Synthesis of Heterocyclic Compounds with the Aid of Nitrile Oxides

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A number of recent preparative improvements have made nitrile oxides, $R{-}C{\equiv}N{\rightarrow}O$, easily accessible starting materials for the synthesis of a wide variety of heterocyclic systems, some of them almost inaccessible by any other route. The vast majority of the reactions discussed in this review are 1,3-dipolar cycloadditions leading to five-membered rings. The survey concludes with a selected number of reactions which do not fall under the above classification, but which are considered to be of preparative interest.

In jüngerer Zeit haben eine Anzahl verbesserter Verfahren zur Gewinnung von Nitriloxiden, $R{-}C{\equiv}N{\rightarrow}O$, diese Stoffklasse zu einem leicht zugänglichen Ausgangsmaterial für die Synthese einer größeren Zahl heterocyclischer Systeme gemacht. Einige der so erhältlichen Heterocyclen können auf andere Weise nur unter großen Schwierigkeiten hergestellt werden. Die meisten der in dieser Übersicht abgehandelten Reaktionen sind 1,3-dipolare Cycloadditionen, die fünfgliedrige Heterocyclen ergeben. Am Schluß des Artikels werden einige präparativ interessante Nitriloxid-Reaktionen anderen Typs besprochen.

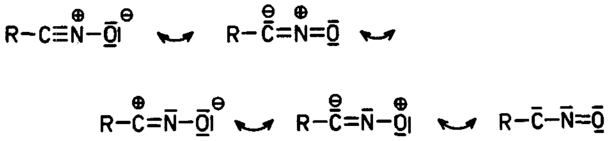
Although nitrile oxides have been known since the turn of the century[1]–and the parent compound, fulminic acid, since the dawn of organic chemistry–very little synthetic use of these extremely reactive compounds was made until 1946, when Quilico[2] began to study the formation of 1,2-oxazoles from nitrile oxides (including fulminic acid) and unsaturated compounds. This type of reaction was much later classified by Huisgen[3,4] as a typical 1,3-dipolar cycloaddition, and was shown to occur not only with olefins and acetylenes, but also with many other types of unsaturated systems; challenging synthetic possibilities for the synthesis of heterocyclic systems heretofore often almost inaccessible were opened[5].

Another important factor in the promotion of nitrile oxides as tools in organic synthesis was the simultaneous development of several methods for the *in situ* generation of the (generally very unstable) nitrile oxides in the presence of the desired acceptor. A further spur to the synthetic use of nitrile oxides was the discovery that these compounds can be stabilized by use of a controlled degree of steric hindrance; this does not affect the general reactivity, but supresses the tendency to spontaneously dimerize to furoxans (1,2,5-oxadiazole-1-oxides)[7]:

(*1*)

This article contains a survey of recent and as yet unreviewed procedures[6,7] for the preparation or *in situ* generation of nitrile oxides, followed by a discussion of the synthesis of (mainly five-membered) heterocyclic compounds by 1,3-dipolar cycloaddition reactions. Finally, some other reactions of nitrile oxides which are also considered to provide interesting synthetic routes to various heterocyclic systems are covered.

Nitrile oxides may only be correctly represented as a resonance hybrid of the following structures:



$$R-C\equiv\overset{\oplus}{N}-\overline{\underline{O}}|^{\ominus} \leftrightarrow R-\overset{\ominus}{\underline{C}}=\overset{\oplus}{N}=\underline{O} \leftrightarrow R-\overset{\oplus}{C}=\overline{N}-\overline{\underline{O}}|^{\ominus} \leftrightarrow R-\overset{\ominus}{\underline{C}}=\overline{N}-\overset{\oplus}{\underline{O}}| \leftrightarrow R-\overline{C}-\overline{N}=\underline{\overline{O}}$$

For the sake of brevity, in this article the abbreviation

$R{-}C{\equiv}N{\rightarrow}O$

will be used whenever practical.

1. Preparation of Nitrile Oxides

In this section, only such methods and improvements of older methods will be considered which were published after the literature deadline [C.A. **60**, (1967)] of the corresponding chapter in HOUBEN-WEYL[7], to which implicit reference is made throughout the article.

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[1] A. WERNER, H. BUSS, Chem. Ber. **27**, 2193 (1894). H. WIELAND, Chem. Ber. **40**, 1667 (1907).

[2] A. QUILICO, G. SPERONI, Gazz. Chim. Ital. **76**, 148 (1946).

[3] R. HUISGEN, Proc. Chem. Soc. **1961**, 577.

[4] R. HUISGEN, Angew. Chem. **75**, 604, 742 (1963).

[5] For comprehensive reviews of the chemistry of nitrile oxides, see: C. GRUNDMANN, Fortschr. Chem. Forsch. **7**, 62 (1966).
C. GRUNDMANN, *Nitrile Oxides* in: *The Chemistry of the Cyano Group*, Z. RAPPOPORT, editor, Interscience Publishers, London, 1970.
C. GRUNDMANN, P. GRÜNANGER, *Nitrile Oxides*, Springer Verlag, New York · Heidelberg, in press.

[6] C. GRUNDMANN, *The Chemistry of Nitrile Oxides*, Fortschr. Chem. Forsch. **7**, 62 (1966).

1.1. Isolation of Nitrile Oxides

Unless special reasons require isolation of these compounds prior to use, it is recommended to attempt isolation only in cases in which the nitrile oxide is stabilized by the presence of bulky groups near the nitrile oxide group.

The use of N-bromosuccinimide (NBS) in dimethylformamide (DMF) in the presence of sodium methoxide or triethylamine as base to dehydrogenate sterically hindered aldoximes to nitrile oxides is an improvement over the procedure involving an alkali metal hypobromite as active reagent[8,9]. Especially in the preparation of aliphatic and bifunctional nitrile oxides and of nitrile oxides possessing a methoxy group or a basic nitrogen function such as a heterocyclic nitrogen atom or a tertiary amine, the former procedure is the method of choice.

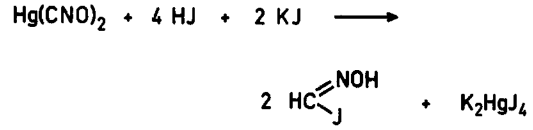
Dehydrogenation of Aldoximes to Nitrile Oxides[8]**:** To a solution or suspension of the aldoxime (5 mmol) in dimethylformamide (8–15 ml) is added sodium methoxide (5 mmol for each oxime group). The reaction mixture is cooled to 10–15° and a solution of N-bromosuccinimide in dimethylformamide (5 mmol for each oxime group in 5 ml DMF) is added with vigorous stirring over 10–15 min. If triethylamine is used as base, the NBS solution is first added to the solution or suspension of the aldoxime, and the solution of triethylamine in dimethylformamide (5 mmol for each oxime group in 5 ml of DMF) over 5 min. To complete the reaction, stirring is continued for an additional 30 min. The reaction mixture is then diluted with ice-water and, in the preparation of crystalline nitrile oxides, kept at 0° for several hours. The crude solid is washed thoroughly with ice-cold water. After one recrystallization from an appropriate solvent, the product is analytically pure. Liquid nitrile oxides are extracted with petroleum ether immediately after the dilution of the reaction mixture with water; the organic layer is washed several times with ice-cold water and then dried over sodium sulfate. Nitrile oxides boiling below 70° at reduced pressures can usually be distilled[9]. The yields are generally 70–80%.

In addition to the reagents so far recommended for the dehydrogenation of oximes, lead tetraacetate may be used[10,11]. In this case, only *syn*-oximes lead to nitrile oxides, the reaction has to be carried out at an initial temperature of $-78°$, and the acetic acid generated neutralized with a suitable base, e.g., pyridine or triethylamine. This modification seems to offer little advantage, except for the possibility of operating at very low temperatures which might make the procedure suitable for the generation of very unstable (aliphatic) nitrile oxides.

2,4,6-Trimethylbenzonitrile Oxide (Mesitonitrile Oxide)[10]**:** A cold solution of lead tetraacetate (3.46 g, 7.8 mmol) in dichloromethane (30 ml) is added with stirring to a cooled ($-78°$) solution of 2,4,6-trimethylbenzaldoxime (1.4 g, 7.0 mmol, 89% *syn*-oxime) in dichloromethane (30 ml). The cold bath is then removed and the reaction mixture allowed to come to 0°. Ether (20 ml) is added and the mixture stirred for another 5 min. The resultant suspension is transferred with ether (100 ml) into a separatory funnel and washed successively with ice-cold water (25 ml) and an ice-cold saturated solution of sodium bicarbonate (4 x 5 ml). The organic layer is dried over magnesium sulfate and concentrated to ~1/2 of its original volume using a stream of dry nitrogen at 0°. At this point, a by-product has separated; it is removed by filtration (80 mg). The rest of the solvent is evaporated from the filtrate in the same manner as above; colorless needles are thus obtained (978 mg). After one recrystallization from aqueous methanol, the pure nitrile oxide is obtained; yield: 900 mg (73% based on *syn*-oxime); m.p. 111.5–112°.

1.2. Generation of Nitrile Oxides *in situ*

The preparation of fulminic acid (formonitrile oxide), $HC{\equiv}N{\rightarrow}O$, usually first involves the synthesis of its mercury or silver salt[12]. Because of their complex character (both salts actually contain the anion $[M(CNO)_2]$, M = Ag or Hg), these compounds are not suitable starting materials for most organic syntheses involving fulminic acid. For this purpose, the silver or mercury salts must be converted into the sodium salt by treatment with sodium amalgam. However, sodium fulminate is not a stable compound; in the solid state, it is very explosive and quickly decomposes. Even in dilute aqueous solution, it decomposes rapidly. Thus, the salt must be used immediately after its preparation. These inconveniences may be avoided by *in situ* generation of fulminic acid. For this purpose, mercury fulminate is first converted into iodoformoxime (formic acid iodide oxime) using hydroiodic acid/potassium iodide:



(2)

$$Hg(CNO)_2 + 4\,HJ + 2\,KJ \longrightarrow 2\,HC\begin{smallmatrix}\nearrow NOH\\ \searrow J\end{smallmatrix} + K_2HgJ_4$$

Iodoformoxime is a reasonably stable precursor for fulminic acid; upon treament with tertiary bases, e.g., triethylamine, in ether at 0°, the free acid is generated immediately[13].

Iodoformoxime from Mercury Fulminate[14,15]**:** Mercury fulminate, freshly prepared according to Beckmann[12,16] from mercury (40 g, 0.2 g-atom) is freed from the bulk of the water present by decantation. The slurry thus obtained (mercury fulminate can be handled in this form without danger of explosion) is added in portions to a well-stirred mixture of hydroiodic acid (56.7%; 105 ml, 0.8 mol) and potassium iodide (83 g, 0.5 mol) cooled to −40°. The reaction temperature must not exceed −30°. After 30 min., the mixture is allowed to warm to 0°, and the crystalline

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[7] C. Grundmann, *Methoden zur Herstellung und Umwandlung von Nitriloxiden*, in Houben-Weyl, Methoden der Organischen Chemie, 4th Ed., Eu. Müller, editor, Vol. X/3, p. 838–870, Georg Thieme Verlag, Stuttgart, 1965.

[8] C. Grundmann, R. Richter, J. Org. Chem. **33**, 476 (1968).

[9] C. Grundmann, S. K. Datta, J. Org. Chem. **34**, 2016 (1969).

[10] G. Just, K. Dahl, Tetrahedron Letters **1966**, 2411; Tetrahedron **24**, 5251 (1968).

[11] G. Just, W. Zehetner, Tetrahedron Letters **1967**, 3389.

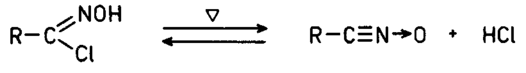
[12] P. Kurtz, *Methoden zur Herstellung und Umwandlung von Knallsäure*, in Houben-Weyl, *Methoden der Organischen Chemie*, 4th. Ed., Eu. Müller, editor, Vol. VIII, p. 355–358, Georg Thieme Verlag, Stuttgart, 1952.

slurry filtered. The moist crystals are transferred to a separatory funnel and dissolved in ether. The ethereal solution is washed with an ice-cold dilute solution of sodium thiosulfate, then twice with water, and dried over sodium sulfate at −25°. The solution thus prepared contains 30–40 g (42–57%) of iodoformoxime. The product is best stored in form of this solution at a temperature below −20°. The crystalline solid, obtained on evaporation of the ether at reduced pressure (water pump) at 10° (water bath) may deflagrate mildly if warmed to room temperature after a prolonged storage at −20°; m.p. 60–65° (with violent decomposition).

For each experiment, the approximate amount of the stock solution should be evaporated in the manner described above, the residue quickly weighed, and immediately redissolved in the required solvent.

A promising route for the *in situ* generation of nitrile oxides is based on the fact that the equilibrium between hydroximic acid chlorides and nitrile oxides plus hydrogen chloride (equation *3*) which, even at elevated temperatures, normally lies far to the left, can be shifted to the right by heating a solution or suspension of the hydroximic acid chloride in a solvent in which hydrogen chloride is virtually insoluble, e.g., toluene[17,18,19]:

(*3*)



$$R-C\overset{\nearrow NOH}{\underset{\searrow Cl}{}} \underset{\longleftarrow}{\xrightarrow{\nabla}} R-C\equiv N\rightarrow O + HCl$$

If this equilibration is carried out in the presence of a suitable acceptor, the nitrile oxide, which is only present at a very low stationary concentration, is immediately consumed; thus, the criteria for successful *in situ* reactions of sensitive nitrile oxides postulated by Huisgen[4,20–23] are met. An example of this reaction type is given in section 2.2.1.

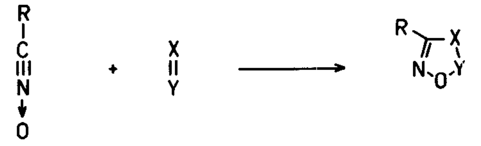
2. Heterocyclic Compounds from Nitrile Oxides by 1,3-Dipolar Cycloaddition

2.1. General

For a detailed discussion of the mechanism of 1,3-dipolar cycloaddition in general as well as in specific relation to nitrile oxides, reference is made to the literature[3,4,24,25]. Although this subject is still under discussion, the following conclusions may be drawn and are of particular interest to the chemist engaged in organic synthesis:

(1) The reaction proceeds according to the following scheme:

(*4*)



(2) The 1,3-dipolar cycloaddition is a concerted four-center reaction in which the unsaturated character of the dipolarophile X—Y is not lost sufficiently long enough to allow configurational rearrangement; thus, the reaction is strictly stereospecific, *cis*- and *trans*-olefins yield the corresponding adducts.

(3) The reaction is only moderately, if at all, influenced by solvent polarity. It generally proceeds without catalyst. In cases in which the double bond character of the dipolarophile is enhanced by bases (e.g., enoles[2,26]) the use of suitable bases, e.g. alkali alkoxides, is indicated. In other cases, the reactivity of the double bond in certain dipolarophiles, e.g., oximes, is increased by a Lewis acid catalyst, e.g., boron trifluoride. This effect is apparently due to an increase of charge separation[27–30]:

$$\overset{\delta+}{X}=\overset{\delta-}{Y}$$

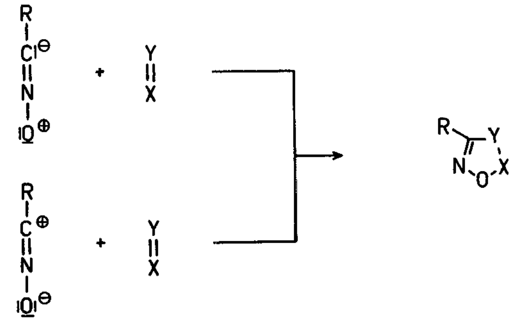
Examples of such catalyzed reactions are described in sections 2.2.2. and 3.

(4) Only a mild influence by either electron-withdrawing or electron-releasing substituents on the dipolarophile or on the nitrile oxide has been observed.

(5) Steric effects are apparently of far greater importance than electronic ones, especially with regard to the orientation of the dipolarophile towards the nitrile oxide in the cycloaddition reaction. Originally, only one orientation (as in equation *5*) was believed to play a role in the reaction, but more recent investigations[31] have demonstrated that in many cases in which X=Y represents an olefin or an acetylene the "inverse" addition product may also be ovserved (equation *6*):

(*5*)

(*6*)



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[13] R. Huisgen, M. Christl, Angew. Chem. **79**, 471 (1967); Angew. Chem., Internat. Ed. **6**, 456 (1967).

[14] R. Huisgen, M. Christl, private communication.

[15] M. Christl, Dissertation, Universität, München, 1969.

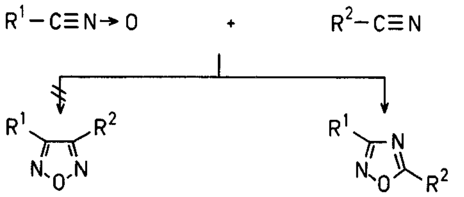
[16] E. Beckmann, Chem. Ber. **19**, 993 (1886).

[17] R. Lenaers, F. Eloy, Helv. Chim. Acta **46**, 1067 (1963).

[18] M. Arbasino, P. Grünanger, Ric. Sci., [A] **7**, 561 (1964) C.A. **63**, 6985 (1965).

Whether this effect arises from a reversal of the polarity of the nitrile oxide, from one of the dipolarophile, or possibly from the steric requirements of the four-center intermediate, which also may play an important role, is not yet completely clear.

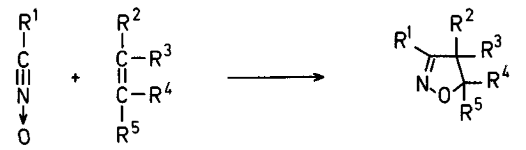
(6) Dipolarophiles containing hetero atoms are often less reactive in cycloaddition than the corresponding C=C unsaturated analogs. The orientation in this case is unambiguous and obeys the principle of maximum gain in σ-bond energy[4], viz. the reactants join in that direction that better allows compensation of the π-bond energy lost by the energy of the two new σ-bonds formed. Thus, the electronegative end of the heterodipolarophile becomes joined to the carbon atom of the nitrile oxide. For example, nitrile oxides and nitriles add to form 1,2,4-oxadiazoles and not 1,2,5-oxadiazoles (furazans):



2.2. 1,2-Oxazoles

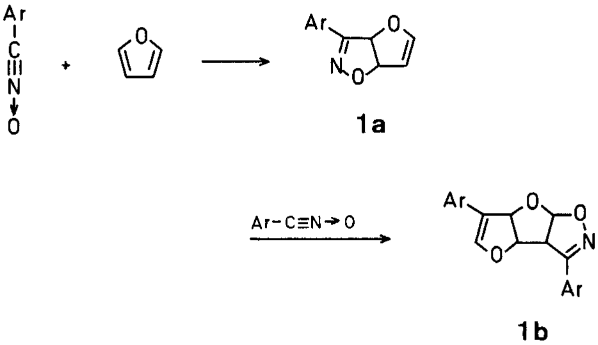
2.2.1. 4,5-Dihydro-1,2-oxazoles (Δ^2-Isoxazolines)

The title compounds are obtained by the addition of nitrile oxides to olefins:

(7)


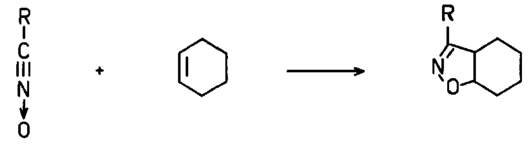
$$R^1-C\equiv N\rightarrow O + R^2(R^5)C=C(R^3)(R^4) \longrightarrow$$

The reaction proceeds smoothly and usually with good to excellent yields at room temperature or below, and is the most general method of preparation of 4,5-dihydro-1,2-oxazoles. Indeed, benzonitrile oxide has been suggested as a suitable reagent for the identification of olefinic compounds[32]. At present, more than 800 1,2-oxazolines obtained by this reaction have been reported in the literature[33]. Thus, it is best to describe the limitations of the reaction. The rate of reaction of an olefinic double bond decreases dramatically with increasing substitution. This leads to considerably lower yields of adduct, since the 1,3-dipolar cycloaddition reaction (equation 7) is always (except in the case of sterically hindered stable nitrile oxides) in competition with spontaneous dimerization (equation 1) and other modes of transformation of the nitrile oxide. Tetrasubstituted olefins react so slowly that they can be considered inert for all practical purposes[9,34]. Similarly, the "double bonds" of true aromatic systems such as benzenoid or heteroaromatic rings do not react with nitrile oxides under standard conditions[35]; however, cycloaddition to furans, pyrrole, and even thiophene can be forced by treating the heterocyclic compound with a nitrile oxide generated *in situ*[36]. Furan, for instance, yields as main product (Scheme **B**) either the monoadduct **1a** arising from attack of the electrophilic carbon of the nitrile oxide on the α-positions of furan, or the bis-adduct **1b**, in which a second molecule of nitrile oxide has added to the vinyl ether bond of **1a**:



Scheme **B**

Cyclohexenes exhibit a particularly low reactivity as compared with more strained cyclic olefins such as cyclobutene, cyclopentene, norbornene, or acenaphthylene[37]; however, even cyclohexenes can be forced to undergo the reaction (equation *8*) by using benzonitrile oxide or trimethylacetonitrile oxide generated *in situ*:

(8)


$$R-C\equiv N\rightarrow O + \text{cyclohexene} \longrightarrow$$

Polyolefins can usually be made to react either at one or at two or more double bonds, provided that none of these is unreactive due to its degree of substitution as mentioned above. Bis- and poly-adducts can often be easily separated from monoadducts, because the former in contrast to the latter are usually only slightly soluble in ether[38]. Fulvenes only react at the two endocyclic bonds[39]. Cyclooctatetra-

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[19] F. Eloy, R. Lenaers, Bull. Soc. Chim. Belges **72**, 719 (1963).

[20] R. Huisgen, W. Mack, E. Anneser, Angew. Chem. **73**, 656 (1961).

[21] R. Huisgen, W. Mack, Tetrahedron Letters **1961**, 583.

[22] P. Grünanger, P. Vita Finzi, Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat. **31**, 277 (1961); C. A. **57**, 2214 (1962).

[23] L. A. Simonyan, U. F. Zeiffman, P. Gambaryan, Izv. Akad. Nauk SSSR **1968**, 1916.

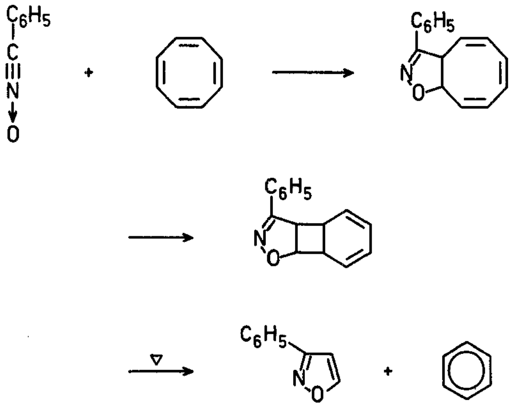
[24] R. A. Firestone, J. Org. Chem. **33**, 2285 (1968).

[25] R. Huisgen, J. Org. Chem. **33**, 2291 (1968).

[26] A. Quilico, G. Stagno d'Alcontres, P. Grünanger, Gazz. Chim. Ital. **80**, 479 (1950).

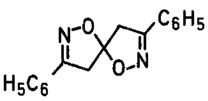
[27] S. Morocchi, A. Ricca, L. Velo, Tetrahedron Letters **1967**, 331.

ene and benzonitrile oxide only yield a bicyclic monoadduct which isomerizes at room temperature to give a tricyclic compound (Scheme **C**) the structure of which was proven by a clean thermal degradation into benzene and 3-phenyl-1,2-oxazole[31,40]:



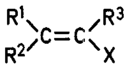
Scheme **C**

Conjugation of a C=C double bond, either with another C=C double bond or with a carbonyl group, enhances the rate of the cycloaddition reaction. Allenic double bonds normally react to yield spiro compounds, e.g., **2**, obtained from propadiene and benzonitrile oxide[41]:



2

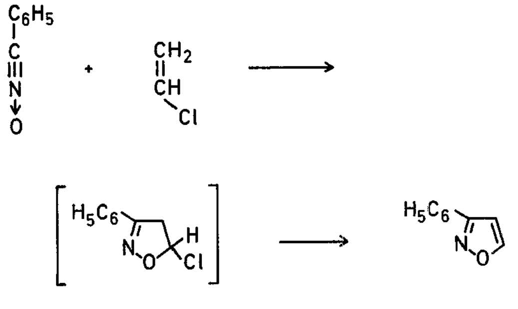
A complication sometimes arises in attempted syntheses of 4,5-dihydro-1,2-oxazoles from ethylenes of type **3** in which R^1 or R^2 is hydrogen and X is a potential leaving group such as halogen, oxygen (e.g., in enols, vinyl ethers, and vinyl esters), nitrogen (e.g., in enamines or nitroolefins), or sulfur (e.g., in ketene Dercaptals):



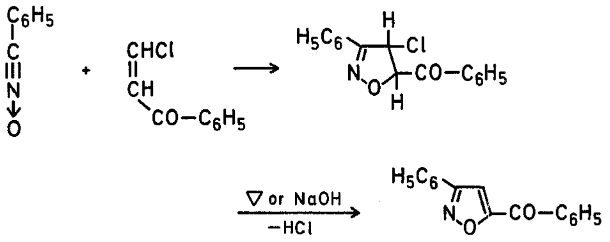
$R^1R^2C{=}CR^3X$

3

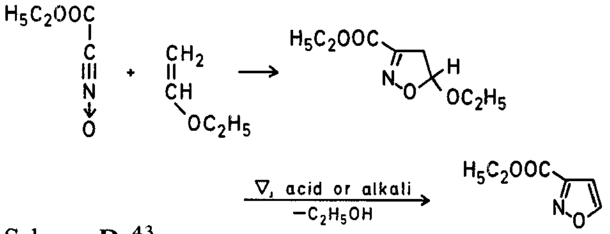
In such cases, the reactions often proceed beyond the 1,2-oxazoline stage to the 1,2-oxazole. The following examples (Schemes D_1–D_7) illustrate this reaction sequence; in those cases where the 1,2-oxazoline is set into brackets, it decomposed spontaneously under the reaction conditions to the 1,2-oxazole:



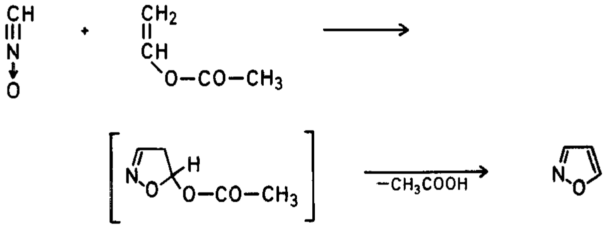
Scheme D_1[15,32]



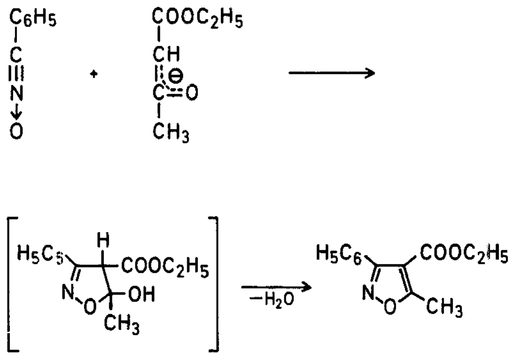
Scheme D_2[42]



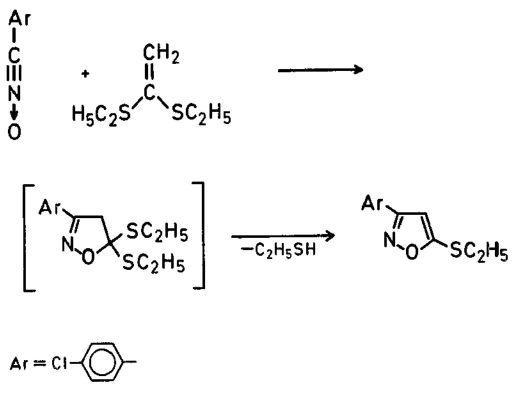
Scheme D_3[43]



Scheme D_4[13]



Scheme D_5[2,26]



Scheme D_6[44]

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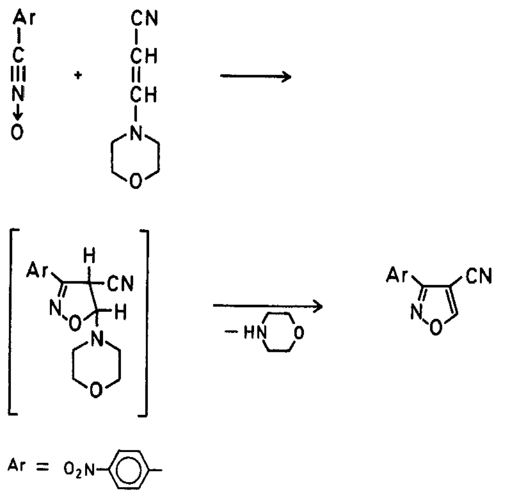
[28] S. Morocchi, A. Ricca, Chim. Ind. (Milano) **49**, 629 (1967). S. Morocchi, A. Ricca, A. Zanarotti, Chim. Ind. (Milano) **50**, 352 (1968).

[29] C. Grundmann, R. Richter, Tetrahedron Letters **1968**, 963.



Scheme D_7[45]

The most serious limitation of the usefulness of this synthesis of Δ^2-1,2-oxazolines is, however, the structural ambiguity of the product when an unsymmetrical olefin of type **4** is used (see also the general remarks in Section 2.1.). In such cases, the synthesis often leads to a mixture of the isomers **5** and **6**:

$$R^1{-}C{\equiv}N{\to}O \quad + \quad R^2{-}CH{=}CH{-}R^3 \longrightarrow$$

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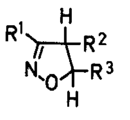

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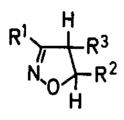
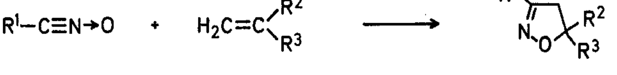


5 **6**

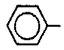
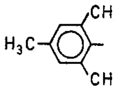
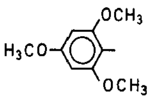
The formation of mixtures of products **5** and **6** has also been observed with monosubstituted ethylenes of type $R^3-CH{=}CH_2$ as starting materials, but never with 1,1-disubstituted ones (**7**). In the latter case, only the 5,5-disubstituted Δ^2-1,2-oxazolines (**8**) appear to be formed:



7 **8**

Table 1 gives the product ratios obtained in some typical cycloadditions of this sort[31]. Separation of the isomers was possible by thin-layer chromatography and structure elucidation was most conveniently carried out by N.M.R. spectroscopy.

Table 1. Ratio and Total Yield of Isomeric 4,5-Dihydro-1,2-oxazoles **5** and **6** formed in the Cycloaddition Reaction of Nitrile Oxides and α,β-unsaturated Methyl Carboxylates (**4**, $R^3{=}COOCH_3$)[31]

R^1	$R^2=H$		$R^2=CH_3$		$R^2=C_6H_5$	
	Ratio **6:5**	Total Yield %	Ratio **6:5**	Total Yield %	Ratio **6:5**	Total Yield %
H	0 :100	93	38:62	36	76:24	23
H_3C	5.1: 94.9	85	64:36	81	70:30	70
$t-C_4H_9$	0 :100	95	86:14	83	78:22	75
$N{\equiv}C-$	2 : 98	72	56:44	43	85:15	5
$HON{=}CH-$			55:45	31		
	3.6: 96.4	99	66:34	84	70:30	89
	6.6: 93.4	100	73:27	97	64:36	93
	6.5: 93.5	86				

***cis*-3-(4-Nitrophenyl)-4,5-dihydro-1,2-oxazole-4,5-dicarboxylic Acid**[46]: A solution of 4-nitrobenzonitrile oxide[47] (3.65 g) in anhydrous benzene (150 ml) is added to a solution of maleic anhydride (2.2 g) in benzene (10 ml). The mixture is refluxed (water bath) with exclusion of moisture for 90 min. and the precipitate formed is separated by filtration and washed with benzene. This crude, slightly yellowish anhydride of *cis*-3-(4-nitrophenyl)-4,5-dihydro-1,2-oxazole-4,5-dicarboxylic acid (m.p. 184–186°, softening around 170°) is treated with a little cold water which slowly transforms it into the desired dicarboxylic acid. This is then purified by repeated recrystallization from acetic acid; yield: 7.0 g (85%); small tufted needles containing 1 mol of water after drying at 100°, m.p. 217–218° (dec.).

3-(5-Nitro-2-furyl)-3a,4,5,6,7,7a-hexahydro-⟨benzo[d]-1,2-oxazole⟩[48]: A solution of 5-nitrofuran-2-carbohydroxamoyl chloride[17] (1.16 g) and cyclohexene (2 ml) in toluene (20 ml) is refluxed under exclusion of moisture for 12 hr. After distillation of the solvent under reduced pressure, the residue is recrystallized from ethanol; yield: 1.32 g (92%); m.p. 145–146°.

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[30] T. Sasaki, T. Yoshioka, Bull. Chem. Soc. Japan **42**, 258 (1969).

[31] M. Christl, R. R. Huisgen, Tetrahedron Letters **1968**, 5209.

[32] A. Quilico, G. Stagno d'Alcontres, P. Grünanger, Nature **166**, 226 (1950).

[33] For a complete listing, see: C. Grundmann, P. Grünanger, *Nitrile Oxides*, Springer Verlag, New York·Heidelberg, in press.
See also: A. Quilico, *Isoxazoles and Related Compounds* in: *The Chemistry of Heterocyclic Compounds*, A. Weissberger, editor, Vol. XVII, p. 1–176, Interscience Publishers, New York, 1962.

[34] C. Grundmann, H. D. Frommeld, K. Flory, S. K. Datta, J. Org. Chem. **33**, 1464 (1968).

[35] P. Grünanger, I. Grasso, Gazz. Chim. Ital. **85**, 1272 (1955).

[36] A. Corsico Coda, P. Grünanger, G. Veronesi, Tetrahedron Letters **1966**, 2911.

[37] N. Barbulescu, P. Grünanger, M. R. Langella, A. Quilico, Tetrahedron Letters **1961**, 89.
N. Barbulescu, P. Grünanger, Gazz. Chim. Ital. **92**, 138 (1962).
G. Bianchi, R. Gandolfi, personal communication (1969).

[38] G. Stagno d'Alcontres, Gazz. Chim. Ital. **82**, 627 (1952).

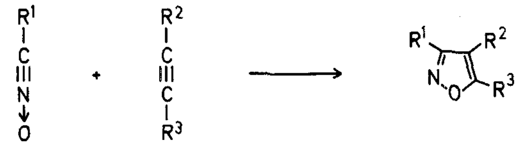
[39] A. Quilico, P. Grünanger, R. Mazzini, Gazz. Chim. Ital. **82**, 349 (1952).

[40] G. Bianchi, R. Gandolfi, P. Grünanger, Chim. Ind. (Milano) **49**, 757 (1967).

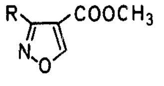
2.2.2. 1,2-Oxazoles (Isoxazoles)

1,2-Oxazoles are formed from nitrile oxides and acetylenic compounds in a reaction as general as that described in Section 2.2.1.[33]:

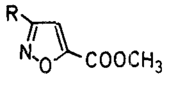
(9)



The cycloaddition of nitrile oxides to acetylenes is in general subject to the same influences as the cycloaddition to ethylenic compounds; monosubstituted acetylenes usually react faster than disubstituted ones, conjugation significantly accelerates the reaction, and adducts of acetylenes of low reactivity can be prepared by treating the addend with an *in situ* generated 1,3-dipole. Monosubstituted acetylenes – unlike the corresponding olefins – afford 5-substituted 1,2-oxazoles exclusively; the formation of the isomeric 4-substituted derivatives has never been observed. As with the corresponding olefins, however, unsymmetrical disubstituted acetylenes may lead to a mixture of isomeric compounds. In the cycloaddition of methyl propiolate to various nitrile oxides, for example, the two possible isomers **9** and **10** were obtained in the ratios given in Table 2:

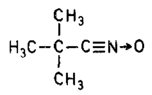
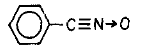
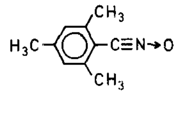


9



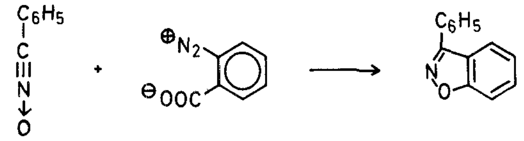
10

Table 2. Isomer Ratios in the Cycloaddition of Nitrile Oxides to Methyl Propiolate[15,49].

Nitrile Oxide	Solvent	Actual Total Yield %	Isomer Ratio **10:9**
$H-C\equiv N\rightarrow O$	Ether	50	84 : 16
 $(CH_3)_3C-C\equiv N\rightarrow O$	Ether	95	91 : 9
$N\equiv C-C\equiv N\rightarrow O$	Ether/water	69	68.5 : 31.5
	Ether	98	72 : 28
	Methanol	97	44 : 56
	Ether	97	28 : 72
	Cyclohexane	96.5	25 : 75

In general, triple bonds react with nitrile oxides more slowly than double bonds. In the case of substrates containing both types of bonds, such as enynes, the bond which is less sterically hindered usually seems to react first, regardless of whether it is a triple or double bond[5,50]. The "triple bond" in benzyne is very reactive; here, the products are benzo[d]-1,2-oxazoles (indoxazenes)[51,52]:

(10)



On the whole, the cycloaddition of acetylenes to nitrile oxides is one of the more important routes to 1,2-oxazoles, but in spite of its wide applicability its synthetic value is slightly less than that of the corresponding reaction with olefins for the following reasons:

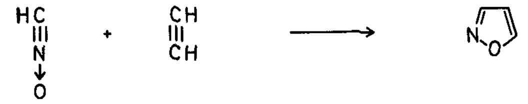
(1) Acetylenes are often less accessible and less stable than the corresponding olefins.

(2) The generally slower reaction rate with acetylenes usually leads to lower yields, as pointed out in Section 2.1.

For these reasons, 1,2-oxazoles are often prepared via cycloaddition to olefins rather than to acetylenes with subsequent conversion of the Δ^2-1,2-oxazolines obtained into the corresponding 1,2-oxazoles. This conversion can be achieved in two different ways:

(a) A suitably substituted ethylene, $R^1-CH=CR^2X$, where XH can later be easily removed from the intermediate 1,2-oxazoline, may be used. Examples are given in Section 2.2.1., Schemes $\mathbf{D}_1$–$\mathbf{D}_7$. The advantage of this technique is strikingly demonstrated by the fact that the parent compound, 1,2-oxazole, is only obtained in 5% yield[53] from acetylene and fulminic acid (equation *11*), whereas the procedure involving generation of fulminic acid from iodoformoxime (see Section 1.2.) in the presence of vinyl acetate and subsequent elimination of acetic acid (compare Scheme $\mathbf{D}_1$) raises the yield to 90%[13,49].

(11)



(b) Δ^2-1,2-Oxazolines having at least one hydrogen atom at each of the positions 4 and 5 are easily dehydrogenated to the corresponding 1,2-oxazoles by oxidation with chromic acid[54,55] or bromination

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[41] G. Stagno d'Alcontres, G. Lo Vecchio, Gazz. Chim. Ital. **90**, 1239 (1960).
G. Stagno d'Alcontres et. al., Gazz. Chim. Ital. **98**, 203 (1968).

[42] P. Vita Finzi, M. Arbasino, Ann. Chim. (Roma) **54**, 1165 (1964).

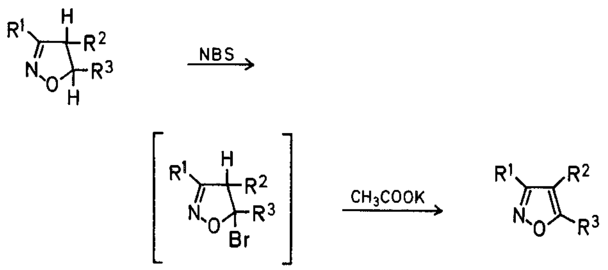
[43] R. Paul, S. Tchelitcheff, Bull. Soc. Chim. France **1962**, 2215.

[44] M. E. Kuehne, S. J. Weaver, P. Franz, J. Org. Chem. **29**, 1582 (1964).

[45] T. Sasaki, T. Yoshioka, Bull. Chem. Soc. Japan **41**, 2212 (1968).

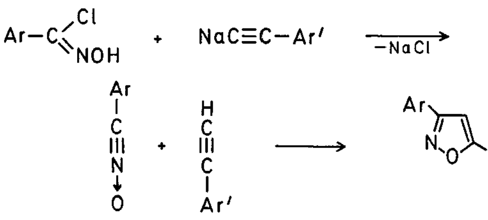
[46] A. Quilico, P. Grünanger, Gazz. Chim. Ital. **85**, 1449 (1955).

with N-bromosuccinimide followed by dehydrobromination with bases (e.g., potassium acetate; Scheme **E**). The latter method is more generally applicable; the yields vary between 70 and 90% depending on the substituents:



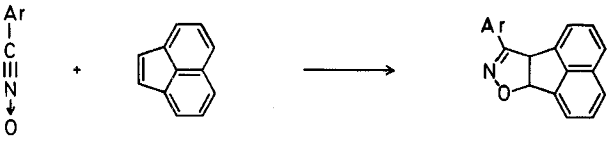
Scheme **E**

The long-known synthesis of 1,2-oxazoles[56] from hydroximic acid chlorides and sodium arylacetylenides involves an intermediate nitrile oxide which is generated from the hydroxamoyl chloride by the strongly basic sodium arylacetylenide (Scheme **F**):



Scheme **F**

Support for this mechanism[2] was obtained by trapping the nitrile oxide with acenaphthylene[57]:



3-(2,4,6-Trimethylphenyl)-5-phenyl-1,2-oxazole[58]: A solution of 2,4,6-trimethylbenzonitrile oxide (10 mmol) and phenylacetylene (11 mmol) in benzene (150 ml) is refluxed (15 min.). The solvent and excess phenylacetylene are evaporated; the final conditions are: b.p.$_{0.1}$: 50°. The 1,2-oxazole remaining is obtained analytically pure after one recrystallization from methanol; yield: 80%; m.p. 94°.

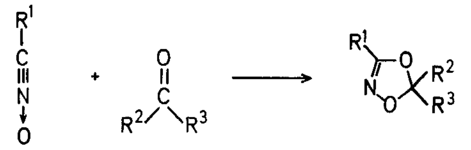
Ethyl 5-methyl-3-phenyl-1,2-oxazole-4-carboxylate[2]: Benzonitrile oxide[2,7] (2.0 g) is dissolved in ethanol (10 ml); then ethyl acetoacetate (2.2 g) is added. Upon addition of a few drops of 20% aqueous sodium hydroxide solution to the reaction mixture, an exothermic reaction with accompanying yellow discoloration starts immediately. The mixture is allowed to stand for 2 days at room temperature; a part of the formed 1,2-oxazole ester has by then crystallized out in pure form (1.0 g; m.p. 49°); a second, slightly yellowish crop of crystals (2.0 g) is obtained by concentration of the mother liquid on the steam bath; yield: 77%.

5-Phenyl-1,2-oxazole[14,15]: Iodoformoxime (4.2 g, 24.6 mmol) dissolved in phenylacetylene (50 ml) is added dropwise, with stirring and cooling with ice, to a solution of triethylamine (4 ml, 29 mmol) in phenylacetylene (20 ml). The reaction mixture is stirred for an additional 30 min.; it is then diluted with ether and extracted with water. Ether and excess dipolarophile are removed by vacuum distillation of the organic layer; the residual oil is distilled at 50–60° (bath temperature)/0.001 mm. The product is a yellow liquid, which is obtained in colorless form after repeated vacuum distillation; yield: 1.85 g (52%); b.p.$_{15}$: 128°.

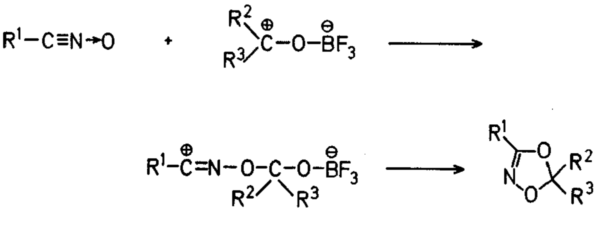
2.3. 1,3,4-Dioxazoles

This ring system is formed by the 1,3-dipolar cycloaddition of a nitrile oxide to a carbonyl bond in a ketone or an aldehyde (equation *12*). The C=O double bond must be activated by the presence of an adjacent electron-withdrawing group[21,22,23], or by addition of boron trifluoride to the reaction mixture[27,59]:

(*12*)



In the latter case, a two-step cycloaddition mechanism is conceivable, since Lewis acids give coordination compounds with aldehydes and ketones:



Among the carbonyl compounds which react according to equation (*12*) are chloral, aromatic aldehydes, α-diketones, and α-oxoesters. The carbonyl function in esters or amides is unreactive, even in the presence of boron trifluoride. Ketenes react only with the C=C double bond[60].

Both the carbonyl groups and the ethylenic double bonds of quinones may react, although this reactivity is structure-dependent. In the case of *o*-benzoquinone, one carbonyl group and both double bonds can undergo 1,3-dipolar additions[61]. In 1,2-naphthoquinone, both carbonyl groups react faster than the C=C double bond, and the initial reaction

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[47] F. Eloy, R. Lenaers, Bull. Soc. Chim. Belges **74**, 129 (1965).

[48] T. Sasaki, T. Yoshioka, Bull. Chem. Soc. Japan **40**, 2604 (1967).

[49] C. Grundmann, P. Grünanger, *Nitrile Oxides*, Springer Verlag, New York · Heidelberg, in press.

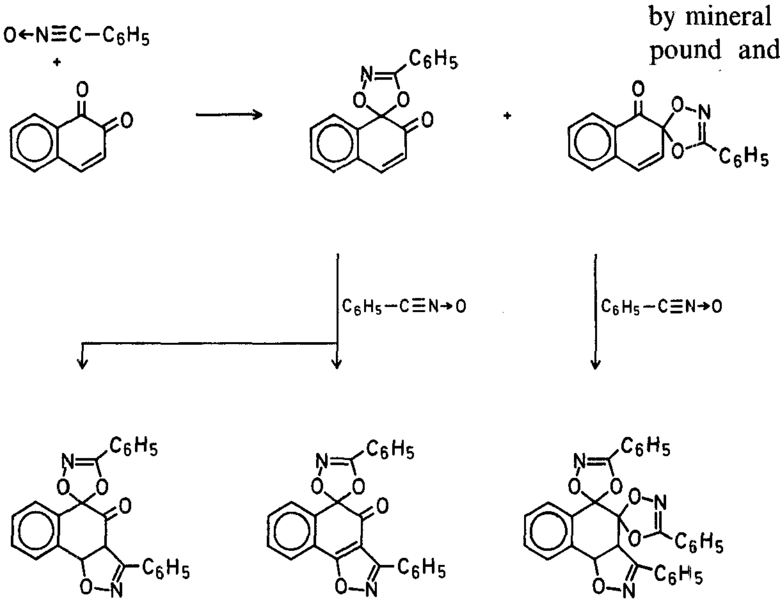
[50] A. Quilico, P. Grünanger, Rend. Ist. Lombardo Sci. Lettere **88**, 990 (1955).
V. N. Chistikletov, A. T. Troshchenko, A. A. Petrov, Doklady Akad. Nauk SSSR **135**, 631 (1960); Zh. Obshch. Khim. **33**, 789 (1963); **34**, 1891 (1964).
O. K. Vagina, V. N. Chistokletov, A. A. Petrov, Zh. Org. Khim. **2**, 417 (1966).
G. N. Bondarev, V. A. Ryzhov, V. N. Chistokletov, A. A. Petrov, Zh. Org. Khim. **3**, 821 (1967).

[51] F. Minisci, A. Quilico, Chim. Ind. (Milano) **46**, 428 (1964).

[52] T. Sasaki, T. Yoshioka, Bull. Chem. Soc. Japan **42**, 826 (1969).

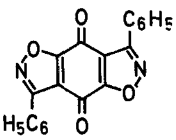
[53] A. Quilico, G. Stagno d'Alcontres, Gazz. Chim. Ital. **79**, 703 (1949).

products are the two isomeric monoadducts. In the case of the initial adduct resulting from attack of the carbonyl group next to the aromatic ring, an excess of nitrile oxide attacks only the chalkone-like C=C double bond to yield a mixture of the bis-adduct and its oxidation product. Initial attack on the β-carbonyl group, however, yields a product in which both the remaining C=O bonds and the C=C bonds are still reactive, and a 1:3 adduct is the final product (Scheme G):

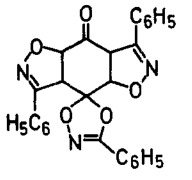


Scheme G

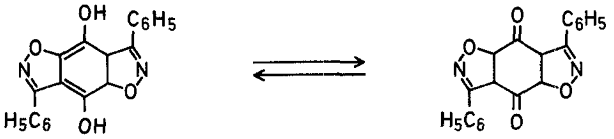
The uncatalyzed reaction of benzonitrile oxide with the double bond of p-benzoquinone yields only the bis-adduct **11**[59,62] arising from the oxidation of the primary 1,2-oxazoline derivative **12a** ⇄ **12b** by air or by excess quinone. In the presence of boron trifluoride etherate, however, it is possible to isolate the easily oxidable **12b** together with a second compound (**13**) containing 3 molecules of nitrile oxide per molecule of quinone; thus, in the latter case, one carbonyl group of the quinone has also reacted[63]:



11



13

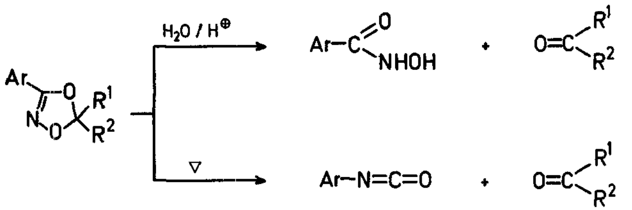


12 b **12 a**

Analogous results have been obtained with 1,4-naphthoquinone.

When the quinone does not contain ethylenic bonds, as in the case of anthracene-9,10-quinone or chrysene-5,6-quinone, the reaction with nitrile oxides can lead to mono-[64] as well as bis-adducts[61] depending on the solvent used.

Prior to discovery of the nitrile oxide synthesis, 1,3,4-oxadiazoles were only known in the form of their 2-oxo-derivatives[65], and the above synthesis is still the only route of importance to this ring system. As cyclic acetals, these compounds are readily cleaved by mineral acids to give the original carbonyl compound and a hydroxamic acid, whereas thermal decomposition yields an aryl isocyanate along with the original carbonyl compound[21,66] (Scheme H):

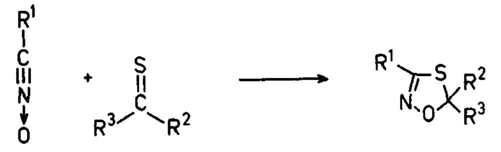


Scheme H

2.4. 1,4,2-Oxathiazoles

Representatives of this ring system are obtained by the reaction of nitrile oxides (preferably generated *in situ*) with thiocarbonyl compounds[20] (equation *13*):

(13)



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[54] G. Bianchi, P. Grünanger, Tetrahedron **21**, 817 (1965).

[55] C. Grundmann, V. Mini, J. M. Dean, H. D. Frommeld, Liebigs Ann. Chem. **687**, 191 (1965).

[56] C. Weygand, E. Bauer, Liebigs Ann. Chem. **459**, 123 (1927).

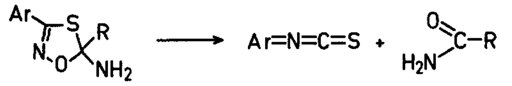
[57] G. F. Bettinetti, private communication (1969).

[58] C. Grundmann, J. M. Dean, J. Org. Chem. **30**, 2089 (1965).

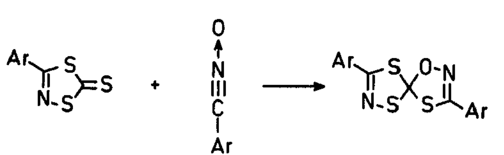
[59] T. Sasaki, T. Yoshioka, Bull. Chem. Soc. Japan **41**, 2206 (1968).

Because the polar character of the C=S double bond is more pronounced than that of the C=O bond, a larger variety of thiocarbonyl than of carbonyl compounds are reactive in the cycloaddition, among them thioketones, thionocarbonates, and trithiocarbonates. These compounds do not require activation either by electron-withdrawing groups or by Lewis acids. Thioamides also react, but the 5-amino-1,4,2-oxadiazoles obtained are unstable and decompose into the corresponding amide and an isothiocyanate (equation *14*):

(14)

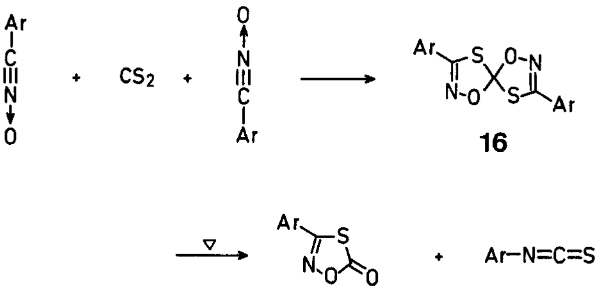


The reaction of 5-thiono-3-aryl-1,4,2-dithiazoles (**14**)[67] with nitrile oxides affords spiro compounds **15**:



14 **15**

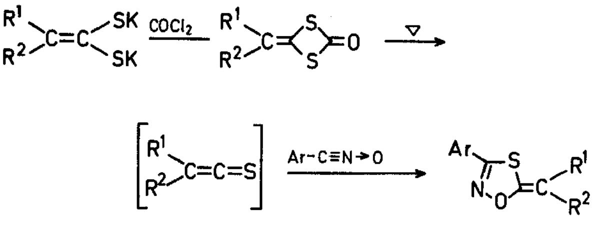
Both double bonds of carbon disulfide take part in the reaction with 2,4,6-trimethylbenzonitrile oxide; the product is the spiro compound **16** which decomposes spontaneously to 5-oxo-3-(2,4,6-trimethylphenyl)-1,4,2-oxathiazole (**17**) and 2,4,6-trimethylphenyl isothiocyanate[68]:



16 **17**

Scheme I

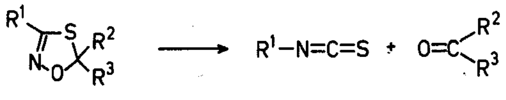
Under the same conditions, carbon oxysulfide is unreactive. In contrast to the behaviour of ketenes, thioketenes generated *in situ* (Scheme J) react with nitrile oxides at the C=S double bond[69]:



Scheme J

All 1,4,2-oxathiazoles are characterized by their easy thermal decomposition into isothiocyanates and the oxygen analogue of the thiocarbonyl compound used to synthesize them (equation *15*; also *14*, and **16**→**17**):

(15)

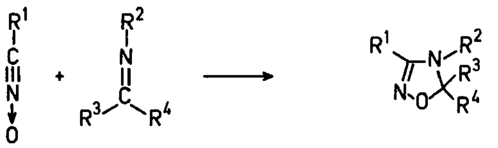


2.5. 1,2,4-Oxadiazoles[70]

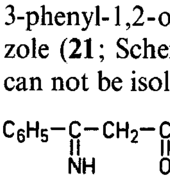
2.5.1. 4,5-Dihydro-1,2,4-oxadiazoles

The title compounds are obtained by cycloaddition of nitrile oxides to aldimines or ketimines (Schiff bases), which can be unsubstituted or contain an N-substituent (equation *16*)[17,71,72]:

(16)

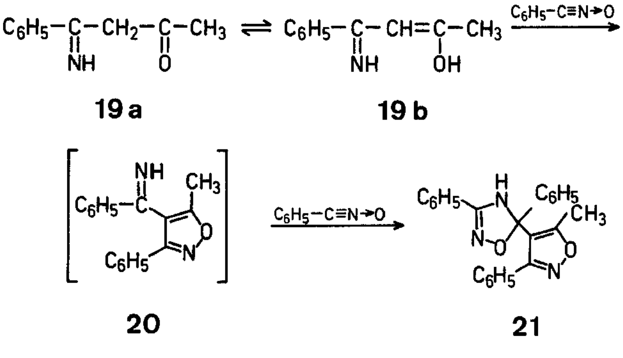


The C=N double bond of alkyl- or aryl-substituted imines is a more powerful dipolarophile than the C=O and C=S double bonds and needs no activation to react with nitrile oxides. Yields are usually very good. In competitive cycloaddition reactions involving a C=O and a C=N double bond, the C=N double bond reacts preferentially. Thus, the reaction of phenanthrene-9,10-quinone monoimine with benzonitrile oxide affords compound **18**[64]:



18

The enolimino form (**19b**) of 3-oxo-1-imino-1-phenylbutane (**19a**) reacts with 2 moles of benzonitrile oxide to immediately yield 3,5-diphenyl-5-(5-methyl-3-phenyl-1,2-oxazol-4-yl)-4,5-dihydro-1,2,4-oxadiazole (**21**; Scheme **K**). The assumed intermediate **20** can not be isolated[72]:



$$C_6H_5-\underset{NH}{\underset{\|}{C}}-CH_2-\underset{O}{\underset{\|}{C}}-CH_3 \rightleftharpoons C_6H_5-\underset{NH}{\underset{\|}{C}}-CH=\underset{OH}{\underset{|}{C}}-CH_3 \xrightarrow{C_6H_5-C\equiv N\rightarrow O}$$

19a **19b** **20** **21**

Scheme **K**

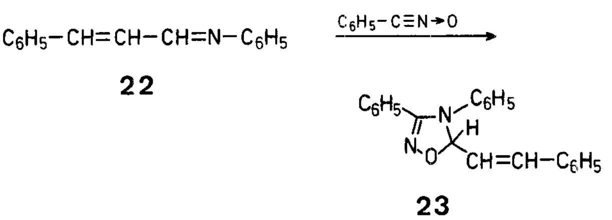
---

[60] R. Scarpati, P. Sorrentino, Gazz. Chim. Ital. **89**, 1525 (1959).

[61] S. Morocchi, A. Ricca, A. Selva, A. Zanarotti, Gazz. Chim. Ital. **99**, 565 (1969).

[62] A. Quilico, G. Stagno d'Alcontres, Gazz. Chim. Ital. **80**, 140 (1950).

Owing to the higher reactivity of the C=N double bond as compared to that of an analogous C=C double bond[73], cinnamylideneaniline (**22**) only reacts at the C=N double bond[74], and the product is **23**:

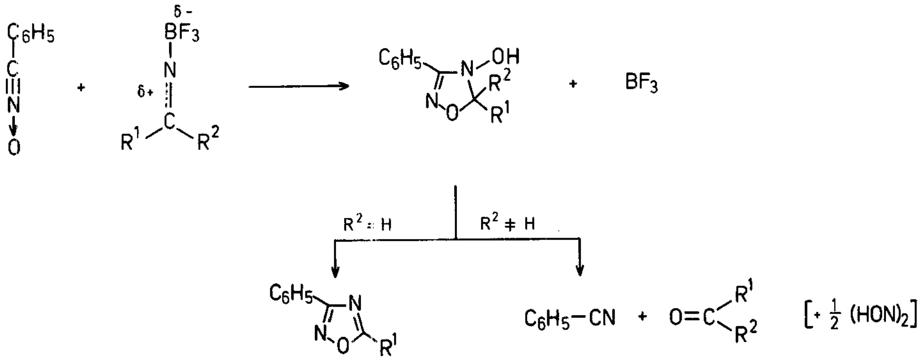


22

23

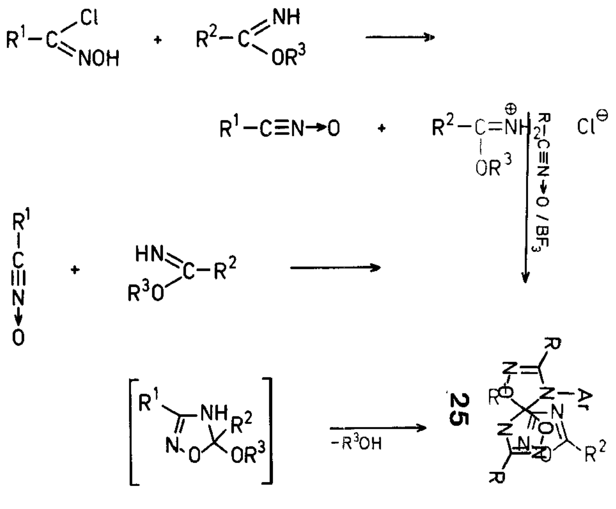
The same type of cycloaddition reaction presumably takes place in the previously reported formation of 1,2,4-oxadiazoles by the reaction of hydroximic acid chlorides with an excess of alkyl imidate; in this case, the nitrile oxide is probably formed *in situ* by the strongly basic dipolarophile[6,19]. The reaction of hydroximic acid chlorides and benzamidine, affording 3,5-disubstituted 1,2,4-oxadiazoles[76], presumably proceeds via a similar mechanism.

The C=N double bond of oximes is only reactive toward nitrile oxides in the presence of an acidic catalyst, e.g., boron trifluoride etherate[28]. Both aldoximes and ketoximes undergo cycloaddition; the latter compounds give lower yields. The hitherto unknown 4-hydroxy-4,5-dihydro-1,2,4-oxadiazoles obtained as products are characterized by their behaviour toward acids (Scheme **M**):



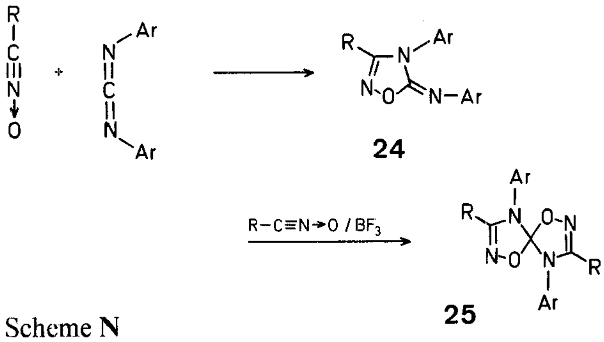
Scheme M

Alkyl imidates react with nitrile oxides to give the dihydro derivatives of 3,5-disubstituted 1,2,4-oxadiazoles as the initial products; these eliminate alcohol spontaneously to afford the parent oxadiazoles[72,75] (Scheme **L**):



Scheme L

The multiple C=N double-bond system of aromatic carbodiimides reacts spontaneously with nitrile oxides to give 5-imino-4,5-dihydro-1,2,4-oxadiazoles (**24**). In the presence of boron trifluoride etherate, these initial products react with a further mole of nitrile oxide to afford the spiro compounds **25** (Scheme N)[29,71]:



24

25

Scheme N

Aliphatic carbodiimides do not react spontaneously with nitrile oxides; however, in the presence of nitrile oxides generated *in situ* by thermal dissociation of hydroximic acid chlorides, cycloaddition occurs.

---

[63] S. Morocchi, A. Quilico, A. Ricca, A. Selva, Gazz. Chim. Ital. **98**, 891 (1968).

[64] W. I. Awad, S. M. A. R. Omran, M. Sobhy, J. Org. Chem. **31**, 331 (1966).
W. I. Awad, M. Sobhy, Canad. J. Chem. **47**, 1473 (1969).

[65] G. Peck, Chem. Ber. **84**, 668 (1951).

[66] O. Exner, Chem. Listy **50**, 779 (1956).

[67] D. Noël, J. Vialle, Bull. Soc. Chim. France **1967**, 2239.

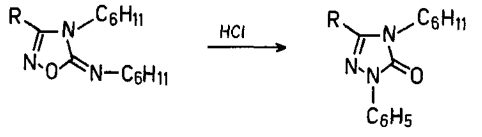
[68] W. O. Foye, J. M. Kaufman, J. Org. Chem. **31**, 2417 (1966).

[69] K. Dickoré, R. Wegler, Angew. Chem. **78**, 1023 (1966); Angew. Chem., Internat. Edit. **5**, 970 (1966).

[70] For a survey of the chemistry of 1,2,4-oxadiazoles, including other synthetic approaches, see F. Eloy, *A Review of the Chemistry of 1,2,4-Oxadiazoles*, Fortschr. Chem. Forsch. **4**, 807 (1965).

[71] L. Fabbrini, F. DeSarlo, Chim. Ind. (Milano) **45**, 242 (1963). F. Lavria, V. Vecchietti, G. Tosolini, Gazz. Chim. Ital. **94**, 480 (1964).

The initially produced 5-imino-4,5-dihydro-1,2,4-oxadiazoles, e.g., **26a**, apparently rearrange under the influence of the hydrogen chloride present to give 5-oxo-4,5-dihydro-1,2,4-triazoles, e.g., **26b** as the final products[30]:



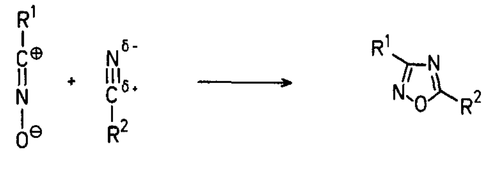
26 a **26 b**

The C=N double bond of cyclic amidines such as 1,5-diazabicyclo[4.3.0]non-5-ene and 1,6-diazabicyclo[5.4.0]undec-5-ene is a good dipolarophile; the products obtained are the corresponding condensed dihydro-1,2,4-oxadiazoles[77].

2.5.2. 1,2,4-Oxadiazoles

The C≡N triple bond adds nitrile oxides to afford 1,2,4-oxadiazoles. The addition direction is invariably determined by the polarization of the reaction partners as illustrated in equation *(17)*; the presence of isomers in the reaction product has never been recorded. Nitriles are more reactive dipolarophiles than carbonyl compounds[22,78], but much less reactive than the structurally analogous alkenes and alkynes[4,79], and less reactive by several orders of magnitude than the comparable C=N systems discussed in Section 2.5.1.

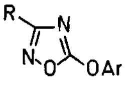
(17)



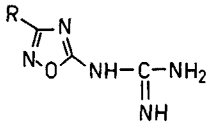
Because of this relatively low order of reactivity of nitriles, it is always advisable and often absolutely necessary to carry out the cycloaddition by generating the nitrile oxide *in situ*. Under these conditions, aromatic, heterocyclic, and aliphatic nitriles, activated by electron-withdrawing substituents, react spontaneously to give moderate to good yields of cycloaddition product[78,80,81,82]. Non-activated aliphatic nitriles react when catalyzed by boron trifluoride etherate[27]. In spite of the use of *in situ* generated nitrile oxides and/or Lewis-acid catalysis, some combinations of nitriles and nitrile oxides still afford low yields of cycloaddition product. In such cases, it may be best to first convert the nitrile oxide into the corresponding alkyl imidate and thence to the desired oxadiazole according to Scheme **L**.

3,5-Diphenyl-1,2,4-oxadiazole[19]: A solution of benzhydroxamoyl chloride (15.5 g, 0.1 mol) and ethyl benzimidate (29.8 g, 0.2 mol) in anhydrous benzene (250 ml) is allowed to stand for several hours at room temperature until the ethyl benzimidate hydrochloride formed has completely precipitated. The hydrochloride is removed by filtration, the filtrate is evaporated, and the residue recrystallized from aqueous ethanol; yield: 20 g (90%); m.p. 108–109°.

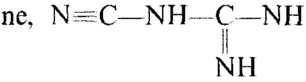
The same compound may be prepared from isolated benzonitrile oxide and benzonitrile in 56% yield[80]; when the reaction is carried out using *in situ* generated benzonitrile oxide, the yield is 65–69%[17,18,59,78,85].



27



28

The highly reactive aryl cyanates, Ar—O—C≡N, undergo smooth cycloaddition with nitrile oxides to give 5-aryloxyl-1,2,4-oxadiazoles **(27)**[83]. When N-cyanoguanidine,  $N{\equiv}C{-}NH{-}\underset{\underset{NH}{\|}}{C}{-}NH_2$, however, only the C≡N group reacts with a nitrile oxide, the products are 5-guanidino-1,2,4-oxadiazoles **(28)**[17,18,59,84,85].

Aromatic nitrile oxides dimerize under the influence of protic or aprotic acids (e.g., hydrogen chloride or boron trifluoride etherate) to yield 1,3-diaryl-1,2,4-oxadiazole-4-oxides[86,87] **(30)**; acid concentrations ranging from traces up to 0.5 equivalent, depending on the solvent and the nitrile oxide, are required. Excess boron trifluoride leads to a different reaction (see Section 3.3.). The dimerization reaction can be rationalized on the basis of a common mechanism (Scheme **O**). When hydrogen chloride is used, the intermediate is the hydrochloride **29**;

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[72] S. Morocchi, A. Ricca, L. Velo, Chim. Ind. (Milano) **49**, 168 (1967).

[73] W. Mack, K. Bast, unpublished work; cited by A. Dondoni, Tetrahedron Letters **1967**, 2397.

[74] N. Singh, J. S. Sandhu, S. Mohan, Tetrahedron Letters **1968**, 4453.

[75] P. Rajagopalan, Tetrahedron Letters **1969**, 311.

[76] C. Musante, Gazz. Chim. Ital. **68**, 331 (1938).

[77] A. Gamba, P. Grünanger, private communication.

[78] R. Huisgen, W. Mack, E. Anneser, Tetrahedron Letters **1961**, 587.

[79] G. Stagno d'Alcontres, P. Grünanger, Gazz. Chim. Ital. **80**, 741 (1950).

[80] G. Leandri, Bull. Sci. Fac. Chim. Ind. Bologna **14**, 80 (1956). G. Leandri, M. Pallotti, Ann. Chim. (Roma) **47**, 376 (1957).

[81] F. Eloy, Bull. Soc. Chim. Belges **73**, 973 (1964).

[82] M. S. Chang, J. U. Lowe, J. Org. Chem. **32**, 1577 (1967).

[83] D. Martin, H. J. Hermann, S. Rackow, K. Nadolsky, Angew. Chem. **77**, 96 (1965); Angew. Chem., Internat. Edit. **4**, 73 (1965). D. Martin, A. Weise, Chem. Ber. **99**, 317 (1966).

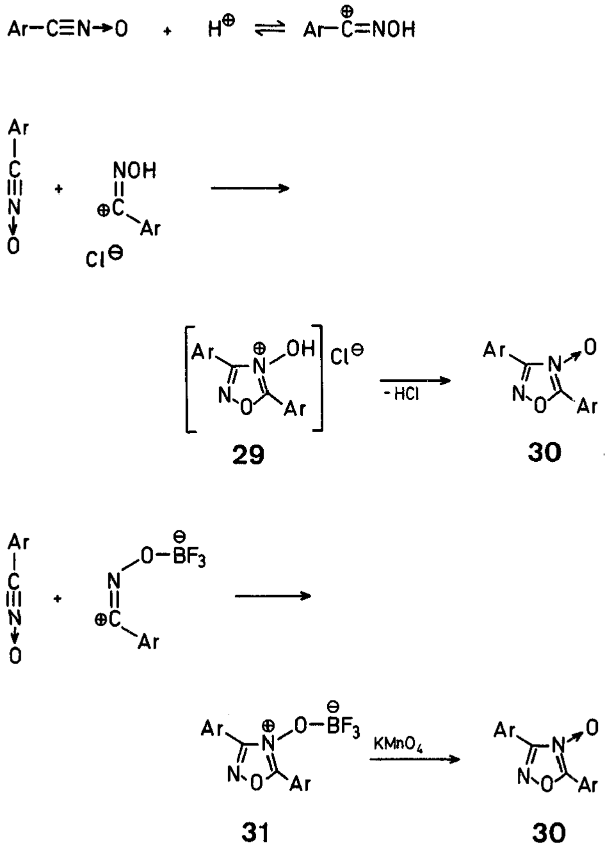
[84] L. Fabbrini, G. Speroni, Chim. Ind. (Milano) **43**, 807 (1961). J. Plenkiewicz, Z. Eckstein, Bull. Acad. Polon. Sci. **15**, 99 (1967).

[85] G. Rembarz, M. Brandner, E. M. Bebenroth, J. prakt. Chem. [4] **31**, 221 (1966).

[86] H. Wieland, Chem. Ber. **41**, 1667 (1907).

[87] S. Morocchi, A. Ricca, A. Selva, A. Zanarotti, Chim. Ind. (Milano) **50**, 558 (1968); Gazz. Chim. Ital. **99**, 165 (1969).

with boron trifluoride, the intermediate adduct **31** is isolable and can be converted into the final product **30** by treatment with potassium permanganate in acetone:

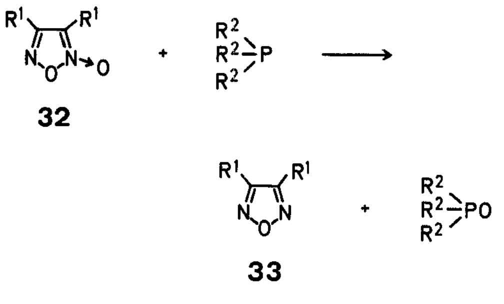


Scheme **O**

2.6. 1,2,5-Oxadiazoles

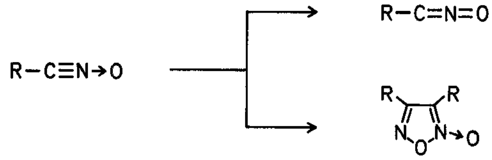
1,2,5-Oxadiazoles (**33**, furazans) are not directly obtainable from nitrile oxides but their 5-oxides, the furoxans (**32**), are readily available by the dimerization of nitrile oxides (equation *1*). Furoxans can in turn be deoxygenated, generally in very good yields, by the specific reducing action of trivalent phosphorus compounds, e.g., phosphines or phosphites[88] (eqation *18*):

(18)



As much interest as the dimerization reaction deserves from a mechanistic point of view[5,34,89], as little needs to be said about its preparative aspects. The reaction is spontaneous, slightly exothermic, is unaffected by the proton concentration of the medium and by catalysts. Solvents have some effect on the rate: the less polar the solvent, the faster the dimerization[89]. The dimerization reaction is, however, limited to those nitrile oxides which are not so sterically hindered by bulky neighbouring groups that they can not approach each other sufficiently to effect ring closure[5,34]. Even in such cases, the reaction is not completely suppressed, but its rate is very low in comparison with that of the competing reaction (*19*), isomerization to isocyanates:

(19)



When $R = C_6H_5$, and under the most favourable circumstances (heating of the nitrile oxide in toluene quickly to > 100°), the ratio of isocyanate to furoxan is ~ 1 : 10[90], whereas when R = 2,4,6-trimethylphenyl, the ratio under optimum conditions (65°, 24 hr) changes to ~8 : 1.

2.7. 1,2,3,5-Oxatriazoles

Representatives of this ring system are formed by the cycloaddition of nitrile oxides to azo compounds. Although aromatic azo compounds appear to be unreactive[5,91], certain esters of azodicarboxylic acid even react with aromatic nitrile oxides at −15° to give dialkyl 4-aryl-2,3-dihydro-1,2,3,5-oxatriazole-2,3-dicarboxylates (**34**). These compounds, however, are unstable and sometimes not isolable even at low temperatures; they quickly undergo ring cleavage, probably via dipole **35**, to afford the open-chain com-

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[88] C. Grundmann, Chem. Ber. **97**, 575 (1964).

[89] G. Barbaro, A. Battaglia, A. Dondoni, private communication.
A. Dondoni, A. Mangini, S. Ghersetti, Tetrahedron Letters **1966**, 4789.

[90] C. Grundmann, P. Kochs, G. F. Kite, unpublished results.

[91] C. Grundmann, P. Grünanger, R. Richter, unpublished results.

[92] P. Rajagopalan, Tetrahedron Letters **1964**, 887.

[93] R. Huisgen, H. Blaschke, E. Brunn, Tetrahedron Letters **1966**, 405.

[94] P. Rajagopalan, H. U. Daenicker, Angew. Chem. **75**, 91 (1963).
U.S. Pat. 3118902-3 (1964), E. E. Schmitt (American Cyanamide Co.); C. A. **60**, 10691 (1964).
P. Rajagopalan, G. B. Advani, J. Org. Chem. **30**, 3369 (1965).

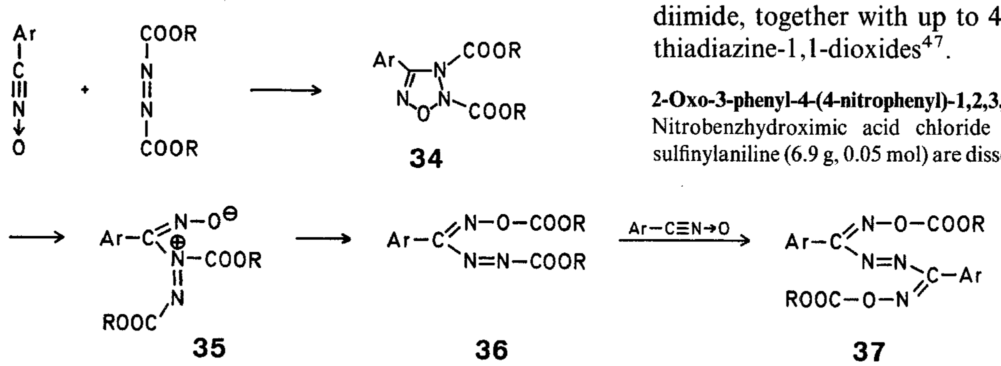
[95] F. Eloy, Helv. Chim. Acta **48**, 380 (1965).

[96] P. Beltrame, A. Commoti, R. Veglio, Chem. Commun. **1967**, 996.
P. Beltrame, private communication.

[97] C. Grundmann, unpublished results.

[98] P. I. Paetzold, W. M. Simson, Angew. Chem. **78**, 825 (1966); Angew. Chem. Internat. Edit. **5**, 842 (1966).
P. I. Paetzold, Angew. Chem. **79**, 583 (1967); Angew. Chem., Internat. Edit. **6**, 572 (1967).
P. I. Paetzold, G. Stohr, Chem. Ber. **101**, 2874 (1968).

pound **36**, which may then add a second mole of nitrile oxide to yield **37** as a by-product[92,93] (Scheme **P**):

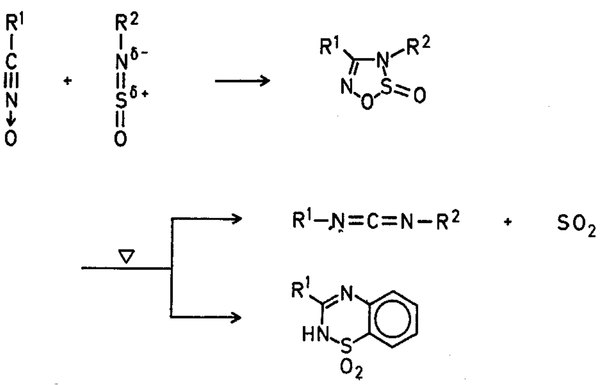


Scheme **P**

When the cycloaddition was carried out at −15° in ether, the heterocyclic primary product **34** ($Ar = C_6H_5$, $R = CH_3$) could be isolated in 67% yield as colorless needles (m.p. 75°, dec.); in benzene or ethyl acetate solution at room temperature, this material turned yellow within minutes. After the solution had been allowed to stand for several hours, the isomerization of **34** to the yellow azo compound **36** was complete. The corresponding ethyl ester (**34**, $Ar = C_6H_5$, $R = C_2H_5$) could not be isolated, but isomerized spontaneously to **36**. Compounds **34** only seem to be isolable when they are crystalline and reasonably insoluble in the reaction medium used.

2.8. 1,2,3,5-Oxathiadiazoles

The N=S double bond of both aliphatic and aromatic N-sulfinylamines is a good dipolarophile for aliphatic and aromatic nitrile oxides; the products are 1,2,3,5-oxathiadiazoles[47,94,95] (Scheme **Q**). Recent kinetic studies, however, cast some doubt as to whether this reaction can be considered a true example of concerted 1,3-dipolar cycloaddition[96]:



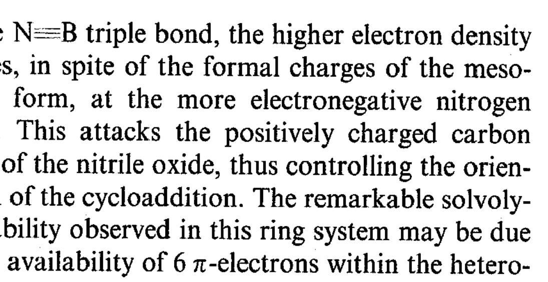
Scheme **Q**

Heating the initial heterocyclic product (Scheme **Q**) readily cleaves this material; sulfur dioxide is split off, and rearrangement of the remaining fragment affords an unsymmetrical carbodiimide. The method is generally applicable. When R^1 is an aliphatic group and R^2 an aryl group, pyrolysis of the initial product leads to the expected corresponding carbodiimide, together with up to 40% of benzo[e]-1,2,4-thiadiazine-1,1-dioxides[47].

2-Oxo-3-phenyl-4-(4-nitrophenyl)-1,2,3,5-oxathiadiazole[47,97]: 4-Nitrobenzhydroximic acid chloride (10 g, 0.05 mol) and N-sulfinylaniline (6.9 g, 0.05 mol) are dissolved in anhydrous benzene (150 ml), and triethylamine (5 g) added with stirring at 15–25° over a period of 1 hr. The reaction mixture is kept at 25° overnight, the triethylamine hydrochloride formed is removed by filtration, and the filtrate evaporated under reduced pressure. The residue is dissolved in the minimum amount of methanol, and ether added until crystallization just begins. The small crystalline fraction thus obtained consists mainly of triethylamine hydrochloride and is immediately filtered off. The oxathiadiazole crystallizes from the filtrate upon addition of more ether; it is recrystallized from benzene/hexane; yield: 8.5 g (52%); m.p. 140°.

2.9. 1,3,5,2-Oxadiazaboroles

Although neither dimeric nor trimeric boron imides undergo cycloaddition with nitrile oxides, the recently prepared monomeric B-pentafluorophenyl-N-arylborimides react with benzonitrile oxide almost quantitatively even at room temperature to form 1,3,5,2-oxadiazaboroles[98] (equation *20*):



(20)

In the N≡B triple bond, the higher electron density resides, in spite of the formal charges of the mesomeric form, at the more electronegative nitrogen atom. This attacks the positively charged carbon atom of the nitrile oxide, thus controlling the orientation of the cycloaddition. The remarkable solvolytic stability observed in this ring system may be due to the availability of 6 π-electrons within the heterocyclic ring.

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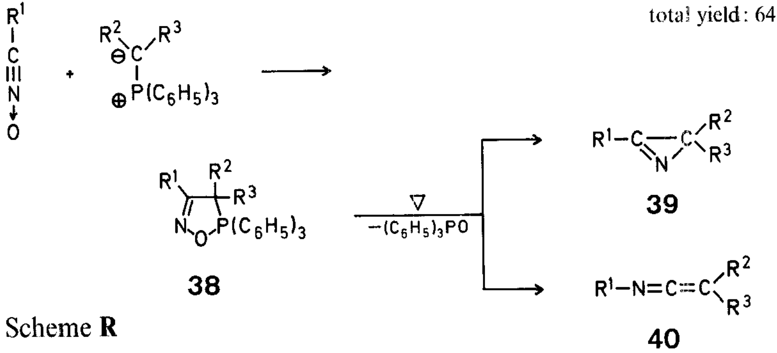
[99] R. Huisgen, J. Wulff, Tetrahedron Letters **1967**, 917.
H. J. Bestmann, R. Kunstmann, Angew. Chem. **78**, 1059 (1966); Angew. Chem., Internat. Edit. **5**, 1039 (1966).
A. Umani-Ronchi, M. Acampora, G. Gaudiano, A. Bravo, Chim. Ind. (Milano) **49**, 388 (1967).

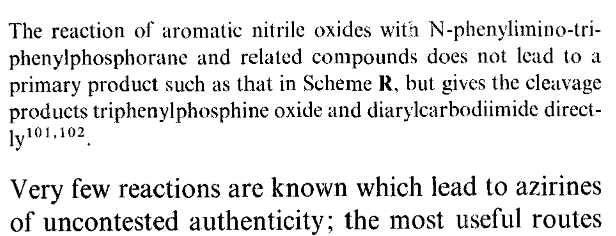
2.10. 4,5-Dihydro-1,2,5-oxazaphospholes

This ring system is probably initially formed in all reactions between a nitrile oxide and a phosphorus ylide (methylenephosphorane), as in Scheme **R**; however, only in certain cases can the primary product be isolated[99,100]. The stability of 4,5-dihydro-1,2,5-oxazaphospholes (**38**) depends on the nature of the substituents. When R^2 and R^3 are electron-donating substituents, the cycloadduct is isolable; only at higher temperatures does elimination of the phosphine oxide take place, leading to the azirine **39**. When R^2 and R^3 are electron-withdrawing groups, cleavage takes place even at room temperature; migration of R^1 then gives the ketimine **40**:



Scheme **R**

The nature of the nitrile oxide may also influence the fragmentation path of the cycloadduct: compound **41a** (Scheme S) affords the ketene-N-phenylimine **42** whereas **41b** is cleaved to afford the azirine **43**, presumably because of the lack of migratory ability of the ethoxycarbonyl group:



Scheme S

The reaction of aromatic nitrile oxides with N-phenylimino-triphenylphosphorane and related compounds does not lead to a primary product such as that in Scheme **R**, but gives the cleavage products triphenylphosphine oxide and diarylcarbodiimide directly[101,102].

Very few reactions are known which lead to azirines of uncontested authenticity; the most useful routes employ photolysis or pyrolysis of vinyl azides[103].

Thus, the reaction sequence depicted in Scheme **R** could in many cases present an attractive alternative to standard procedures as far as availabilty of starting materials, inherent danger, versatility, and yields are concerned.

3,5,5,5-Tetraphenyl-4,5-dihydro-1,2,5-oxazaphosphole[100]: Triethylamine (4.0 g, 39.4 mmol) is added to a stirred solution of benzhydroximic acid chloride (3.02 g, 19.4 mmol) in a mixture of anhydrous benzene (200 ml) and toluene (150 ml) at −30°. After 30 min., the triethylammonium chloride formed is filtered off and the cold filtrate is added with stirring and under nitrogen over a period of 5 min. to a freshly prepared solution of methylenephosphorane[104] (8.3 mmol) in benzene (50 ml). The initially yellow solution turns dark brown, but fades again to yellow after the reaction is complete. The solvent is evaporated under reduced pressure from a 50° water bath, and the residue recrystallized from methanol; yield: 1.54 g; m.p. 128–129° (dec.). From the mother liquor, an additional 0.54 g is obtained; total yield: 64%.

3. Heterocyclic Compounds by Other Reactions of Nitrile Oxides

A number of reactions of nitrile oxides with various nucleophilic compounds lead from the initial product via a number of assumed or isolable intermediates to heterocyclic rings. These final products are often only obtained in low yields, as by-products, or are so structurally simple that their synthesis is easier by other routes. Reviews of the reactions of nitrile oxides with diazoalkanes, sulfur ylids, and arsenic ylids have appeared in the literature[5,6,7].

Only a few reactions, selected for their preparative interest, are considered here.

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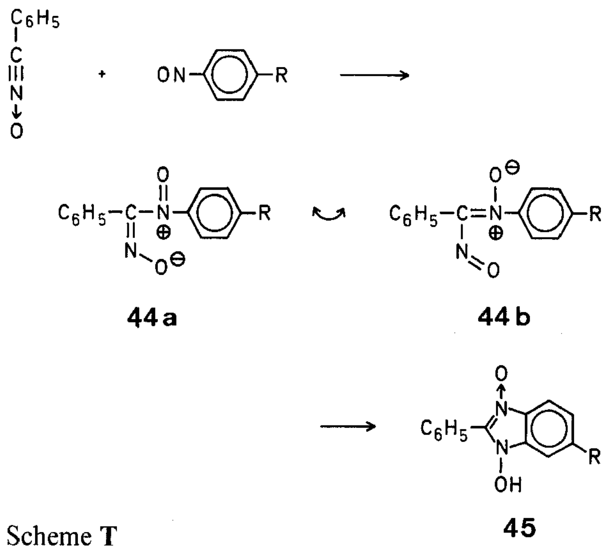
3.1. 1-Hydroxybenzimidazole-3-oxides

These substituted benzimidazoles (**45**), which have only recently also become readily available by another route[105], may be obtained[106] by the reaction of nitrile oxides with nitrosobenzene [R=H, $N(CH_3)_2$]:

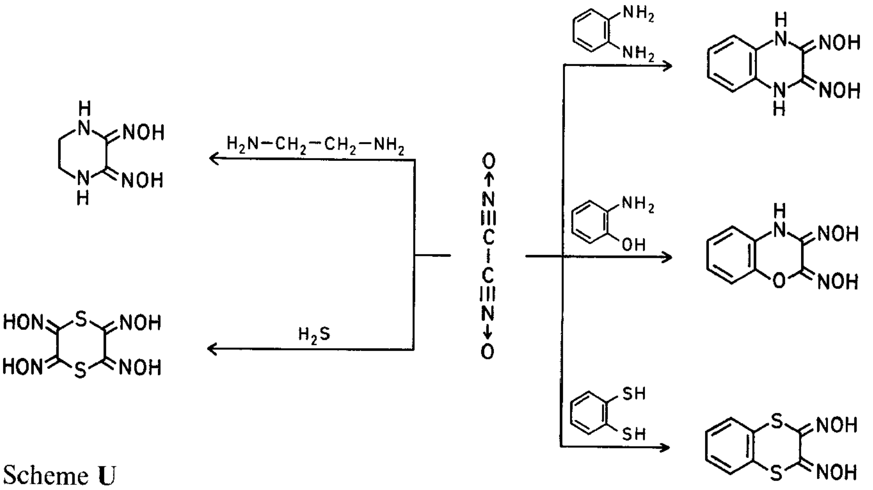


Scheme T

At −20° and when R = H, the intermediate **44** was isolable[105].

3.2. 1,4-Diazines, 1,4-Oxazines, and 1,4-Dithiins (Hydrogenated Derivatives)

These ring systems are all available via nucleophilic addition reactions of cyanogen-N,N′-dioxide (Scheme U)[55,107]. There exist numerous other routes to the basic heterocyclic structures thus preparable, but none which is so convenient.

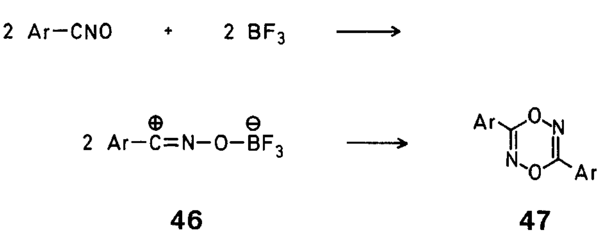


Scheme U

2,3,5,6-Tetraoximino-1,4-dithian[55]: A freshly prepared solution of cyanogen-N,N′-dioxide (~0.45 g) in carbon tetrachloride (50 ml) is stirred at 0° with a solution of sodium sulfide nonahydrate (2.4 g) in water (20 ml). After 1 hr, the organic phase is separated, the aqueous phase is acidified with 2 *N* sulfuric acid, and extracted with ether (3 x 50 ml). The combined ether extracts are dried over sodium sulfate, concentrated to 30 ml, and ligroin (15 ml, b.p. 60–70°) is added. The dithian (170 mg, 14%) is separated by filtration and recrystallized from ether/petroleum ether; m.p. 225–230°.

3.3. 1,4,2,5-Dioxadiazines

If aromatic nitrile oxides are treated with an excess of boron trifluoride in a non-coordinating solvent such as hexane, the dimerization to 1,2,5-oxadiazoles (see Section 2.6) or to 1,2,4-oxadiazoles (see Section 2.5.2) does not take place, and a different dimer, a 3,6-diaryl-1,4,2,5-dioxadiazine (**47**) is formed[87]. The intermediate appears to be the boron trifluoride adduct of the nitrile oxide (**46**); whether the reaction proceeds via an open-chain dipolar intermediate or by a concerted 1,3:1,3 head-to-tail cycloaddition is not known. The compound **47** ($Ar = C_6H_5$) was obtained much earlier (although its structure was not recognized) by the action of pyridine on benzonitrile oxide[108].



Scheme V

Simple derivatives of this ring system are so far only available via dimerization of nitrile oxides.

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