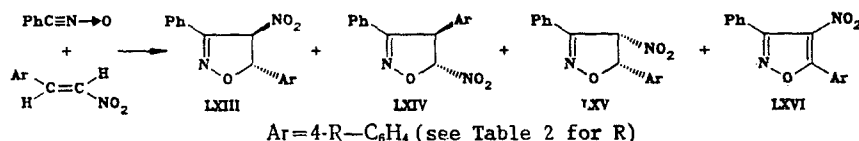
TABLE 2. Compositions of the Products of the Reaction of Benzonitrile N-Oxide with trans- β -Nitrostyrenes [103, 104]

R	Yields of adducts, %			
	LXII	LXIV	LXV	LXVI
H	47	23	3	—
CH ₃	54	19	—	—
Cl	34	16	11	10
Br	36	17	12	7

The regioselectivity of this reaction was explained from the position of boundary orbital theory.

A number of communications regarding the cycloaddition of aromatic nitrile N-oxides to β -nitrostyrenes have been published [92, 94, 100-105].

The regiochemistry and stereochemistry of the cycloaddition of benzonitrile N-oxide to various trans- β -nitrostyrenes have been investigated in detail [94, 103-105]. It was established that the composition of the reaction products depends on the nature of the substituent in the ring of the β -nitrostyrene (Table 2). The primary cycloaddition products are, however, regioisomeric trans-5-aryl-4-nitro-3-phenyl- (LXIII) and trans-4-aryl-5-nitro-3-phenyl- Δ^2 -isoxazolines (LXIV), in addition to which cis-5-aryl-4-nitro-3-phenyl- Δ^2 -isoxazolines LXV and 5-aryl-4-nitro-3-phenylisoxazoles LXVI were isolated in some cases. The latter are formed as a result of epimerization and oxidation of regioisomers LXIII [103, 106].



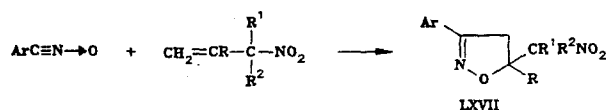
In the investigated cases 4-nitro- Δ^2 -isoxazolines LXIII were formed in the greatest amounts. This is evidently associated with the fact that the approach of the 1,3-dipole to the C=C bond of the dipolarophile in the transition state, which leads to the formation of 5-nitro- Δ^2 -isoxazoline LXIV, is sterically more hindered than in the formation of LXIII. On refluxing in xylene or butylbenzene nitro- Δ^2 -isoxazolines LXIII-LXV give 3,5-diaryl- and 3,4-diarylisoxazoles in good yields as a result of the elimination of HNO₂ [92, 103, 107].

A study of the kinetics of cycloaddition showed that the reactivities of β -nitrostyrenes in the reaction with benzonitrile N-oxide increase with an increase in the Hammett σ constant of the substituent in the phenyl ring of the alkene [104].

The reaction of α -nitrostilbene with benzonitrile N-oxide in ether at 20°C leads directly to a dehydronitration product - 3,4,5-triphenylisoxazole [100].

3-Aryl-4-nitro-5-(3-indolyl)- Δ^2 -isoxazolines were synthesized in 44-53% yields as a result of the cycloaddition of β -(3-indolyl)nitroethylene to aromatic nitrile N-oxides [108].

Δ^2 -Isioxazolines LXVII, which contain nitroalkyl fragments in the 5 position, were obtained in high yields by the reaction of aromatic nitrile N-oxides with unconjugated nitroalkenes [86, 109-111].

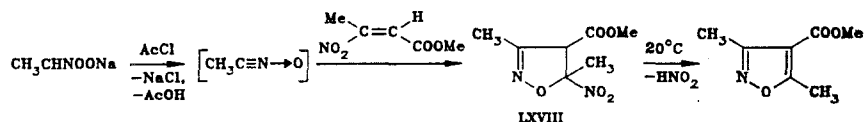


R = R¹ = R² = H; R = Me, R¹ = R² = H; R = H, R¹ = Me, R² = NO₂; Ar = Ph, 3-NO₂- and 4-NO₂-C₆H₄, 4-MeOC₆H₄, 4-F, 4-Cl- and 4-BrC₆H₄, 5-nitro-2-furyl

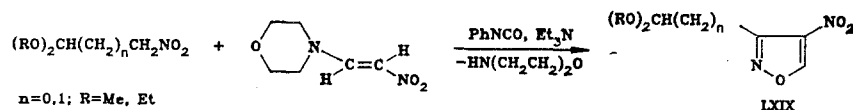
A study of the kinetics of the reaction of p- and m-substituted benzonitrile N-oxides with 3-nitro-1-propene showed that the reactivities of the N-oxides decrease with an increase in the Hammett σ constant of the substituent in the phenyl ring of the N-oxide [112].

Information regarding 1,3-dipolar cycloaddition reactions of conjugated and unconjugated nitroalkenes with aliphatic nitrile N-oxides is available [113, 114]. The latter are usually generated from primary nitro compounds by the action of phenyl isocyanate in the presence of triethylamine or other reagents (POCl_3 , AcCl , BzCl , Ac_2O , etc.) and are introduced in situ into the reaction with the dipolarophiles [115].

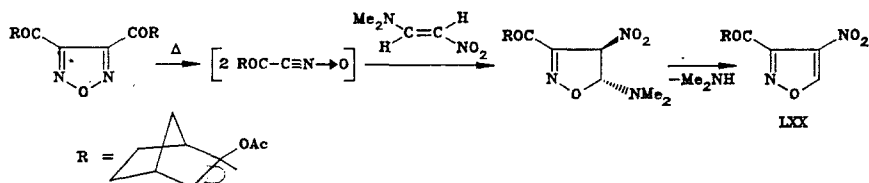
For example, the cycloaddition of acetonitrile N-oxide generated by treatment of the Na salt of the anti form of nitroethane with acetyl chloride to methyl β -nitrocrotonate gives the unstable 5-nitro- Δ^2 -isoxazoline LXVIII (in low yield), which, after standing at 20°C for 7 weeks, is converted to 3,5-dimethyl-4-methoxycarbonylisoxazole [113].



A method for obtaining 3-formyl- and 3-formylmethyl-4-nitroisoxazole acetals LXIX from nitroacetaldehyde or β -nitropropanal acetals, trans- β -morpholinoethylene, and phenyl isocyanate was recently described [114]. Nitroisoxazoles LXIX are formed in high yields after brief refluxing of the reagents in benzene in the presence of triethylamine.



In 1980 it was shown [116] that upon thermolysis diacylfuroxanes are converted to α -keto nitrile N-oxides, which in situ give cycloadducts with various dipolarophiles. Brittelli and Boswell [116] used this method to obtain 4-nitro-3-(2-acetoxy-2-bornylcarbonyl)-isoxazole (LXX), which is formed in 50% yield by refluxing bis(2-acetoxy-2-bornylcarbonyl)-furoxane with excess trans- β -dimethylaminonitroethylene in toluene.



The material presented in this review provides evidence for the extensive possibilities of the use of conjugated and unconjugated nitroalkenes as dipolarophiles in 1,3-dipolar cycloaddition for the preparative synthesis of various five-membered heterocycles. In some cases nitroalkenes can also serve as the source of 1,3-dipoles; this significantly expands the synthetic possibilities of compounds of this type [117-121]. Reactions involving the intramolecular 1,3-dipolar cycloaddition of unconjugated nitroalkenes [119] and reactions using nitroalkenes as heteroanalogs of conjugated dienes [8, 122-124], which open up possibilities for the synthesis of more complex heterocyclic structures, are also of definite theoretical and practical interest. The indicated aspects seem to us to be extremely promising directions in modern organic synthesis.

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SYNTHESIS AND PROPERTIES OF 5-PHENYLETHYNYLFURAN-2-ALDEHYDE

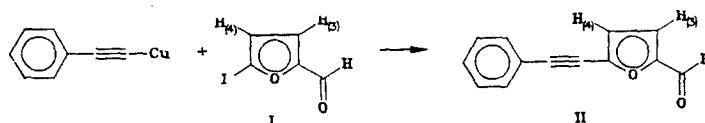
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Phenylethynylation of 5-halofurfurals gives 5-phenylethynylfuran-2-aldehyde which can be converted into the corresponding acid and several of its derivatives with retention of the triple bond.

5-Phenylethynylfuran-2-aldehyde was prepared in 1966 [1, 2] in 64% yield by the reaction of 5-iodofurfural with copper phenylacetylide in boiling pyridine (4 h); there is however only one publication relating to its derivatives [3].

The object of the present work was to select conditions which would provide an increased yield of the aldehyde II and to study its reactions involving the aldehyde group and the triple bond.



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