

# 1 Nitrile Oxides

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The chemistry of nitrile oxides is well documented. Several important monographs either specially devoted to nitrile oxides or including corresponding comprehensive chapters should be mentioned (1–5). Several reviews appeared (6–8), which concern preparation, reactivity, and synthetic applications of nitrile oxides. Some books and reviews devoted to individual aspects of nitrile oxide chemistry will be cited elsewhere.

The topics of the present presentation is closest to that of the monograph written by Torrsell (4). Therefore, the aim of this chapter is to update the information concerning nitrile oxides published after the monograph (4). The literature was followed by *Chemical Abstracts* database (1988–2001) and indices from Vol. 136 (2002) till Vol. 144 (2006). As to the period 1988–2002, references will be given practically only to data omitted in Reference 5.

## 1.1. PHYSICOCHEMICAL PROPERTIES

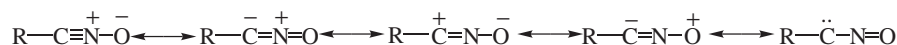
Nitrile oxides,  $\text{RNCO}$ , are derivatives of fulminic acid ( $\text{R}=\text{H}$ ). They can be named as *fulmido-substituted parent molecules*, but usually their names are derived from corresponding nitriles, for example, benzonitrile oxide, mesitonitrile oxide, thiophene-2-carbonitrile oxide.

Specific properties of nitrile oxides depend on the structure of the functional group, which have highly polarized  $\text{C}-\text{N}$  and  $\text{N}-\text{O}$  bonds (Scheme 1.1).

Most nitrile oxides are unstable, some of them are explosive. This fact hinders the study of their physical properties. Nevertheless, there are a number of publications concerning not only stable but also unstable nitrile oxides. In particular, mass spectral data for nitrile oxides among other unstable compounds containing an  $\text{N}^+-\text{X}^-$  bond are summarized in a review (9). In such studies, the molecular ions must be generated using indirect procedures, including dissociative electron ionization, online flash-vacuum pyrolysis mass spectrometry, or ion-molecular reactions. Their characterization is mainly based on collisional activation and ion-molecular reactions.

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*Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis,*  
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Scheme 1.1

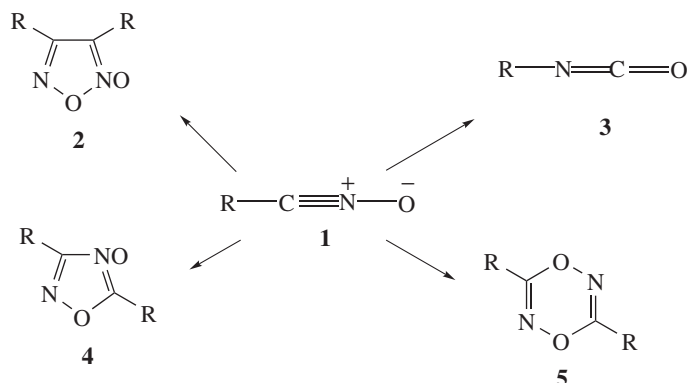
Unstable nitrile oxides XCNO, X = ONC, NC, Cl, Br, and Me, were generated and studied in the gas phase by He I photoelectron spectra (10) and by other methods, such as low resolution mid-IR, high-resolution IR, and microwave spectroscopy (11, 12). In particular, the unstable BrCNO molecule and its stable dibromofuroxan dimer were generated in the gas phase and studied by He I photoelectron, mid-IR, photoionization mass spectra as well as by *ab initio* calculations (13). Gas-phase IR and *ab initio* investigation were performed for the unstable CF<sub>3</sub>CNO molecule and corresponding stable furoxan (14). Cyano- and isocyanofulminates were studied by *ab initio* calculations at the MP2/6-31G\* level (15). It should also be noted that the electronic structure of fulminic acid was studied experimentally, using He I photoelectron and two-dimensional Penning ionization electron spectroscopies (16).

Thermochemical parameters of some unstable nitrile oxides were evaluated using corresponding data for stable molecules. Thus, for 2,4,6-trimethylbenzonitrile N-oxide and 2,4,6-trimethoxybenzonitrile N-oxide, the standard molar enthalpies of combustion and sublimation at 298.15 K were measured by static-bomb calorimetry and by microcalorimetry, respectively, this made it possible to derive the molar dissociation enthalpies of the N–O bonds, D(N–O) (17).

On the basis of published data for enthalpies of formation, sublimation, and vaporization, the dissociation enthalpies of terminal N–O bonds, DH°(N–O), in various organic compounds including nitrile oxides, were calculated and critically evaluated (18). The derived DH°(N–O) values can be used to estimate enthalpies of formation of other molecules, in particular nitrile oxides. N–O Bond energy in alkyl nitrile oxides was evaluated using known and new data concerning kinetics of recyclization of dimethylfurazan and dimethylfuroxan (19).

Evidently, stable nitrile oxides can be investigated by spectral and X-ray methods using ordinary procedures. As examples, X-ray diffraction studies of *o*-sulfamoylbenzonitrile oxides (20), 5-methyl-2-(methylsulfonyl)-3-thiophene-carbonitrile oxide (21), β,β-diphenylacrylonitrile oxide (22), and (dimorpholino-phosphoryl) carbonitrile oxide (23) can be cited. It should be underlined that structures of the latter compounds differ from those of classical stable *o,o'*-disubstituted arylcarbonitrile oxides and *tert*-alkylcarbonitrile oxides. Therefore, not only purely steric shielding of the CNO group but also electrostatic or donor–acceptor interactions between the atoms of the latter and adjacent polar substituents (21, 23) and also electron delocalization in π-systems (20, 22) enhance the stability of nitrile oxide.

Main routes of chemical transformations of nitrile oxides **1** in the absence of other reagents with multiple bonds have been well generalized in Reference 4 and are presented in Scheme 1.2.



Scheme 1.2

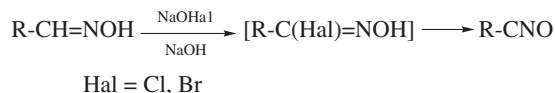
These routes are dimerization to furoxans **2** proceeding at ambient and lower temperatures for all nitrile oxides excluding those, in which the fulmido group is sterically shielded, isomerization to isocyanates **3**, which proceeds at elevated temperature, is practically the only reaction of sterically stabilized nitrile oxides. Dimerizations to 1,2,4-oxadiazole 4-oxides **4** in the presence of trimethylamine (4) or  $BF_3$  ( $1:BF_3 = 2:1$ ) (24) and to 1,4,2,5-dioxadiazines **5** in excess  $BF_3$  (1, 24) or in the presence of pyridine (4) are of lesser importance. Strong reactivity of nitrile oxides is based mainly on their ability to add nucleophiles and particularly enter 1,3-dipolar cycloaddition reactions with various dipolarophiles (see Sections 1.3 and 1.4).

## 1.2. METHODS FOR GENERATION AND PREPARATION OF NITRILE OXIDES

In this section, *generation* means formation, usually succeeded by *in situ* transformation of an unstable nitrile oxide, while *preparation* relates to stable nitrile oxides, which can be isolated and stored for a long time. A review including data on formation of nitrile oxides was published recently (25).

It is quite natural to consider that nitrile oxides could be generated or prepared from fulminic acid or fulminates. However, until recently, only one example of such a reaction is known, namely the formation of stable triphenylacetone nitrile oxide from trityl chloride and silver fulminate. Other attempts to generate nitrile oxides from organic halides and metal fulminates gave the corresponding isocyanates (1, 4). In 1982, a successful synthesis of trimethylsilanecarbonitrile oxide from trimethylsilyl bromide and  $Hg(II)$  fulminate was reported (26). This nitrile oxide possesses all of the characteristic properties of nitrile oxides and, moreover, its use is equivalent to that of fulminic acid, owing to the hydrolytic cleavage of the Si–C bond. In addition the conditions were elaborated, which

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**Scheme 1.3**

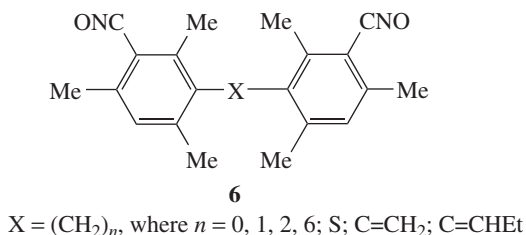
allowed one to hydrolyse the mentioned organosilicon nitrile oxide (27) and to introduce fulminic acid generated in some reactions (28). Nevertheless, because of the explosive nature of metal fulminates, their synthetic use is very limited and no data on their application for generation or formation of nitrile oxides were found in the literature published through the last 20 years.

##### 1.2.1. Formation from Aldoximes

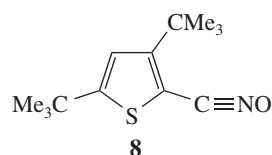
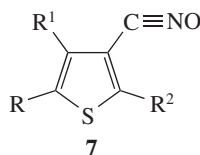
The transformation of aldoximes to nitrile oxides is essentially a dehydrogenation process.

Different procedures of this dehydrogenation are thoroughly discussed in the monograph (4). It is only necessary to note here that the process is carried out mainly as halogenation–dehydrohalogenation. The intermediate hydroximoyl halide is frequently not isolated (Scheme 1.3). The reaction is convenient for both the generation of unstable nitrile oxides (in the presence of a dipolarophile) and the preparation of stable nitrile oxides. It is usually carried out in a two-phase water–organic solvent system with methylene dichloride as the preferred solvent.

The latter procedure was used in syntheses of stable nitrile oxides such as  $\beta,\beta$ -diphenylacrylonitrile oxide and 2,6-diphenylbenzonitrile oxide (22), a series of functionally substituted 2,6-dimethylbenzonitrile oxides (29), as well as 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide (29), stable bis(nitrile oxides) of a novel structure **6**, in which two benzene rings, bearing hindered fulmido groups are connected with a bridge (30), tetrachloroisophthalo- and terephthalonitrile oxides (31). Stable *o*-sulfamoylbenzonitrile oxides with only one shielding substituent were also prepared using NaOCl/NaOH in a two-phase system (20, 32).



Stable 2,4-disubstituted thiophene-3-carbonitrile oxides **7** and 3,5-di(*t*-butyl)-thiophene-2-carbonitrile oxide **8** were synthesized from respective aldoximes by the similar one-pot procedure (33–35).



$R = R^2 = \text{Me}, R^1 = \text{H, Alk};$

$R = \text{H, Me, MeO, MeSO}_2, R^2 = \text{H, Br}, R^1 = \text{SMe, SO}_2\text{Me, OMe}$

The above-mentioned procedure and some of its modifications were also used for the generation of various unstable nitrile oxides. In this section, only those reactions in which nitrile oxides were isolated or identified by physical methods will be discussed in detail. References will be given only if nitrile oxides are transformed *in situ* to other products.

Thus, the bromoformonitrile oxide  $\text{BrCNO}$  was generated in the gas phase from dibromoformaldoxime by pyrolysis or by a chemical reaction with  $\text{HgO(s)}$  or  $\text{NH}_3(\text{g})$  (13). Polyfluoroalkanecarbonitrile oxides were generated from the respective hydroximoyl bromides and triethyl amine (36). Generation of ethoxycarbonylformonitrile oxide from ethyl chloro(hydroxyimino)acetate in the ionic liquids (1-butyl-3-methyl-1*H*-imidazolium tetrafluoroborate or hexafluorophosphate) and its *in situ* reaction with ethyl acrylate gave 4,5-dihydro-3,5-isoxazole-dicarboxylic acid diethyl ester (37). Recently, a procedure was used for the generation of nitrile oxides from aldoximes, in water or in aqueous tetrahydrofuran (THF), and subsequent *in situ* transformations by intra- or intermolecular 1,3-cycloaddition reactions. This simple though prolonged (18–72h) procedure gives practically quantitative yields (38).

Hydroximoyl halides can be readily prepared by halogenation of oximes using various reagents. As one of rather new reagents, the hydrogen chloride/*N*,*N*-dimethylformamide/ozone system (39) was used for the preparation of different hydroximoyl chlorides  $\text{RCCl=NOH}$  ( $R = \text{Ar, 5-nitro-2-furyl, PhCO, } t\text{-Bu}$ ) as precursors of nitrile oxides. However, most useful for both two-step and one-step (usually in the presence of  $\text{Et}_3\text{N}$ ) procedures are *N*-bromo- (40, 41) and *N*-chlorosuccinimides (42–44). Other *N*-halogen-substituted compounds such as chloramine-T (45), trichloroisocyanuric acid (46), and *N*-(*t*-butyl)-*N*-chlorocyanamide (47) were also used for the oxidative dehydrogenation of aldoximes.

Dehydrochlorination of hydroximic acid chlorides for generation of nitrile oxides can also be performed using organotin compounds such as  $(\text{SnBu}_3)_2\text{O}$  or  $\text{SnPh}_4$  (48, 49). The reaction proceeds under mild conditions, *O*-stannylated aldoximes like  $\text{RCH=NOSnBu}_3$  being thought to be key intermediates.

Thermal dehydrochlorination of hydroximoyl chlorides affords nitrile oxides (50–52). *O*-Ethoxycarbonylbenzohydroximoyl chloride, generating benzonitrile oxide, was used as a stable nitrile oxide precursor, which was efficiently used in 1,3-cycloaddition reactions with alkenes (53).

Direct oxidation of oximes is prospective promising procedure for the generation of nitrile oxides. Mercury(II) acetate (54), dimethyldioxirane (55), ceric

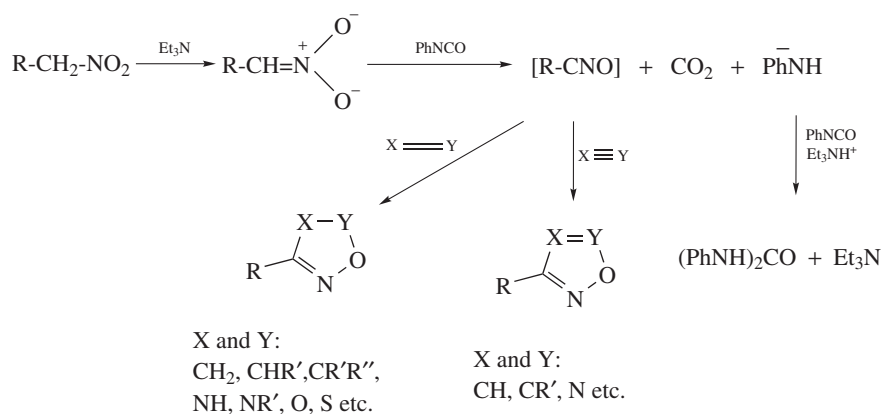
ammonium nitrate (56), and hypervalent iodine compounds, such as iodobenzene dichloride (57), iodosylbenzene (58), diacetoxy iodobenzene (59) were used as oxidants. Manganese(IV) oxide was also found to oxidize aldoximes to nitrile oxides, the best results being obtained with hydroximinoacetates as nitrile oxide precursors (60).

### 1.2.2. Formation from Aliphatic Nitro Compounds

Generation of nitrile oxides by the Mukaiyama procedure, *viz.*, dehydration of primary nitroalkanes with an aryl isocyanate, usually in the presence of  $\text{Et}_3\text{N}$  as a base, is of high importance in nitrile oxide chemistry. Besides comprehensive monographs (4, 5), some data concerning the procedure and its use in organic synthesis can be found in References 61 and 62.

Dehydration of primary nitroalkanes results in unstable nitrile oxides and, therefore, is limited by *in situ* transformation of the latter, for the preparation of various stable products, mainly those of 1,3-dipolar cycloaddition (Scheme 1.4).

As an example of the “classic” Mukaiyama procedure, one might mention cycloaddition of nitrile oxides, generated by reaction of primary nitroalkanes with *p*-chlorophenylisocyanate in the presence of a catalytic amount of  $\text{Et}_3\text{N}$ , to diethyl vinylphosphonate or diethyl propargylphosphonate affording the corresponding 2-isoxazolines or isoxazole, bearing the phosphonate group, in good yields (63). Many reagents, other than arylisocyanates, have been tested for the dehydration of nitroalkanes, among them  $\text{POCl}_3$ ,  $\text{AcCl}$ ,  $\text{Ac}_2\text{O}$ ,  $\text{BzCl}$ , and  $\text{MeSO}_2\text{Cl}$  (64). A rather “exotic” *p*-toluenesulfonyl chloride –  $\text{K}_2\text{CO}_3$  – 18-crown-6 system was used in the synthesis of annulated  $\Delta^2$ -isoxazolines starting from primary nitroalkanes (including functionalized ones) and cyclopentenes (65). There was also reported (66) the successful generation of nitrile oxides from primary nitro compounds by using thionyl chloride and triethylamine. Generation of nitrile oxides from nitromethyl ketones by the action of Ce(III) or Ce(IV) ammonium



Scheme 1.4

nitrate in the presence of formic acid has been described (67). Formation of nitrile oxides was also reported for the action of Mn(III) acetate on nitroacetate esters (68) and for the reaction of phosphorus trichloride with nitronate anion generated from  $\beta$ -nitrostyrene (69).

Nitrile oxides can be generated not only from primary but also from some functionalized secondary nitroalkanes. Thus, ethyl 2-nitroacetoacetate readily eliminates the acetic acid moiety using a AcOH–Ac<sub>2</sub>O mixture in the presence of a catalytic amount of strong mineral acid, for example, H<sub>2</sub>SO<sub>4</sub>, at room temperature to give ethoxycarbonylformonitrile oxide (70). Aroylformonitrile oxides were generated in a nitrating mixture from 1,3-diketones such as 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1,3-butanedione and its 4,4-difluoro and 4,4,4-trifluorosubstituted derivatives (71).

Generation of nitrile oxides can also proceed by the action of “neutral” or basic reagents, for example, *tert*-butyl carbonate (72) or 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, both in the presence of a catalytic amount of 4-(dimethylamino)pyridine (73), the latter with microwave activation. Some primary nitro compounds, are activated by electron-withdrawing substituents in a vicinal position such as in acetylnitromethane, benzoylnitromethane, ethyl nitroacetate, and nitro(phenylsulfonyl)methane generate nitrile oxides by the action of tertiary amines, preferably, 1,4-diazabicyclo[2.2.2]octane (DABCO) (74).

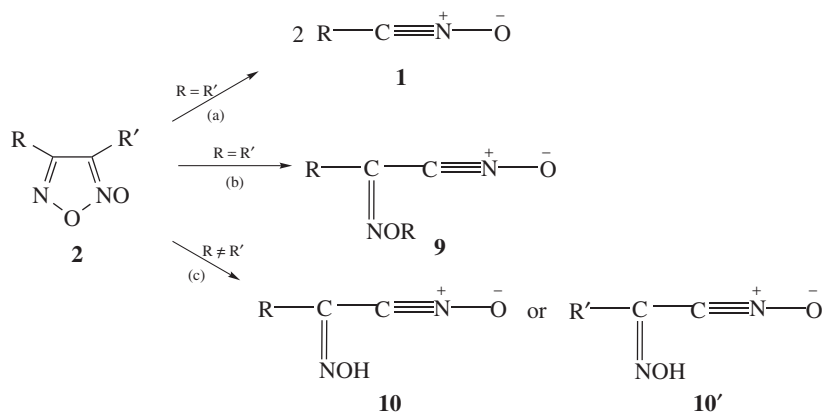
Highly efficient modifications of Mukaiyama’s procedure, convenient for combinatorial syntheses, were reported recently, namely *the polymer-supported synthesis of isoxazolines via nitrile oxides*, starting from primary nitroalkanes, in a one-pot process (75) and by microwave activation of the process (73).

### 1.2.3. Formation by Cycloreversion

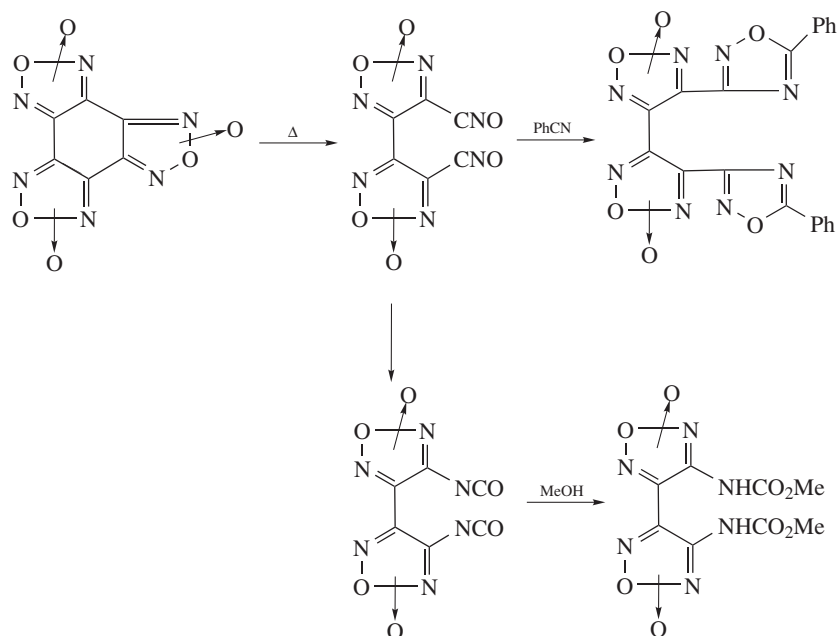
Dimerization of nitrile oxides to furoxans (Scheme 1.2) becomes reversible at elevated temperatures, by photolysis or electron impact, the first two methods being used in synthesis. The data concerning vacuum pyrolysis and photolysis of furoxans summarized in (76) are of great interest. Both formation of furoxans and their thermolytic transformation to nitrile oxides are comprehensively presented in a two-volume monograph (77, 78) and in a review (79). Three modes of the cycloreversion, depending on the nature of substituents in the furoxan molecule (5) are shown in Scheme 1.5. The cycloreversion of furoxan **2** to form two nitrile oxides **1** molecules [route (a)] is of main interest. Rearrangement [route (b)], which occurs mainly in diacylfuroxans affording  $\alpha$ -acyloximinonitrile oxides **9** as well as fragmentation [route (c)] leading to a mixture of  $\alpha$ -hydroximinonitrile oxides **10** and **10'** are of limited interest.

Stable furoxans are convenient starting compounds for generating short-lived nitrile oxides XCNO (X = ONC, NC, Cl, Br, and Me) by thermolysis (10, 11, 80, 81). The thermolysis of benzotrifuroxan (200°, in excess PhCN) proceeds (Scheme 1.6) with the cleavage of the C–C and O–N(O) bonds in only one furoxan ring to give bifuroxan bis(nitrile oxide). The latter undergoes further reactions such as cycloaddition with PhCN or conversion to bisisocyanate (82).

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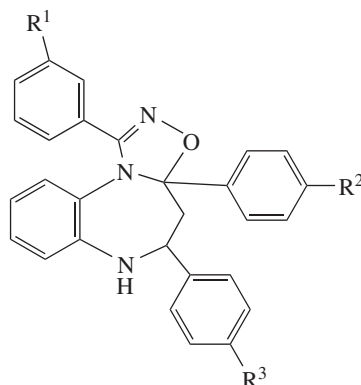


Scheme 1.5



Scheme 1.6

Cycloreversion with nitrile oxide formation is known not only in furoxans but also in isoxazolines, 1,2,4-oxadiazoles, furazans, and some other five-membered heterocycles (76). Such process, eliminating nitrile oxide fragment  $3-R^1C_6H_4C \equiv N^+O^-$ , was observed mass spectrometrically in 3a,4,5,6-tetrahydro-[1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine derivatives **11** (83).



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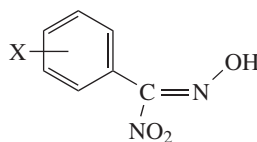
( $R^1 = \text{H, Br}$ ;  $R^2 = \text{H, OMe}$ ;  $R^3 = \text{H, OMe}$ )

#### 1.2.4. Other Methods

The methods considered in this section concern mainly reactions of nitro compounds.

The reaction of dinitrogen tetroxide with substituted dinitromethane salts  $\text{RC}(\text{NO}_2)=\text{NO}_2\text{K}$  [ $\text{R} = \text{Ph, 3-O}_2\text{NC}_6\text{H}_4, 3,5-(\text{O}_2\text{N})_2\text{C}_6\text{H}_3, 4\text{-MeO-3,5-(O}_2\text{N})_2\text{C}_6\text{H}_2, \text{EtO}_2\text{C, Me, MeO}_2\text{C}$ ] was carried out in the generation of nitrile oxides  $\text{RCNO}$  (84, 85). Using  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{14}\text{N}$  nuclear magnetic resonance (NMR) spectroscopy, it was shown that this reaction proceeds through dinitronitrosomethyl intermediates, of which one was isolated. The reaction occurs only when substituents capable of conjugation with the nitrile oxide fragment are present.

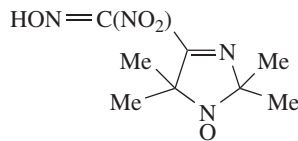
*Z*-Acetonitrolic acid rapidly loses  $\text{NO}_2^-$  to form unstable acetonitrile oxide, which could be detected by monitoring its subsequent reactions (86). Arylnitrolic acids **12** ( $\text{X} = p\text{-Cl, } m\text{-NO}_2, o\text{-NO}_2$ ) exist in the *E*-configuration and undergo slow loss of  $\text{NO}_2^-$  to give nitrile oxides. Subsequently it was shown (87) that nitrolic acids are converted to nitrile oxides in practically quantitative yields under neutral conditions (heating in THF).



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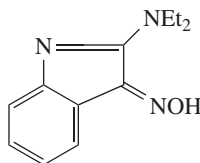
( $\text{X} = p\text{-Cl, } m\text{-NO}_2, o\text{-NO}_2$ )

Thermolysis of a stable radical 4-[(hydroxyimino)nitromethyl]-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl **13** gives the corresponding spin-labeled nitrile oxide. It was also identified in isoxazolines formed in cycloadditions with olefins (88).

**13**

Nitrile oxides are generated by photolysis of 1,2-diaryl-substituted nitroethylenes through the formation of an oxazetidine 2-oxide and its fragmentation (Scheme 1.7) (89).

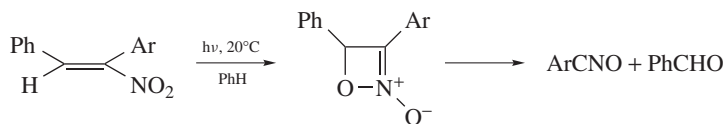
Nitro(imidoyl)ketene  $\text{PhN}=\text{C}(\text{NEt}_2)\text{C}(\text{NO}_2)=\text{CO}$  eliminates  $\text{CO}_2$  on heating and rearranges to 2-diethylamino-3-hydroximino-3*H*-indole **14**, presumably via nitrile oxide  $\text{PhN}=\text{C}(\text{NEt}_2)\text{C}-\text{N}^+\text{O}^-$  (90).

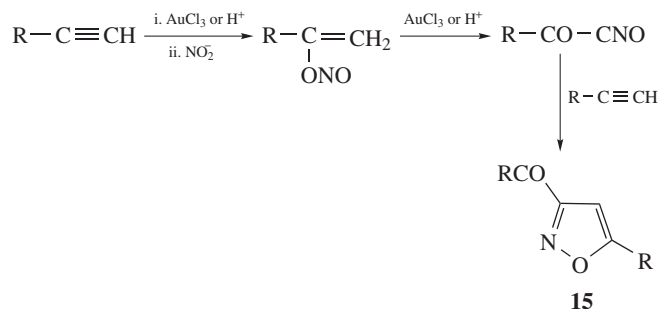
**14**

In alkali solutions, 5-nitro-2-furaldehyde forms an anion of (5-nitrofuran-2-yl)methanediol, which undergoes an irreversible redox ring-opening reaction to give mono(nitrile oxide) of  $\alpha$ -ketoglutaconic acid  $\text{HO}_2\text{CCOCH}=\text{CH}-\text{CNO}$ ,<sup>o</sup> the latter was identified as furoxan (91).

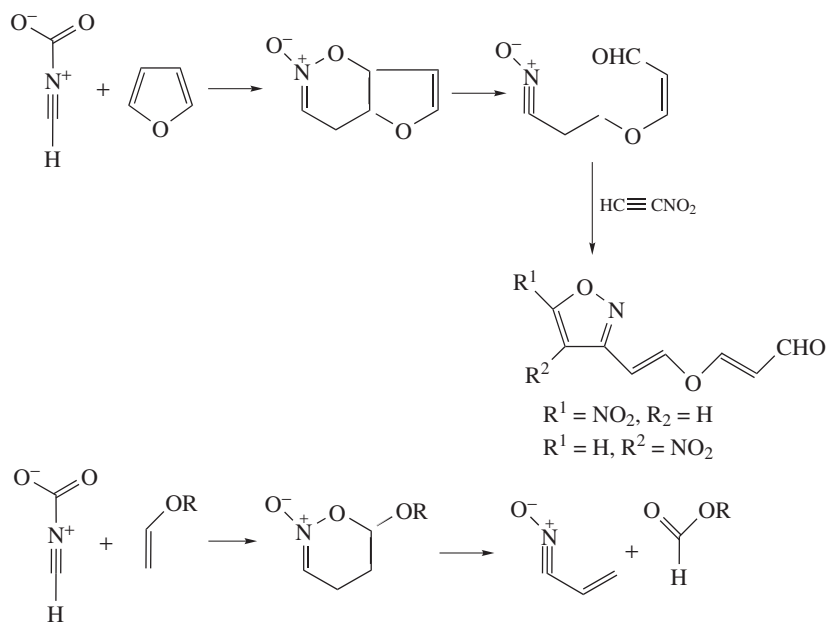
Very interesting transformations were reported in terminal alkynes  $\text{RC}\equiv\text{CH}$  ( $\text{R} = \text{alkyl, aryl, alkoxy, carboxylate, etc.}$ ). They react readily with nitric acid, in aqueous nitromethane (1:1) and in the presence of catalytic amounts of tetrabutylammonium tetrachloroaurate to give 3,5-disubstituted isoxazoles **15** in 35% to 50% isolable yield (92). The reaction might proceed via a nitrile oxide intermediate by attack of an electrophile ( $\text{AuCl}_3$  or  $\text{H}^+$ ) and of a nucleophile ( $\text{NO}_2^-$ ) on the triple bond to form a vinyl nitrite, which is converted to a nitrile oxide by the action of gold(III) or of nitric acid (Scheme 1.8).

Intermediate formation of nitrile oxides is, also proposed in reactions of nitroacetylene with furan and vinyl ethers (Scheme 1.9) (93) and of lithium (phenyl)acetylide with  $\text{N}_2\text{O}_4$  (94).

**Scheme 1.7**



Scheme 1.8



Scheme 1.9

Dehydration of O-silylated hydroxamic acids is used as a general method in the synthesis of nitrile oxides (95) in the presence of trifluoromethanesulfonic anhydride and triethylamine.

Methoxycarbonylformonitrile oxide is smoothly generated by  $\beta$ -elimination of methanol from *E*-N-methoxy-N-(methoxycarbonylmethylene)amine N-oxide,  $\text{MeO}_2\text{CCH}=\text{N}(\text{OMe})\text{O}$ , in the presence of a catalytic amount of boron trifluoride etherate (96).

Phosphorylated and thiophosphorylated diazo compounds,  $i\text{-Pr}_2\text{P}(\text{X})\text{C}(\text{N}_2)\text{SiMe}_3$  ( $\text{X} = \text{O}, \text{S}$ ) react with nitrosyl chloride to give  $\alpha$ -nitroso-diazo derivatives

which rapidly eliminate nitrogen to form  $i\text{-Pr}_2(\text{X})\text{CNO}$  (97). Similarly phosphorylated nitrile oxide,  $\text{R}_2\text{P}(\text{O})\text{CNO}$  ( $\text{R} = \text{morpholino}$ ) was prepared by treatment of  $\text{R}_2\text{P}(\text{O})\text{CHXCHO}$  ( $\text{R} = \text{morpholino}$ ;  $\text{X} = \text{Cl, Br}$ ) with  $\text{HNO}_2$  in  $\text{AcOH}$  (98).

Ammonium cerium(IV) nitrate on reaction with acetone or acetophenone generates acetyl- or benzoylformonitrile oxides, respectively (99). These nitrile oxides dimerize to furoxans and give, in the presence of alkenes and alkynes, 3-acetyl- or 3-benzoyl-4,5-dihydroisoxazoles and 3-acetyl- or 3-benzoylisoxazoles, respectively; the yield of the isoxazole derivatives was improved on using ammonium cerium(III) nitrate tetrahydrate–formic acid (99).

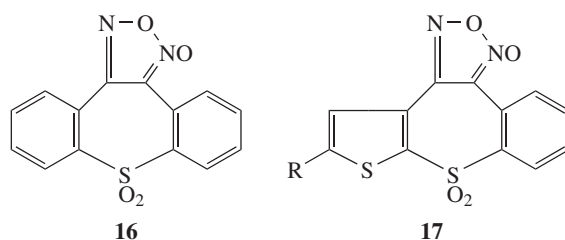
### 1.3. REACTIONS OF NITRILE OXIDES

Some routes of chemical transformations of nitrile oxides connected with the problem of their stability were briefly discussed in Section 1.2. Here only two types of such reactions, proceeding in the absence of other reagents, *viz.*, dimerization to furoxans and isomerization to isocyanates, will be considered. All other reactions of nitrile oxides demand a second reagent (in some cases the component is present in the same molecule, and the reaction takes place intramolecularly): namely, *deoxygenation*, *addition of nucleophiles*, and *1,3-dipolar cycloaddition reactions*. Also, some other reactions are presented, which differ from those mentioned above.

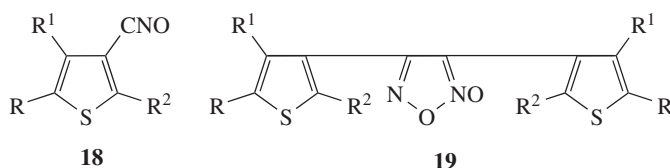
Probably, the diversity of nitrile oxide chemistry is not conducive to writing reviews related to all aspects of their reactivity. Therefore, only several references can be mentioned, which are connected with several topics in this section. Among these are the reviews devoted to the photochemistry of N-oxides (including nitrile oxides) (100) and reactions of nitrilium betaines with heteroaromatic compounds (101). Other references on reviews will be given in corresponding subsections or paragraphs.

#### 1.3.1. Dimerization and Isomerization

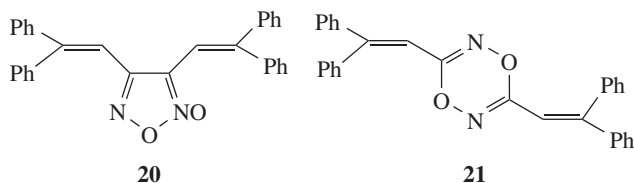
Dimerization and isomerization are conveniently considered together, since reaction routes for the same group of nitrile oxides frequently depends on reaction conditions or differences in substituent(s). Dimerization of unstable nitrile oxides proceeds during their generation, when another reaction partner is absent, while isomerizations demand, thermal or photostimulation (97). As a rule, sterically stabilized nitrile oxides do not give furoxans, and their heating leads to isomeric isocyanates. This is the case, for example, for stable bis(nitrile oxides) of the benzene series (30). However, there are stable nitrile oxides, which can dimerize. Thus, stable *o*-sulfonylbenzonitrile oxides undergo thermal dimerization to furoxans, (2,2'-sulfonylbis(benzonitrile oxide) on heating rearranges to tetracyclic furoxan **16**, a dibenzothiepinofurazane derivative (32). Similarly, 2-thienylphenylsulfon-3,2'-dicarbonitrile oxides give benzothienothiepinofurazan trioxides **17** ( $\text{R} = \text{H, Me}$ ) at reflux in benzene (102).



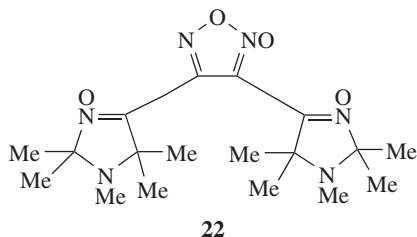
The stability of *o*-sulfonylbenzonitrile oxides and their thiophene analogs probably depends on electronic factors. The same factors do not prevent dimerization, as can be seen from data concerning several differently substituted nitrile oxides of the thiophene series (103). Sterically stabilized 3-thiophenecarbonitrile oxides **18** ( $R = R^1 = R^2 = \text{Me}$ ;  $R = R^2 = \text{Me}$ ,  $R^1 = i\text{-Pr}$ ), when boiled in benzene or toluene, isomerized to isocyanates (isolated as ureas on reaction with aniline) while nitrile oxides **18** with electron-withdrawing substituents ( $R^1$  and/or  $R^2 = \text{SO}_2\text{Me}$ , Br) dimerized to form furoxans **19**.



3,3-Diphenylacrylonitrile oxide, exhibiting unexpected stability, presumably due to delocalization, dimerized to furoxan **20** or 1,4,2,5-dioxadiazine **21** (22).



Diaryl- (85), diaroyl- (71), bis(4-substituted-1,2,5-oxadiazol-3-yl)furoxans (104) as well as “exotic” 1,2,2,5,5-pentamethyl-4-(nitromethyl)-3-imidazoline 3-oxide-derived furoxan **22** (105) were obtained via corresponding nitrile oxides.



Dimethyl furoxan-3,4-dicarboxylate was obtained from methoxycarbonylformonitrile oxide (96). Treatment of nitroacetamides  $RR^1NCOCH_2NO_2$  [ $R, R^1 = H, Me; Me, Me; H, Ph; RR^1 = (CH_2)_4$ ] with  $SOCl_2$  afforded furoxan-3,4-dicarboxamides (106).

The nitrile oxide dimerization mechanism was subjected to quantum chemical investigation. Semiempirical methods MNDO for acetonitrile oxide and AM1 for dimethoxyphosphorylformonitrile oxide (107) as well as density functional theory (DFT) calculations (B3LYP/6-31G\*) for acetonitrile oxide and *p*-chlorobenzonitrile oxide (108) agree that these reactions proceed in two steps. They involve dinitroso alkene intermediates, the limiting stage depending on C–C bond formation. The retardation of dimerization in aromatic nitrile oxides arises from the interruption of conjugation between the nitrile oxide and aryl groups in the C–C bond formation step (108).

There are very interesting experimental data demanding theoretical interpretations: both dimerization and cycloaddition with dipolarophiles of some aromatic nitrile oxides  $RCNO$  ( $R = Ph, 2-ClC_6H_4, 2,6-Cl_2C_6H_3$ ) can be inhibited by a catalytic amount of  $(4-BrC_6H_4)_3N^+ SbCl_6^-$  (109).

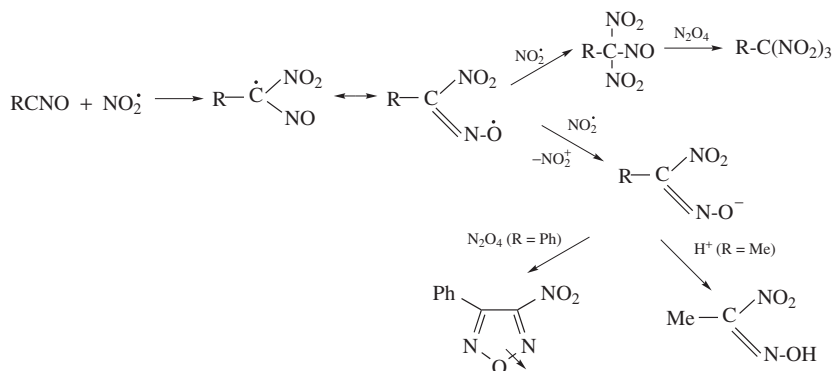
### 1.3.2. Deoxygenation

Deoxygenation of nitrile oxides demands a reducing agent. Amongst those, compounds of phosphorus(III) like  $PPh_3$  (97) are useful. The reaction gives respectively, nitrile and P-oxide. Reactions of nitrile oxides with phospholes is of special interest. Phospholes undergo Diels–Alder reactions at high pressure rather than 1,3-dipolar cycloadditions with nitrile oxides but the latter are deoxygenated in the process (110).

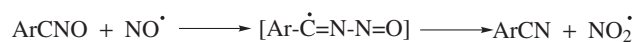
Intriguing results, concerning both deoxygenation and dimerization of nitrile oxides were obtained on investigation of reactions of the latter and of furoxannitric acids with nitrogen oxides (111–113). Reaction of acetonitrile oxide with  $N_2O_4$  in  $CH_2Cl_2$  led to the corresponding nitrolic acid  $MeC(:NOH)NO_2$  while hydroxyiminonitrile oxide  $PhC(:NOH)CNO$  gave a mixture of 4-nitro-3-phenyl- and 3-nitro-4-phenylfuroxans (111). Under similar conditions, benzonitrile oxides  $RC_6H_4CNO$  ( $R = H, 3-, 4-O_2N, 4-Br$ ) afforded aryltrinitrosomethanes  $RC_6H_4C(NO)_3$  (111). A probable mechanism of the reactions, taking into account the radical nature of nitrogen dioxide (111), is presented in Scheme 1.10.

Previously unknown deoxygenation was reported with *o*-, *m*-, and *p*-nitrobenzonitrile oxides on reactions with NO (112); this was interpreted as being due to the radical nature of the latter (Scheme 1.11).

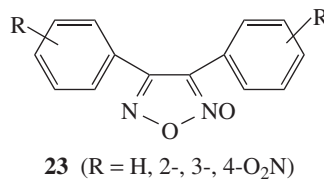
Deoxygenation by NO proceeds rather slowly, and nitrile oxides take part simultaneously in two other reactions: (a) dimerization to furoxans **23** and (b) interaction with  $NO_2$  which is formed in the reaction, to give aryltrinitromethanes. The most unstable of the known arenecarbonitrile oxides, benzonitrile oxide, owing to its fast dimerization gives no phenyltrinitromethane but only furoxans. Products similar to both cited reactions are formed with  $N_2O_3$  because of its known equilibrium with NO and  $NO_2$  (112).



Scheme 1.10



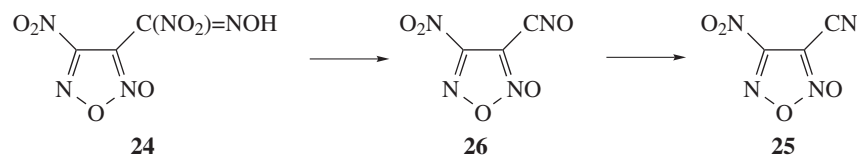
Scheme 1.11



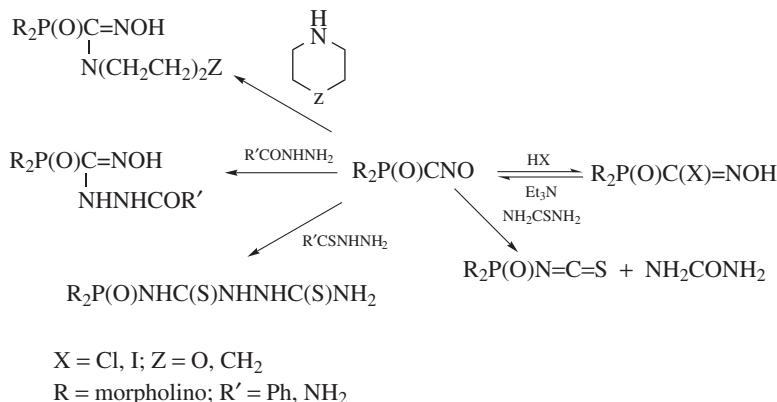
Investigation of the reaction of furoxannitrolic acids with nitrogen tetroxide (113) showed that the first step is the formation of the corresponding intermediate nitrile oxides followed by their transformations. Thus, treating nitrolic acid **24** with N<sub>2</sub>O<sub>4</sub> in CHCl<sub>3</sub> resulted in furoxancarbonitrile **25** via intermediate nitrile oxide **26** (Scheme 1.12). It seems probable that nitrogen tetroxide plays the role of a reducing agent in the nitrile oxide deoxygenation.

### 1.3.3. Addition of Nucleophiles and Further Transformations

Nucleophiles react with nitrile oxides in a 1,3-nucleophilic addition pattern. The carbon atom of the CNO group is being attacked by the negatively polarized part



Scheme 1.12



Scheme 1.13

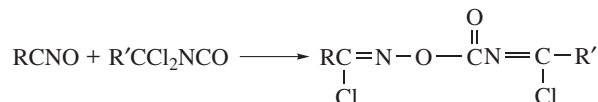
of the nucleophile (by an anion as a limiting case), while its positively polarized or charged part (proton in the simplest case) adds to the oxygen atom of the fulminate moiety. 1,3-Addition reactions proceed with halogen, N-, O-, S-, C-, and other nucleophiles. The adducts formed might undergo further transformations.

Thus, (dimorpholinophosphoryl)formonitrile oxide undergoes 1,3-addition reactions with HCl, HI, primary and secondary amines, acylhydrazines, and even with thiourea or thiosemicarbazide (Scheme 1.13) (98). The former gives (dimorpholinophosphoryl)isothiocyanate and urea. Those products might arise from a retro destruction of the unstable 1,3,5-oxathiazoline. The latter transforms to the isothiocyanate, the product of addition of a second molecule of thiosemicarbazide. (98).

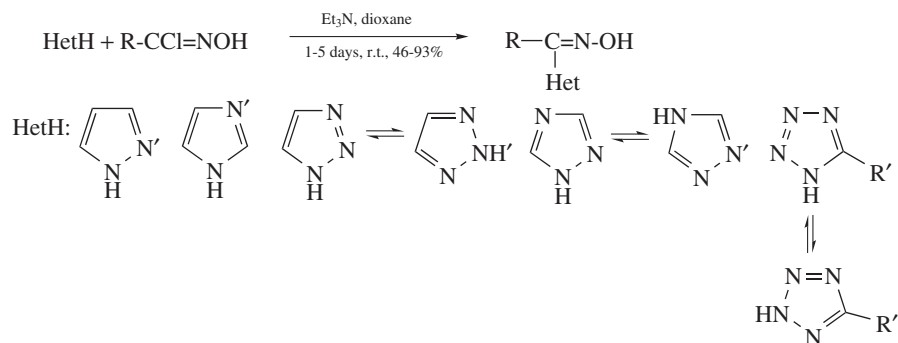
Related (diisopropoxyphosphoryl)- and (diisobutoxyphosphoryl)formonitrile oxides (114), generated in basic media from the corresponding oximes react *in situ* with alcohols, phenols, alkanethiols, thiophenols, aliphatic and aromatic primary amines, hydrazines and hydrazides as well as 4-aminoantipyrine to give hydroxymates, thiohydroxymates, and amidoximes, respectively. It is important to note that the addition is stereoselective and gives *E*-adducts with the exception of (i-PrO)<sub>2</sub>P(O)C(:NOH)OMe, which is formed as a 1:1 mixture of *E* and *Z* isomers.

3-Arylsydnone-4-carbonitrile oxides add hydrogen chloride to give the corresponding hydroximoyl chlorides on treatment with HCl/EtOH (115). Reactions of nitrile oxides, RC-NO (R = mesityl, duryl, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, PhCO) with 1,1-dichloroalkyl isocyanates, R'CCl<sub>2</sub>NCO (R' = CCl<sub>3</sub>, CF<sub>3</sub>) in benzene containing Et<sub>3</sub>N lead by [2 + 3] cycloaddition (116) to the corresponding O-acylated chloro-oximes RCCl=NO<sub>2</sub>CN=CClR in 58% to 89% yield, rather than to oxadiazolidinone adducts (Scheme 1.14).

Nitrile oxides add to various N-nucleophiles, bearing N-H bonds to give amidoximes. These nucleophiles comprise primary and secondary amines, amides, N-heterocycles and so on. Thus, N-unsubstituted pyrazole, imidazole, 1,2,3- and



Scheme 1.14



R = *t*-Bu, Ph<sub>2</sub>CH, Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 2-pyridyl

R' = H, Me, Et, *i*-Pr, Ph, 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, PhH<sub>2</sub>, MeO, MeS, EtS, Me<sub>2</sub>NH, PhNH, NH<sub>2</sub>

Scheme 1.15

1,2,4-triazoles or tetrazoles and its 5-substituted derivatives give hydroximoylazoles (Scheme 1.15) on addition to nitrile oxides, which are generated from the corresponding hydroximoyl chlorides (117).

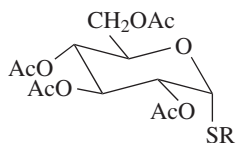
The 1,3-dipoles were generated by the addition of Et<sub>3</sub>N' in 20% excess. Only imidazole was basic enough to generate a nitrile oxide in the absence of triethylamine. Due to prototropic tautomerism, reactions of triazoles and tetrazoles led to mixtures of two isomers. With unsubstituted pyrazole and imidazole only one hydroximoylazole was formed (117).

Interesting examples of the addition of N-nucleophiles to nitrile oxides are syntheses of chelated *Z*-amidoxime, N-[2-(dimethylaminomethyl)phenyl]mesitylene-carboamidoxime (118), and pyranosyl amidoximes (119) from the respective nitrile oxides and amines. Aromatic aldoximes undergo unusual reactions with chloramine-T (4 equiv, in refluxing MeOH). N-(*p*-tolyl)-N-(*p*-tosyl)benzamides are formed via addition of 2 equiv of chloramine-T to the intermediate nitrile oxide followed by elimination of sulfur dioxide (120).

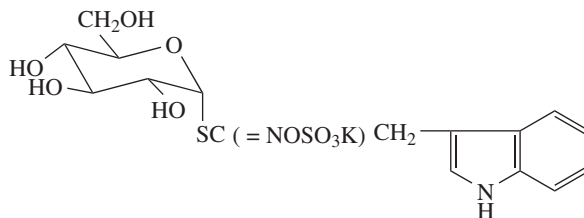
Addition of ammonia as a model nucleophile to nitrile oxides was studied by a semiempirical MNDO method, for fulminic acid and acetonitrile oxide (121). The reaction is exothermic and proceeds in two steps. The first (and rate-determining) step is the formation of a zwitterionic structure as intermediate. The second step, which involves transfer of a proton, is very fast and leads to the formation of *Z*-amidoximes in accordance with experimental data. Similar results were

obtained by the same authors, for nitrile oxides, cited above, and for benzonitrile oxide considering water as an O-nucleophile (122).

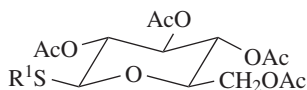
S-Nucleophiles are very reactive in 1,3-addition reactions with nitrile oxides. A series of  $\alpha$ -glucosinolates **27** ( $R = CR^1=NOH$ ;  $R^1 = Ph, CH_2Ph, CH_2CH_2Ph, (E)-CH=CHPh, 3\text{-indolylmethyl}$ ) was prepared by addition reactions of thiol **27** ( $R = H$ ) with nitrile oxides (123). The indolyl-substituted glucosinolate was then converted to  $\alpha$ -glucobrassicin **28**.

**27**

$R = CR^1 = NOH$ ;  $R^1 = Ph, CH_2Ph, CH_2CH_2Ph, (E)-CH=CHPh, 3\text{-indolylmethyl}$

**28**

Similarly, adducts **29** were prepared starting from 2,3,4,6-tetra-O-acetyl-1-thio- $\beta$ -D-glucopyranose (124).

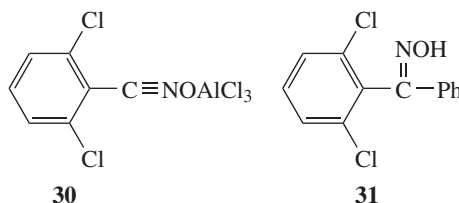
**29**

Nitrile oxides were generated from oximes  $RCH:NOH$  by successive treatment with chlorine and  $Et_3N$  and used *in situ* without further purification. Only benzonitrile oxide and phenylacetone nitrile oxide afforded normal adducts in high yields. The reactions generated from nitrile oxides with *p*-, *m*-, and *o*-methoxybenzaldehyde oximes gave adducts, chlorinated in the benzene ring, while the reactions with nitrile oxides, generated from *p*-chloro- and *p*-nitrobenzaldehyde oximes gave no adducts.

Addition of C-nucleophiles to nitrile oxides is of special interest. There are examples of reactions with both carbanions and neutral carbon nucleophiles. To the former group belong reactions of nitrile oxides with organometallic

compounds leading to corresponding oximes (125). These reactions proceed with or without the aid of a Lewis acid depending on the nucleophilic nature. Thus, reactions of aromatic nitrile oxides with BuLi, without a Lewis acid catalyst or with Et<sub>2</sub>Zn catalyzed by BF<sub>3</sub>·OEt<sub>2</sub> afford ketoximes ArC(:NOH)R (Ar = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, R = Bu, Et) in 94% to 99% yield.

Similar reactions proceeding with aromatic and heteroaromatic compounds can be classified as unconventional types of aromatic electrophilic substitution. Extremely reactive aromatic substrates react with nitrile oxides without a catalyst. In other cases reactions demand stimulation with a Lewis acid. Thus, ethyl cyanoformate N-oxide EtO<sub>2</sub>CC≡NO reacts at the 3-position of 2,5-dimethyl- and 2,5-diphenylpyrrole to give the corresponding hydroxyimino esters (126). Nitrile oxides complexed with Lewis acids have increased electrophilic character at the nitrile carbon atom and are used as hydroxynitrilium ion equivalents with common aromatic compounds. Thus, treating 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CCl=NOH with AlCl<sub>3</sub> gives the nitrile oxide–Lewis acid complex **30**, which reacts with benzene to afford oxime **31** in 70% yield (127).



Nitrile oxide–BF<sub>3</sub> complexes can also be used as electrophilic moieties with aromatic systems. Introducing BF<sub>3</sub> into a mixture of 2,6-dichlorobenzonitrile oxide and mesitylene in hexane, gave 88% *Z*-2',6'-dichloro-2,4,6-trimethylbenzophenone oxime (128).

Nitrile oxides react *in situ* with formaldehyde dimethylhydrazone (129) to give oxime-hydrazones RC(:NOH)CH:NNMe<sub>2</sub> (R = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, MeCO, MeC(:NOH)). The reaction is performed on treatment of oximes with CH<sub>2</sub>:NNMe<sub>2</sub> in the presence of Et<sub>3</sub>N without isolation of the intermediate nitrile oxides.

### 1.3.4. 1,3-Dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition reactions are of main interest in nitrile oxide chemistry. Recently, reviews and chapters in monographs appeared, which are devoted to individual aspects of these reactions. First of all, problems of asymmetric reactions of nitrile oxides (130, 131), including particular aspects, such as asymmetric metal-catalyzed 1,3-dipolar cycloaddition reactions (132, 133), development of new asymmetric reactions utilizing tartaric acid esters as chiral auxiliaries (134), and stereoselective intramolecular 1,3-dipolar cycloadditions (135) should be mentioned. Other problems considered are polymer-supported 1,3-dipolar cycloaddition reactions, important, in particular, for combinatorial chemistry

(136, 137), application of cyclodextrin-based catalysts and molecular reactors in 1,3-dipolar cycloaddition reactions of nitrile oxides (138, 139).

In the scope of this subsection, competitive 1,3-cycloaddition of nitrile oxides to carbon-carbon and carbon-heteroatom multiple bonds are of special interest. Competition between carbon-carbon and carbon-nitrogen double bonds in 1,3-cycloaddition reactions with benzonitrile oxides is the subject of a review (140). 1,3-Dipolar cycloaddition reactions of *o*-benzoquinones are summarized in Reference 141. Depending on the nature of the substrates and of the substituents, benzonitrile oxides add to both C=C and C=X bonds.

Several papers concerning modern modifications of 1,3-cycloaddition reactions of nitrile oxides should be also mentioned. An efficient solution-phase combinatorial synthesis of isoxazoles and isoxazoles, using [2 + 3] cycloaddition reaction of nitrile oxides with olefins and alkynes, followed by precipitation of the products as HCl salts has been developed (142). A general method for the liquid-phase syntheses of isoxazoles and isoxazoles via a 1,3-dipolar cycloadditions is elaborated. Poly(ethylene glycol)-supported alkyne or alkene react with nitrile oxides, generated *in situ* from aldioximes followed by elimination from the poly(ethylene glycol) support, to give target products in good yield and purity (143).

One-pot 1,3-dipolar cycloaddition of nitrile oxides generated *in situ* on solid phase, in the presence of a variety of dipolarophiles, provided a library of isoxazoles and isoxazoles (144). (4*S*)-*p*-Hydroxybenzyl-1,3-oxazolidin-2-one was used as a solid-supported chiral auxiliary in asymmetric 1,3-dipolar cycloadditions (145). It was also shown that Mg(II) cation (from magnesium perchlorate) catalyzes asymmetric 1,3-dipolar cycloaddition reactions using solid-supported oxazolidinone chiral auxiliaries (146). The results obtained support a reaction mechanism, which proposes the coordination of the Mg(II) to the dicarbonyl fragment of the chiral auxiliary. The resin-bound chiral auxiliaries could be recycled once, with little loss in regio- or stereoselectivity, but a second recycle gave products with significantly decreased regio- and stereoselectivities.

It was found that 2-propenyloxymagnesium bromide reacts much more readily with nitrile oxides than other known dipolarophiles of electron-deficient, electron-rich, and strained types, including 3-buten-2-one, ethyl vinyl ether, and norbornene, respectively (147). Therefore, this BrMg-alkoxide is highly effective in various nitrile oxide cycloaddition reactions, including those of nitrile oxide/Lewis acid complexes.

An unusual solvent effect was observed in cycloadditions of aromatic nitrile N-oxides with alkyl-substituted *p*-benzoquinones in ethanol-water (60:40): the reaction rates were 14-fold greater than those in chloroform (148). The use of ion pairs to control nitrile oxide cycloadditions was demonstrated. A chiral auxiliary bearing an ionic group and an associated counterion provides enhanced selectivity in the cycloaddition: the intramolecular salt effect controls the orientation of the 1,3-dipolar reagent (149).

Microwave irradiation promotes the 1,3-dipolar activity of nitrile oxides generated from hydroximoyl chlorides. They interacted *in situ* over alumina with alkenes and alkynes (150). The effect was demonstrated in reactions of

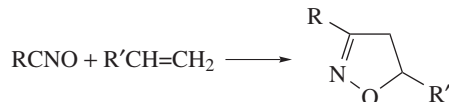
4-chlorobenzhydroximoyl chloride with dimethyl 2-butenedioate and dimethyl acetylenedicarboxylate. Cycloadditions of mesitonitrile oxide to various dipolarophiles in supercritical carbon dioxide were studied. The magnesium bromide-mediated cycloaddition to pent-1-en-3-ol gave higher stereoselectivity than reactions in most conventional solvents (151).

1,3-Dipolar cycloaddition reactions of nitrile oxides were studied using various computational methods. Thus, tendency of some thiophene nitrile oxides to undergo intramolecular 1,3-dipolar cycloaddition was evaluated by quantitative structure-activity relationship (QSAR) indices (152), and some nitrile oxides and dipolarophiles were characterized quantitatively by the global electrophilicity power,  $\omega$  (153). For several nitrile oxides, *ab initio* (4–31G\*) and semiempirical (MNDO, AM1) quantum chemical calculations demonstrated that all the nitrile oxides including phosphoryl nitrile oxides are electron-donating dipoles, for which in their competing electronic and steric interactions in [2 + 3] cycloaddition reactions, the latter are determinant (154). Theoretical studies of stereoselectivity of intramolecular 1,3-dipolar cycloaddition using *ab initio* methods, semiempirical methods, and a tandem quantum mechanic-molecular mechanic method were also performed (155). In a review (156) data, concerning transition-state modeling with empirical force fields were analyzed for various reactions including nitrile oxide cycloaddition.

**1.3.4.1. Intermolecular Cycloaddition at the C=C Double Bond** Addition at the C=C double bond is the main type of 1,3-cycloaddition reactions of nitrile oxides. The topic was treated in detail in Reference 157. Several reviews appeared, which are devoted to problems of regio- and stereoselectivity of cycloaddition reactions of nitrile oxides with alkenes. Two of them deal with both inter- and intramolecular reactions (158, 159). Important information on regio- and stereochemistry of intermolecular 1,3-dipolar cycloaddition of nitrile oxides to alkenes was summarized in Reference 160.

Individual aspects of nitrile oxide cycloaddition reactions were the subjects of some reviews (161–164). These aspects are as follows: preparation of 5-hetero-substituted 4-methylene-4,5-dihydroisoxazoles by nitrile oxide cycloadditions to properly chosen dipolarophiles and reactivity of these isoxazolines (161), 1,3-dipolar cycloaddition reactions of isothiazol-3(2*H*)-one 1,1-dioxides, 3-alkoxy- and 3-(dialkylamino)isothiazole 1,1-dioxides with nitrile oxides (162), preparation of 4,5-dihydroisoxazoles via cycloaddition reactions of nitrile oxides with alkenes and subsequent conversion to  $\alpha,\beta$ -unsaturated ketones (163), and [2 + 3] cycloaddition reactions of nitroalkenes with aromatic nitrile oxides (164).

Cycloaddition with nitrile oxides occur with compounds of practically any type with a C=C bond: alkenes and cycloalkenes, their functional derivatives, dienes and trienes with isolated, conjugated or cumulated double bonds, some aromatic compounds, unsaturated and aromatic heterocycles, and fullerenes. The content of this subsection is classified according to the mentioned types of dipolarophiles. Problems of relative reactivities of dienophiles and dipoles, regio- and stereoselectivity of nitrile oxide cycloadditions were considered in detail by Jaeger and



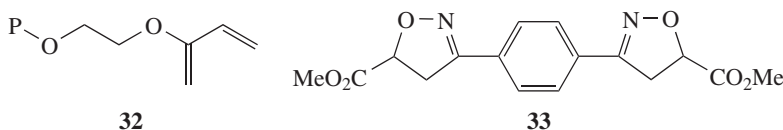
Scheme 1.16

Colinas (5). These aspects are not treated here separately but data omitted in Reference 5 or published after 2001 are included in individual reactions and types of dipolarophiles.

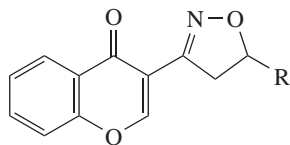
**1.3.4.1.1. Alkenes** Unsubstituted ethylene, though highly reactive as a dipolarophile (5), is not conveniently used because of its physical state. Its adducts are of lower interest compared to those formed from other olefins. Terminal alkenes ( $\text{R}'$  is various alkyl, cycloalkyl, aryl groups) add to nitrile oxides regioselectively to give 3,5-disubstituted isoxazolines (Scheme 1.16) and frequently serve for trapping unstable and characterizing stable nitrile oxides. Styrene is one of the most popular dipolarophiles. (30–33, 105, 165–167).

This regioselectivity is practically not influenced by the nature of substituent  $\text{R}$ . 3,5-Disubstituted isoxazolines are the sole or main products in [3 + 2] cycloaddition reactions of nitrile oxides with various monosubstituted ethylenes such as allylbenzene (99), methyl acrylate (105), acrylonitrile (105, 168), vinyl acetate (168) and diethyl vinylphosphonate (169). This is also the case for phenyl vinyl selenide (170), though subsequent oxidation–elimination leads to 3-substituted isoxazoles in a one-pot, two-step transformation. 1,1-Disubstituted ethylenes such as 2-methylene-1-phenyl-1,3-butanedione, 2-methylene-1,3-diphenyl-1,3-propanedione, 2-methylene-3-oxo-3-phenylpropanoates (171), 2-methylene-1,3-dichloropropane, 2-methylenepropane-1,3-diol (172) and 1,1-bis(diethoxyphosphoryl) ethylene (173) give the corresponding 3-R-5,5-disubstituted 4,5-dihydrooxazoles.

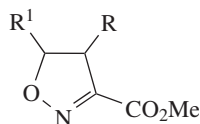
An efficient one-pot synthesis of isoxazolines, using soluble polymer-supported acrylate has been described (174). Thus, the addition of 1,4-benzenedicarbonitrile  $\text{N,N}'$ -dioxide (generated from  $\text{N,N}'$ -dihydroxy-1,4-benzenedicarboximidoyl dichloride) to polyethylene glycol-supported 2-propenoic acid 2-hydroxyethyl ester **32** ( $\text{P}$  = polyethylene glycol support) followed by cleavage of the bond with the support gave 3,3'-(1,4-phenylene)bis[4,5-dihydro-5-isoxazolecarboxylic acid] di-Me ester (**33**) in 97% yield.



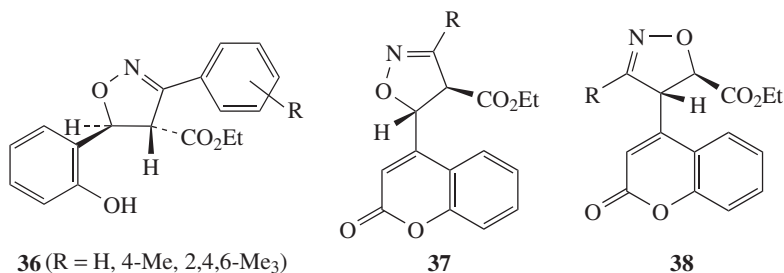
Chromone-3-carbonitrile oxide obtained from 3-formylchromone oxime by bromination and subsequent dehydrobromination underwent cycloaddition reactions with terminal alkenes to give isoxazolines **34** (175).

**34** (R = CN, Ph, *p*-Tol, CH<sub>2</sub>Br, Ac)

Reaction of methoxycarbonylformonitrile oxide (generated from MeO<sub>2</sub>CCCl=NOH in the presence of Et<sub>3</sub>N in Et<sub>2</sub>O) with methyl undec-10-enoate gave 90% of isoxazoline **35** [R = (CH<sub>2</sub>)<sub>8</sub>CO<sub>2</sub>Me, R<sup>1</sup> = H] whereas a similar reaction with methyl oleate gave a 40% isomeric mixture of **35** [R = 1-octyl, R<sup>1</sup> = (CH<sub>2</sub>)<sub>7</sub>CO<sub>2</sub>Me and R = (CH<sub>2</sub>)<sub>7</sub>CO<sub>2</sub>Me, R<sup>1</sup> = 1-octyl] (176).

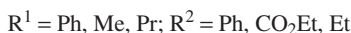
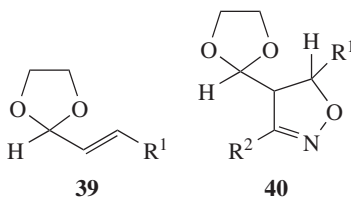
**35**

Formation of mixtures of the above type, which is common with internal olefins, do not occur with many functionalized alkenes. Thus, tertiary cinnamates and cinnamides undergo cycloadditions with benzonitrile oxides to give the 5-Ph and 4-Ph regioisomers in a 25–30:75–70 ratio. This result is in contrast to that obtained when methyl cinnamate was used as the dipolarophile (177). 1,3-Dipolar cycloaddition of nitrile oxides to ethyl *o*-hydroxycinnamate proceeds regioselectively to afford the corresponding ethyl *trans*-3-aryl-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylates **36** (178). Reaction of 4-[(*E*)-(2-ethoxycarbonylvinyl)] coumarin with acetonitrile oxide gives **37** (R = Me) and **38** in 73% and 3% yields, respectively, while reaction of the same dipolarophile with 4-methoxybenzonitrile oxide affords only **37** (R = 4-MeOC<sub>6</sub>H<sub>4</sub>) (85%) (179).

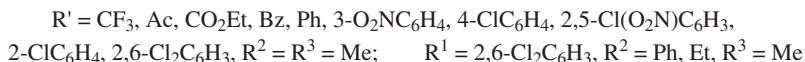
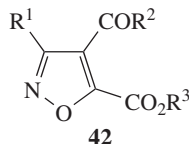
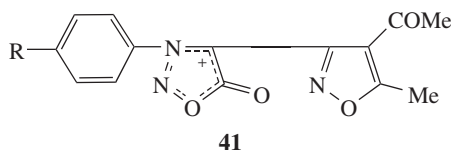
**36** (R = H, 4-Me, 2,4,6-Me<sub>3</sub>)**37****38**

1,3-Dioxolanes **39** derived from  $\alpha,\beta$ -unsaturated aldehydes react with nitrile oxides R<sup>2</sup>CNO to give the corresponding isoxazolines **40** with the 1,3-dioxolan-2-yl substituent in position 4 as main products, and their 5-isomers as minor products with good regioselectivity and synthetically useful yields. The corresponding

aldehydes are being inactive as dipolarophiles (180). The 1,3-dipolar cycloaddition reactions of nitrile oxides and  $\alpha,\beta$ -unsaturated 1,3-dioxolanes **39** are effectively accelerated by ultrasound irradiation to give isoxazolines **40** with yields and regioselectivities surpassing those from the corresponding thermal reactions (181).



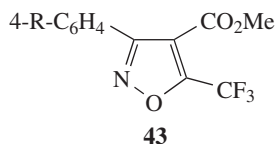
Reactions of nitrile oxides with 1,3-dicarbonyl compounds are of a specific character: the latter enter the interaction in enol form, and cycloaddition is followed by dehydration to give isoxazole derivatives. Thus, 3-arylsydnone-4-carboxyhydroxamic acid chlorides react with acetylacetone in the presence of  $\text{Et}_3\text{N}$  to give arylisoxazolyl sydnones **41** (182). Cycloaddition of nitrile oxides  $\text{R}^1\text{CNO}$  with  $\beta$ -acylpyruvates,  $\text{R}^2\text{COCH}=\text{C}(\text{OH})\text{CO}_2\text{R}^3$ , results in isoxazole derivatives **42** (183).  $\beta$ -Acylpyruvates, unlike ordinary  $\beta$ -diketones, show high dipolarophilic reactivity toward nitrile oxides in the absence of base.



Other compounds, with  $\text{C}=\text{C}$  bond activated by an electron-withdrawing group and bearing a good leaving group in the  $\beta$ -position also give isoxazoles, rather than oxazolines, on 1,3-dipolar cycloaddition reactions with nitrile oxides. Thus, methyl 3-(*p*-nitrobenzoyloxy)acrylate was used as a methyl propiolate equivalent with reverse regioselectivity, giving 3-aryl-4-methoxycarbonylisoxazoles on reactions with a variety of substituted benzonitrile oxides, in moderate to good yields (184). A reversal in regioselectivity was also observed when  $\beta$ -dimethylamino-

vinyl phenyl sulfone was used as a dipolarophile in cycloadditions with nitrile oxides. The sulfone gives rise mainly to 4-substituted isoxazoles, after elimination of dimethylamine, while phenyl vinyl sulfone is known to give 5-substituted isoxazolines (185).

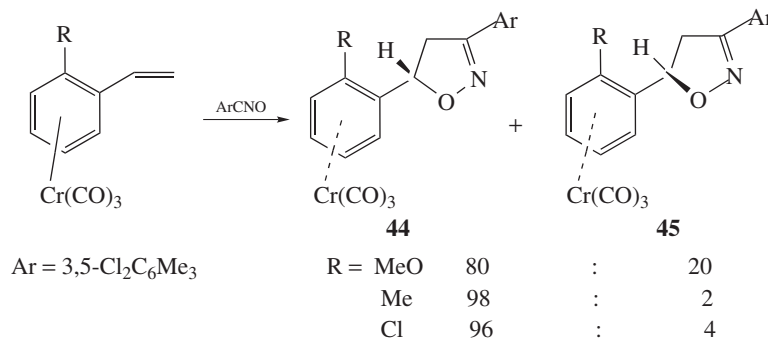
A Wang resin-bound  $\beta$ -bromo- $\beta$ -trifluoromethylacrylate, (Z)-F<sub>3</sub>CCBr=CHCO<sub>2</sub>Me, was used in the solid-phase synthesis of trifluoromethylated isoxazolecaboxylates using aromatic nitrile oxides generated *in situ* from hydroxymoyl chlorides (4-RC<sub>6</sub>H<sub>4</sub>C(Cl)=NOH) and Et<sub>3</sub>N, followed by removing the resin with trifluoroacetic acid. Methylation of the free acid with diazomethane in diethyl ether gave aryltrifluoromethylisoxazolecaboxylates **43** as major products in 21% to 48% yields and in 8:1–14:1 regioselectivities (186).



A promising magnesium ion catalysis in nitrile oxide cycloadditions has been observed, using allylic alcohols and stable mesitonitrile oxide as models (187). Such a catalysis was applied to asymmetric syntheses of a variety of isoxazolines from achiral nitrile oxides using chiral alkenes with MgBr<sub>2</sub> (188, 189), achiral alkenes with Lewis acid complexes with chiral ligands, the role of Lewis acid being played by MgBr<sub>2</sub> (190), Et<sub>2</sub>Zn (191, 192), and ytterbium triflate (193). Recently, a novel chiral reaction strategy was designed by the intensive assembling of characteristically functionalized metals, which play specific roles in controlling the stereochemical course. In particular, 1,3-dipolar cycloaddition of nitrile oxides to allylic alcohols was achieved by using zinc and magnesium metal and diisopropyl (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding 2-isoxazolines with excellent enantioselectivity (194).

However, most asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides with alkenes are carried out without Lewis acids as catalysts using either chiral alkenes or chiral auxiliary compounds (with achiral alkenes). Diverse chiral alkenes are in use, such as camphor-derived chiral N-acryloylhydrazide (195), C<sub>2</sub>-symmetric 1,3-diacryloyl-2,2-dimethyl-4,5-diphenylimidazolidine, chiral 3-acryloyl-2,2-dimethyl-4-phenyloxazolidine (196, 197), sugar-based ethenyl ethers (198), acrylic esters (199, 200), C-bonded vinyl-substituted sugar (201), chirally modified vinylboronic ester derived from D-(+)-mannitol (202), (1*R*)-menthyl vinyl ether (203), chiral derivatives of vinylacetic acid (204), (*E*)-1-ethoxy-3-fluoroalkyl-3-hydroxy-4-(4-methylphenylsulfinyl)but-1-enes (205), enantiopure  $\gamma$ -oxygenated- $\alpha,\beta$ -unsaturated phenyl sulfones (206), chiral ( $\alpha$ -oxyallyl)silanes (207), and (*S*)-but-3-ene-1,2-diol derivatives (208). As a chiral auxiliary, diisopropyl (*R,R*)-tartrate (209, 210) has been very popular.

A rather rare case is the use of chiral nitrile oxide, derived from N-glyoxyloyl-(2*R*)-bornane-10,2-sultam (211). Several nitrile oxides of the latter type, bearing

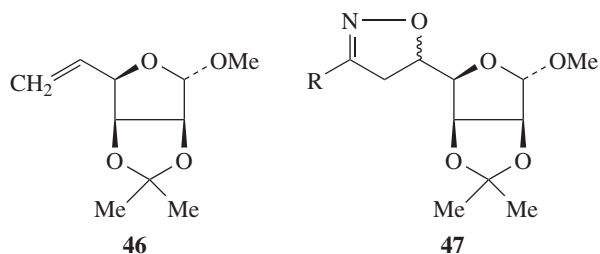


Scheme 1.17

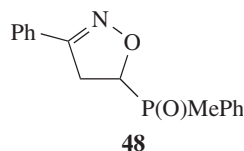
a chiral terpene-based unit X, were generated from oximes and nitro compounds and were subjected to 1,3-dipolar cycloaddition with (*E*)-hex-3-ene to give the corresponding 2-isoxazolines in good yields. However, stereoselectivities were only moderate (212).

The cycloaddition of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide to tricyclobonylchromium complexed styrenes proceeds with high stereoselectivity (Scheme 1.17), thus offering a new synthetic route to optically active 3,5-disubstituted 4,5-dihydroisoxazoles (213). The preferred formation of cycloadducts **44** rather than **45** shows that nitrile oxide attacks the  $\pi$  face opposite to Cr(CO)<sub>3</sub> and the reactive rotamer of the dipolarophile is transoid (213).

$\pi$ -Facial selectivity occurs in regio- and diastereoselective cycloaddition reactions of benzonitrile oxide and ethoxycarbonylformonitrile oxide to  $\alpha$ -methyl dideoxy-D-lyxo-hexenofuranoside **46** giving isoxazolines **47** (R = Ph, CO<sub>2</sub>Et), respectively (214).



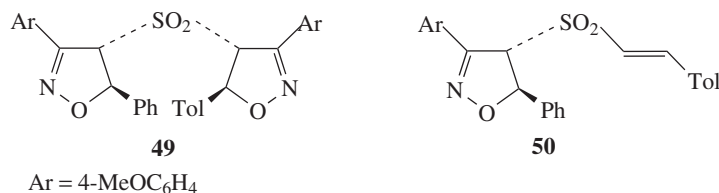
Considerable (ca 40% de) diastereofacial selectivity was found in 1,3-dipolar cycloaddition reactions of nitrile oxides with racemic methylphenylvinylphosphine oxide, providing phosphinylisoxazolines in high yields. The five substituted regioisomers, for example, **48**, either prevailed or were the only product formed (215). The crystal structure of **48** showed, in agreement with spectral assignments, that it has the *erythro* configuration and exists in a conformation with *anti*-arranged C–O and P=O bonds.



An interesting antibody-catalyzed intermolecular asymmetric 1,3-dipolar cycloaddition reaction between 4-acetamidobenzonitrile N-oxide and N,N-dimethylacrylamide generating the corresponding 5-acylisoxazoline was observed (216). Reversed regioselectivity of nitrile oxide cycloaddition to a terminal alkene was reported in the reaction of 4-*tert*-butylbenzonitrile oxide with 6A-acrylamido-6A-deoxy- $\beta$ -cyclodextrin in aqueous solution, leading to the formation of the 4-substituted isoxazoline, in contrast to the predominance of the 5-substituted regioisomer from reactions of monosubstituted alkenes (217).

Baker's yeast catalyzed the regioselective cycloaddition of stable aromatic nitrile oxides ArCNO [Ar = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, 2,4,6-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>] to ethyl cinnamate, ethyl 3-(*p*-tolyl)acrylate, and *tert*-butyl cinnamates (218). Reactions of dichloro- and trimethoxybenzonitrile oxides with all three esters proceeded regio- and stereoselectively to form exclusively alkyl *trans*-3,5-diaryl-4,5-dihydrooxazole-4-carboxylates. However, mesitonitrile oxide gave an analogous result, only with *tert*-butyl cinnamate, whereas from the two other esters mixtures of isomeric 3,4-diaryl-4,5-dihydrooxazole-5-carboxylate (65:35) were obtained. An attempt to improve regioselectivity of the reactions of ethyl cinnamates with mesitonitrile oxide, by using  $\beta$ -cyclodextrin as an artificial enzyme along with baker's yeast resulted in the reversal of regioselectivity (218). Baker's yeast also catalyzed the asymmetric cycloaddition reactions of above-mentioned nitrile oxides to 2- and 4-vinylpyridines to afford optically active 3-aryl-5-pyridyl-4,5-dihydroisoxazoles. The stereoselectivity was enhanced by directing the geometry of both the dipole and dipolarophile, using  $\beta$ -cyclodextrin as an additional binding cavity along with baker's yeast (219).

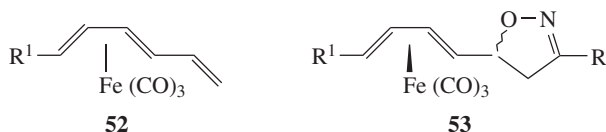
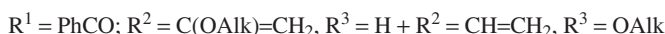
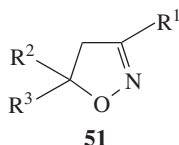
**1.3.4.1.2. Alkadienes and -trienes** 1,3-Dipolar cycloaddition of bis(styryl) sulfone (*E,E*)-PhCH=CHSO<sub>2</sub>CH=CHC<sub>6</sub>H<sub>4</sub>Me-4 with 4-MeOC<sub>6</sub>H<sub>4</sub>CH=NOH, in the presence of chloramine-T, gave a mixture of bis(isoxazolinyl) sulfone **49** and (styrylsulfonyl)isoxazoline **50** (220).



1,3-Dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide to unsymmetrical 1,5-hexadien-3-ol proceeds regioselectively to some extent due to the hydrogen

bonding effect. The chelation of Mg metal instead of H bonding, in the same reaction, results in excellent regioselectivity in addition to a good diastereoselectivity (221).

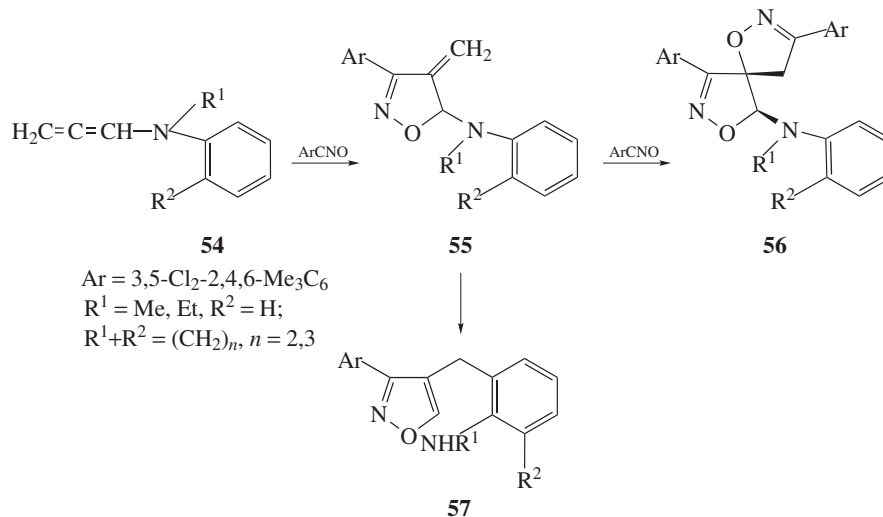
Cycloaddition of 2-alkoxy-1,3-butadienes,  $\text{H}_2\text{C}=\text{C}(\text{OAlk})\text{CH}=\text{CH}_2$ , and nitrile oxides to give isoxazolines **51** proceeds with the participation of only one of the conjugated  $\text{C}=\text{C}$  bonds. With benzonitrile oxide, only the vinyl group in alkoxydienes participates in cycloaddition reactions while in the case of phenylglyoxylonitrile oxide both double bonds react (222). Nitrile oxides  $\text{RC}\equiv\text{NO}$  react with iron complexed trienes **52**. The reaction proceeds with good yield and diastereoselectivity ( $\sim 90/10$ ) to give isoxazolines **53** (223).



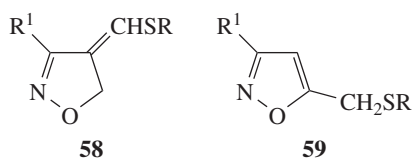
Allenes add nitrile oxides either to one or two double bonds. For mono- and 1,1-disubstituted allenes, relative activity of the two bonds depends on the nature of substituents. The reaction (Scheme 1.18) of N-propadienylanilines **54** with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide proceeds site- and regioselectively to give 5-substituted 4-methylene-4,5-dihydroisoxazoles **55**, which add a second molecule of nitrile oxide to afford 4,5'-spirobi-(4,5-dihydroisoxazoles) **56**. Dihydroisoxazoles **55** isomerize to 4-(2-aminobenzyl)isoxazoles **57** via a Claisen-type rearrangement (224).

N,N-diarylaminosallenes **54** ( $\text{R}^1 = 2\text{-R}^3\text{-3-R}^4\text{-C}_6\text{H}_3$ ,  $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$ ;  $\text{R}^2 + \text{R}^3 = \text{CH}=\text{CH}$ ,  $\text{CH}_2\text{CH}_2$ ,  $\text{R}^4 = \text{H}$ ), undergo similar transformations with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide affording methyleneisoxazolines **55** and 4,5'-spirobi-(4,5-dihydroisoxazoles) **56**, respectively (225). The difference is that only **55** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ) undergoes a Claisen rearrangement to **57** on treatment with Lewis acids while under similar conditions complicated rearrangements and degradation reactions are observed with other compounds **55**.

Allenyl sulfides  $\text{RSCH}=\text{C}=\text{CH}_2$  and the same nitrile oxide undergo cycloadditions which occur exclusively or predominantly at the external double bond to give 4-alkylidenedihydroisoxazoles **58** and 5-(methylthio)isoxazoles **59** (226).

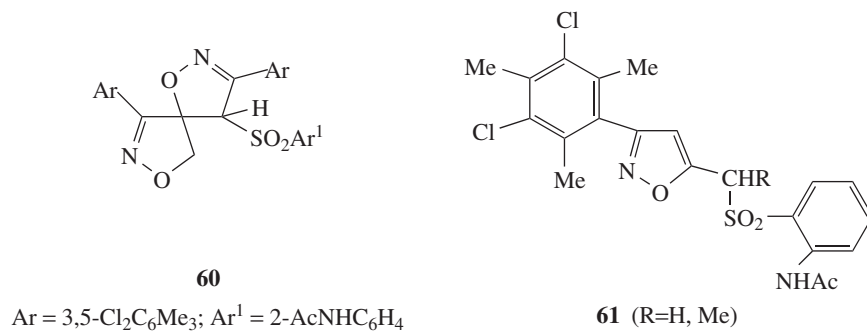


Scheme 1.18



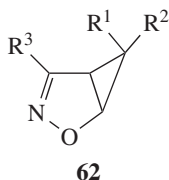
R = 2-AcNHC<sub>6</sub>H<sub>4</sub>, 2,4-(O<sub>2</sub>N)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, benzothiazol-2-yl; R<sup>1</sup> = 3,5-Cl<sub>2</sub>C<sub>6</sub>Me<sub>3</sub>

Reactions of arylsulfonylallenes with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (227) proceed in a manner similar to that of the above-mentioned sulfides. Probably, both 4- and 5-alkylidene-4,5-dihydroisoxazole cycloadducts are initially formed which then undergo different transformations. 4-Alkylidene isomers give spiro adducts such as **60** with an additional molecule of nitrile oxide, while 5-isomers convert to isoxazoles **61**, products of their prototropic rearrangement.

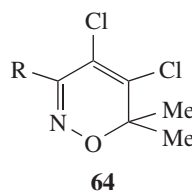
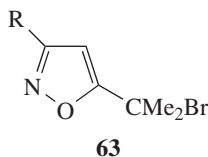


Selective nitrile oxide addition at the internal  $C_{(4)}=C_{\alpha}$  double bond, to give the spiro compound, is described for 4-vinylideneoxazolidin-2-one (228).

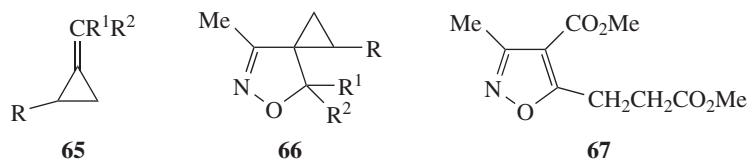
**1.3.4.1.3. Cycloalkene Derivatives** Cyclopropenes readily interact with nitrile oxides. Reactions of a broad series of 3,3-disubstituted cyclopropenes with 4-substituted benzonitrile, methoxycarbonyl- and cyanoformonitrile oxides (229) as well as with di(isopropoxy)phosphorylformonitrile oxide (230) give 2-oxa-3-azabicyclo[3.1.0]hexene derivatives **62**. Stereoselectivity of the cycloaddition is governed by both steric and polar factors. In particular, steric factors are supposed to prevail for 3-methyl-3-phenylcyclopropene affording **62** [ $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ,  $R^3 = (\text{Me}_2\text{CHO})_2\text{P}(\text{O})$ ] with *endo*-Ph, whereas electrostatic factors control cycloadditions to 3-methyl-3-cyanocyclopropene leading to adducts **62** [ $R^1 = \text{CN}$ ,  $R^2 = \text{Me}$ ,  $R^3 = (\text{Me}_2\text{CHO})_2\text{P}(\text{O})$ ] with an *exo*-oriented cyano group (230). 1,2-Dichloro-3-(chloromethyl)-3-methylcyclopropene undergoes dipolar cycloadditions with nitrile oxides to produce 2-oxa-3-azabicyclo[3.1.0]hex-3-enes, **62**, in which the  $6\text{-ClCH}_2$  substituent occupies the *endo* position (231). It should be noted that reactions of (diisopropoxyphosphoryl)formonitrile oxide with 1-bromo-3,3-dimethylcyclopropene and 3,3-dimethyl-1,2-dichlorocyclopropene lead to isoxazole **63** and oxazine **64** [ $R = (\text{Me}_2\text{CHO})_2\text{PO}$ ], respectively (232).



$R^1 = \text{Me}$ ,  $R^2 = \text{Me}$ ,  $\text{Ph}$ ,  $4\text{-BrC}_6\text{H}_4$ ,  $\text{CH}:\text{CH}_2$ ,  $\text{CH}_2:\text{CMe}$ ,  $\text{Me}_2\text{C}:\text{CH}$ ,  $\text{CN}$ ;  
 $R^1 = R^2 = \text{Ph}$ ;  $R^1 = \text{Ph}$ ,  $R^2 = \text{CN}$ ;  $R^3 = \text{CN}$ ,  $(\text{Me}_2\text{CHO})_2\text{P}(\text{O})$



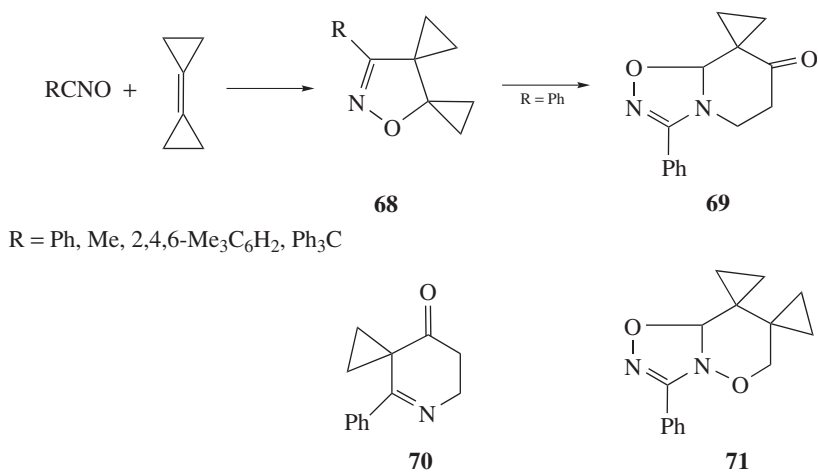
1,3-Dipolar cycloadditions of acetonitrile oxide to alkylidenecyclopropanes **65** ( $R = \text{H}$ ;  $R^1 = \text{H}$ ,  $R^2 = \text{Ph}$ ;  $R^1 = \text{Me}$ ,  $R^2 = \text{CH}_2\text{CH}_2\text{Ph}$ ) give mainly or exclusively spirocyclopropaneisoxazolines **66**. However, **65** ( $R = R^1 = \text{CO}_2\text{Me}$ ;  $R^2 = \text{H}$ ) affords isoxazole **67** originating from the rearrangement of the regioisomer of **66** (233).



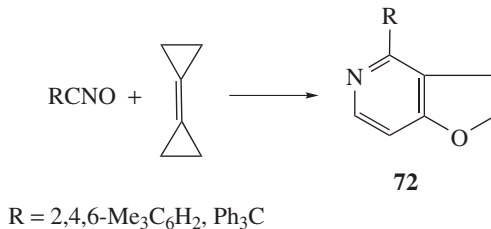
Bicyclopropylidene smoothly undergoes 1,3-dipolar cycloaddition to nitrile oxides to give rather stable bispirocyclopropaneisoxazolines **68** (Scheme 1.19). Formation of side product **69** was observed for **68** (R = Ph). The yield of **69** depended on temperature and duration of the reaction rising from 5% (THF, 66°C, 7h) to 14% (PhH, 80°C, 14h). Two routes were suggested for the side reaction: (a) rearrangement of **68** to **70** followed by reaction of the latter with a second molecule of PhCNO to give **69**, and (b) reaction with a second molecule of PhCNO to give **70** with subsequent rearrangement of the latter to **69** (234).

On the basis of previously published data (235), concerning thermal rearrangement of **68** (R = Ph and mesityl) to furo[3,2-*c*]pyridine derivatives, reactions of mesitonitrile oxide and triphenylacetonitrile oxides were carried out (*o*-Cl<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 170°C, 5 days) leading to compounds **72** (R = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, Ph<sub>3</sub>C) in 7% and 21% yields, respectively (Scheme 1.20) (234).

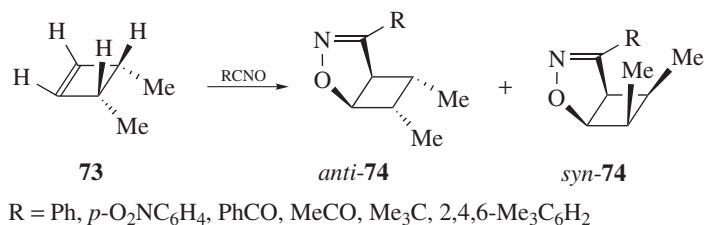
Facial selectivity in 1,3-dipolar cycloadditions to *cis*-3,4-dimethylcyclobutene (**73**) (Scheme 1.21) was studied. Only phenylglyoxylo- and pyruvonnitrile oxides lacked facial selectivities (*anti:syn* = 1:1). All other nitrile oxides formed preferably *anti*-**74**. The *anti:syn* ratio increased from 60:40 (R = *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>) and 65:35 (R = Ph) to 87:13 and 92:8 for bulky *tert*-Bu and mesityl substituents, respectively. The transition-state structure of the cycloaddition of formonitrile oxide was determined using both HF/6-31G\* and B3LYP/6-31G\* methods. The



Scheme 1.19



Scheme 1.20

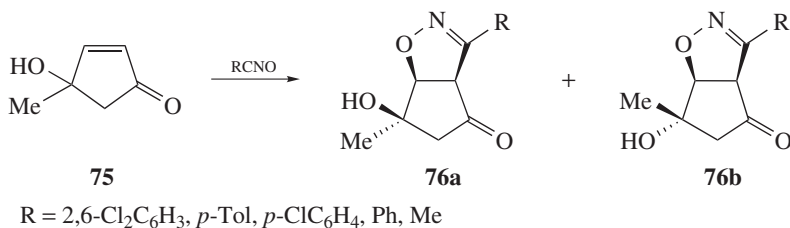


Scheme 1.21

calculated relative free enthalpies of these transition states satisfactorily reproduce, at both levels the observed facial selectivity (236).

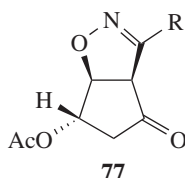
Dimethyl 7-10-tetrahaaptotricyclo[4.2.2.0<sup>2,5</sup>]deca-3,7,9-triene-7,8-dicarboxylate tricarbonyliron reacted readily with several 1,3-dipoles nitrile oxides, at the cyclobutene double bond, to give adducts from which the tricarbonyliron group could be easily removed by oxidative decomplexation with trimethylamine N-oxide (237).

Regio- and diastereoselectivity in 1,3-dipolar cycloadditions of nitrile oxides to 4-substituted cyclopent-2-enones was studied (238, 239). The reactions are always regioselective, while the diastereofacial selectivity depends on the nature of the substituents. Thus, 4-hydroxy-4-methylcyclopent-2-enone (**75**) gives preferably adducts **76a**, the **76a**:**76b** ratio varying from 65:35 to 85:15 (Scheme 1.22).



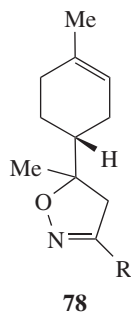
Scheme 1.22

It was also shown that for some other related 4-substituted cyclopent-2-enone derivatives the regiofacial selectivity is lower, and completely reversed in the case of 4-acetoxycyclopent-2-enone, giving 100% of the adduct **77**.



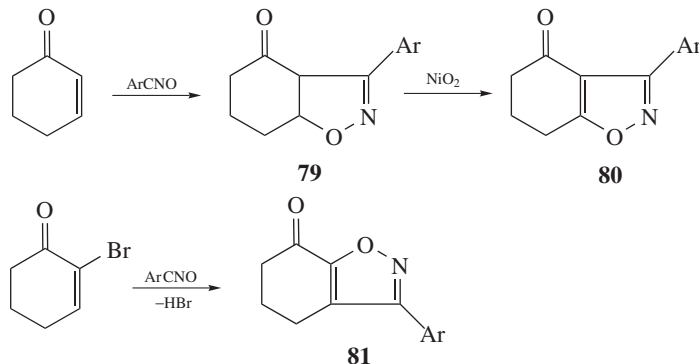
The study of benzonitrile oxide additions to 4-benzoylaminocyclopent-2-en-1-ol and its derivatives (**240**) demonstrated that mainly anti-adducts are formed. This was interpreted as the result of the *syn*-directing ability of the cyclopentene substituents by strong intramolecular hydrogen bonding. Indeed, removal of the intramolecular hydrogen bond, by OH protection or oxidation, activates the *syn*-directing ability of the amido substituent and provides a route for obtaining *syn*-adducts (**240**).

The cycloaddition of nitrile oxides RCNO (R = alkyl, alkenyl, aryl), generated *in situ* from either RCH<sub>2</sub>NO<sub>2</sub>/PhNCO or RCH=NOH/NaOCl to (*R*)-(+)-limonene, proceeds regioselectively at the extracyclic double bond, but not stereospecifically, to form (*5R/S*)-isoxazoles **78** in 64% to 81% isolated yield (**241**).



Isoxazolines **79**, obtained from aromatic nitrile oxide cycloadditions to cyclohex-2-enone, reacted with nickel peroxide to give 3-aryl-6,7-dihydro[1]benzoxisoxazol-4(*5H*)-ones **80**. In contrast, the corresponding 2-bromocyclohex-2-enone underwent nitrile oxide cycloaddition, followed by dehydrobromination, to afford the regioisomeric 3-aryl-4,5-dihydro[1]benzoxisoxazol-7(*6H*)-ones **81** (Scheme 1.23) (**242**).

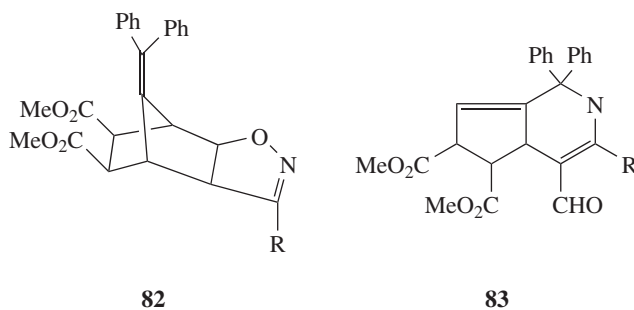
The 1,3-dipolar cycloaddition reactions of nitrile oxides to unsymmetrically substituted norbornenes (**243**) and to dicyclopentadiene and its derivatives (**244**) proceed with complete stereoselectivity. The approach of the dipole takes place exclusively from the *exo*-face of the bicycloheptane moiety, generally



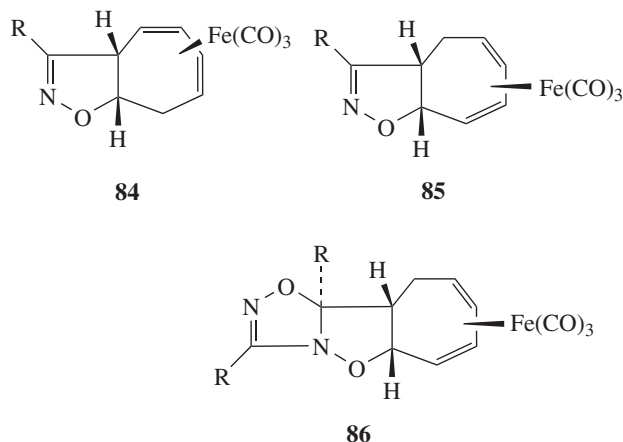
Scheme 1.23

providing mixtures of regioisomers; however some substituted norbornene and dicyclopentadiene derivatives give a single isomer. Experimental observations concerning dicyclopentadiene derivatives were investigated via a gas phase and solvent model, MO calculations on the transition-state geometries at semiempirical (PM3), and hybrid *ab initio*-DFT levels (244).

Reactions of methoxycarbonylformonitrile, furonitrile and substituted benzonitrile oxides (4-Me, 4-OMe, 3-OMe, 4-Cl, 3-Cl, 2,4-di-Cl, 4-F as substituents) with dimethyl 7-(diphenylmethylene)bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate led exclusively to exo cycloadducts **82** ( $R = \text{CO}_2\text{Me}$ , 2-furyl, substituted phenyl), which, on irradiation with a low-pressure mercury lamp, afforded 3-azabicyclo[4.3.0]nonadiene-7,8-dicarboxylates **83** as the only products. The 1,3-dipolar cycloaddition, followed by a photorearrangement, provides a new method for obtaining tetrahydro-2*H*-pyridine derivatives from cyclopentadiene (245).

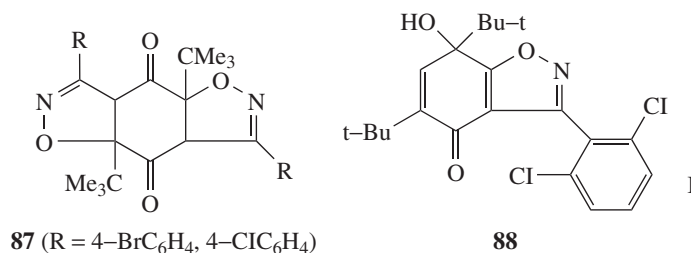


Nitrile oxides react with cycloheptatriene and its tricarbonyliron complex to give mixtures of adducts. In particular, for the complex, these adducts are **84**, **85** (regioisomers at the uncomplexed double bond) and bisadduct **86**. The regioselectivity of the reactions of cycloheptatriene is similar to that of the reactions of its tricarbonyliron derivative (246).



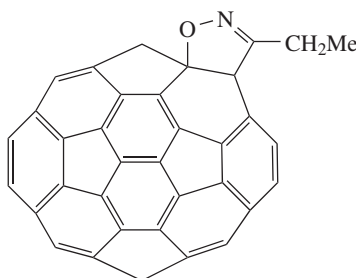
**1.3.4.1.4. Aromatic and Related Compounds** The main part of aromatic compounds, able to undergo 1,3-dipolar cycloaddition reactions with nitrile oxides, are polycyclic hydrocarbons and their derivatives. Dipolarophilic reactivity toward nitrile oxides is known for phenanthrene and pyrene (247). Microwave irradiation in the absence of a solvent improves product yields and reduces reaction times compared with classical heating with and without refluxing solvents (248). Quantum chemical DFT calculations at the B3LYP/6-31G(d) level for reactions of mesitronitrile oxide with anthracene and its aza-analog, acridine, are in agreement with the observed regioselectivity and do not agree with the predictions of frontier molecular orbital (FMO) theory (249).

*p*-Quinones are active dipolarophiles, used in particular in natural product syntheses (250). 2,5-Di(*tert*-butyl)-*p*-benzoquinone is well known as a dipolarophile in reactions with a series of substituted benzonitrile oxides (251, 252). This quinone gives not only 1:1 but also 1:2 cycloadducts, the latter, for example, **87**, with *p*-substituted benzonitrile oxides, probably, because of less steric hindrances (251). Normal 1:1 and 1:2 adducts of the 1,3-cycloaddition at C=C bond(s) are, however, rather unstable and, in particular, undergo base-induced transformations. The structure of one of the final products **88**, obtained from 1,3-dipolar 1:1 cycloadduct of 2,5-di(*tert*-butyl)-*p*-benzoquinone with 2,6-dichlorobenzonitrile oxide was determined by X-ray diffraction analysis. The *t*-Bu group at



the bridgehead position of the 1,3-dipolar cycloadduct migrated to the neighboring carbonyl carbon atom. This base-induced rearrangement takes place with a bulky group, that is, Et, *i*-Pr, *t*-Bu, and Bn at the bridgehead position of nitrile oxide—quinone cycloadducts in an alcohol media. The driving force of this reaction is stabilization by aromatization from isoxazoline derivatives to isoxazole-fused *p*-quinol derivatives (252).

**1.3.4.1.5. Fullerenes** Cycloaddition reactions are very popular for functionalization of fullerenes. Such reactions of fullerenes are compiled and discussed in detail in Reference 253. During the last 10 to 15 years, several communications appeared concerning [3 + 2] cycloaddition of nitrile oxides to fullerene C<sub>60</sub>. Nitrile oxides, generated in the presence of C<sub>60</sub>, form products of 1,3-cycloaddition, fullerene isoxazolines, for example, **89**. The products were isolated by gel permeation chromatography and appear by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy to be single isomers. Yields of purified products are ca 30%. On the basis of <sup>13</sup>C NMR, structures with C<sub>s</sub> symmetry are proposed. These products result from addition of the nitrile oxide across a 6,6 ring fusion (254).



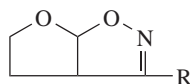
89

Similarly, other cycloadducts of nitrile oxides with C<sub>60</sub> were synthesized. The cycloadducts were characterized by <sup>13</sup>C NMR spectroscopy and high-resolution fast atom bombardment (FAB) mass spectrometry. It should be mentioned that X-ray structure determination of the 3-(9-anthryl)-4,5-dihydroisoxazole derivative of C<sub>60</sub>, with CS<sub>2</sub> included in the crystals, was achieved at 173 K (255). Cycloaddition of fullerene C<sub>60</sub> with the stable 2-(phenylsulfonyl)benzonitrile oxide was also studied (256). Fullerene formed with 2-PhSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CNO 1:1 and 1:2 adducts. The IR, NMR, and mass spectra of the adducts were examined. Di(isopropoxy)phosphorylformonitrile oxide gives mono- and diadducts with C<sub>60</sub> (257). Structures of the adducts were studied using a combination of high performance liquid chromatography (HPLC), semiempirical PM3 calculations, and the dipole moments.

1,3-Dipolar cycloaddition of C<sub>60</sub> with nitrile oxides was modeled at the B3LYP/6-31G(d,p)//AM1 level, and its mechanism and regiochemistry were investigated. Theoretically, the reaction can proceed by four types of additions, *viz.*, closed [6,6], open [5,6], closed [5,6], and open [6,6] additions. Analysis of

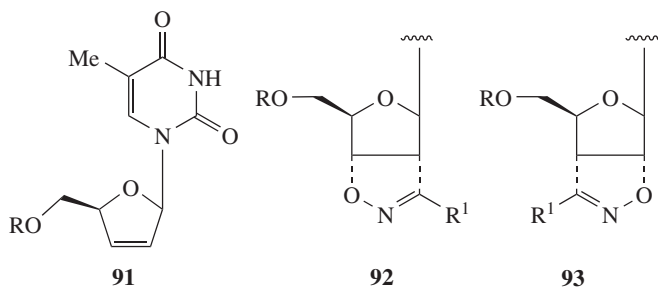
these reactions showed that closed [5,6] and open [6,6] additions are not probable and that closed [6,6] addition is the most favored one (258).

**1.3.4.1.6. Heterocycles** Both non-aromatic unsaturated heterocycles and hetero-aromatic compounds are able to play the role of ethene dipolarophiles in reactions with nitrile oxides. 1,3-Dipolar cycloadditions of various unsaturated oxygen heterocycles are well documented. Thus, 2-furonitrile oxide and its 5-substituted derivatives give isoxazoline adducts, for example, **90**, with 2,3- and 2,5-dihydrofuran, 2,3-dihydropyran, 1,3-dioxep-5-ene, its 2-methyl- and 2-phenyl-substituted derivatives, 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hept-2-ene, and 1,4-epoxy-1,4-dihydronaphthalene. Regio- and *endo-exo* stereoselectivities have also been determined (259).

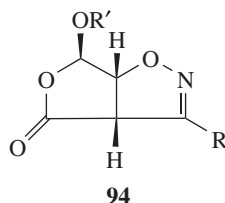


**90** (R = H, NO<sub>2</sub>, 4-, 3-nitrophenyl)

1,3-Dipolar cycloaddition reactions of 2,6-dichlorobenzonitrile oxide with 2',3'-didehydro-2',3'-dideoxythymidine **91** (R = H, Me<sub>3</sub>CMe<sub>2</sub>Si), at its 2,5-dihydrofuran double bond, gave nucleosides **92** and **93** in 67% yield and 3:2 ratio and 96% yield and 3:1 ratio, respectively (260).

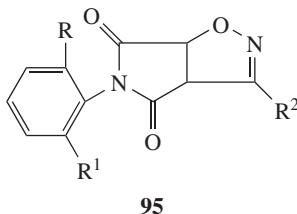


1,3-Dipolar cycloadditions of benzonitrile oxide, its substituted derivatives as well as 9-anthro- and 2-furonitrile oxides to 5-alkoxy- and 5-hydroxy-2(5*H*)-furanones afforded regiospecifically furoisoxazoles **94**. 5-Methoxy- and 5-ethoxy-furanones gave exclusively *exo*-**94**, whereas 5-hydroxyfuranone gave a 52:48 mixture of *exo*-**94** (R = Ph, R' = H) and its *endo* diastereomer (261). Reaction of benzonitrile oxide with 5-(*R*)-(1-menthyloxy)-2(5*H*)-furanone proceeds regioselectively to give (3*aS*,6*R*,6*aR*)-3*a*,6*a*-dihydro-4-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyloxy]-3-phenylfuro[3,4-*d*]isoxazol-4(3*aH*)-one and its regioisomer, (3*aR*,4*R*,6*aS*)-3*a*,6*a*-dihydro-4-[(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyloxy]-3-phenylfuro[3,4-*d*]isoxazol-6(4*H*)-one, in a 68:32 ratio (262).



1,3-Dipolar cycloaddition of 2,4-(trimethylsilyl)- and 2,4-(trimethylgermyl)-substituted thiophene-1,1-dioxides as well as silylated 2,2'-bithiophene-1,1-dioxides was investigated. It was shown that only the  $C_{(4)}=C_{(5)}$  double bond of 2,4-disubstituted thiophene-1,1-dioxides interacts with acetonitrile oxide to give thienoisoxazoline dioxides. Bithiophene derivatives were inactive or their reaction with nitrile oxide was accompanied by desilylation. Cycloaddition of benzonitrile oxide with all mentioned sulfones did not occur. The molecular structure of 3a-methyl-5,6a-bis(trimethylgermyl)-3a,6a-dihydrothieno[2,3-*d*]isoxazole 4,4-dioxide was established by X-ray diffraction (263).

N-Arylmaleimides are useful reagents for trapping and characterization of nitrile oxides (see, e.g., Ref. 165). However, their cycloadducts can also be target products. Thus, a series of 3,5-diaryl-4,6-dioxo-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*]isoxazoles **95** was obtained by 1,3-dipolar cycloaddition of substituted benzonitrile oxides with N-(2,6-dialkylphenyl)maleimides. Certain compounds **95** showed bactericidal and fungicidal activity (264).



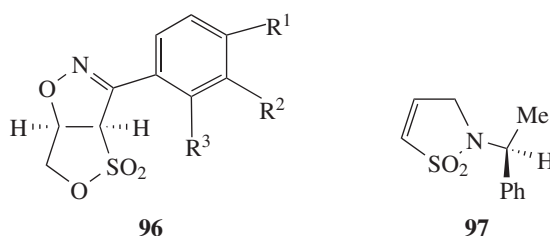
$R = R^1 = \text{Me, Et}; R = \text{Me}, R^1 = \text{Et};$

$R^2 = \text{Ph, 2-MeOC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 3\text{-O}_2\text{NC}_6\text{H}_4,$   
 $4\text{-O}_2\text{NC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 3,4\text{-(OCH}_2\text{O)C}_6\text{H}_3,$   
 $3\text{-MeOC}_6\text{H}_4, 3,5,2\text{-Cl}_2(\text{MeO})\text{C}_6\text{H}_2, 3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2$

4-[Chloro(hydroxyimino)methyl]-3-phenyl-1,2,3-oxadiazolium-5-olate-(3-phenylsydnone-4-carbohydroximoyl chloride) reacts *in situ* (through nitrile oxide) with N-arylmaleimides or 2-methyl-N-phenylmaleimide to give 5-aryl-3-(3-phenylsydnone-4-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-diones or 6a-methyl-5-phenyl-3-(3-phenylsydnone-4-yl)-3a,6a-dihydropyrrolo[3,4-*d*]isoxazole-4,6-diones, respectively (265).

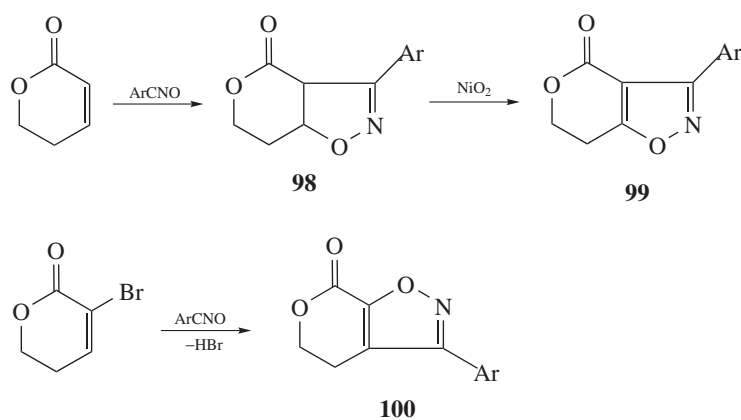
The cycloaddition of prop-1-ene-1,3-sultone to a variety of nitrile oxides (generated from corresponding  $\alpha$ -chlorobenzaldoximes and used *in situ*) afforded

oxathiolisoxazolines **96** ( $R^1 = \text{H, Cl, F, Me, MeO}$ ;  $R^2 = R^3 = \text{H}$ ;  $R^1 = R^3 = \text{H}$ ;  $R^2 = \text{Cl, Br, O}_2\text{N, Me}$ ;  $R^1 = R^2 = \text{H}$ ;  $R^3 = \text{Cl}$ ;  $R^1 = R^3 = \text{Cl}$ ;  $R^2 = \text{H}$ ;  $R^1 R^2 = \text{OCH}_2\text{O}$ ;  $R^3 = \text{H}$ ) in good yield and with excellent regioselectivity (266). The scope and limitations of dipolar cycloaddition reactions between nitrile oxides and prop-1-ene-1,3-sultone was also studied by other authors (267), who observed a remarkably high regioselectivity and stereoselectivity. It should be noted that low diastereoselectivity was only observed in 1,3-dipolar cycloaddition reactions between nitrile oxides and chiral  $\alpha,\beta$ -unsaturated  $\gamma$ -sultams, for example, **97** (268).

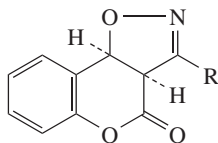


Cycloaddition of 5,6-dihydropyran-2-one with aromatic nitrile oxides leads to 3-aryl-3a,6,7,7a-tetrahydropyrano[3,4-*d*]isoxazol-4(*4H*)-ones **98**. The latter react with nickel peroxide to give the corresponding dihydropyranoisoxazolones **99**. Similar to 2-bromocyclohex-2-enone, 3-bromo-5,6-dihydropyran-2-one undergoes nitrile oxide cycloaddition, followed by dehydrobromination, to form regioisomeric 3-aryl-5,7-dihydropyrano[4,3-*d*]isoxazol-7(*4H*)-ones **100** (Scheme 1.24) (242).

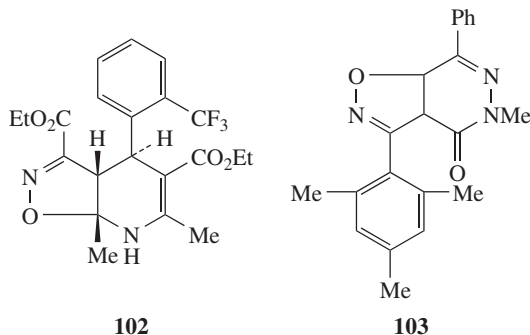
Coumarin reacts with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide affording a single regioisomer **101** ( $R = 3,5\text{-Cl}_2\text{C}_6\text{Me}_3$ ) in high yield (269).



Scheme 1.24

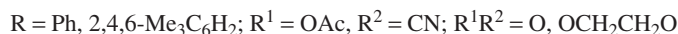
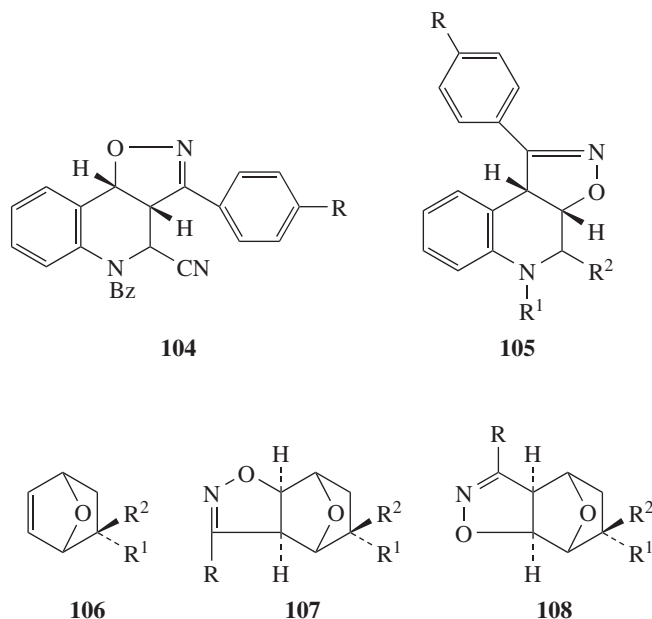
**101** (R = 3,5-Cl<sub>2</sub>C<sub>6</sub>Me<sub>3</sub>)

Cycloaddition reactions of nitrile oxides with 5-unsubstituted 1,4-dihydropyridine derivatives produced isoxazolo[5,4-*b*]pyridines in moderate to good yield. In each case examined, the reaction produced only a single isomer, the structure of which was assigned by NMR spectra and confirmed by X-ray diffraction analysis of **102** (270). A study of the cycloaddition behavior of substituted pyridazin-3-ones with aromatic nitrile oxides was carried out (271). Nitrile oxides undergo position and regioselective 1,3-dipolar cycloaddition to the 4,5-double bond of pyridazinone to afford 3a,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4-ones, for example, **103**.

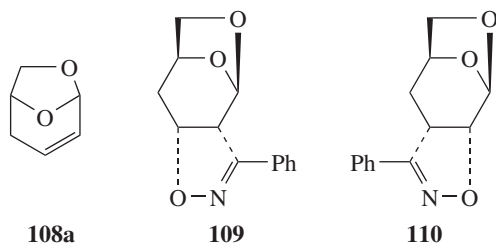
**102****103**

Reactions of benzonitrile oxide and its 4-substituted derivatives with 1-benzoyl-2-cyanodihydroquinoline gave mixtures of regioisomers **104** and **105** (R<sup>1</sup> = Bz, R<sup>2</sup> = CN). In contrast, the reaction with dihydroquinoline, bearing the phenyl substituent in the position 2 and the benzyl group in the position 1, gave only one regioisomer **105** (R<sup>1</sup> = PhCH<sub>2</sub>, R<sup>2</sup> = Ph) (272). The 1,3-dipolar cycloaddition of aromatic nitrile oxides (generated *in situ* from aromatic aldoxime precursors in a two-phase CHCl<sub>3</sub>/NaOCl system) to 1,2-dihydroisoquinoline derivatives proceeds regioselectively and results in 3-aryl-3a,8,9,9a-tetrahydroisoxazolo[5,4-*c*]isoquinolines (273). The latter undergo ring cleavage, under the action of silica gel or refluxing in ethanol in the presence of an acid, to give aryl 1,2-dihydro-4-isoquinolyl ketone oximes.

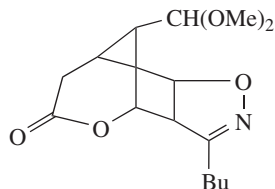
There are a few communications concerning cycloadditions of nitrile oxides to unsaturated oxa and aza cage systems. Benzo- and mesitonitrile oxides RCNO give, with five substituted 7-oxanorbornenes **106**, mixtures of the corresponding *exo*-adducts **107** and **108** in nearly quantitative yields. No traces of compounds resulting from the *endo*-face attack was detected (274). Substituents at positions 5 and 6 of **106** render the process highly regioselective.



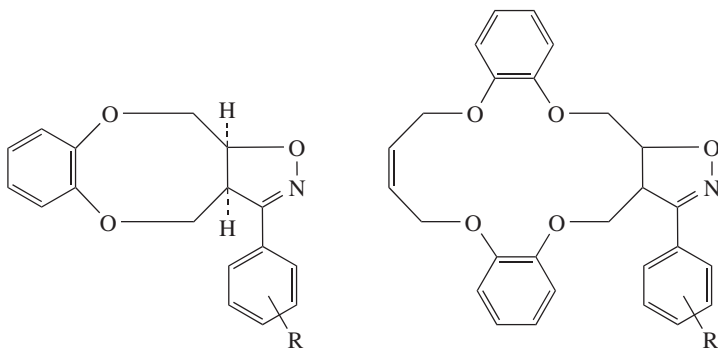
Benzonitrile oxide, generated by dehydrochlorination of benzohydroximoyl chloride, undergoes regio- and face-selective cycloadditions to 6,8-dioxabicyclo [3.2.1]oct-3-ene **108a** yielding a 4:1 mixture of 4,5-dihydroisoxazoles **109** and **110**. Both products have *exo*-stereochemistry, resulting from the approach of the nitrile oxide from the face opposite to the methyleneoxy bridge. Structures of the adducts were determined by  $^1\text{H}$  NMR spectroscopy and, in the case of compound **109**, by X-ray diffraction analysis (275).



Pentanenitrile oxide, BuCNO, formed *in situ* from 1-nitropentane, PhNCO and  $\text{Et}_3\text{N}$  in benzene, added stereo- and regioselectively to 8-*syn*-(dimethoxymethyl)-3-oxo-2-oxabicyclo[3.2.1]oct-6-ene to give 75% of the tricyclic lactone **111** (276). Introduction of a methoxycarbonyl group into the plane asymmetrical double bond of 2,3-dioxa- and 2,3-oxazabicyclo[2.2.2]oct-5-enes, brought about a clear-cut increase in syn selectivity of their reactions with 1,3-dipoles (277).

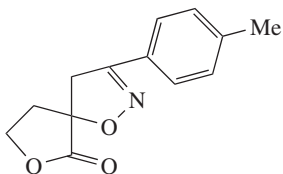
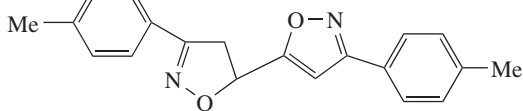
**111**

Isoxazolobenzodioxocines **112** were prepared in 29% to 65% yields by the 1,3-dipolar cycloaddition of the corresponding benzenenitrile oxides to 2,5-dihydro-1,6-benzodioxocine. Similarly, monoadducts **113** were obtained from the 16-membered tetraether as the dipolarophile (278).

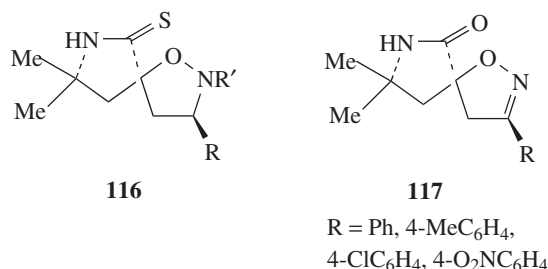
**112****113**

R = H, 4-OMe, 4-Me, 4-Cl, 4-NO<sub>2</sub>, 4-Br, 4-F, 3-Cl      R = H, 4-Cl, 4-NO<sub>2</sub>, 3-Cl

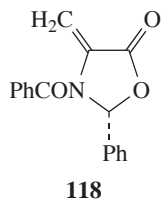
Alkylidene-substituted heterocycles readily enter 1,3-cycloaddition reactions with nitrile oxides to give the corresponding spiroadducts. Thus, reaction of methylene- $\gamma$ -butyrolactones with aromatic nitrile oxides proceeds at room temperature producing spiroheterocycles, for example **114** (279). However, cycloaddition with 5-methylene-5*H*-furan-2-one, carried out in refluxing toluene gives the unexpected product **115** (279). Some 4-substituted benzonitrile oxides undergo 1,3-dipolar cycloadditions with 3-methylenephthalide affording expected spiroisoxazolines. These spiroadducts can be converted to the corresponding 2-(3-arylisoxazol-5-yl)benzoic acids by various methods, including thermal and acidic treatments, as well as electrooxidation (280).

**114****115**

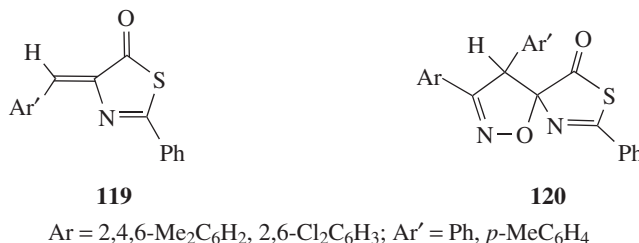
5,5-Dimethyl-3-methylenepyrrolidine-2-thione, which reacts with nitrones regio- and stereoselectively at its exocyclic C=C bond to give only spirocycloadducts **116**, behaves more complicatedly with nitrile oxides. The latter undergo 1,3-dipolar cycloaddition both to the exocyclic C=C and C=S double bonds with subsequent cycloreversion and formation of spiro-lactams **117** (281).



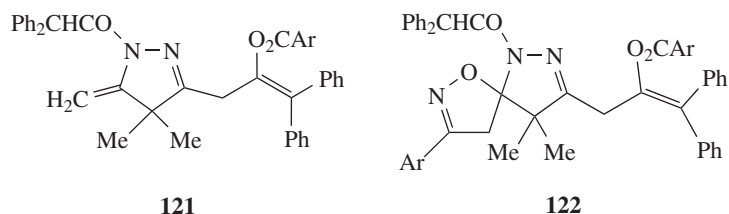
The 1,3-dipolar cycloaddition reactions of the chiral 3-benzoyl-4-methylene-2-phenyloxazolidin-5-one **118** and nitrile oxides RCNO ( $R = \text{Ph}, \text{Me}$ ) had the expected stereochemistry, addition of the 1,3-dipole having occurred from the less hindered  $\pi$ -face of the exocyclic methylene of **118** (282).



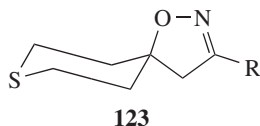
Stable mesito- and 2,6-dichlorobenzonitrile oxides,  $\text{ArCNO}$ , add to the C=C bond of 4-arylidene-2-phenyl-5(4*H*)-thiazolones **119** ( $\text{Ar}' = \text{Ph}, p\text{-MeC}_6\text{H}_4$ ) affording spiroisoxazolines **120**. The cycloaddition reactions are regioselective and only one of the two possible regioisomers has been isolated (283).



Substituted 3-alkenyl-5-methylene-4,5-dihydro-1*H*-pyrazole **121** reacts with 4- $\text{MeC}_6\text{H}_4\text{CNO}$  to give the spiro compound **122** ( $\text{Ar} = 4\text{-C}_6\text{H}_4\text{Me}$ ) (284).

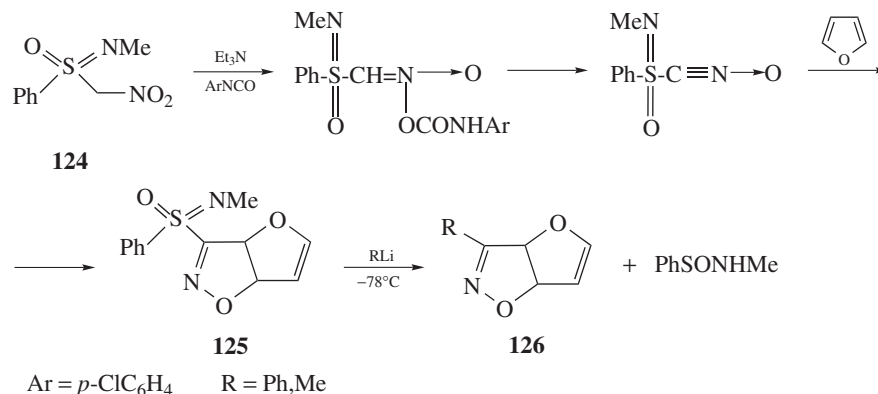


The cycloaddition of nitrile oxides to 4-methylenetetrahydrothiopyran proceeds regioselectively with the formation of spiro-substituted isoxazolines **123** ( $R = H, Cl, NO_2$ ). Semiempirical calculations (AM1) were used to analyze the electronic structure of reactants, energies of products, and activation barriers leading to these products, in order to rationalize this exclusive regioselectivity. It was shown that the main factor responsible for the high stereoselectivity of this reaction is not frontier orbital control, but mainly electrostatic and steric interactions. Spiro compounds **123** were cleaved by hydrogenolysis to  $\gamma$ -amino alcohols which were recycled to spiro-oxazines (285). Cycloadditions of nitrile oxides to 4-methylene-1-methylpiperidine gave spiro-substituted isoxazoline derivatives. NMR studies confirmed that only one regioisomer was formed selectively. X-ray structure analysis, carried out for one of these products, showed the occurrence of only one stereoisomer, explicable by comparing AM1-calculated  $\Delta H_f$  values of all possible cycloadducts (286).

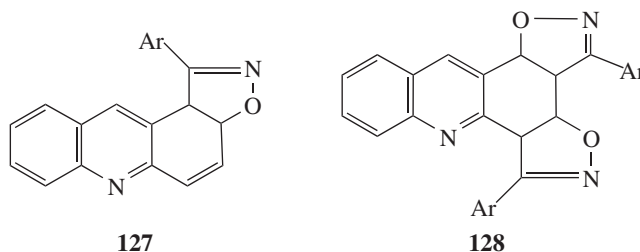


Among heteroaromatic compounds able to react with nitrile oxides as dipolarophiles, furan, probably, is the best known. Recently, a novel nitrile oxide was generated from a sulfoximine and converted *in situ* to a cycloadduct with furan (Scheme 1.25) (287). The starting racemic N-methyl-S-nitromethyl-S-phenylsulfoximine **124** was prepared in 87% yield via nitration of N,S-dimethyl-S-phenylsulfoximine. Reaction of **124** with *p*-chlorophenyl isocyanate and a catalytic quantity of triethylamine, in the presence of furan, afforded dihydrofuroisoxazole **125**, the product of nitrile oxide cycloaddition, in 42% yield (65:35 diastereomer ratio). The reaction of **125** with phenyllithium and methyllithium afforded compounds **126**, which are products formed by replacement of the sulfoximine group by Ph and Me, respectively.

Mesitonitrile oxide and acridine (1:2 ratio) react site- and regioselectively to give mono-cycloadduct **127**. The reaction of the same reagents in a 10:1 ratio afforded the mono-cycloadduct **127**, and the bis-cycloadduct **128** with the opposite regiochemistry to that of the mono-cycloadduct (288).



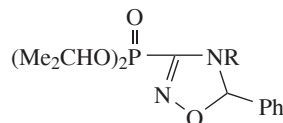
Scheme 1.25



**1.3.4.2. Intermolecular Cycloaddition at C=X or X=Y Bonds** Cycloaddition reactions of nitrile oxides to double bonds containing heteroatoms are well documented. In particular, there are several reviews concerning problems both of general (289) and individual aspects. They cover reactions of nitrile oxides with cumulene structures (290), stereo- and regiocontrol of 1,3-dipolar cycloadditions of imines and nitrile oxides by metal ions (291), cycloaddition reactions of *o*-benzoquinones (292, 293) and aromatic seleno aldehydes as dipolarophiles in reactions with nitrile oxides (294).

**1.3.4.2.1. Aldimines, Ketimines, and Related Compounds as Dipolarophiles**

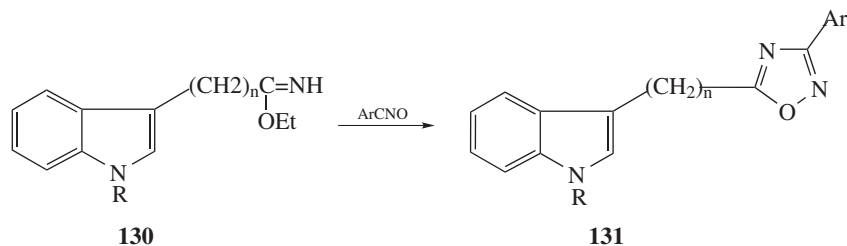
Reactions of aldimines with nitrile oxides proceed readily to give 1,2,4-oxadiazolines independently of the nature of substituents both in dipole and dipolarophile molecules. 1,2,4-Oxadiazolines were prepared by the regioselective 1,3-dipolar cycloaddition of nitrile oxides with fluoro-substituted aldimines (295). Phosphorylnitrile oxides gave with azomethines, PhCH:NR, phosphorylated 1,2,4-oxadiazolines **129** (296). Expected 1,2,4-oxadiazolines were also obtained from azomethines, derived from 4-formylcoumarine (179) and 1,3-diphenylpyrazole-4-carbaldehyde (297).

**129** (R = Ph, C<sub>6</sub>H<sub>4</sub>Br-4, Bu)

1,3-Dipolar cycloaddition of nitrile oxide at the C=N bond of indole imino esters **130**, followed by elimination of the alcohol moiety gives oxadiazole derivatives **131** (Scheme 1.26) (298). Reaction of N-arylbenzamidines with arenenitrile N-oxides (generated *in situ* from oximoyl chlorides) produce unstable 5-amino-4,5-dihydro-1,2,4-oxadiazoles which, on aqueous acidic treatment hydrolyze to open-chain N-benzoyloxy-N'-arylareneamidines (299).

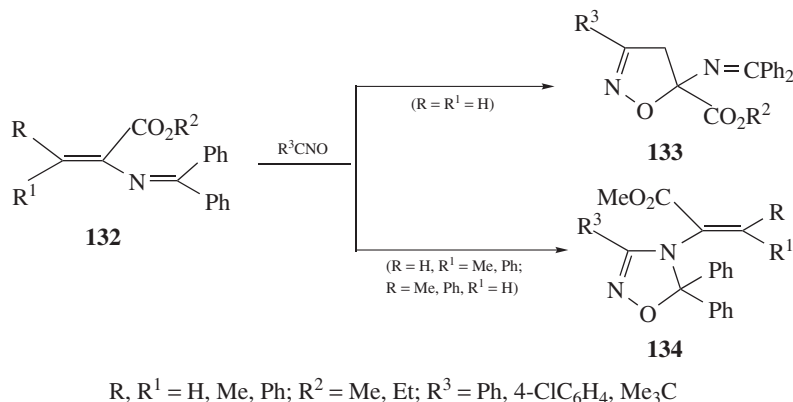
Poly(ethylene glycol) supported liquid-phase syntheses by both the reaction of (polyethylene glycol (PEG))-supported imines with nitrile oxides, generated *in situ* from aldoximes, (300) and 1,3-dipolar cycloadditions of nitrile oxide, generated *in situ* on soluble polymers with a variety of imines (301, 302) have been described. The solid-phase synthesis of 1,2,4-oxadiazolines via cycloaddition of nitrile oxide generated *in situ* on solid support with imines has also been elaborated (303). These syntheses of 1,2,4-oxadiazolines provide a library of 1,2,4-oxadiazolines in good yields and purity.

Cycloaddition reactions of ketimines have interesting features, especially with N-substituted imines. Results of 1,3-dipolar cycloaddition reactions of 1,1-diphenyl-2-aza-1,3-butadiene derivatives **132** with nitrile oxides depend on the type and on the stereochemistry of the β-substituents (304, 305). With the unsubstituted compounds **132** (R = R<sup>1</sup> = H, R<sup>2</sup> = Me, Et) the reaction occurs at the C=C double bond, providing a good method for the synthesis of 4,5-dihydro-isoxazole derivatives **133** (R<sup>2</sup> = Me, Et, R<sup>3</sup> = Ph; R<sup>2</sup> = Me, R<sup>3</sup> = CMe<sub>3</sub>). The β-substituted compounds **132** undergo reactions at the N=C double bond, thus giving, with R<sup>3</sup>CNO (R<sup>3</sup> = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>), the 4,5-dihydro-1,2,4-oxadiazole derivatives **134** (Scheme 1.27). All the reactions occur with high site- and regioselectivity. The crystal structure of **134** (R = Me, R<sup>1</sup> = H, R<sup>3</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>) has been determined (304).



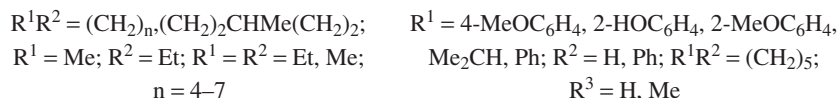
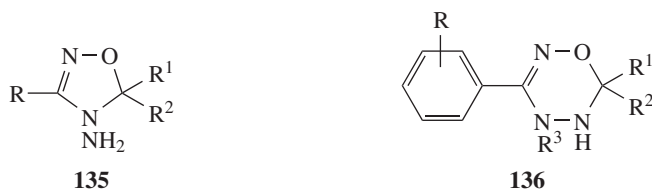
R = H, n = 0, 1; R = Me, n = 0. Ar = Ph, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 3-MeC<sub>6</sub>H<sub>4</sub>, 5-nitro-2-furyl

**Scheme 1.26**



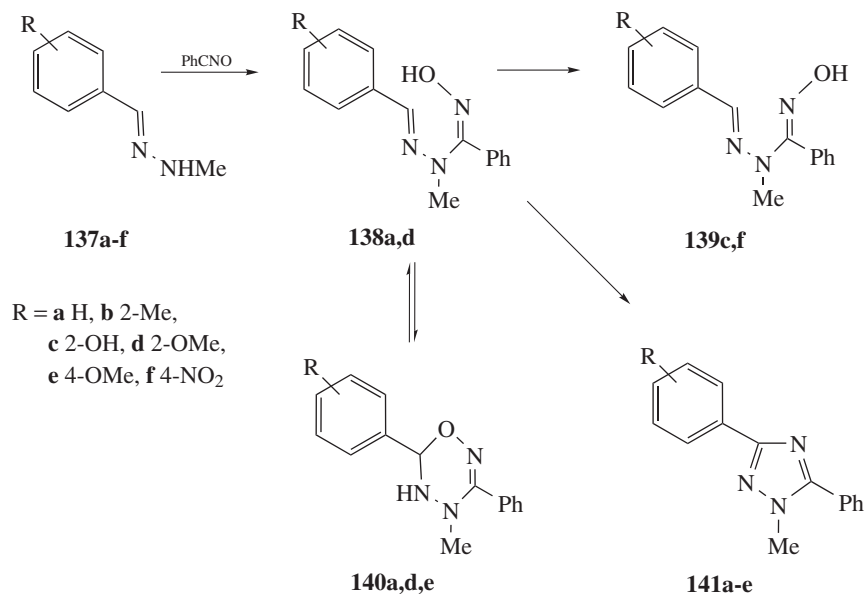
Scheme 1.27

Some data reporting reactions of nitrile oxides with hydrazones seem to be contradictory to each other. It was communicated that 1,3-dipolar cycloaddition of aromatic nitrile oxides  $RCNO$  ( $R = Ph$ , substituted  $Ph$ ), generated *in situ* from respective hydroxymoyl chlorides, with ketone hydrazones  $R^1R^2C=NNH_2$  proceed in a quite “normal” fashion to give 4-amino-4,5-dihydro-1,2,4-oxadiazolines **135** (306). However, products of reactions of similar nitrile oxides with other hydrazones, mainly N-substituted,  $R^1R^2C=NNHR^3$ , were described by the same investigator as 5,6-dihydro-4*H*-1,2,4,5-oxatriazines **136** (307).



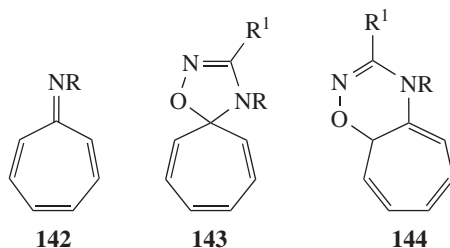
Later it was shown in reactions of aromatic aldehyde methylhydrazones **137a-f** with benzonitrile oxide that the initially formed *Z*-adduct **138**, depending on the reaction procedure and the substituents, undergoes either isomerization to the thermodynamically stable *E*-adduct **139**, tautomerization to an oxatriazine **140** or irreversible cyclization to a triazole **141** (Scheme 1.28). The structure of 4-methyl-3,6-diphenyl-5,6-dihydro-4*H*-1,2,4,5-oxatriazines **140a** was confirmed by an X-ray study (308).

Some features are characteristic of reactions of nitrile oxides with 2,4,6-cycloheptatrien-1-imines (8-azaheptafulvenes). 1,3-Dipolar cycloaddition to the  $C=N$  double bond of N-aryl-2,4,6-cycloheptatrien-1-imines **142** ( $R = Ar$ ), affording

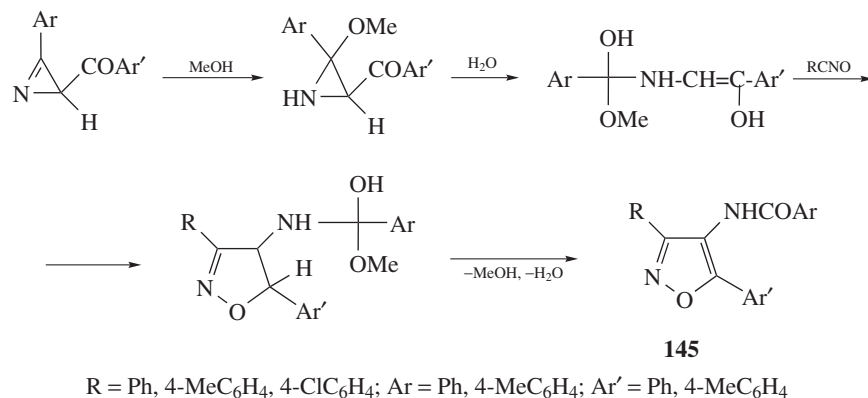


Scheme 1.28

1,2,4-oxadiazaspiro[4.6]undeca-6,8,10-trienes **143**, is described for *p*-substituted benzonitrile oxides (309, 310). The study of a more extended series of azaheptafulvenes **142** ( $\text{R} = \text{Me, 4-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$ ) and nitrile oxides  $\text{R}^1\text{CNO}$  ( $\text{R}^1 = \text{alkyl, Ph, substituted Ph, MeCO, Bz, CO}_2\text{Et}$ ) show that the above-mentioned reactions give, as a rule, only adducts derived from a reaction involving the  $\text{C}=\text{N}$  moiety of **142**. However, the adducts consist of a mixture of rapidly equilibrating spiro and fused isomers, that is, **143** and **144**, whose ratio is found to be dependent on substituents, temperature, and solvent (311). It is interesting to note that only products arising from the spiro isomer **143** are obtained in high yields in the catalytic hydrogenation of **143/144** (310, 311).



In the reaction of *o,o'*-disubstituted benzonitrile oxides with 8-(*p*-tolyl)-8-azaheptafulvene (**142**,  $\text{R} = 4\text{-MeC}_6\text{H}_4$ ) in cyclohexane, there is a competition between attack by the nitrile oxides on the  $\text{C}=\text{N}$  moiety (to give a mixture of

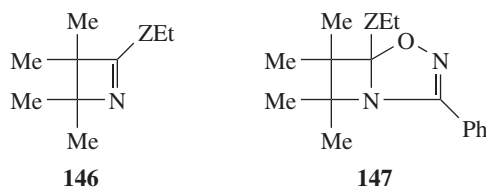


Scheme 1.29

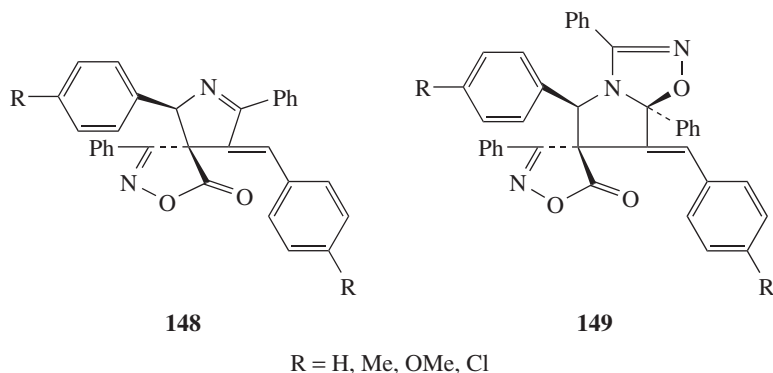
equilibrating fused and spiro adducts) and on the  $\text{C}_{(2)}=\text{C}_{(3)}$  double bond of **142**. Site selectivity is highly enhanced by carrying out the reaction in polar solvents, only the attack at the  $\text{C}=\text{N}$  moiety has been observed in methanol (312). The relative stabilities of rapidly equilibrating mixtures of fused (**144**) and spiro (**143**) isomers have been well reproduced by B3LYP/6–31G\* calculations (313).

**1.3.4.2.2. Nonaromatic Unsaturated Heterocycles** Reactions of aromatic nitrile oxides with 1-azirines are followed by the ring opening of the latter to give 4-benzamidoisoxazoles **145** (314). The structure of **145** ( $\text{R} = 4\text{-ClC}_6\text{H}_4$ ,  $\text{Ar} = \text{Ar}' = \text{Ph}$ ) was established by single-crystal X-ray analysis. A mechanism for the formation of **145** has been proposed, (see Scheme 1.29).

1,3-Dipolar cycloadditions of 2-ethoxy- and 2-ethylthio-1-azetines **146** ( $\text{Z} = \text{O}, \text{S}$ ) with nitrile oxides give 4,5,6,6a-tetrahydroazeto[1,2-*d*]oxadiazoles, for example **147** (315, 316).



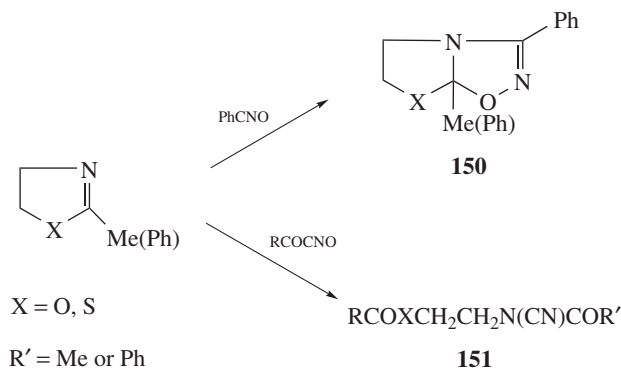
Cyclic imidate esters, 2-ethoxypyrrolin-5-one and 2-ethoxy-1*H*-indol-3-one, undergo 1,3-dipolar cycloaddition reactions with nitrile oxides, the reaction site being at the pyrroline  $\text{C}=\text{N}$  bond (317). Rigid and sterically congested pyrroline spiro compounds **148** demonstrate complete diastereofacial selection in site and regiospecific cycloaddition reactions with nitrile oxides to give products **149** (318).



2-Methyl-4,5-dihydrooxazole (319), 2-phenyl-4,5-dihydrooxazole (320), and 2,4,4-trimethyl-4,5-dihydrooxazole (319), which are examples of cyclic imide esters, undergo 1,3-dipolar cycloaddition reactions with benzonitrile N-oxide to give the 7a-substituted 3-phenyl-5,6-dihydro-7aH-oxazolo[3,2-*d*]-1,2,4-oxadiazoles **150**. 2-Methyl-4,5-dihydrothiazole gives the thia analog of **150** (319). Alkanoyl- and aroylformonitrile oxides (RCOCNO), 2-methyl- 4,5-dihydro-oxazole, 2-methyl-4,5-dihydrothiazole (319) as well as 2-phenyl-4,5-dihydro-oxazole (320) give the open-chain compounds **151** ( $X = O$  and  $S$ , respectively) (Scheme 1.30).

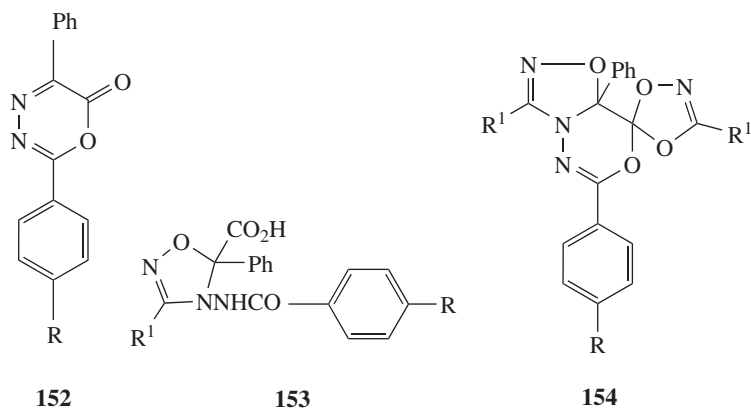
Among six-membered unsaturated nitrogen heterocycles, cycloaddition reactions of nitrile oxides at the  $C=N$  bond have been described for individual 3,4-dihydroisoquinolines, such as the reactions of 6,7-dimethoxy-3,4-dihydro-isoquinoline and its 1-methyl- and 1-cyanomethyl-substituted derivatives with acylcarbonitrile oxides (321). They have also been described for 1,3,4-oxadiazin-6-ones (322), and for fused dihydro-1,3-oxazine derivatives (323, 324).

Reactions of 2,5-diaryl-1,3,4-oxadiazin-6-ones **152** ( $R = H, Me, MeO, Cl, NO_2$ ) with stable nitrile oxides  $R^1CNO$  ( $R^1 = 2,4,6-Me_3C_6H_2, 2,6-Cl_2C_4H_3$ )

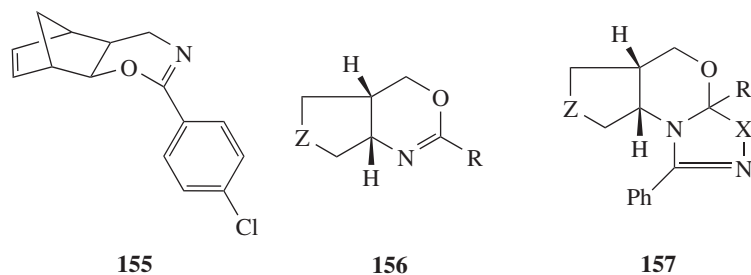


Scheme 1.30

gave 1,2,4-oxadiazoles **153**. When mesitonitrile oxide was used, bis-adducts **154** (at C=N and C=O bonds) were also formed. The cycloadditions showed a remarkable site selectivity toward one of two carbon–nitrogen double bonds. The structures of both adducts were confirmed by X-ray analysis (322).

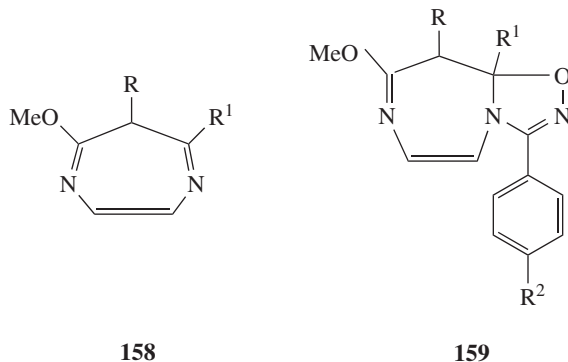


Cycloaddition of benzonitrile oxide to di-*exo*- and di-*endo*-norbornane and norbornene-fused dihydro-1,3-oxazine structural isomers gave tetracyclic 1,3-oxazino-1,2,4-oxadiazolines. With norbornene dipolarophiles, which contain C=N and C=C bonds, the cycloaddition with PhCNO takes place at the olefinic bond. The di-*exo* compound yields one tetracyclic isoxazoline, regioselectively, whereas the di-*endo*-isomer gives an isomeric mixture of isoxazolines. The di-*exo*-norbornene derivative **155** and PhCNO, however, gave a bis-adduct (323). *cis*-5,6-Tetramethylene-1*H*-1,3-dihydrooxazines **156** ( $Z = \text{CH}_2\text{CH}_2$ ,  $R = 4\text{-ClC}_6\text{H}_4$ ,  $4\text{-MeC}_6\text{H}_4$ ), and analogs unsaturated in the carbocyclic ring **156** ( $Z = \text{CH}:\text{CH}$ ) gave adducts at the hetero-double bond with benzonitrile oxide, furnishing 1,3-oxazino-1,2,4-oxadiazolines **157** ( $Z = \text{CH}_2\text{CH}_2$ ,  $\text{CH}:\text{CH}$ ;  $X = \text{O}$ ,  $R = 4\text{-MeC}_6\text{H}_4$ ). The site selectivity of the cycloaddition differs from that of the above-mentioned norbornene-fused dihydrooxazines, where the nitrile oxide dipole attacks first the C:C rather than the C:N bond (324).



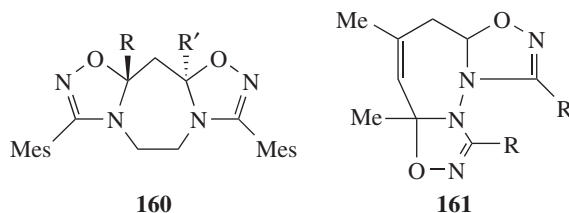
Methoxymethyldiazepines **158** ( $R = \text{Me}$ ,  $R^1 = \text{H}$ ;  $R = \text{H}$ ,  $R^1 = \text{Me}$ ) undergo regioselective 1,3-cycloaddition with benzonitrile oxide and its 4-substituted

derivatives  $4\text{-R}^2\text{C}_6\text{H}_4\text{CNO}$  ( $\text{R}^2 = \text{Me}, \text{Cl}$ ) to give good yields of dihydrooxadiazolodiazepines **159** ( $\text{R} = \text{Me}, \text{R}^1 = \text{H}, \text{R}^2 = \text{H}, \text{Me}, \text{Cl}; \text{R} = \text{R}^2 = \text{H}, \text{R}^1 = \text{Me}$ ). The crystal structure of **159** ( $\text{R} = \text{Me}, \text{R}^1 = \text{H}, \text{R}^2 = \text{Cl}$ ) has also been reported (325).

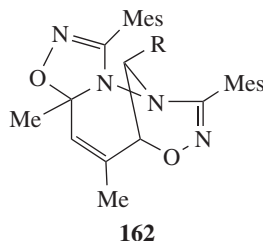


Reactions of 2,3-dihydro-1*H*-1,4-diazepines with mesitronitrile oxide proceed with site- and regiospecific 1,3-dipolar cycloaddition leading to bis[1,2,4]oxadiazolo[1,4]diazepine derivatives **160** (326). Of the three compounds **160** only the one with  $\text{R} = \text{R}' = \text{Ph}$  is formed with *trans* arranged substituents. The two other products ( $\text{R} = \text{R}' = \text{Me}$  and  $\text{R} = \text{Me}, \text{R}' = \text{Ph}$ ) are mixtures of diastereoisomers. The heterotricyclic 6,10a,11,11a-tetrahydro-5*H*-bis[1,2,4]oxadiazolo[4,5-*d*:5',4'-*g*][1,4]diazepine structure **160** of the obtained bis-adducts indicates that the hetero double bonds are much more reactive than the olefinic ones. No evidence for the formation of monoadducts was obtained.

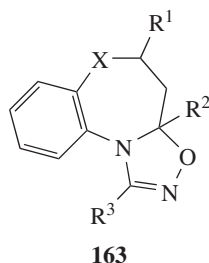
Bis[1,2,4]oxadiazolino[4,5-*b*;5',4'-*g*][1,2]diazepines **161** ( $\text{R} = \text{mesityl}, \text{CF}_3$ ) were prepared by a one-step cycloaddition of mesitronitrile and trifluoroacetonitrile oxides, with 5,7-dimethyl-4*H*-(or 2*H*)-1,2-diazepines (327).



Reactions of 1,2-diazepines with nitrile oxides are sometimes difficult to elucidate because they give mixtures (328) or unexpected products. Thus, reactions of 3-methyl- and 3,7-dimethyl-1,2-diazepines with mesitronitrile oxide leads to 5,10-dioxa-1,2,4,11-tetrazatricyclo[7,3,1,0<sup>2,6</sup>]trideca-3,7,11-triene derivatives **162** ( $\text{R} = \text{H}, \text{Me}$ , respectively) (329). Such structures were determined by X-ray diffraction studies (330).

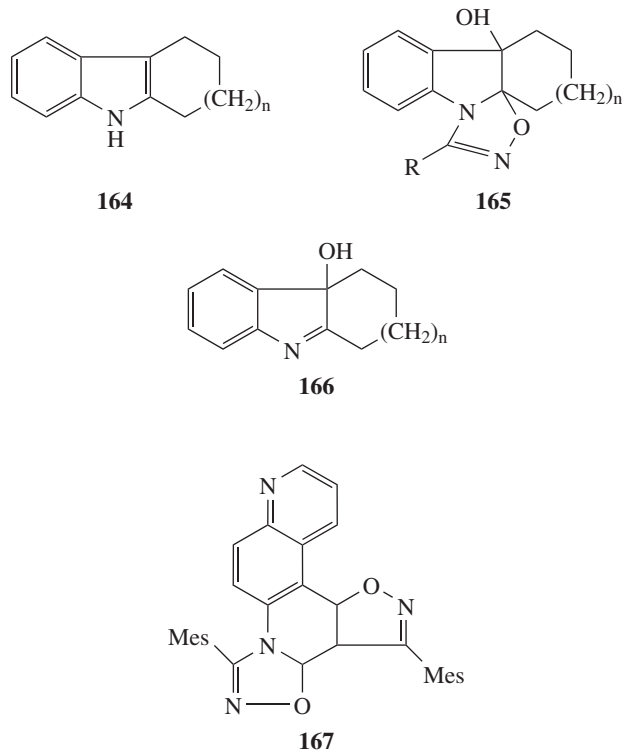


The 1,3-dipolar cycloaddition of 1,5-benzodiazepine to a nitrile oxide occurs at the N=C double bond at the 1 and 2 positions of the benzodiazepine system (331, 332). A second nitrile oxide molecule adds at the C<sub>(4)</sub>=N<sub>(5)</sub> bond (333). Behavior of 1,5-benzothiazepines is similar to that of 1,5-benzodiazepines. 3a,4,5,11-Tetrahydro-1,2,4-oxadiazolo[4,5-*d*][1,5]benzothiazepines **163** (X = S, R<sup>1</sup> = Ph, 2-, 3-, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, Me, R<sup>2</sup> = Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, R<sup>3</sup> = Ph, 3-BrC<sub>6</sub>H<sub>4</sub>, CO<sub>2</sub>Et) and 3a,4,5,11-tetrahydro-6H-1,2,4-oxadiazolo[4,5-*d*] [1,5]benzodiazepines **163** (X = NH) were obtained by 1,3-dipolar cycloaddition reactions of 2,3-dihydro-1,5-benzothiazepines and 2,3-dihydro-1H-1,5-benzodiazepine with benzonitrile oxides, respectively (332, 334).

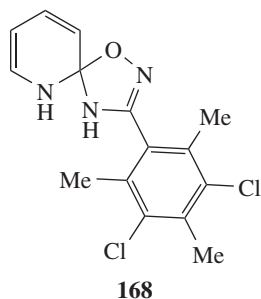


*1.3.4.2.3. Nitrogen-containing Hetarenes* Reactions of RCNO (R = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>) with cycloalkano[*b*]indoles **164** (n = 1, 2, 3) gave mainly the oxadiazolo[4,5-*a*]indoline adducts **165**. The structure elucidation of the adducts was based on their spectral data, chemical behavior and in the case of **165** (R = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, n = 1) by X-ray analysis (335). The suggested mechanism takes into account the ability of 2,3-disubstituted indoles, especially, of 1,2,3,4-tetrahydrocarbazoles, to autooxidation and proposes the intermediate formation of compounds **166** which react with nitrile oxides to give the final products **165** (335).

Mesitronitrile oxide, but not benzonitrile oxide, adds to aza-analogs of phenanthrene, *viz.*, benzo[*h*]quinoline, 1,10-, 1,7-, and 4,7-phenanthrolines to give low yields of mono-cycloadducts at the C<sub>(5)</sub>=C<sub>(6)</sub> bond. Only 4,7-phenanthroline gave minor products, of which one the bisadduct **167** was isolated in approximately 7% yield. Phenanthridine reacts with two nitrile oxides but affords phenanthridin-6-one rather than a cyclo-adduct (336).

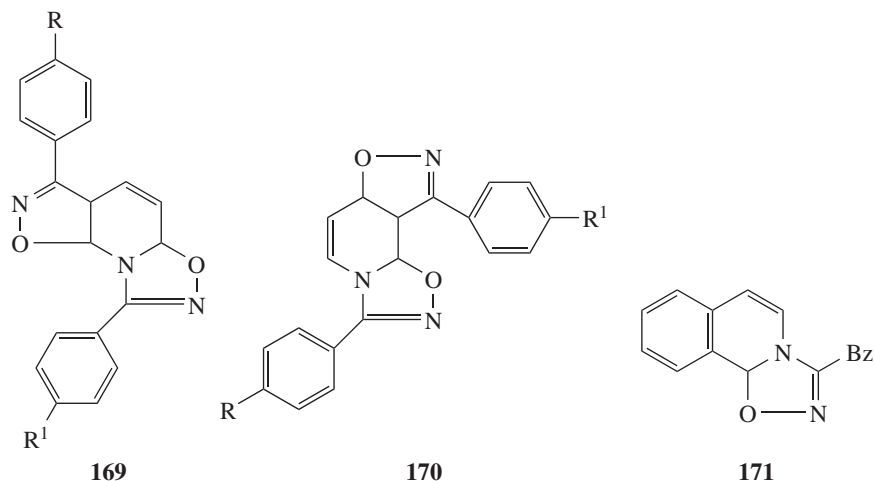


Stable 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide reacts with 2- and 4-aminopyridines in their imino forms, if acids are present to promote the formation of imine, to give cycloadducts such as **168** (337).

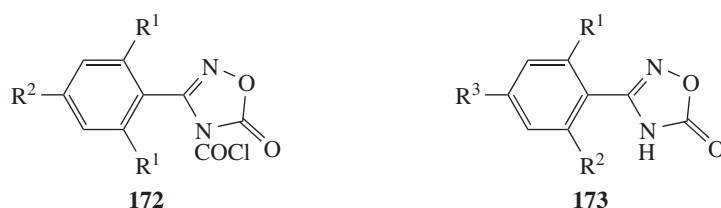


Bis-cycloadducts **169** and **170** ( $R = R^1 = MeO, Me, Cl$ ) obtained from reactions of respective 4-substituted benzonitrile oxides and pyridine have been described. Crossed adducts, such as **169** ( $R = H, R^1 = MeO$ ;  $R = MeO, R^1 = H$ ), were also formed on treating pyridine with mixtures of various nitrile oxides (338). Addition of pyridine to benzoylcarbonitrile oxide affords an unstable

adduct, which slowly reverts to the addends, leading to BzNCO and products deriving from it. A moderately stable cycloadduct **171** has been obtained in the reaction with isoquinoline (339).

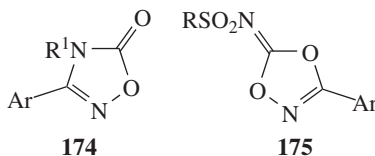


**1.3.4.2.4. Heterocumulenes** The 1,3-dipolar cycloaddition of substituted benzonitrile oxides to the C=N group of chlorocarbonyl isocyanate ClC(O)N=C=O gives 3-aryl-4-chlorocarbonyl-5-oxo-4,5-dihydro-1,2,4-oxadiazoles **172** in 75%–80% yield (340). A similar reaction with chlorosulfonyl isocyanate, ClSO<sub>2</sub>N=C=O, affords 4-unsubstituted oxadiazolinones **173** (341).

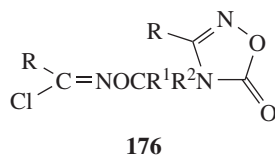


R = R<sup>1</sup> = Me, OMe; R = Cl, R<sup>1</sup> = H R<sup>1</sup> = Cl, OMe, Me; R<sup>2</sup> = Cl, OMe, Me; R<sup>3</sup> = H, OMe, Me

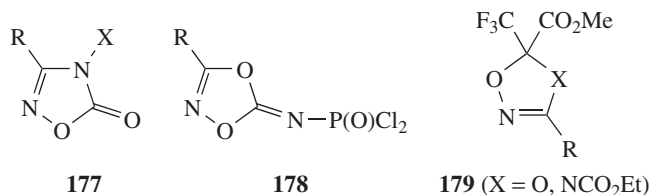
The study of the above reaction by different authors (342) showed that besides oxadiazolones **172**, open-chain products from the 1,3-addition of chlorocarbonyl isocyanate to the fulminic group, RCCl=N-O<sub>2</sub>CN=C=O (R = mesityl, duryl), were formed (342). Reactions of aromatic nitrile oxides with various sulfonyl isocyanates RSO<sub>2</sub>NCO (R = Pr, Cl, substituted Ph) gave oxadiazoles **174** (R<sup>1</sup> = RSO<sub>2</sub>) and dioxazoles **175**, the latter being formed on cycloaddition at the C=O bond (343). The hydrolysis of **174** (R<sup>1</sup> = RSO<sub>2</sub>) gave **174** (R<sup>1</sup> = H).



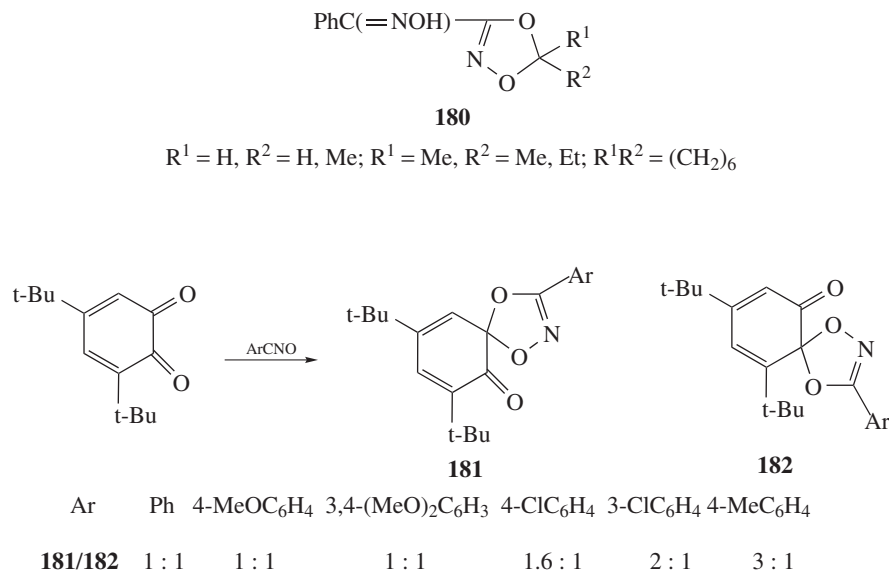
Reactions of stable mesito- and duronitrile oxides with 1-chloroalkyl isocyanates  $R^1R^2CCINCO$  ( $R^1 = CF_3$ ,  $R^2 = Ph$ , 4-MeC<sub>6</sub>H<sub>4</sub>;  $R^1 = CCl_3$ ,  $R^2 = H$ ) gave oxadiazolones **176**. The double adducts are formed by the cycloaddition of one nitrile oxide molecule at the isocyanate C=N bond and the nucleophilic addition of the chloroalkyl moiety to a second nitrile oxide molecule (344).



Cycloaddition of aromatic nitrile oxides, RCNO ( $R = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$ , 2,3,5,6-Me<sub>4</sub>C<sub>6</sub>H, 3,5-Cl<sub>2</sub>-2,4,6-Me<sub>3</sub>C<sub>6</sub>) to isocyanatophosphoric dichloride occurs at both the C=N and C=O bond of the isocyanato group to afford an inseparable mixture of heterocyclic products, consisting of 3-aryl-4-dichlorophosphinoyl-4,5-dihydro-1,2,4-oxadiazol-5-ones **177** ( $X = P(O)Cl_2$ ) and 5-aryl-2-dichlorophosphinoylimino-2H-1,3,4-dioxazoles **178**. The structure of these compounds was confirmed by spectral data and chemical transformations, in particular, by hydrolysis of **177** ( $R = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$ ,  $X = P(O)Cl_2$ ) to give **177** ( $X = H$ ) (345). Reactions of methyl trifluoropyruvate and its (methoxycarbonyl)imine CF<sub>3</sub>C(:X)CO<sub>2</sub>Me ( $I$ ;  $X = O$ , NCO<sub>2</sub>Me) with aromatic nitrile oxides RCNO ( $R = \text{mesityl}$ , duryl) gave dioxazoles and oxadiazoles **179** (346).



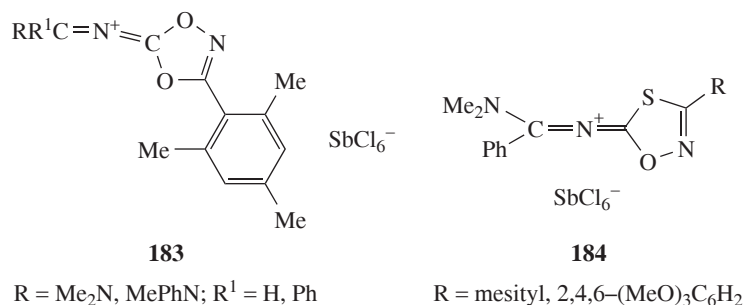
**1.3.4.2.5. Carbonyl and Thiocarbonyl Compounds**  $\alpha$ -(Hydroxyimino)phenyl-acetonitrile oxide (generated *in situ* at room temperature from PhC(:NOH)C(:NOH)Cl in the presence of NaHCO<sub>3</sub> or Et<sub>3</sub>N) reacts with simple aldehydes and ketones  $R^1R^2CO$  to give 1,4,2-dioxazoles **180** (347). Related dioxazoles, formed by cycloaddition of benzonitrile oxide to aromatic aldehydes, upon treatment with *t*-BuOK, undergo cyclo-reversion, allowing direct conversion to substituted benzoic acids or their esters (348).



Scheme 1.31

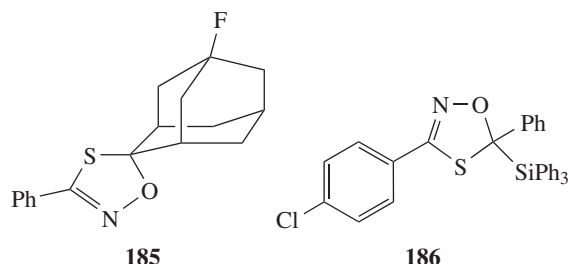
A synthesis of novel spirodioxazole systems by the 1,3-dipolar cycloaddition reactions of 3,5-di-*tert*-butyl-1,2-benzoquinone with aromatic nitrile oxides has been described (Scheme 1.31). Though yields are high (80%–100%), the regioselectivity is low, the regioisomer ratio **181:182** being dependent on the Ar nature (349).

Mesitronitrile oxide undergoes a reversible cycloaddition to the carbonyl group of the 1-oxo-3-azoniabutatriene salts  $\text{RR}^1\text{C}=\text{N}^+=\text{C}=\text{O} \text{ SbCl}_6^-$  to give the 2-azoniaallene salts **183**. X-ray structural analysis of **183** ( $\text{R} = \text{NMePh}$ ,  $\text{R}^1 = \text{H}$ ) confirmed the proposed structure (350). 1-Thia-3-azoniabutatriene salts,  $\text{RR}^1\text{C}=\text{N}^+=\text{C}=\text{S} \text{ SbCl}_6^-$  ( $\text{R}, \text{R}^1 = \text{H, Me}_2\text{N}$ ;  $\text{Ph, Me}_2\text{N}$ ) react with nitrile oxides at the  $\text{C}=\text{S}$  double bond to yield 2-azoniaallene salts **184** (351).

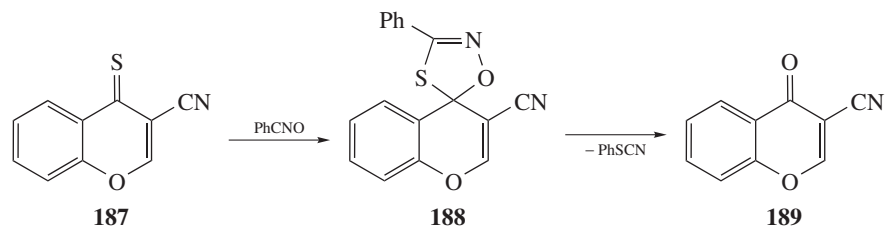


Face selectivity in the 1,3-dipolar cycloaddition reactions of benzonitrile oxide and its *p*-substituted derivatives with 5-substituted adamantane-2-thiones,

N-benzyladamantyl-2-imines, and 2-methyleneadamantanes were studied (352, 353). In particular, X-ray single-crystal analysis confirmed the configuration of the oxathiazoline **185**, resulting from the favored attack of nitrile oxide on the 5-fluoroadamantane-2-thione. 2-Silyl-substituted oxathiazole **186** was synthesized by the 1,3-dipolar cycloaddition reaction of phenyl triphenylsilyl thioketone with 4-chlorobenzonitrile oxide (354).

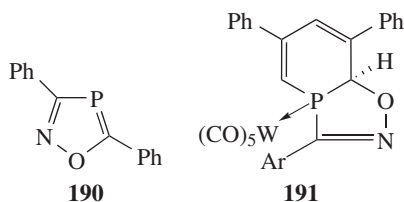


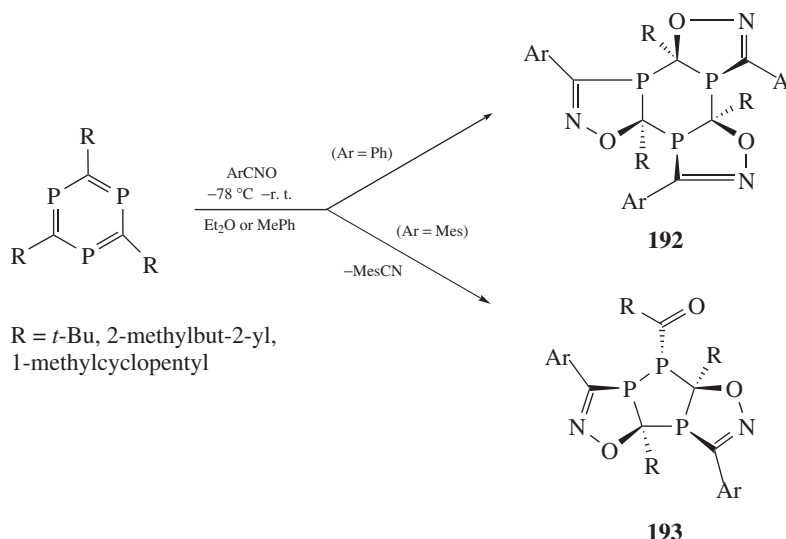
1,3-Dipolar cycloaddition of 3-cyano-4*H*-1-benzopyran-4-thione **187** with benzonitrile oxide proceeded regioselectively to give cycloadduct **188** (involving the thione function). The unstable cycloadduct fragmented to yield 3-cyanochromone **189** and phenyl isothiocyanate (Scheme 1.32) (355).



Scheme 1.32

**1.3.4.2.6. Compounds with Unusual Double Bonds** 1,3-Dipolar cycloaddition of 1-chloro-2-phenyl-2-trimethylsilyl-1-phosphaethene with nitrile oxides, followed by elimination of Me<sub>3</sub>SiCl, results in 3,5-diphenyl-1,4,2-oxaphosphazole **190** (356). Chromium, molybdenum, and tungsten pentacarbonyls of 3,5-diphenyl- $\lambda^3$ -phosphinins react with nitrile oxides to give the corresponding 1,3-dipolar cycloadducts, at the P=C bond, see **191** (Ar = Ph, Mes) (357).



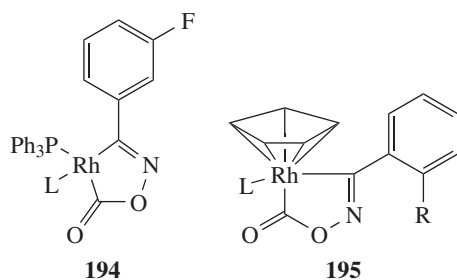


Scheme 1.33

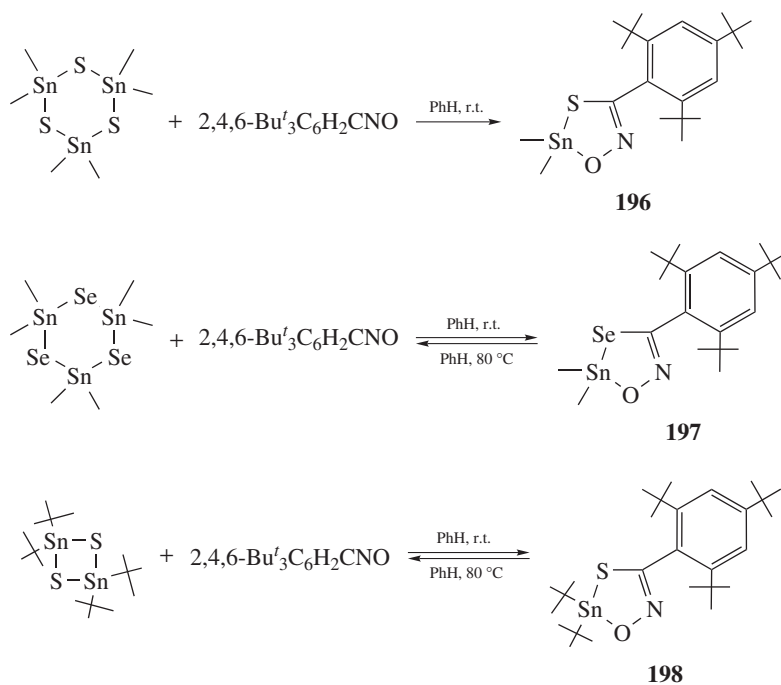
Benzonitrile oxide and mesitronitrile oxide undergo 1,3-dipolar cycloaddition reactions with 1,3,5-triphosphinines under mild conditions to afford fused heterocyclic compounds (Scheme 1.33), for example, **192** and **193**. Oxaphosphazoles and oxadiphospholes have become accessible by thermal fragmentation reactions of such fused heterocyclic compounds (358).

Low-valence metal carbonyl complexes give in good yield (50%–85%), five-membered metalacycles by 1,3-dipolar cycloaddition of aromatic nitrile oxides to a M–CO bond. Synthesis of metalacycles from metalacarborane carbonyl anions [*closo*-3- $\text{PPh}_3$ -3-(CO)-3,1,2- $\text{MC}_2\text{B}_9\text{H}_{11}$ ] $^-$  (M = Ir, Rh) and [*closo*-2- $\text{PPh}_3$ -2-(CO)-2,1,7- $\text{RhC}_2\text{B}_9\text{H}_{11}$ ] $^-$ , from a number of pentamethylcyclopentadienyl and cyclopentadienyl complexes of Co, Rh, and Ir of the type  $(\eta^5\text{-C}_5\text{R}_5)\text{ML}(\text{CO})$  (R = H, Me; L =  $\text{PPh}_3$ ,  $\text{PMe}_3$ , CO) and from the metal carbonyl anions  $\text{M}(\text{CO})_5^-$  (M = Mn, Re) have been described (359). Single-crystal X-ray diffraction studies of the rhodaisoxazolinone metalacycles, for example, **194** (L is carborane ligand) have also been reported. The reaction of rhodium complex  $\text{C}_5\text{H}_5\text{Rh}(\text{CO})(\text{L})$  [L =  $\text{P}(\text{CHMe}_2)_3$ ], which is prepared from  $\text{C}_5\text{H}_5\text{Rh}(\text{CO})_2$  and neat triisopropylphosphine, with benzonitrile oxide and 2-chlorobenzonitrile oxide affords metalaheterocycles **195** in 90% to 95% yield. The X-ray structural analysis of **195** (R = H) reveals the presence of an almost planar  $\text{RhCONC}$  heterocycle in which the two Rh–C distances differ by 0.045 Å (360).

Kinetically stabilized germanothiones  $\text{Tbt}(\text{Tip})\text{Ge}=\text{S}$ ,  $\text{Tbt}(\text{Dis})\text{Ge}=\text{S}$  and germanoselones  $\text{Tbt}(\text{Tip})\text{Ge}=\text{Se}$ ,  $\text{Tbt}(\text{Dis})\text{Ge}=\text{Se}$  [Dis = bis(trimethylsilyl)methyl, Tbt = 2,4,6-tris(bis(trimethylsilyl)methyl)phenyl, Tip = 2,4,6-tris(isopropyl)phenyl], have been synthesized and have shown to enter 1,3-dipolar cycloaddition reactions with mesitronitrile oxide (361).



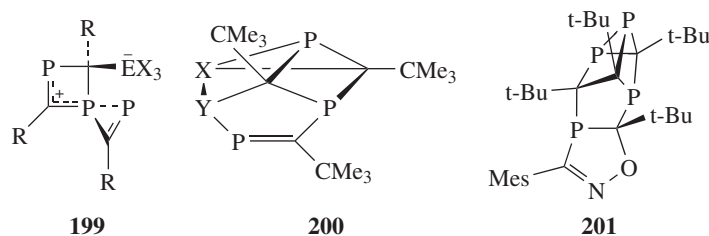
Reactions of 2,2,4,4,6,6-hexamethyl-1,3,5-trithia- and -1,3,5-triseleno-2,4,6-tristannins with 2,4,6-tri-*t*-butylbenzonitrile oxide, at room temperature, gave 2,2-dimethyl-1,3,5,2-oxathiazastannole **196** and 2,2-dimethyl-1,3,5,2-oxaselenastannole **197**, respectively. The reaction of 2,2,4,4-tetra-*t*-butyl-1,3,2,4-dithiadistannetane with 2,4,6-tri-*t*-butylbenzonitrile oxide gave 2,2-di-*t*-butyl-1,3,5,2-oxathiazastannole **198**, which was characterized by X-ray crystallography (362). The reactions yielding oxachalcogenazastannoles **197** and **198**, are reversible; the equilibrium is shifted to the addends at 80°C (Scheme 1.34). In these reactions, trichalcogenatristannines and dithiadistannetane can be regarded as cyclic forms of unstable stannanethiones and stannaneselones.



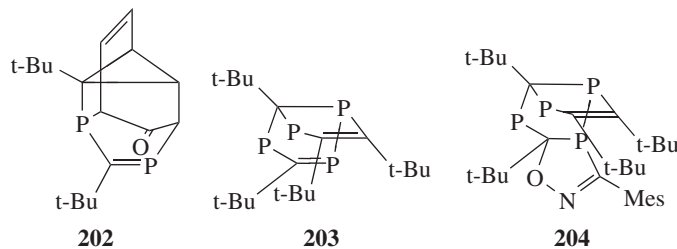
Scheme 1.34

The reaction of a highly crowded 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl-dihydrostilbine (TbtSbH<sub>2</sub>) with elemental sulfur, in the presence of nitrile oxides, results in the formation of [2 + 3] cycloaddition reaction products of a thioxostilbine TbtSb = S and a dithioxostiborane TbtSb(S) = S (363).

Some interesting transformations of cage organophosphorus compounds, including their 1,3-cycloaddition reactions with nitrile oxides at the C=P bond have been described. In the presence of aluminum halides and gallium chloride, phosphalkynes undergo spiro-cyclotrimerization, with incorporation of the corresponding Lewis acid, to form the betaines **199** (R = CMe<sub>3</sub>, CMe<sub>2</sub>Et, 1-adamantyl, EX<sub>3</sub> = AlCl<sub>3</sub>; R = CMe<sub>3</sub>, EX<sub>3</sub> = AlBr<sub>3</sub>, AlI<sub>3</sub>, GaCl<sub>3</sub>). The reaction of **199** (R = CMe<sub>3</sub>, EX<sub>3</sub> = AlCl<sub>3</sub>) with DMSO allows the selective generation of two isomeric triphospha Dewar benzene derivatives. Both are trapped efficiently, by further reaction with the phosphalkyne, to the phosphalkyne cyclotetramers **200** (X = CCMe<sub>3</sub>, Y = P; X = P, Y = CCMe<sub>3</sub>). In the case of **200** (X = P, Y = CCMe<sub>3</sub>), further functionalization of the phosphalkene unit is possible by [3 + 2] cycloaddition with mesitonitrile oxide, to give annulated isoxazoline **201** (364).



On heating at 95°, in the presence of tropone, *tert*-butylphosphaacetylene, P≡C–Bu formed along with the tetracyclic adduct **202** gave 5% of tetraphosphasemibullvalene **203**. The latter reacted with mesitonitrile oxide to give oxaphosphazole **204**, which was characterized by X-ray crystallography (365).

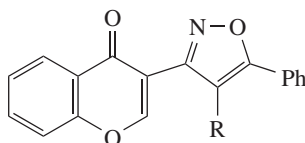


### 1.3.4.3. Intermolecular Cycloaddition at C≡C, C≡N, and C≡P Bonds

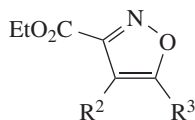
**1.3.4.3.1. Cycloaddition at C≡C Bonds** Cycloaddition of nitrile oxides to triple carbon–carbon bonds is a rather trivial reaction. Therefore, most attention is to new types of dipoles and dipolarophiles as well as to unusual reaction routes

and modern preparative procedures. In particular, reagents and approaches in nitrile oxide chemistry become closer to those of organometallic and coordination chemistry.

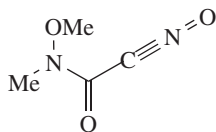
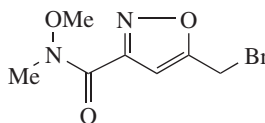
Chromone-3-carbonitrile oxide undergoes cycloaddition reactions with phenyl- and diphenylacetylenes to give isoxazoles **205** ( $R = H, Ph$ ). The nitrile oxide is obtained from 3-formylchromone oxime by bromination and subsequent dehydrobromination (175).

**205**

The reaction of ethoxycarbonylformohydroximinoyl chloride  $EtO_2CCl:NOH$  with acetylene derivatives gave isoxazoles **206** ( $R^2 = H, CO_2Et, CO_2Me, COC_6H_4NO_2-4$ ;  $R^3 = CO_2Et, CO_2Me, Ph, C(Ph)_3$ ) (366).

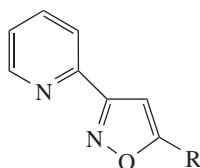
**206**

The cycloaddition of Weinreb amide functionalized nitrile oxide with a range of dipolarophiles has been studied. N-Methoxy-N-methylcarboncyanidic amide, nitrile oxide **207** (i.e., a nitrile oxide of Weinreb amide type derivative) was generated from 2-chloro-2-(hydroxyimino)-N-methoxy-N-methylacetamide as intermediate and used *in situ*. Thus, addition of 3-bromo-1-propyne as dipolarophile to this precursor of **207**, followed by quenching with triethylamine, gave 5-(bromomethyl)-N-(methoxy)-N-methyl-3-isoxazolecarboxamide **208** in 55% to 60% yield (367).

**207****208**

Iodoacetylene (prepared *in situ* from ethynylmagnesium bromide or tributyl (ethynyl)tin with iodine) was used as a dipolarophile in the 1,3-dipolar cycloaddition reactions with nitrile oxides to produce 2-(5-iodoisoxazol-3-yl)pyridine and 3-(4-fluorophenyl)-5-iodoisoxazole in good yield (70%–90%). Subsequently,

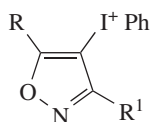
several 5-substituted 3-(pyridin-2-yl)isoxazole derivatives **209** ( $R = C\equiv C\text{SiMe}_3$ , Ph, 2-thienyl,  $\text{CH}=\text{CH}_2$ ) were obtained by Pd-catalyzed coupling reactions. The crystal structure of 2-(5-iodoisoxazol-3-yl)pyridine has been determined (368).



$R = C\equiv C\text{SiMe}_3$ , Ph, 2-thienyl, vinyl

**209**

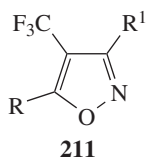
Arylethynyl(phenyl)iodonium salts,  $\text{RC}\equiv\text{C}^+\text{I}^-\text{Ph}$   $4\text{-MeC}_6\text{H}_4\text{SO}_3^-$ , react as 1,3-dipolarophiles with nitrile oxides  $\text{R}^1\text{CNO}$  to afford phenyl(substituted isoxazolyl)iodonium salts **210**, which give iodoisoxazoles on reaction with nucleophiles. The crystal structure of **210** ( $R = \text{Ph}$ ,  $\text{R}^1 = \text{mesityl}$ ) has been determined (369).



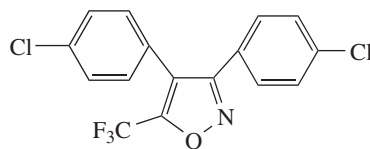
$R = \text{Ph}$ ,  $4\text{-ClC}_6\text{H}_4$ ,  $4\text{-MeOC}_6\text{H}_4$ ;  $\text{R}^1 = \text{mesityl}$ ,  $2,6\text{-Cl}_2\text{C}_6\text{H}_3$

**210**

Syntheses of 1-aryl-3,3,3-trifluoro-1-propynes and their reactions with nitrile oxides to give 3,5-diaryl-4-trifluoromethylisoxazoles have been carried out. In particular, 1-(4-chlorophenyl)-3,3,3-trifluoro-1-propyne, on reaction with 4-chlorobenzohydroximinoyl chloride in the presence of  $\text{Et}_3\text{N}$  in PhMe, give a 45% mixture of **211** ( $R = \text{R}^1 = 4\text{-ClC}_6\text{H}_4$ ) and the regioisomer **212** in the ratio of 97:3, respectively (370).



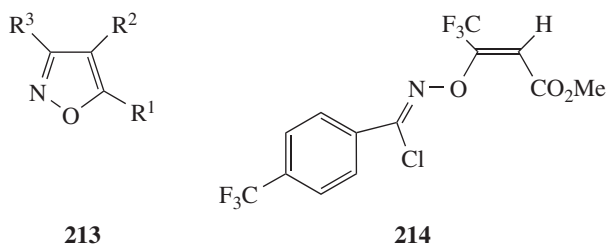
**211**



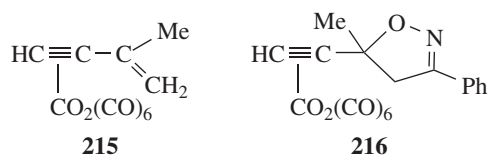
**212**

The triethylamine-induced reaction of benzohydroximinoyl chlorides, precursors of nitrile oxides, with  $\beta$ -trifluoromethyl-substituted acetylenic esters gives rise to three products: 5-trifluoromethyl-4-isoxazolecarboxylates, **213** ( $\text{R}^1 = \text{CF}_3$ ,

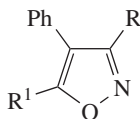
$R^2 = \text{MeO}_2\text{C}$ ,  $R^3 = 4\text{-F}_3\text{CC}_6\text{H}_4$ ), regioisomeric 4-trifluoromethyl-5-isoxazole-carboxylates, **213** ( $R^1 = \text{MeO}_2\text{C}$ ,  $R^2 = \text{CF}_3$ ,  $R^3 = 4\text{-F}_3\text{CC}_6\text{H}_4$ ) and unexpectedly oximinoyl chloride **214**, resulted by 1,4-addition. Product distribution is rationalized in terms of two competing reactions, either 1,4-addition of the oximate anion to the acetylenic ester or formation of the nitrile oxide followed by 1,3-dipolar cycloaddition. Anionic 1,4-addition of the oximinoyl chloride to the acetylenic ester is favoured at low temperatures, while nitrile oxide formation, followed by cycloaddition, occur at temperatures above  $0^\circ$  (371).



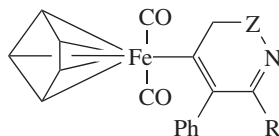
A characteristic feature of contemporary investigations in the field under consideration, is the interest in cycloaddition reactions of nitrile oxides with acetylenes in which properties of the  $\text{C}\equiv\text{C}$  bond are modified by complex formation or by an adjacent metal or metalloid atom. The use of such compounds offers promising synthetic results. In particular, unlike the frequently unselective reactions of 1,3-enynes with 1,3-dipoles, nitrile oxides add chemo-, regio- and stereoselectively to the free double bond of  $(1,3\text{-enynes})\text{Co}_2(\text{CO})_6$  complexes to provide 5-alkynyl-2-oxazoline derivatives in moderate to excellent yield. For example, enyne **215** reacts with *in situ* generated  $\text{PhCNO}$  to give 80% yield of isoxazoline **216** (372).



$\eta^1$ -Ethynyl complexes  $\text{Cp}(\text{CO})_n\text{LMC}\equiv\text{CPh}$ , ( $\text{Cp} = \eta\text{-cyclopentadienyl}$ ;  $n = 1, 2$ ;  $\text{L} = \text{CO}$ ,  $\text{PPh}_3$ ;  $\text{M} = \text{Fe}$ ,  $\text{Mo}$ ) react with nitrile oxides  $\text{RCNO}$  ( $\text{R} = \text{Ph}$ ,  $\text{CO}_2\text{Et}$ ) to give the  $\sigma$ -isoxazolyl transition metal derivatives **217** [same  $\text{R}$ ,  $\text{R}^1 = \text{Cp}(\text{OC})_n\text{LM}$ ]. An X-ray diffraction study of **217** [ $\text{R} = \text{Ph}$ ,  $\text{R}^1 = \text{Cp}(\text{OC})(\text{Ph}_3\text{P})\text{Fe}$ ] has been performed (373). Treatment of iron complex  $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{CH}_2\text{C}\equiv\text{CPh}$  with nitrile oxides yields six-membered  $\sigma$ -heterocyclic iron complexes, **218** ( $\text{R} = \text{Ph}$ ,  $\text{CO}_2\text{Et}$ ,  $\text{Z} = \text{O}$ ), arising from cycloaddition and subsequent 1,2-migration of the  $(\eta^5\text{-C}_5\text{H}_5)_2\text{Fe}(\text{CO})$  group (374).



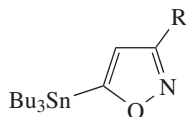
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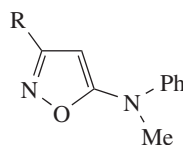
218

2-Alkynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes participate in 1,3-dipolar cycloaddition reactions with mesito-, benzonitrile oxide or *tert*-butylformonitrile oxide to provide isoxazoleboronic esters in good yield and with excellent levels of regiocontrol. In addition, these potentially valuable synthetic intermediates have been shown to participate efficiently in Suzuki coupling reactions (375). The [3 + 2] cycloaddition reaction of nitrile oxides and alkynylboronates provide direct access to a wide variety of isoxazole boronic esters with high levels of regiocontrol. For example, mesitonitrile oxide reacts with 2-(1-hexynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, in refluxing diethyl ether, giving 5-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)isoxazole in 73% yield. The application of this methodology in the synthesis of non-steroidal anti-inflammatory agents has also been described (376).

3-Substituted 5-(tributylstannyl)isoxazoles have been synthesized in good yields by the 1,3-dipolar cycloaddition reaction of ethynyltributylstannane with nitrile oxides, generated *in situ*.  $\text{Bu}_3\text{SnC}\equiv\text{CH}$  and  $\text{RCNO}$  ( $\text{R} = \text{Me}, \text{Ph}, \text{CO}_2\text{Et}$ ) give isoxazoles **219** in 85% to 100% yield. 3-Methyl-5-(tributylstannyl)isoxazole is easily converted to the corresponding 5-benzoyl- and 5-arylisoxazoles by a Pd-catalyzed reaction (377). Ynamines, such as,  $\text{PhNMeC}\equiv\text{CH}$ , react with nitrile oxides to give the 5-aminoisoxazoles **220** ( $\text{R} = \text{Me}_3\text{C}, \text{Ph}, \text{substituted Ph}$ ). The stannyl-substituted ynamine  $\text{PhNMeC}\equiv\text{CSnBu}_3$  also furnishes the compounds, **220** on reaction with hydroximoyl chlorides (378).



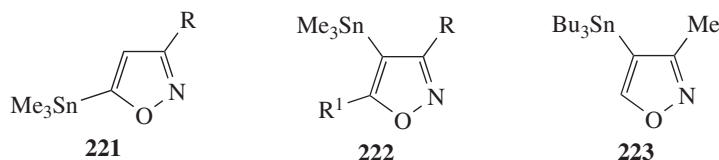
219



220

1,3-Dipolar cycloaddition reaction of trimethylstannylacetylene with nitrile oxides yielded 3-substituted 5-(trimethylstannyl)isoxazoles **221**. Similar reactions of (trimethylstannyl)phenylacetylene, 1-(trimethylstannyl)-1-hexyne, and bis(trimethylsilyl)acetylene give the corresponding 3,5-disubstituted 4-(trimethylstannyl)isoxazoles **222**, almost regioselectively (379). The 1,3-dipolar cycloaddition reaction of bis(tributylstannyl)acetylene with acetonitrile oxide, followed by treatment with aqueous ammonia in ethanol in a sealed tube, gives 3-methyl-4-(tributylstannyl)isoxazole **223**. The palladium catalyzed cross coupling reaction of

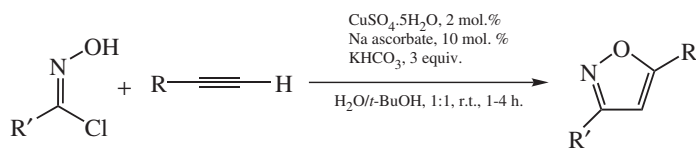
**223** with 2-iodonitrobenzene, followed by reductive cyclization give 3-acetylintole (380). 1,3-Dipolar cycloaddition reactions between nitrile oxides and stannylalkynes proceed in a regiospecific manner to afford 4-stannylisoxazoles in good yields. No reaction has been observed with vinyl- or allylstannanes (381).



R = Me, Ph, CO<sub>2</sub>Et; R<sup>1</sup> = Bu or Ph, Me<sub>3</sub>Si, Me<sub>3</sub>Sn

Exciting results have been obtained by using copper(I)-catalyzed 1,3-cycloaddition reactions with 1-alkynes (382). The process is apparently mediated by species like R-C≡C-Cu, formed *in situ* by reduction of copper(II) sulfate with sodium ascorbate, and proceeds at room temperature to give products, in high yield and with high regioselectivity (Scheme 1.35). For example, thermal cycloaddition of 4-methoxybenzonitrile oxide to phenylacetylene results, after 8h at 60°C, in a 4:1 mixture of 3,5- and 4,5-isomers in 62% yield, whereas only a single regioisomer has been obtained in 92% yield after 1h at ambient temperature, using Cu(I) as a catalyst. Different alkynes have been employed in the Cu(I)-catalyzed cycloadditions. In particular, a steroidal isoxazole has been obtained from 17-ethynylestradiol and 4-methoxybenzonitrile oxide in 98% yield.

A number of publications have appeared concerning polymer-supported syntheses of isoxazoles via 1,3-dipolar cycloadditions. In particular, soluble polymer-supported alkynes react with nitrile oxides, generated *in situ*, to give isoxazoles in good yield (383). A library of isoxazoles and 5-isoxazol-4-yl-[1,2,4]oxadiazoles has been prepared by combined solution- and solid-phase syntheses (384). Acetylenic sulfones attached to solid supports by means of ester linkers [polymer-supported 4-(alkynylsulfonyl)benzenemethanol benzoate derivatives] have been employed in cycloaddition reactions with mesitonitrile oxide, followed by cleavage of the products from the resin by ester hydrolysis or reductive desulfonylation (385). Solid-phase synthesis of 3-hydroxymethylisoxazoles, by cycloaddition of alkynes to resin-bound nitrile oxides, give the products in moderate yields and fair to good purity, depending on the alkyne substituents (386).



**Scheme 1.35**

Different aspects of 1,3-dipolar cycloaddition reactions of nitrile oxides at the  $C\equiv C$  bond have been studied using quantum chemical methods. Quantitative predictions of substituent and solvent effects on the regioselectivities of nitrile oxide cycloadditions to electron-deficient alkynes have been made, using hybrid DFT calculations, with the B3LYP/6-31G\* method, to calculate the activation barriers of nitrile oxide cycloadditions to the unsymmetrical alkynes, cyanoacetylene and Me propiolate. Both, inherent electronic effects and solvent polarity have been shown to influence regioselectivity (387). 1,3-Dipolar cycloaddition reactions of substituted nitrile oxides RCNO, (R = F, NO<sub>2</sub>, OMe, OH, CO<sub>2</sub>Me, CHO, CONH<sub>2</sub>, H, Me) with propyne were studied, using the DFT at the 6-311++G\*\* level. The reaction rates have been calculated at different temperatures from 200 to 400 K. The conclusions are that formation of 5-methyl-substituted isoxazoles is dominant at low temperatures, while 4-methyl-substituted isoxazoles are favored at relatively high temperatures (388).

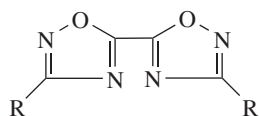
The mechanism for the 1,3-dipolar cycloaddition of benzonitrile oxide to ethynyl- and propynylboronate has been studied by DFT at the B3LYP/6-31G\* level. These reactions are concerted [3+2] processes. The presence of the two oxygens on the boronic ester precludes the participation of the B atom in the [3+3] processes. The two pathways leading to the formation of the regioisomeric isoxazoles, bearing the boronic ester unit on the 4- or 5- positions, have been characterized. The activation parameters are in acceptable agreement with experiments, allowing the explanation of the factors controlling these regioselective cycloadditions (389).

It is of interest to mention that DFT study performed, prior to experimental observations, revealed for Cu(I)-catalyzed cycloaddition of nitrile oxides to 1-alkynes, a stepwise mechanism involving unprecedented metalacycle intermediates, which appear to be common for a variety of dipoles (382).

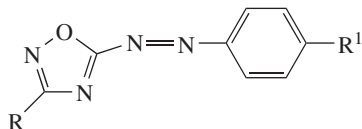
*1.3.4.3.2. Cycloaddition at  $C\equiv N$  and  $C\equiv P$  Bonds* Important information concerning cycloadditions of nitrile oxides to  $C\equiv N$  and  $C\equiv P$  bonds is collected in review (289). Here, recent data and those concerning individual unconventional types of nitriles and phosphacetylenes are presented.

Reactions of hydroximinoyl chlorides, R<sub>2</sub>CCl:NOH, with cyanogen and diazocyanides, 4-R<sup>1</sup>C<sub>6</sub>H<sub>4</sub>N=NCN gave bi[1,2,4]oxadiazoles **224** or arylazooxadiazoles **225** (390). The reaction of dialkylcyanamides with EtO<sub>2</sub>CCl:NOH gave (dialkylamino)oxadiazolecarboxylates **226**; the reaction of arylcarbohydroximinoyl, chlorides R<sub>2</sub>CCl:NOH, with N-cyanomorpholine gave 3-aryl-5-morpholino-1,2,4-oxadiazoles **226** (366).

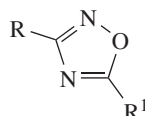
The carbon-nitrogen triple bond of aryl thiocyanates acts as a dipolarophile in 1,3-dipolar cycloadditions. Reactions with nitrile oxides yield 5-arylthio-1,2,4-oxadiazoles **227** (X = O; Y = S). Aryl selenocyanates behave similarly forming 5-arylseleno-1,2,4-oxadiazoles **227** (X = O; Y = Se). Reactions of 5-aryl-1,2,4-oxadiazoles with secondary amines, such as piperidine, yield 5-piperidino-1,2,4-oxadiazoles **227** (X = O; YR<sup>1</sup> = piperidino) (391).



224



225



226

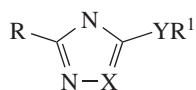
R = Ph, 3-FC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; R = EtO<sub>2</sub>C;

R<sup>1</sup> = Cl, Br, NO<sub>2</sub>

R<sup>1</sup> = NMe<sub>2</sub>, morpholino, piperidino

R = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 3-FC<sub>6</sub>H<sub>4</sub>, 2-FC<sub>6</sub>H<sub>4</sub>;

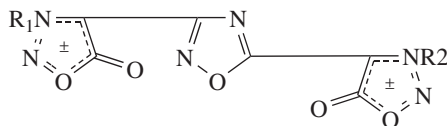
R<sup>1</sup> = morpholino



227

R = Ph, 3-MeC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; R<sup>1</sup> = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 1-naphthyl

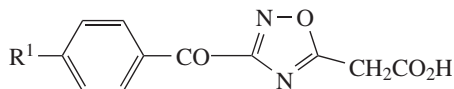
3-Arylsydnone-4-carbonitrile oxides, which are generated *in situ* by thermal dehydrochlorination of the corresponding hydroximic acid chlorides, undergo 1,3-dipolar cycloadditions with sydnone-4-carbonitriles to give 3-aryl-4-[5-(3-arylsydnonyl)-1,2,4-oxadiazol-3-yl]sydnones **228** (392).



228

R<sup>1</sup> = *p*-EtOC<sub>6</sub>H<sub>4</sub>, Ph, *p*-tolyl; R<sup>2</sup> = *p*-anisyl, *p*-tolyl, *p*-EtOC<sub>6</sub>H<sub>4</sub>, Ph, cyclohexyl

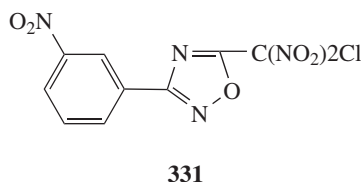
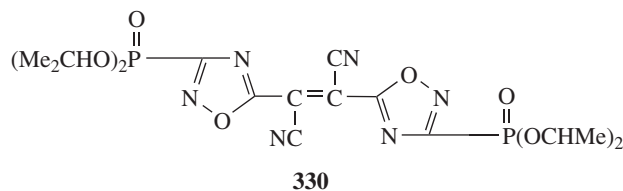
Aroyl glyoxylonitrile oxides 4-R<sup>1</sup>C<sub>6</sub>H<sub>4</sub>COCNO, undergo a cycloaddition reaction with CH<sub>2</sub>(CN)<sub>2</sub>. The 3-aryl-1,2,4-oxadiazole-5-acetonitrile obtained are converted to the corresponding (3-aryl-1,2,4-oxadiazol-5-yl)acetic acids **229** (393).



229

R<sup>1</sup> = H, Me, OMe, Cl, F

A phosphorylnitrile oxide  $(\text{Me}_2\text{CHO})_2\text{P}(\text{O})\text{CNO}$  reacts with tetracyanoethylene to give the bisadduct **330** (296). Reaction of cyanodinitrochloromethane with 3-nitrobenzonitrile oxide gives 5-chlorodinitromethyl-3-(3-nitrophenyl)-1,2,4-oxadiazole **331** (394).



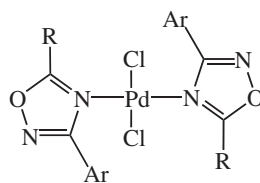
A significant acceleration of 1,3-dipolar cycloaddition of nitriles with nitrile oxides is shown, in the absence of solvent, at microwave irradiation (395). The reactions are finished within 2 to 10 min, to give 1,2,4-oxadiazoles in good yields.

A new route to 1,2,4-oxadiazoles and their complexes via Pt- and Pd-mediated 1,3-dipolar cycloaddition of nitrile oxides to organonitriles, has been reported. The sequence of the metal-mediated [2 + 3] cycloaddition offers an alternative route for the preparation of oxadiazoles.

Significant activation of the CN group in organonitriles upon their coordination to a Pt(IV) center has been found in the reaction of  $[\text{PtCl}_4(\text{RCN})_2]$  ( $\text{R} = \text{Me}, \text{Et}, \text{CH}_2\text{Ph}$ ) with stable aromatic nitrile oxides,  $\text{ArCNO}$  ( $\text{Ar} = 2,4,6\text{-R}'_3\text{C}_6\text{H}_2$ ;  $\text{R}' = \text{Me}, \text{OMe}$ ), to give the (1,2,4-oxadiazole)platinum(IV) complexes,  $\text{PtCl}_4.\text{HetH}$  ( $\text{HetH} = 3\text{-Ar-5-R-1,2,4-oxadiazole}$ ;  $\text{Ar}$  and  $\text{R}$  see above). The [2 + 3] cycloaddition has been performed under mild conditions even starting from complexed acetonitrile and propionitrile, which exhibit low reactivity in the free state. The reaction between complexes  $\text{PtCl}_4.\text{HetH}$  and one equivalent of  $\text{Ph}_3\text{P}:\text{CHCO}_2\text{Me}$  in  $\text{CH}_2\text{Cl}_2$  leads to the appropriate Pt(II) complexes  $\text{PtCl}_2.\text{HetH}$ ; the reduction fails only in the case of  $\text{PtCl}_4.\text{HetH}$  ( $\text{Ar} = \text{mesityl}, \text{R} = \text{Me}$ ) because it is insoluble in most common organic solvents. The oxadiazoles formed in the metal-mediated reaction are liberated, almost quantitatively, from their Pt(IV) complexes by reaction of the latter with an excess of pyridine in  $\text{CHCl}_3$ , giving free 1,2,4-oxadiazoles and *trans*- $[\text{PtCl}_4(\text{pyridine})_2]$  (396).

The reactions between stable 2,4,6-trisubstituted benzonitrile oxides  $\text{ArCNO}$  and *trans*- $[\text{PdCl}_2(\text{RCN})_2]$  complexes, or  $\text{RCN}$  ( $\text{R} = \text{Me}, \text{Et}, \text{CH}_2\text{CN}, \text{NMe}_2, \text{Ph}$ ), in the presence of  $\text{PdCl}_2$ , proceed under mild conditions and give the 1,2,4-oxadiazole *trans*-complexes of the type **332** in 40% to 85% yields. In  $\text{CH}_2\text{Cl}_2$ , the reaction between the nitrile oxides and  $[\text{PdCl}_2(\text{MeCN})_2]$  furnishes

complexes  $[\text{PdCl}_2(\text{ONCAr})_2]$ , which are the first representatives of metal compounds in which nitrile oxides act as ligands. The liberation of the heterocyclic species from **332** is successfully performed by substitution reactions either with 1,2-bis(diphenylphosphino)ethane or with an excess amount of  $\text{Na}_2\text{S} \cdot 7\text{H}_2\text{O}$  in MeOH (397).

**332**

Ar = 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$ , 2,4,6-( $\text{MeO}$ ) $_3\text{C}_6\text{H}_2$   
 R = Me, Et,  $\text{CH}_2\text{CN}$ ,  $\text{NMe}_2$ , Ph

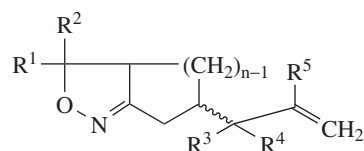
The cycloaddition of nitrile oxides to nitriles, and its Pt(II) and Pt(IV) complexes, *trans*- $[\text{PtCl}_2(\text{NCMe})_2]$  and *trans*- $[\text{PtCl}_4(\text{NCMe})_2]$ , was investigated by quantum chemical methods at different levels of theory, using quasi-relativistic pseudopotentials for the platinum atom. The activation of the nitriles ligated to Pt(IV) can be interpreted in terms of both kinetic (activation parameters) and thermodynamic (reaction energies) viewpoints. The higher reactivity of the Pt(IV) complex, when compared with that of the Pt(II) complex, is kinetically controlled. The calculations predict that the Pt(II) complex should be less reactive than free acetonitrile, and that the relative reactivity of the Pt(II) complex is governed mainly by the entropic factor. The cycloaddition of nitrile oxide to nitriles is mainly controlled by the  $\text{HOMO}_{\text{nitrile oxide}}\text{-LUMO}_{\text{nitrile}}$  type of interaction and occurs via a concerted asynchronous mechanism for both free and bound nitriles rather than via a stepwise mechanism (398).

Mesitylphosphaacetylene 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2\text{C}\equiv\text{P}$ , (synthesized by  $\text{AlCl}_3$ -initiated elimination of  $(\text{Me}_3\text{Si})_2\text{O}$  from  $\text{Me}_3\text{SiP}=\text{C}(\text{OSiMe}_3)\text{C}_6\text{H}_2\text{-2,4,6-Me}_3$ ), undergoes [3 + 2] cycloaddition reactions with nitrile oxides to yield oxazaphosphole derivatives (399).

**1.3.4.4. Intramolecular Cycloaddition** Intramolecular nitrile oxide cycloaddition (INOC) is widely used in the synthesis of various compounds, particularly, natural products. This field is reviewed in detail in Chapter 6 of the monograph/Reference 5 and also in Reference 400 limited to nitrile oxides generated from nitroalkenes. Some features of INOC are illustrated in this subsection by new data and those omitted in Reference 5.

Reactions with participation of the  $\text{C}=\text{C}$  bond are the most studied of INOCs. Normal products of such reactions are annulated isoxazolines. A synthesis of bicyclic isoxazolines via sequential Michael and intramolecular 1,3-dipolar additions (403) are mentioned as an example. Michael addition of 1-nitroalkadiene,  $\text{R}^1\text{R}^2\text{C}=\text{CH}(\text{CH}_2)_n\text{CH}=\text{CHNO}_2$  to allylic stannane  $\text{R}^3\text{R}^4\text{C}=\text{C}(\text{R}^5)\text{CH}_2\text{SnR}^6_3$

( $R^6 = \text{Me, Ph}$ ) was induced by  $\text{TiCl}_4$  at  $-78^\circ$  in  $\text{CH}_2\text{Cl}_2$ . A nitrile oxide, generated by subsequent addition of  $\text{Et}_3\text{N}$  in THF, underwent intramolecular addition to give 8% to 92% of compounds **333** as diastereoisomeric mixtures.

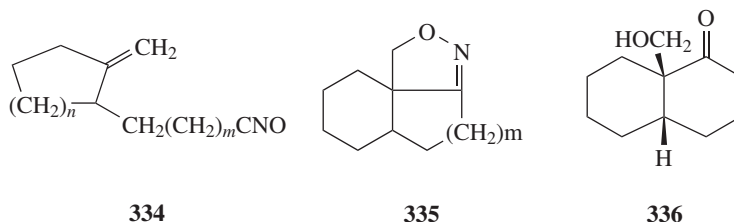
**333**

$R^1 = \text{H, Me, Ph, CH:CH}_2$ ;  $R^2 = \text{H, Me}$ ;  $n = 2, 3$ ;

$R^3 = \text{H, Me, Ph}$ ;  $R^4, R^5 = \text{H, Me}$

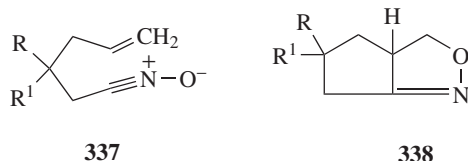
A study of Lewis acid-promoted reactions of 1-nitroalka-1,5-(or 1,6-)dienes with allylic stannanes shows that, in the presence of  $\text{TiCl}_4$ , 1-nitrohexa-1,5-diene reacts smoothly with allyltrimethylstannane to give a diastereoisomeric mixture of 6-allyl-3a,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isoxazoles, while the reaction, using  $\text{AlCl}_3$  as catalyst, leads to allylated cyclohexanone oxime derivatives in good yield. A similar reaction of 1-nitrohepta-1,6-diene, however, gives a bicyclic isoxazoline, irrespective of the Lewis acids employed. In the latter case, nitrile oxides derived from 1-nitroalka-1,6-dienes undergo a stepwise cycloaddition, as shown by the lack of stereospecificity in the reactions of (1*E*,6*Z*)-1-nitro-7-phenylhepta-1,6-diene and (1*E*,6*Z*)-1-nitroocta-1,6-diene (402).

Certain specific steric effects are operative on intramolecular nitrile oxide—olefin cycloadditions. These effects are governed by both ring size and character of substituents. Thus, cycloadditions to the exomethylene group are successful with substituted methylenecyclohexanones **334** ( $m = 1, 2$ ;  $n = 2$ ) and gave tricyclic **335** ( $m = 1, 2$ ), but do not occur with methylenecyclopentanones **334** ( $m = 1, 2, 3$ ;  $n = 1$ ). Activation energies calculated by molecular mechanics are consistent with these results. Cleavage of **335** ( $m = 2$ ) by Raney Ni gives *cis*-decalone **336** (403).

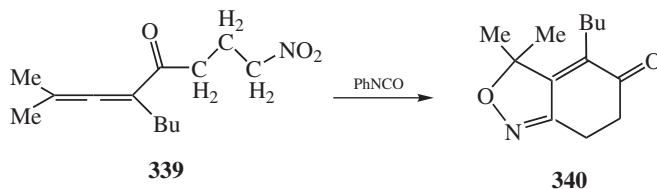
**334****335****336**

Substituent effects on intramolecular dipolar cycloadditions can be illustrated by the *gem*-dicarboalkoxy effect (404). This effect (rel. rate  $> 20$ ) has been

measured for the reaction **337**  $\rightarrow$  **338** ( $R = R' = \text{CO}_2\text{Me}$ ) and good diastereoselectivity (ca 9:1) has been observed in reactions **337**  $\rightarrow$  **338** ( $R = \text{Me, Ph}$ ;  $R' = \text{H}$ ) for the intramolecular dipolar cycloaddition of three substituted 5-hexene nitrile oxides.



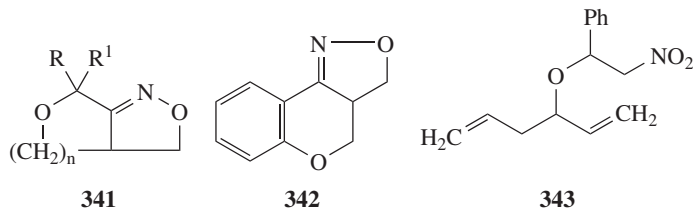
The study of the intramolecular nitrile oxide—allene cycloaddition shows, in particular, that dehydration of nitroallene **339** by  $\text{PhNCO}$ , generates a nitrile oxide *in situ*, which gives isoxazoline **340** (Scheme 1.36). Thus, the reaction of the more remote double bond with the formation of six-membered ring prevails (405).



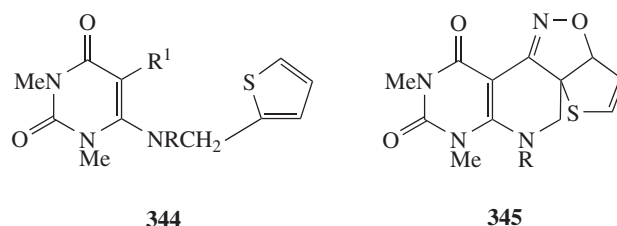
Scheme 1.36

Many investigations are devoted to INOCs leading to fused biheterocyclic systems.

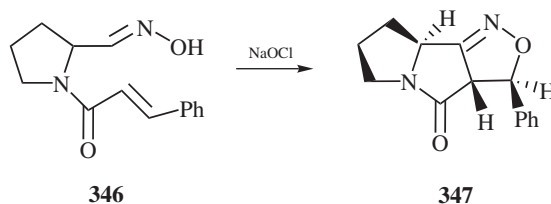
The reaction of O-trimethylsilyl  $\alpha$ -bromoaldoximes,  $\text{RR}^1\text{CBrCH}=\text{NOSiMe}_3$  ( $R = R^1 = \text{Me}$ ;  $R = \text{Ph, Me, } R^1 = \text{H}$ ) with unsaturated alcohols produces oximino ethers  $\text{RR}^1\text{C}(\text{CH}=\text{NOH})\text{O}(\text{CH}_2)_n\text{CH}=\text{CH}_2$  ( $n = 1, 2$ ), which can be readily oxidized with sodium hypochlorite. The intermediate nitrile oxide formed, undergoes cyclization affording fused isoxazolines **341** (406). O-Allylsalicylaldoxime,  $o\text{-CH}_2=\text{CHCH}_2\text{OC}_6\text{H}_4\text{CH}=\text{NOH}$  gives isoxazoline **342** on treatment with iodobenzene dichloride (57). Intramolecular nitrile oxide—olefin cycloaddition of 2-(2-nitro-1-phenylethoxy)-1,5-hexadiene **343** proceeds with high regioselectivity to form a [5,5] ring system (407).



INOCs in biheterocyclic systems, where the CNO group is bonded to one heterocycle and the C=C bond belongs to the second heterocycle, open an elegant route to polyheterocyclic systems. Thus, nitrile oxides **344** ( $R = 4\text{-BrC}_6\text{H}_4$ ,  $4\text{-MeC}_6\text{H}_4$ ,  $4\text{-MeOC}_6\text{H}_4$ , etc.,  $R^1 = \text{CNO}$ ), generated from the corresponding oximes **344** ( $R^1 = \text{CH=NOH}$ ) on treatment with  $\text{Et}_3\text{N-NaOCl}$  in  $\text{H}_2\text{O-CH}_2\text{Cl}_2$  undergo intramolecular cycloaddition to give 75% to 80% heterocycles **345** (408).

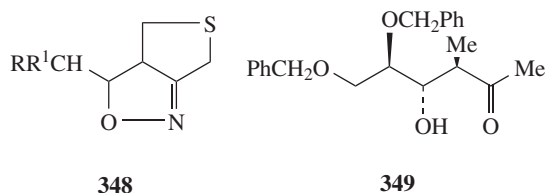


Functionalized, enantiomerically pure 3,4-dihydropyrrolidin-2-one and 1,2-dihydropyrrolizidin-3-one systems, have been prepared by INOC, starting from enamido-oximes **346** (Scheme 1.37) and by subsequent reduction of the obtained cycloadducts, **347** (409). Substituted hexahydroisoxazolo[3,4-*a*]pyrrolizinone **347** has been obtained by an *in situ* INOC procedure in 60% yield, as a mixture (4:1) with its minor diastereoisomer, and purified by semipreparative HPLC.

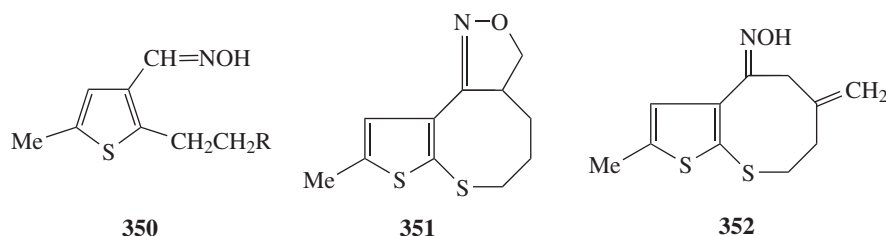


Scheme 1.37

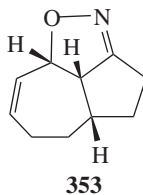
The INOC reaction of chiral olefins with a sulfur atom in the carbon chain, connecting dipole and dipolarophile, occurs with poor to excellent *anti*-stereoselectivity, which is mainly affected by the substituents at the allylic stereocenter. Thus, treating chiral (*E*)- and (*Z*)- $\text{RR}^1\text{CHCH=CHCH}_2\text{S}(\text{CH}_2)_2\text{NO}_2$  with  $4\text{-ClC}_6\text{H}_4\text{NCO}$  and  $\text{Et}_3\text{N}$  leads to isoxazolines **348** as diastereomeric mixtures. Catalytic hydrogenation of **348** ( $R = \text{CH}_2\text{OCH}_2\text{Ph}$ ,  $R^1 = \text{OCH}_2\text{Ph}$ ), using Raney nickel, affords  $\beta$ -ketol **349** quantitatively (410).



Oxidation of (alkenylthio)thiophenecarboxaldehyde oxime **350** (R = allyl) by NaOCl gives the nitrile oxide, which cyclizes to thieno[2,3-*b*]thiocino[4,5-*c*]isoxazole **351**. However, isomeric **350** (R = isopropenyl), under the same conditions, is converted to the unusual product, thieno[2,3-*b*]thiocin **352**. In both reactions, cyclodimerization products of nitrile oxides are also obtained. Structures of compounds **350** (R = isopropenyl) and **352** have been studied by X-ray diffraction analysis (411).



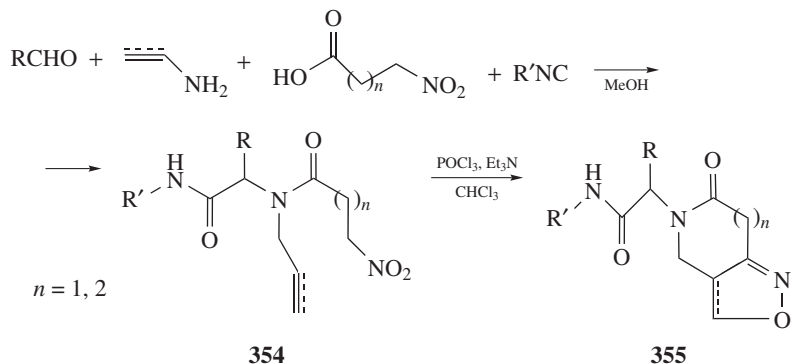
Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and -1,3,5-triene-tethered nitrile oxides give tricyclic isoxazolines, for example, **353**, as a single stereoisomer.



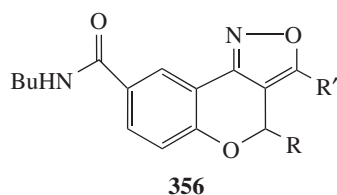
The relative stereochemistry of tricycle-fused isoxazolines resulting from 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides is *cis-cis*, whereas from cyclohepta-1,3,5-triene-tethered nitrile oxides the *cis-trans* isomer predominates (412).

A promising combination of sequential multicomponent Ugi reaction and INOC has been carried out for the preparation of fused isoxazoles and isoxazolines (413). The coupling of these two reactions (Scheme 1.38) provide access to the heterocyclic ring systems in two steps, from easily available starting materials (e.g., R = Ph, R' = PhCH<sub>2</sub>), in moderate to good overall yields (the yields of Ugi reaction products **354** were 50%–70%, those of the INOC products **355** were 27%–64%).

A solid-phase synthesis of substituted benzopyranoisoxazoles **356** (I; R = H, Me, Et, Pr, Ph, CHMe<sub>2</sub>; R<sup>1</sup> = H, Me, decyl, Ph) has been described (414). The six-step synthesis includes a method of generating nitrile oxides on a polymer support, followed by an intramolecular 1,3-dipolar cycloaddition with a tethered alkyne, for assembly of the benzopyranoisoxazole scaffold.

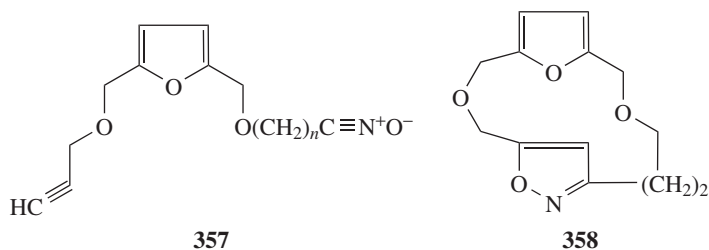


Scheme 1.38

R = H, Me, Et, Pr, Ph, CHMe<sub>2</sub>

R' = H, Me, decyl, Ph

The intramolecular cycloaddition reactions of the nitrile oxides **357** ( $n = 1, 2, 3, 9$ ), obtained *in situ* from the 2,5-difunctional furan hydroximoyl chlorides or nitro compounds (415) has specific features because of the 2,5-arrangement of two open chains bearing acetylenic and fulminic moieties. Only with **357** ( $n = 3$ ) is the expected furanoisoxazolophane **358** formed, in acceptable yield. Compound **357** ( $n = 9$ ) gives a complex product mixture whereas **357** ( $n = 1, 2$ ) gives rise to the exclusive reaction of the dipole with a double bond of the furan system.



### 1.3.5. Miscellaneous

Reactions other than those discussed in subsections 1.3.1. to 1.3.4. are presented here. Transformations of nitrile oxides by the action of reductive agents and

electrophiles as well as processes involving oxidation steps and some unconventional cycloadditions are considered in this subsection.

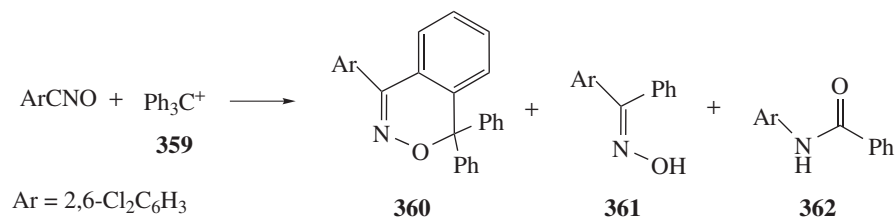
Electrochemical behavior of a series of stable aromatic nitrile oxides as well as benzonitrile oxide and 1-adamantylformonitrile oxide have been studied (416). Radical anions were detected by electron spin resonance (ESR) in the first stage of electrochemical reduction of *p*- and *m*-NO<sub>2</sub>-substituted benzonitrile oxides. Analysis of the splitting constant reveal that the unpaired electron is localized mainly on the nitro group and the aromatic ring. The suggested mechanism of electrochemical reduction of nitrile oxides includes successive stages of radical anion formation, recombination of the latter to dioxime dianion and, finally, the protonation of the dianion to dioxime monoanion RC(=NO<sup>-</sup>)C(=NOH)R, furoxan formation being excluded.

Reactions between nitrile oxides ArCNO and benzylic carbocations **359** produce addition products, such as benzoxazines **360**, oximes **361**, and amides **362** (Scheme 1.39) (417).

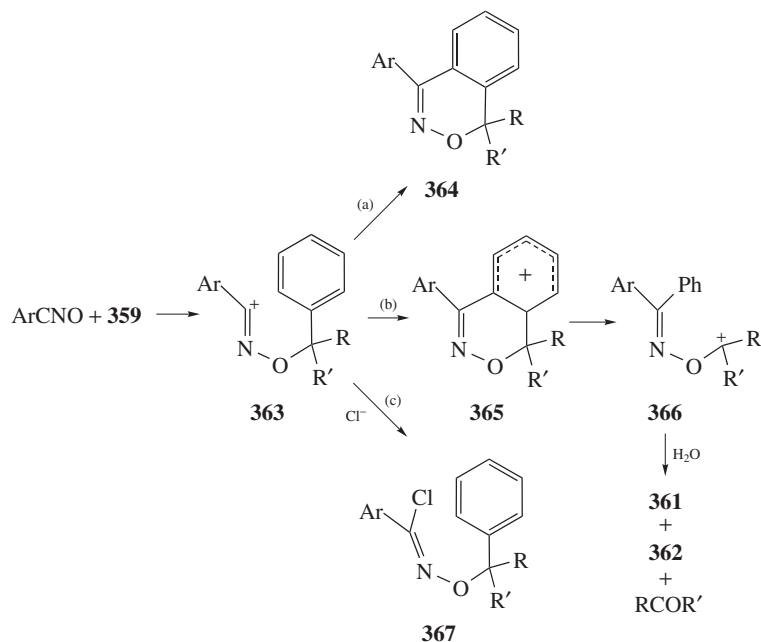
Different results have been obtained when the carbocations are generated from the corresponding chlorides with various Lewis acids. Primary, secondary, and tertiary carbocations showed different reactivities. The product ratios depend strongly on the substituents on the aromatic ring of the benzylic carbocations. The proposed mechanism (417) is illustrated by Scheme 1.40. The key cationic intermediate **363**, formed from ArCNO and **359**, undergoes further transformations. Route (a) leads to benzoxazines **364**, which are isolated for tertiary, for example, **360**, and secondary carbocations, **364** (R = H, R' = 3-MeOC<sub>6</sub>H<sub>4</sub>). Route (b) gives successively cations **365** and **366**. Hydrolysis of the latter affords oximes of the type **361**, amides of the type **362**, and ketones (aldehydes) RCOR'. Finally, route (c) giving O-substituted chlorooximes **367** is confirmed by the isolation of compounds with R = 4-MeOC<sub>6</sub>H<sub>4</sub>.

In the case of primary carbocation, reaction with nitrile oxide gives a mixture of two regioisomeric oximes (Scheme 1.41). Probably, this is a result of the attack of the nitrile oxide – BF<sub>3</sub> complex on neutral 3-chloromethylanisole.

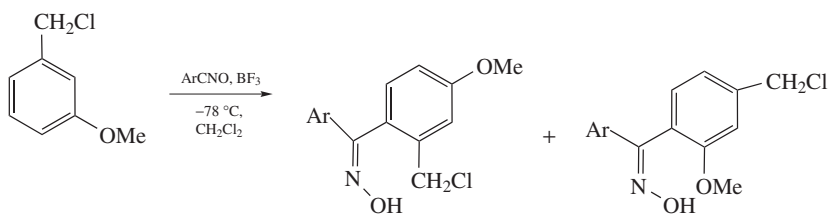
Treatment of  $\gamma$ -nitrothioamides **368** with phenyl isocyanate and triethylamine (nitrile oxide generation conditions) leads to  $\alpha,\beta$ -unsaturated nitriles **369**. The mechanism proposed for this reaction is shown in Scheme 1.42, which includes the dehydration stage of the nitrile oxide formed (418).



Scheme 1.39

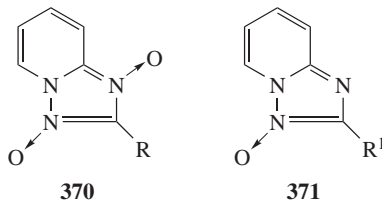


Scheme 1.40

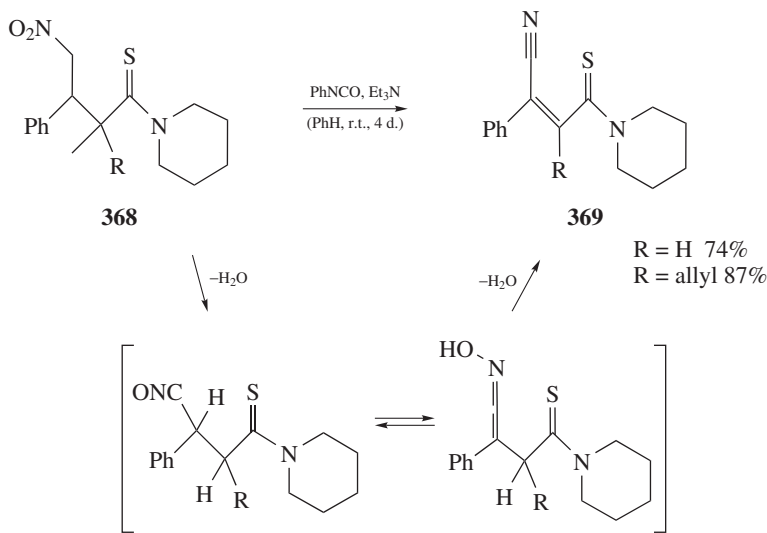


Scheme 1.41

Reactions of 2-nitrosopyridine with nitrile oxides afford, depending on structure of the latter, either 1,2,4-triazolo[1,5-*a*]pyridine 1,3-di-N-oxides (**370**) or the corresponding 1,2,4-triazolo[1,5-*a*]pyridine 3-oxides (**371**) (419).

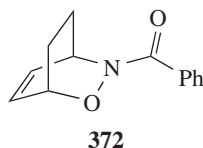


$\text{R} = 2,6\text{-Cl}_2\text{C}_6\text{H}_3, 4\text{-O}_2\text{NC}_6\text{H}_4; \text{R}^1 = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2, \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$



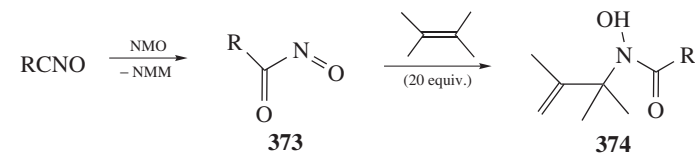
Scheme 1.42

Nitrile oxides are oxidized by tertiary amine N-oxides, for example, N-methylmorpholine N-oxide, in various solvents at room temperature to unstable nitrosocarbonyl compounds. In the presence of dienes, such as 1,3-cyclohexadiene, they afford Diels–Alder adducts, e.g., **372** from  $\text{PhCNO}$ , in fair yields. The mild conditions used in oxidizing a variety of nitrile oxides promise a wide application of this method in synthetic processes (420).



Nitrosocarbonyl intermediates **373**, generated under mild conditions, (r.t., 12h) by the mild oxidation of nitrile oxides  $\text{RCNO}$  with N-methylmorpholine N-oxide, undergo ene reactions with tetramethylethylene and cyclohexene to give N-hydroxy-substituted amides **374** in 95% to 99% yield (Scheme 1.43). Other nitrile oxides  $\text{RCNO}$  ( $\text{R} = 4\text{-MeC}_6\text{H}_4$ ,  $4\text{-MeOC}_6\text{H}_4$ ,  $4\text{-NO}_2\text{C}_6\text{H}_4$ , Me, Pr, Hex,  $\text{PhCH}_2$ ,  $\text{PhCH}=\text{CH}$  and  $\text{PhCO}$ ), also react *in situ*, to give products of ene reactions in high yield. With less substituted ethylenes (1,1-dimethyl-, 1,2-dimethylethylenes and  $\alpha$ -methylstyrene), the ene pathway is still active but the oxidation step of the nitrile oxides competes with the cycloaddition to the olefins. The nitrosocarbonyl intermediates, such as **373**, are claimed as “super-enophiles”, allowing mild carbon–nitrogen bond formations (421).

The synthesis of 1,2,4-oxadiazole-4-oxides with a polystyrene solid phase attached at position 3 of the heterocycle has been performed in cycloadditions



R = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, Mes

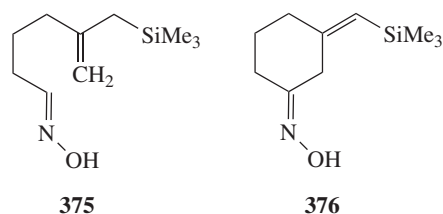
NMO is N-methylmorpholine N-oxide

NMM is N-methylmorpholine

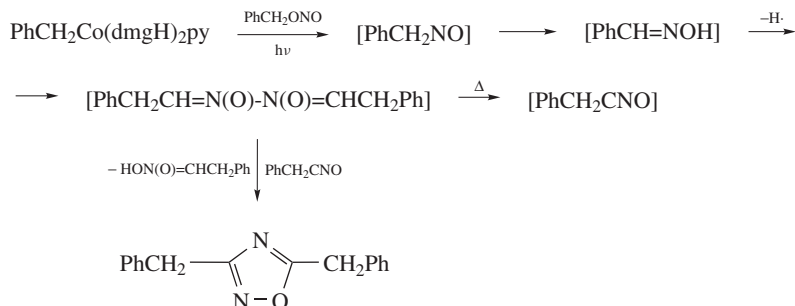
**Scheme 1.43**

of stable supported nitrile oxides to amidoximes. The photochemical cycloreversion of these heterocycles affords free nitrosocarbonyl intermediates, which are trapped by suitable dienes or enes. The method is considered a clean and environmental friendly approach to the fleeting nitrosocarbonyl intermediates, which afford valuable adducts in various synthetic applications. The isomeric heterocycles, adhered at position 5 of the ring, are also obtained by cycloaddition of nitrile oxides to supported amidoximes. Their photolysis affords resin-bound nitroso carbonyls that are trapped with dienes, affording valuable supported adducts suitable for further elaboration in solid-phase chemistry (422).

Rather than the expected [3 + 2] cycloaddition, a novel ene-like cycloisomerization occurs on deprotonation of allyltrimethylsilyl-oxime compounds, when the  $\beta$ -sp<sup>2</sup> carbon atom of the allyltrimethylsilyl moiety is tethered to the oxime unit. The resulting nitrile oxide group serves as an enophile, and the final cyclized product still has two functional groups suitable for further manipulations. Thus, ene-like cycloisomerization of allyltrimethylsilyl-oxime **375** with NaOCl in CH<sub>2</sub>Cl<sub>2</sub> gives 82% of cyclized product **376** (423). See also Reference 424.



DFT studies of the intramolecular ene-like (or the so-called 1,3-dipolar ene) reaction between nitrile oxides and alkenes show that this reaction is a three-step process involving a stepwise carbenoid addition of nitrile oxide to form a bicyclic nitroso compound, followed by a retro-ene reaction of the nitrosocyclopropane intermediate. The competitive reactions, either the intramolecular [3 + 2] cycloaddition between nitrile oxides and alkenes or the intermolecular dimerization of nitrile oxides to form furoxans, can overwhelm the intramolecular 1,3-dipolar ene reaction if the tether joining the nitrile oxide and alkene is elongated, or if substituents such as trimethylsilyl are absent (425).



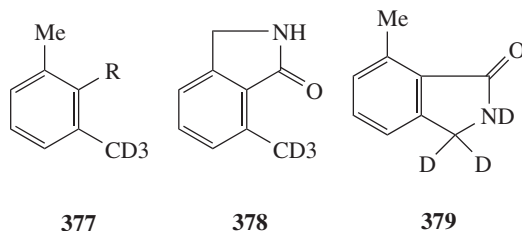
Scheme 1.44

The benzyl ligand of benzylbis(dimethylglyoximate)pyridine cobalt complex has been selectively converted to 3,5-dibenzyl-1,2,4-oxadiazole by a reaction with alkyl nitrite in the presence of light (426). The reaction proceeds by the *in situ* formation of an oxime and a nitrile oxide (Scheme 1.44).

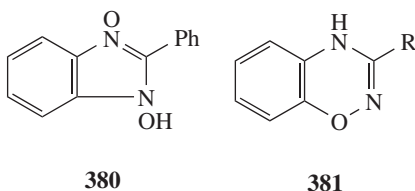
Ion-molecule reactions of ionized nitrile oxide,  $\text{R-C}\equiv\text{N}^+-\text{O}$ , with several neutral nitriles,  $\text{R}'\text{CN}$ , were studied, using both tandem mass spectrometric techniques and *ab initio* MO calculations (427). Ionized oxygen atom transfer and formal substitution of nitric oxide by the neutral reagent in the radical cation are the main processes. Whereas the former reaction yields the corresponding ionized nitrile oxide,  $\text{R}'-\text{C}\equiv\text{N}^+-\text{O}$ , the second process gives an electron species tentatively ascribed, following high-kinetic energy collisional activation experiments, to an aromatic azirinium cation. All the experimental data point to a two-step reaction sequence where the primarily formed intermediate ions competitively dissociate by the loss of nitrile or of nitric oxide, respectively, giving nitrile oxide ions and azirinium ions.

The mechanism of the simplest reaction  $\text{HCNO}^+ + \text{HCN} \rightarrow \text{cyclo-HCCHN}^+ + \text{NO}$  has been explored at the MP2/6-31G(d) level of theory. The most favorable reaction profile involves the formation of a C—N bond between the positively charged carbon atom of  $\text{HCNO}^+$  and the nitrogen atom of hydrocyanic acid giving an  $\text{HCNO}^+/\text{HCN}$  intermediate which isomerizes into an ionized nitrosoazirine before losing NO.

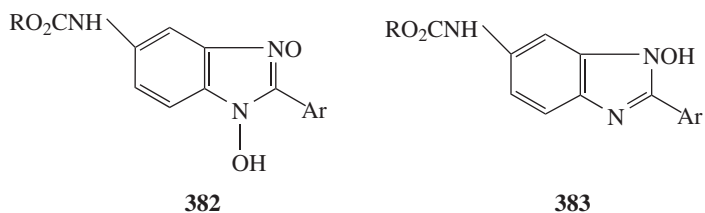
Photolysis of nitrile oxide **377** ( $\text{R} = \text{CNO}$ ) gives acylnitrene **377** ( $\text{R} = \text{CON}$ ), which undergoes intramolecular insertion reactions to give products **378** and **379** (428).



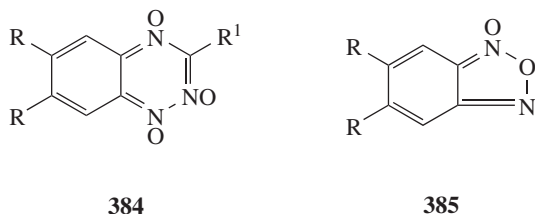
Benzonitrile oxide reacts with nitrosobenzene to give  $\alpha$ -nitrosanitron  $\text{PhN(O)=CPhNO}$ , which cyclizes to hydroxyphenylbenzimidazole oxide **380** and/or benzoxadiazine **381** ( $\text{R} = \text{Ph}$ ). Similar reactions of  $\text{PhNO}$  with  $p\text{-MeC}_6\text{H}_4\text{CNO}$  and  $\text{EtO}_2\text{CCNO}$  give **381** ( $\text{R} = p\text{-tolyl}$  and  $\text{CO}_2\text{Et}$ ). Nitrosomesitylene  $2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{NO}$  reacts with  $\text{PhCNO}$  and  $p\text{-MeC}_6\text{H}_4\text{CNO}$  to give  $\alpha$ -nitrosanitrones  $2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{N(O)=CRNO}$  ( $\text{R} = \text{Ph}, p\text{-tolyl}$ ), which do not undergo cyclization reactions (429).



Arenecarbonitrile oxides react with alkyl ( $p$ -nitrophenyl)carbamates at the nitro group, the nitrogen atom of the latter being the nucleophilic center. Tautomeric  $N$ -hydroxybenzimidazole  $N$ -oxides **382** and **383** form as the final products (430).

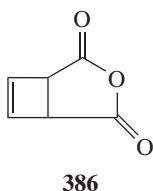


Benzo-*as*-triazine tri- $N$ -oxides **384** ( $\text{R} = \text{H}, \text{Me}$ ;  $\text{R}^1 = \text{mesityl}, 2,6\text{-Cl}_2\text{C}_6\text{H}_3$ ) are formed from the reaction of nitrile oxides  $\text{R}^1\text{CNO}$  with benzofuroxans **385**. The structure of **384** ( $\text{R} = \text{Me}, \text{R}^1 = \text{mesityl}$ ) has been confirmed by X-ray crystal structure analysis (431).

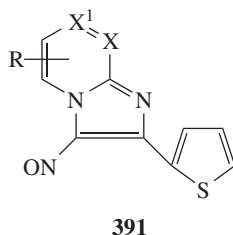
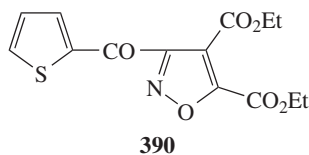
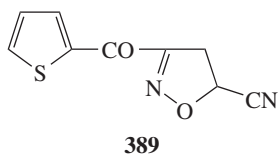
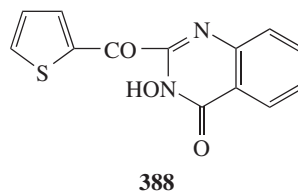
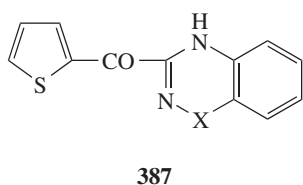


The efficiency and limitations of 3-oxabicyclo[3.2.0]hept-6-ene-2,4-dione **386** (cyclobut-3-ene-1,2-dicarboxylic anhydride) as an acetylene equivalent in 1,3-dipolar cycloadditions has been reported. It reacted readily with a variety of reagents, including nitrile oxides. In all cases, the sterically favored anti-isomers

are formed exclusively. When subjected to flash-vacuum pyrolysis, the adducts undergo thermal fragmentation, either by a retro-cleavage, or by loss of maleic anhydride, to form products that are similar to those from reactions of acetylene in the cycloaddition step. A concerted pathway is proposed for the pyrolytic conversion into the "formal acetylene cycloadduct" rather than a stepwise radical mechanism (432).



2-Thenoylcarbohydroxamoyl chloride, as precursor of 2-thienylglyoxylonitrile oxide undergoes nucleophilic 1,3-addition with *o*-phenylenediamine, *o*-aminothiophenol and methyl anthranilate to afford benzotriazine **387** (X = NH), benzothiadiazine **387** (X = S), and quinazoline **388**, respectively. With acrylonitrile and diethyl acetylenedicarboxylate, 1,3-dipolar cycloaddition proceeds to give 5-cyano-3-thenoylisoxazoline **389** and diethyl 3-thenoylisoxazole-4,5-dicarboxylate **390**, respectively. However, nitroso derivatives of imidazo[1,2-*a*]pyridines **391** (X = X<sup>1</sup> = CH; R = H, 8-Me, 6-Cl), imidazo[1,2-*a*]pyrimidine **391** (X = N, X<sup>1</sup> = CH, R = H), and imidazo[1,2-*a*]pyrazine **391** (X = CH, X<sup>1</sup> = N) have been obtained in good yields by the action of 2-thenoylhydroxamoyl chloride to 2-aminopyridines, 2-aminopyrimidines and 2-aminopyrazines, respectively (433).



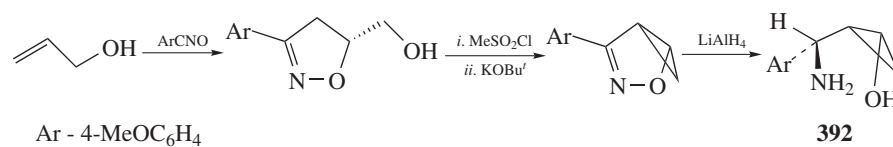
$\beta$ -(2-Aminophenyl)- $\alpha,\beta$ -ynones react with nitrile oxides by domino [3+2] cycloaddition/annulation reactions, giving rise to isoxazolo[4,5-*c*]quinolines in satisfactory yields (434). Nitrile oxides undergo addition to allylzinc bromide to generate 5-butenylisoxazolines in good yields. The domino reaction combines 1,3-cycloaddition with Wurtz coupling (435).

## 1.4. APPLICATIONS OF NITRILE OXIDES

### 1.4.1. Nitrile Oxides in Organic Synthesis

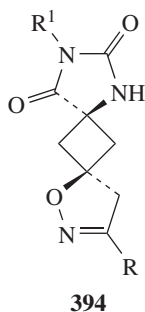
Versatile uses of nitrile oxides in organic synthesis up to year 2000 are well reviewed by Jaeger and Colinas (5). Therefore, this subsection is limited to data published after 2000 with the exclusion of those cited in Reference 5. The contents of the subsection are organized by taking into account the chemical structure (Sections 1.4.1.1 and 1.4.1.2), natural origin of parental compounds (Section 1.4.1.3), and biological activity of synthesized compounds (Section 1.4.1.4).

**1.4.1.1. Syntheses of Carbocyclic Compounds** (1*S*,2*S*)-2[(*S*)-Amino(4-methoxyphenyl)methyl]cyclopropan-1-ol **392** (Scheme 1.45) has been prepared by a stepwise procedure involving a 1,3-dipolar nitrile oxide cycloaddition to allyl alcohol followed by a construction of the cyclopropa[*d*]isoxazole system, and reduction of the bicycle (436).



**Scheme 1.45**

Achiral hydantoin- and isoxazoline-substituted dispirocyclobutanoids **394** have been prepared by solid-phase synthesis (437). The facial and selective Boc-NH-mediated H-bond delivery of nitrile oxides afford dispirocyclobutanoids **394** (R = Bz, Et; R<sup>1</sup> = Ph, PhCH<sub>2</sub>, Bu) as major compounds.



On treatment with a base such as NaOMe or even  $\text{LiAlH}_4$ , mono-cycloadducts of mesitonitrile oxide and polycyclic aromatic hydrocarbons have been cleaved to yield the corresponding oximes, which are oxidized to ketones by the Dess–Martin method. The same ketones have been obtained by reductive ring opening of the mono-cycloadducts with Raney Ni (438).

Anthracene groups have been linked to [60]fullerene by the [3 + 2] cycloaddition of the corresponding nitrile oxides. The anthryl groups of the fullerene derivatives react readily with singlet oxygen to form the 9,10-epidioxides on photo-oxidation (439). The adduct of fullerene  $\text{C}_{60}$  with ferrocenylformonitrile oxide (generated from the corresponding oxime) has been prepared. The ferrocene derivative is bound to  $\text{C}_{60}$  at the 6–6 bond of the isoxazoline ring. The reaction may lead either to a mono- or diadduct (440).

The addition of nitrile oxides to [60]fullerene, leading to fullerenoisoxazolines, can be reversed, using reducing agents such as  $\text{Mo}(\text{CO})_6$  or DIBALH. The liberated nitrile oxide is reduced to the corresponding nitrile. This reaction can be used, in principle, for protection/deprotection of [60]fullerene or for solubilization purposes. The isoxazoline moiety can be removed using  $\text{Mo}(\text{CO})_6$  from the bis-adduct, carrying isoxazoline and pyrrolidine fragments, giving a fullerenopyrrolidine derivative (441).

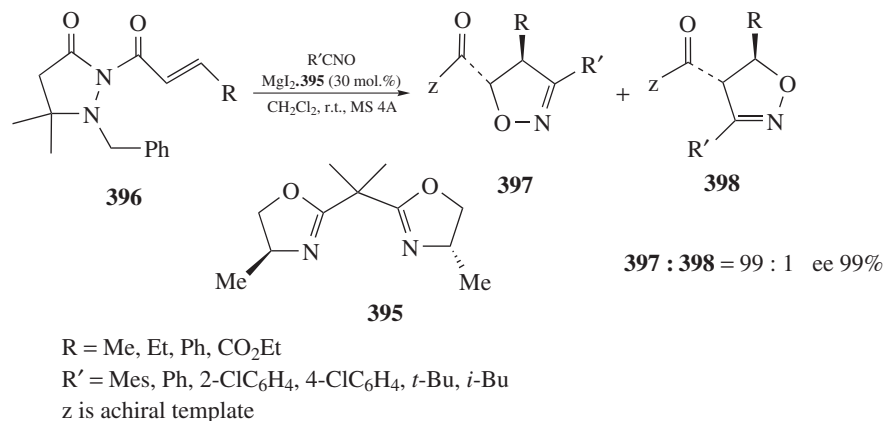
**1.4.1.2. Heterocyclic Compounds** It is useful to begin this paragraph with recent syntheses of rather simple heterocyclic derivatives, important as intermediates for the preparation of more complicated products. These syntheses can also be used as models for elaboration of new syntheses, first of all, those of stereoselective syntheses.

Formyl C-glycosides, prepared in three steps via the thiazole-based formylation of sugar lactones are readily condensed with hydroxylamine to give the corresponding oximes. The latter are the precursors of glycosyl nitrile oxides via the N-bromosuccinimide method (41).

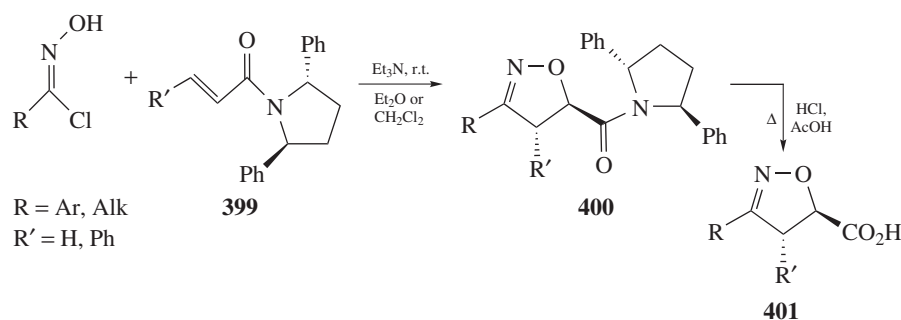
A highly regio- and enantioselective nitrile oxide cycloaddition to alkenes, using sub-stoichiometric amounts of a chiral Lewis acid like  $\text{MgI}_2$ , **395** complex, has been reported (442). Pyrazolidinones **396**, prove to be effective achiral templates in the cycloadditions, providing C-adducts, **397**, in high selectivity (compared to isomers **398**) and enantiomeric excess (Scheme 1.46). To avoid potential problems, involving coordination of the Lewis acid by amine bases, a method for the generation of unstable nitrile oxides from hydroximinoyl chlorides, using Amberlyst 21 as the base, has been developed.

The 1,3-dipolar cycloaddition of a variety of aromatic and aliphatic nitrile oxides to 2,5-*trans*-2,5-diphenylpyrrolidine-derived acrylamide and cinnamamide **399**, efficiently affords the corresponding 4,5-dihydroisoxazole-5-carboxamides **400** in highly regio- and stereoselectivity (Scheme 1.47). Acid hydrolysis of these products affords enantiopure 4,5-dihydroisoxazole-5-carboxylic acids **401** (443).

The cycloaddition of aliphatic nitrile oxides to the analogous methacrylamide also proceeds smoothly to afford the expected cycloadducts in moderate yields



Scheme 1.46

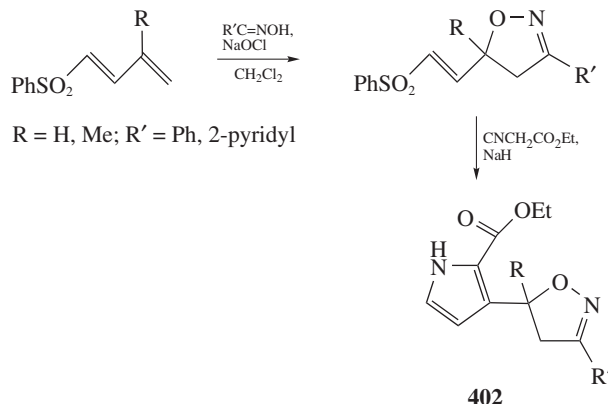


Scheme 1.47

and very high regio- and stereoselectivity. In sharp contrast, aromatic nitrile oxides react with the same amide to afford 5-methyl-4,5-dihydroisoxazole-5-carboxamides in higher yields but with a nearly 1:1 mixture of diastereoisomers (443).

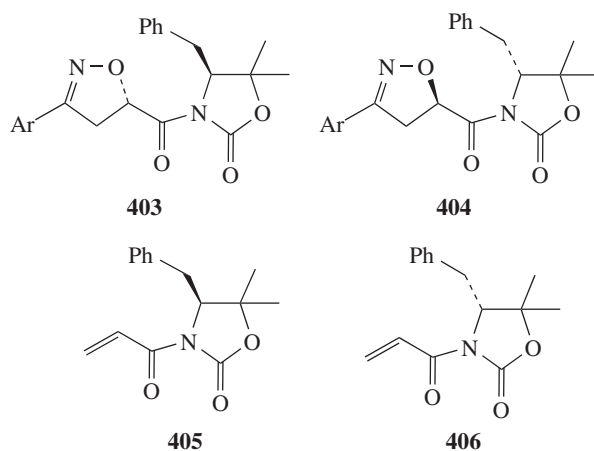
5-(3-Pyrrolyl)-4,5-dihydroisoxazole derivatives **402** have been synthesized (Scheme 1.48) in good yields (66%–78%) by regioselective 1,3-dipolar cycloaddition of nitrile oxides to 1-phenylsulfonyl-1,3-dienes, followed by Barton–Zard pyrrole annulation using ethyl isocyanoacetate anion (444).

Optically active 3-arylisoxazoline-5-carboxylic acid derivatives **403** or **404** have been prepared by the reaction of (*S*)- or (*R*)-3-acryloyl-4-benzyl-5,5-dimethyloxazolidin-2-one (**405** or **406**) with nitrile oxides, obtained from benzo-hydroximoyl chloride and its substituted derivatives in the presence of a catalytic amount of metal salt, for example, Yb(OTf)<sub>3</sub> (445). This procedure improves the diastereoselectivity of compounds **403** or **404**, which are industrially useful as intermediates for various drugs and agrochemicals. It also enables the amount



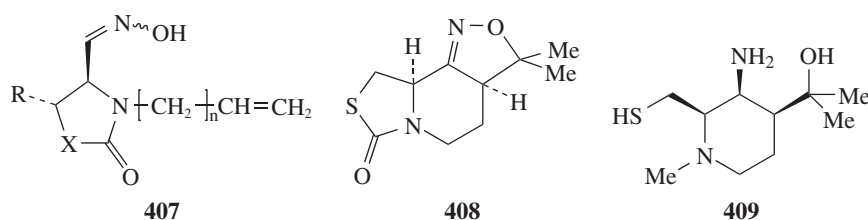
Scheme 1.48

of metal salts to be reduced and thereby makes the reaction industrially applicable. In particular, a mixture (86:14) of diastereomers **403** and **404** (Ar = Ph) was prepared in 71% yield.



Regioselective dipolar cycloadditions of 4-nitro-, 5-nitro-, and 2-methyl-5-nitro-1-vinylimidazoles with nitrile oxides afford the corresponding 5-(imidazol-1-yl)isoxazolines, which are potential intermediates in the synthesis of aminoimidazole analogs of purine nucleosides (446). Isoxazole, isoxazoline and isoxazolidine analogs of C-nucleosides, related to pseudo-uridine, have been synthesized by 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones, derived from mono- and disubstituted uracil-5-carbaldehydes and 2,4-dimethoxypyrimidine-5-carbaldehyde. The dimethoxy derivatives have been easily deprotected to the corresponding uracil, bearing the heterocyclic ring instead of a sugar moiety (447).

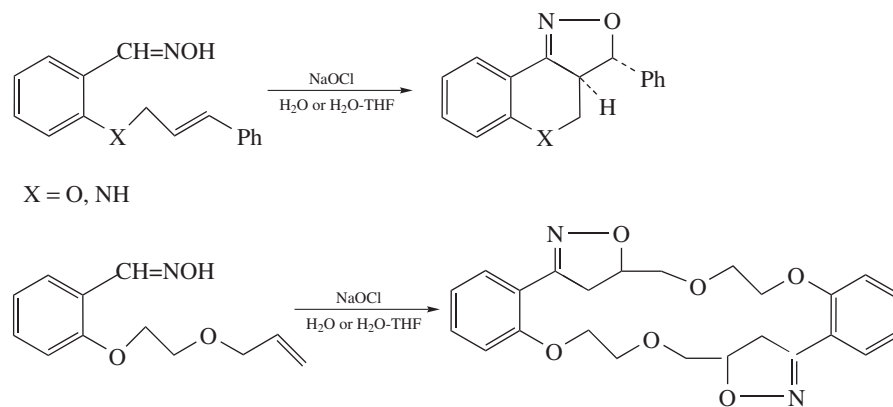
Intramolecular nitrile oxide—olefin cycloaddition of oxazolidine and thiazolidine oximes **407** ( $R = H, Me$ ;  $R^1 = H, Me$ ;  $X = O, S$ ;  $n = 1, 2$ ) proceed stereoselectively, yielding tricyclic fused pyrrolidines and piperidines. Thus, **407** ( $n = 2$ ;  $R = H$ ;  $R^1 = Me$ ;  $X = S$ ) has been oxidized to the nitrile oxides with sodium hypochlorite, in the presence of triethylamine in methylene chloride, to give the isoxazothiazolopyridine **408** in 68% yield. Reduction of **408** with lithium aluminum hydride affords mercaptomethylmethylpiperidine **409** in 24% yield (448).



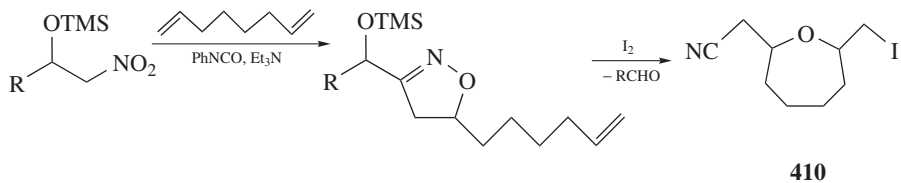
Examples of one-pot 1,3-dipolar cycloaddition in water have been described, affording novel benzopyran, quinoline, and cyclophane isoxazolines (Scheme 1.49) (38).

A variety of cyclic ethers, **410**, have been obtained via both, solution-phase and polymer-supported methods in the  $[3 + 2]$  cycloadditions of nitrile oxides to alkenes and dienes to give isoxazolines (Scheme 1.50). Both simple and substituted dienes have been found suitable for polymer-supported formation of cyclic ethers of ring sizes five through seven (449).

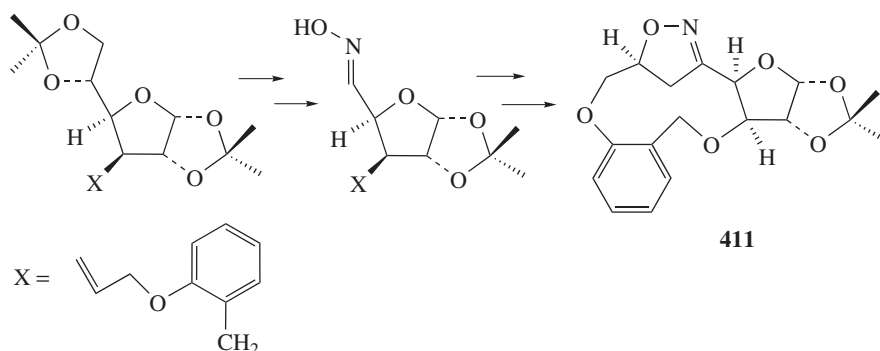
Chiral 10 to 12-membered nitrogen and oxygen heterocycles, fused to isoxazoline rings have been prepared with high regio- and stereoselectivity by INOCs of tethered N- and O-allyl carbohydrate derivatives. The use of a  $-Y-Ar-CH_2$  tether, containing a 1,2-disubstituted aromatic ring between the heteroatom attached to



Scheme 1.49



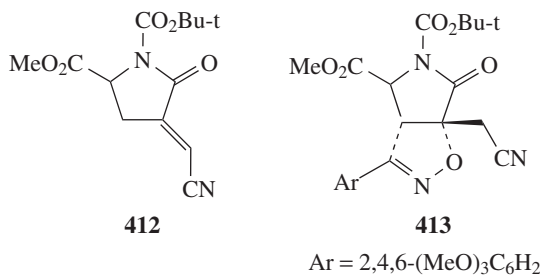
Scheme 1.50



Scheme 1.51

a nitrile oxide-bearing carbohydrate scaffold, and the allyl group, facilitates the formation of medium-sized rings. The cycloaddition affords bridged isoxazolines, **411**, with O-tethered allyl carbohydrate derivatives (Scheme 1.51). But a fused isoxazoline was obtained when a N(Ts)-tethered allyl derivative was used (**450**).

Reactions of (2*S*,4*E*)-4-(cyanomethylidene)-5-oxo-1,2-pyrrolidinedicarboxylate **412** with 2,4,6-trimethoxybenzene nitrile oxide, performed in the presence of a base, afford racemic isoxazolo fused 2-pyrrolidinone **413** in 82% to 86% diastereomeric excess (451).



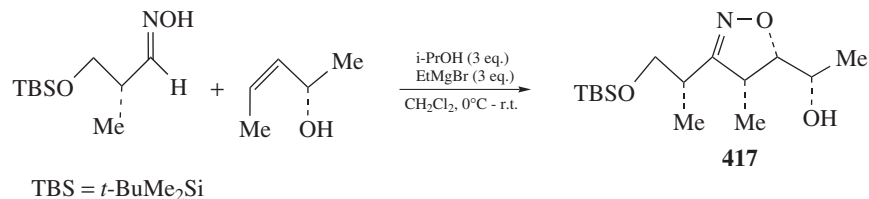
Silacyclophanes **414**, were synthesized (Scheme 1.52) by using quadruple macrocyclization of bis(vinyl dimethyl)disiloxane with an aromatic bis(nitrile oxide) formed from bis(hydroxymoyl chloride) **415** (452).



**Scheme 1.52**

The yields of the first and the second stages were 53% and 48%, respectively. The yields of the *para*-analog of **414** were similar (55% and 35%, respectively). A one-pot reaction with pyridine-2,6-biscarbohydroximinoyl dichloride gives a pyridine analog of **414** as a minor product (8%). The main product **416** (25% yield) arises from an intramolecular nitrile oxide dimerization. The macrocyclic cycloadducts have been characterized spectroscopically and by X-ray crystallography (452).





Scheme 1.53

Macrocycles containing isoxazoline or isoxazole ring systems, potential receptors in host–guest chemistry, have been prepared by multiple (double, triple or quadruple) 1,3-dipolar cycloadditions of nitrile oxides, (prepared *in situ* from hydroxamoyl chlorides) to bifunctional calixarenes, ethylene glycols, or silanes containing unsaturated ester or alkene moieties (453). This one-pot synthetic method has been readily extended to the preparation of different types of macrocycles such as cyclophanes, bis-calix[4]arenes and sila-macrocycles. The ring size of macrocycles can be controlled by appropriate choices of the nitrile oxide precursors and the bifunctional dipolarophiles. Multiple cycloadditive macrocyclization is a potentially useful method for the synthesis of macrocycles.

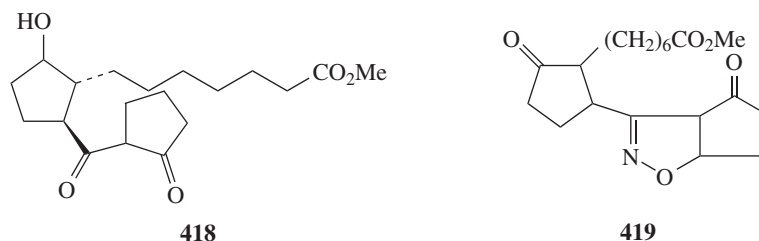
Enantiomerically pure isoxazolines **417** have been prepared (Scheme 1.53) via the stereo- and regioselective cycloaddition of chiral nitrile oxides and allylic alcohols (454). By ring opening with Et<sub>3</sub>SiCl followed by imine hydrolysis with Raney nickel/B(OH)<sub>3</sub>, isoxazolines **417** were converted with stereo integrity to the respective hydroxy ketones, the latter being used as polyketide building blocks. This method has been used to prepare an isoxazoline analog of erythronolide A seco acid. A new procedure for the selective reduction of conjugated Δ<sup>2</sup>-isoxazolines to unsaturated β-hydroxy ketones has been described. The use of SmI<sub>2</sub> as the reducing agent and B(OH)<sub>3</sub> to hydrolyze the resulting imine results in a mild, convenient, and chemoselective protocol for this otherwise difficult transformation. It complements the existing methodology for the preparation of β-hydroxy ketones via nitrile oxides (455).

Intramolecular cycloaddition of nitrile oxides, prepared from 1,2-isopropylidene-protected ether-linked oligo-pentoses leads to the diastereoselective formation of chiral isoxazolines fused to 10–16-membered oxa-cycles (456).

A rapid access to carbocyclic nucleosides, containing a fused isoxazoline ring has been proposed, starting from cyclopentadiene. The route involves a hetero Diels–Alder cycloaddition reaction of nitrosocarbonylbenzene followed by a 1,3-dipolar cycloaddition of nitrile oxides, cleavage of the N–O tether and transformation of the heterocyclic aminols into nucleosides via construction of purine and pyrimidine heterocycles (457).

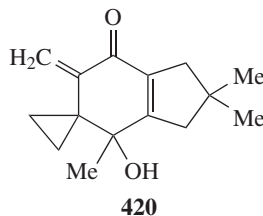
**1.4.1.3. Syntheses of Natural Products and Related Compounds** 1,3-Dipolar cycloaddition reactions of nitrile oxides in the synthesis of natural products and their analogs has been the subject of a recent review (458).

The synthesis of new 11-deoxyprostaglandin analogs with a cyclopentane fragment in the  $\omega$ -chain, prostanoid **418**, has been accomplished by a reaction sequence involving nitrile oxide generation from the nitromethyl derivative of 2-( $\omega$ -carbomethoxyhexyl)-2-cyclopenten-1-one, its 1,3-cycloaddition to cyclopenten-1-one and reductive transformations of these cycloadducts (459). Diastereoisomers of a new prostanoid precursor **419** with a 4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]isoxazole fragment in the  $\omega$ -chain have been synthesized. Reduction of **419** gives novel 11-deoxyprostanoids with modified  $\alpha$ - and  $\omega$ -chains (460).

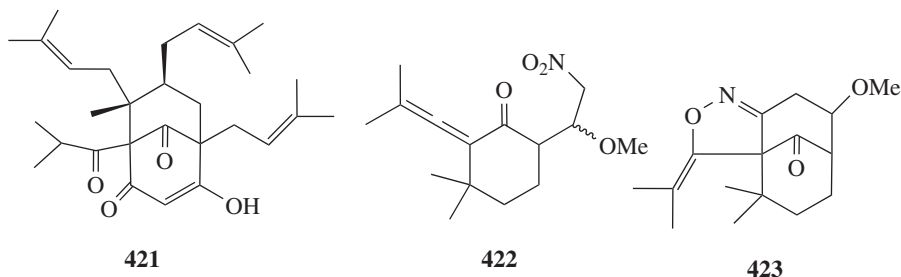


The 1,3-dipolar addition to terminal alkenes of nitrile oxides, generated from nitromethylene derivatives of bicycloheptane, provides 9,11-ethano-13,15-isoxazolinoprostanoids, PGH analogs, with alkyl, phenyl, or additional heterocyclic fragment in the  $\omega$ -chain (461). Chemical transformations of 9,11-ethano-13,15-isoxazolinoprostanoids furnish prostanoids with bifunctional fragments of  $\beta$ -hydroxyketone and  $\alpha$ -aminoalcohol in the  $\omega$ -chain. The reaction of  $\beta$ -hydroxyketones with methanesulfonyl chloride gives rise to prostanoids with an enone component in the  $\omega$ -chain. 9,11-Ethano-16-thiaprostanoids have been prepared, for the first time, by nucleophilic addition of thiols to the polarized double bond in the  $\omega$ -chain. The 1,3-dipolar addition to terminal alkenes of nitrile oxides, generated from nitromethylene derivatives of bicycloheptane provides 9,11-ethano-13,15-isoxazolinoprostanoids with an alkyl, phenyl, or additional heterocyclic fragment in the  $\omega$ -chain (462).

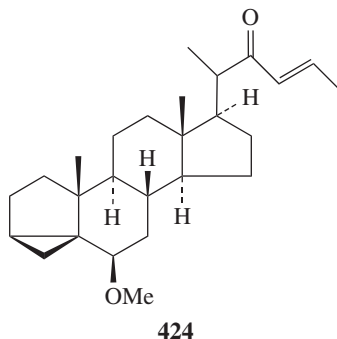
A total synthesis of the sesquiterpene ( $\pm$ )-illudin C **420** has been described. The tricyclic ring system of the natural product is readily quickly assembled from cyclopropane and cyclopentene precursors via a novel oxime dianion coupling reaction and a subsequent intramolecular nitrile oxide—olefin cycloaddition (463).



A synthetic approach to hyperevolutin A **421**, prenylated bicyclo[3.3.1]nonanone derivative, with an acylated phloroglucinol-type fragment, has been described (464). Intramolecular allene–nitrile oxide cycloaddition of **422** has been used to construct the bicyclic framework and the vicinal quaternary centers in cycloadduct **423**.

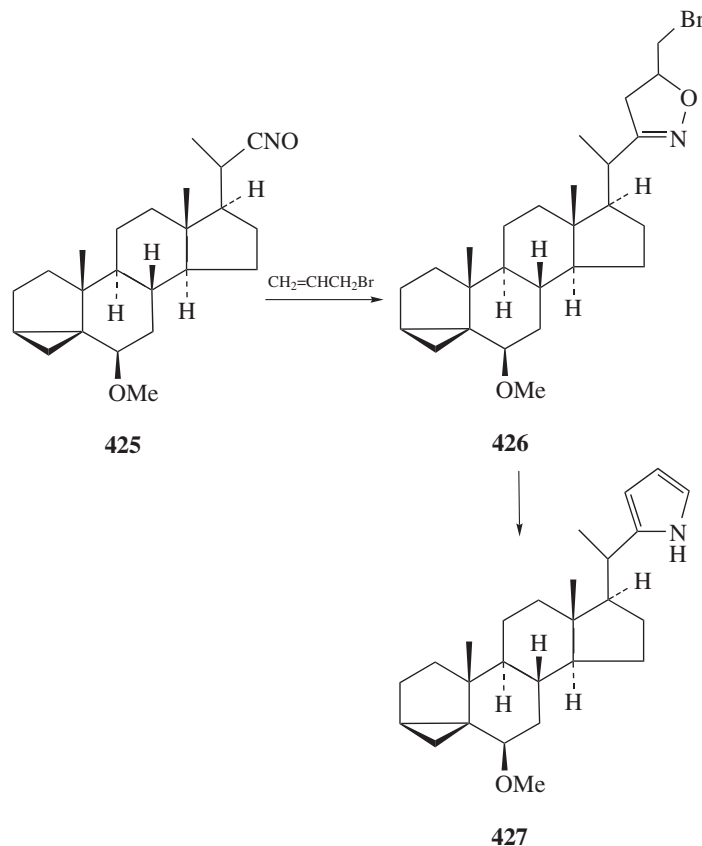


$\Delta^{23}$ -22-Oxo steroids **424** have been synthesized via 1,3-dipolar cycloaddition of steroidal nitrile oxides to low-molecular dipolarophiles. Cycloaddition of 2-propynyl bromide to 20-carbonitrile oxide, followed by hydrogenation of the isoxazole derivative, gives 22-enamino-24-keto steroid. The latter has then been converted into the target enones in several steps (465).



1,3-Dipolar cycloaddition of nitrile oxide **425** with allyl bromide followed by hydrogenation of dihydroisoxazole derivative **426** (Scheme 1.54) gives a pyrrol-substituted steroid derivative **427** (466).

A total synthesis of functionalized 8,14-seco steroids with five- and six-membered D rings has been developed (467). The synthesis is based on the transformation of (S)-carvone into a steroidal AB ring moiety with a side chain at C<sub>(9)</sub>, which allows the creation of a nitrile oxide at this position. The nitrile oxides are coupled with cyclic enones or enol derivatives of 1,3-diketones, and reductive cleavage of the obtained cycloadducts give the desired products. The formation of a twelve-membered ring compound has been reported in the cycloaddition of one of the nitrile oxides with cyclopentenone and as the result of an intramolecular ene reaction, followed by retro-aldol reaction.

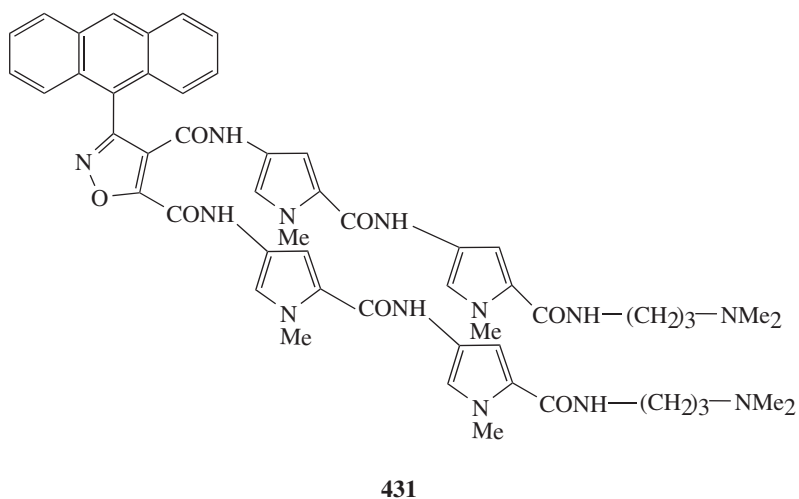
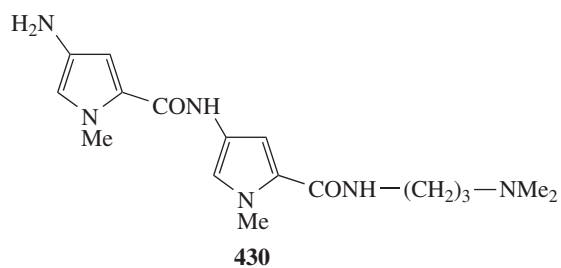
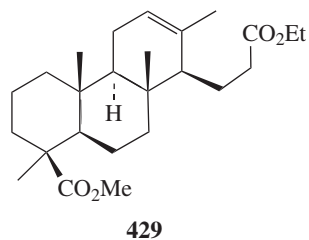
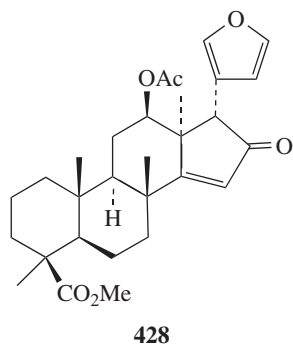


Scheme 1.54

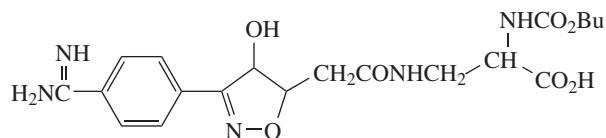
Starting from quinic acid, a highly substituted, *cis*- $\alpha,\beta$  unsaturated nitrile oxide has been synthesized and used in a 1,3-dipolar cycloaddition, to afford a precursor of the *cis*-decalin system of branimycin (**468**).

The stereoselective synthesis of the 12-acetoxy enone **428**, related to the limonoid azadiradione, has been achieved in 12 steps (16% overall yield), starting from tricyclic diester **429**. The key steps involve an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide and a Stille coupling reaction of vinyl iodide with stannylfuran (**469**).

9-Anthracenecarbonitrile oxide, prepared directly from 9-anthracenecarbaldoxime and N-chlorosuccinimide, reacts with dimethyl acetylenedicarboxylate to afford dimethyl 3-(9'-anthracenyl)isoxazole-4,5-dicarboxylate in good yield. Double activation reactions between this diester and hydrogenated lexitropsin **430**, in a 1:2 molar ratio, produce a novel intercalating isoxazolyl bis-lexitropsin conjugate **431** as the major product (**43**).

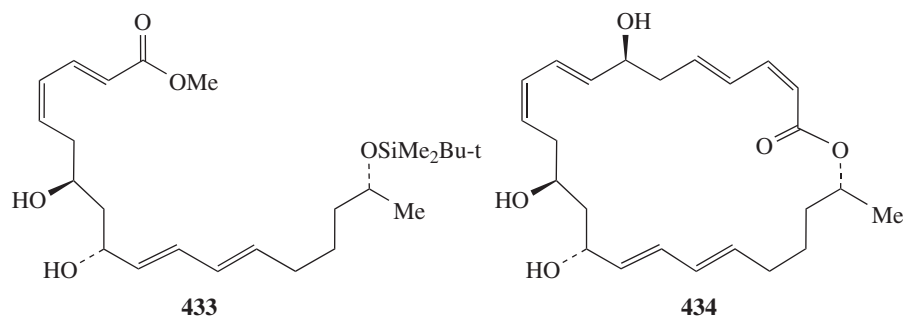


Four diastereoisomers of isoxazolinol **432** have been prepared via [3 + 2] dipolar cycloadditions of nitrile oxides. The ring 4*S*,5*S* isomer shows the configuration of an isolated metabolite of roxifiban, a platelet glycoprotein receptor antagonist (470).



432

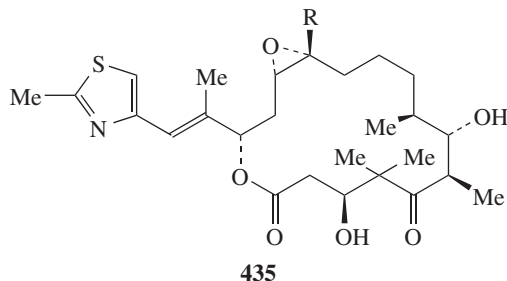
Diastereoselective intermolecular nitrile oxide—olefin cycloaddition has been used in an enantioselective synthesis of the C<sub>(7)</sub>-C<sub>(24)</sub> segment **433** of the 24-membered natural lactone, macrolactin A **434** (471, 472). Two (carbonyl)iron moieties are instrumental for the stereoselective preparation of the C<sub>(8)</sub>-C<sub>(11)</sub> E,Z-diene and the C<sub>(15)</sub> and C<sub>(24)</sub> sp<sup>3</sup> stereocenters. Also it is important to note that the (carbonyl)iron complexation serves to protect the C<sub>(8)</sub>-C<sub>(11)</sub> and C<sub>(16)</sub>-C<sub>(19)</sub> diene groups during the reductive hydrolysis of an isoxazoline ring.



433

434

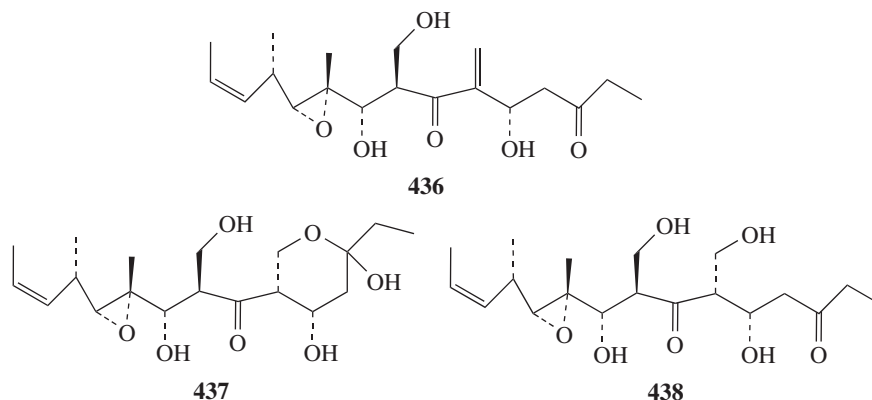
An expedient and fully stereocontrolled synthesis of epothilones A (**435**, R = H) and B (**435**, R = Me) has been realized (473, 474). The routes described, involve an extensive study of nitrile oxide cycloadditions, as substitutes for aldol addition reactions, leading to the realization of a highly convergent synthesis, based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddition.



435

Two stereoselective aldol reactions, followed by a nitrile oxide cycloaddition and a stereoselective late-stage epoxidation are the key steps in the total synthesis of myriaporones 1, 3, and 4 (**436**, **437**, and **438**). The synthesis allows

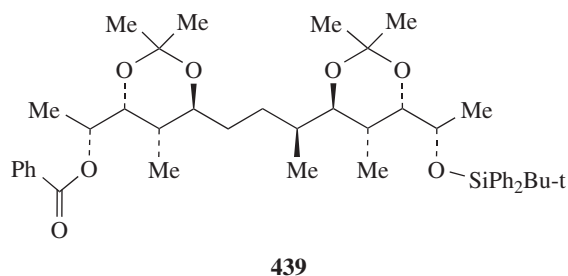
the unambiguous assignment of stereogenic centers, not previously assigned for these compounds (475, 476).



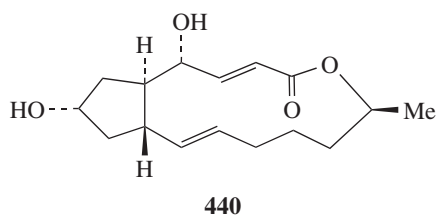
Carbohydrate derivatives with a spiroisoxazoline moiety, present in psammaphysins and ceratinamides (metabolites isolated from marine sponges) have been prepared in good yields and excellent regio- and diastereoselectivity by a route involving Wittig olefination and 1,3-dipolar cycloaddition as key steps (477).

3,4-Di(2,3,4,6-tetra-O-acetyl- $\beta$ -D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide has been synthesized from D-mannose by a route, involving as the key step, dimerization of mannopyranosyl nitrile oxide. Three methods have been used for the generation of the nitrile oxide: isocyanate-mediated dehydration of nitromethylmannose derivative, treatment of aldoxime with aqueous hypochlorite and base-induced dehydrochlorination of hydroximoyl chloride. D-glucose, D-galactose, D-xylose and L-fucopyranosyl analogs have been prepared similarly. The structure of D-mannose-derived 1,2,5-oxadiazole 2-oxide has been established by X-ray crystallography (478).

A strategy based on the diastereoselective dipolar cycloaddition reaction of nitrile oxides and allylic alcoholates, has been applied to the synthesis of bis(isoxazolines) that are precursors to polyketide fragments. These intermediates can be elaborated into protected polyols, for example, **439**, by sequential chemoselective reductive opening of each isoxazoline or, alternatively, by simultaneously, providing access to all stereoisomers of this carbon skeleton (479).

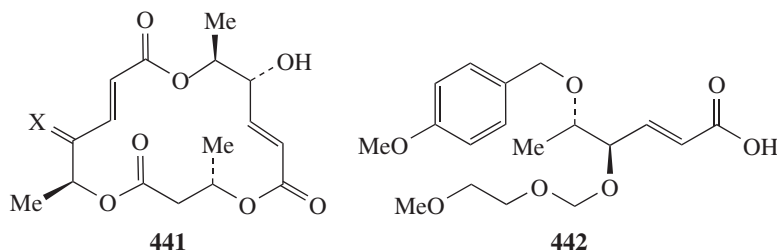


Three novel stereo- and regioselective schemes for the total synthesis of (+)-brefeldin A **440** have been accomplished. Each of them exploit intermolecular nitrile oxide cycloaddition for constructing the open chain and introducing substituents, but differ in subsequent stages. The first (480) and the second (481) use intramolecular cycloaddition for the macrocycle closure. However, in the second scheme INOC is followed by C=C bond *cis-trans*-isomerization. In the third scheme (481) intermolecular cycloaddition is followed by ring closing metathesis as the key step.

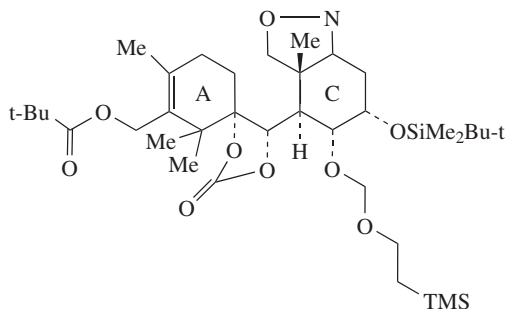


A stereoselective total synthesis of erythronolide A, using two  $Mg^{II}$ -mediated cycloadditions of nitrile oxides has been described. Of broader significance, the strategy not only facilitates the synthesis of specific polyketide targets (i.e., natural products) but also opens up new possibilities for the preparation of nonnatural analogs (482).

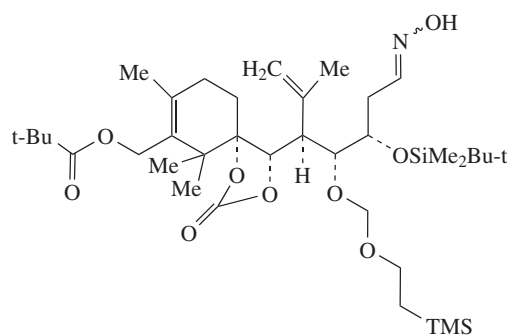
The unified highly convergent total and formal syntheses of (+)-macrophelides B (**441**; X = O) and A (**441**; X =  $\alpha$ -OH,  $\beta$ -H), respectively, have been described (483). Key features of the syntheses include the concise synthesis of the optically active  $\delta$ -hydroxy- $\gamma$ -keto  $\alpha,\beta$ -unsaturated acid fragment **442** via the direct addition of a *trans*-vinyllogous ester anion equivalent to a readily available Weinreb amide, and the facile construction of the 16-membered macrolide core of the macrospinelide series via an INOC.



The stereoselective formation of the C ring of paclitaxel **443** has been accomplished by the nitrile oxide [3+2] cycloaddition of intermediate **444** to the preformed A ring (484).



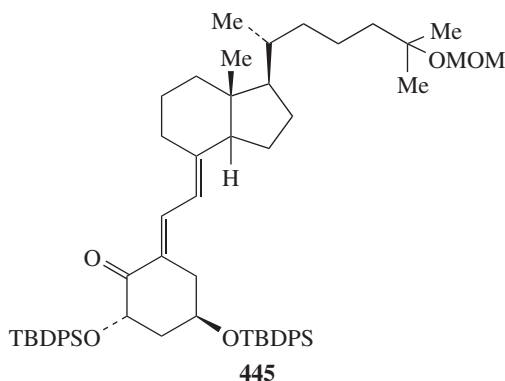
443



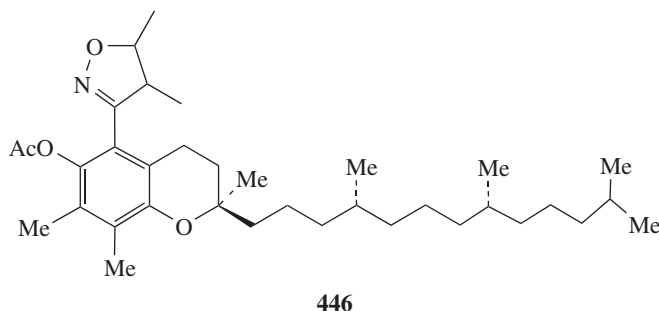
444

Starting from the Ni *meso*-formyloctaethylporphyrin oxime complex, the *meso*-cyanooctaethylporphyrin N-oxide complex has been synthesized for the first time. The double addition of the nitrile oxide to 2,5-norbornadiene afford a porphyrin dimer, whose structure has been established by X-ray diffraction analysis (485). The 1,3-dipolar cycloaddition reaction of *meso*-tetraarylporphyrins with 2,6-dichlorobenzonitrile oxide yields isoxazoline-fused chlorins and stereoisomeric bacteriochlorins. The crystal structure of one of bacteriochlorins has been characterized by X-ray diffraction (486, 487).

An efficient synthetic route to (10*Z*)- and (10*E*)-19-fluoro-1 $\alpha$ ,25-dihydroxy vitamin D<sub>3</sub> has been developed (488). The key feature of this pathway is the introduction of a 19-fluoromethylene group to a (5*E*)-19-nor-10-oxo-vitamin D derivative. The 10-oxo compound **445** has been obtained via a 1,3-dipolar cycloaddition reaction of (5*E*)-1 $\alpha$ ,25-dihydroxyvitamin D with *in situ* generated nitrile oxide, followed by ring cleavage of the formed isoxazoline moiety with molybdenum hexacarbonyl. Conversion of the keto group of (5*E*)-19-nor-10-oxo-vitamin D to the *E* and *Z* fluoromethylene group has been achieved via a two-step sequence, involving a reaction of lithiofluoromethyl phenyl sulfone, followed by the reductive de-sulfonylation of the  $\alpha$ -fluoro- $\beta$ -hydroxysulfone. The dye-sensitized photoisomerization of the (5*E*)-19-fluorovitamin D affords the desired (5*Z*)-19-fluorovitamin D derivatives, (10*Z*)- and (10*E*)-19-fluoro-1 $\alpha$ ,25-dihydroxy-vitamin D<sub>3</sub>.



New isoxazoline derivatives of  $\alpha$ -tocopherol, the main component of vitamin E, have been synthesized in a facile, two-step sequence consisting of nitration followed by 1,3-dipolar cycloaddition. 5-Nitromethyl- $\alpha$ -tocopheryl acetate, obtained from  $\alpha$ -tocopheryl acetate by direct nitration in one step, act as the nitrile oxide precursor in the reaction with various alkenes. The facile conversion proceeds in the presence of equimolar amounts of PhNCO and catalytic amounts of triethylamine to give isoxazolines, **446** (489).



A novel class of activators for chloride conductance in the cystic fibrosis transmembrane conductance regulator protein has been identified. These 3-(2-benzyloxyphenyl)isoxazoles and 3-(2-benzyloxyphenyl)isoxazolines have been synthesized employing the 1,3-dipolar cycloaddition of nitrile oxides with various alkene and alkyne dipolarophiles (490).

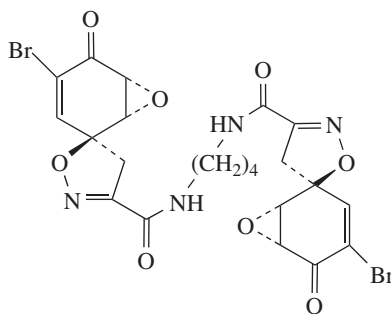
3,4-Diaryl isoxazole analogs of valdecoxib [4-(5-methyl-3-phenylisoxazol-4-yl) benzenesulfonamide], a selective cyclooxygenase-2 (COX-2) inhibitor, have been synthesized by the 1,3-dipolar cycloaddition of arencarbonitrile oxides to the enolate ion of phenylacetone, regioselectively prepared *in situ* with lithium diisopropylamide at 0° (491). The corresponding 3-aryl-5-methyl-4-phenylisoxazoles are easily generated by a dehydration/aromatization reaction, under basic conditions, of 3-aryl-5-hydroxy-5-methyl-4-phenyl-2-isoxazolines and are further transformed into their benzenesulfonamide derivatives. The biochemical COX-1/

COX-2 selectivity was evaluated *in vitro* by using the human whole blood assays of COX isoenzyme activity. Three compounds, not bearing the sulfonamide group present in valdecoxib, have been found to be selective COX-1 inhibitors.

A total synthesis of (+)-vinblastine widely used in cancer chemotherapy, has been reported. It includes the synthesis of (–)-vindoline. 1,3-Dipolar cycloaddition of a nitrile oxide has played an important role in the preparation of the indoloazacycloundecane moiety, whose coupling with (–)-vindoline occurs with the desired stereochemistry, leading to an intermediate readily transformed to the target (+)-vinblastine (492).

The synthesis of multivalent neoglycoconjugates by 1,3-dipolar cycloaddition of nitrile oxides and alkynes has been reported (493). The nitrile oxides have been generated *in situ* in the presence of alkynyl derivatives, allowing the access to homo and hetero multivalent systems containing O- and C-linked glycosides and isoxazole bridges.

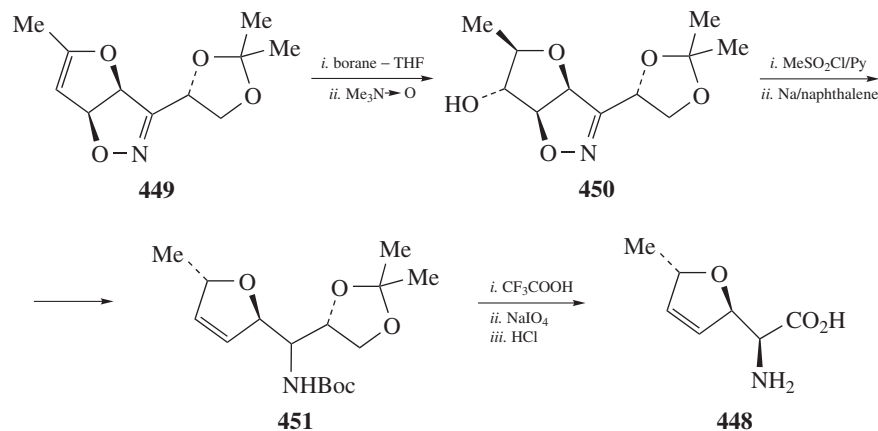
The synthesis of the spiroisoxazoline natural product (+)-calafianin **447** has been reported, using asymmetric nucleophilic epoxidation and nitrile oxide cycloaddition as key steps. Syntheses and spectral analyses of all calafianin stereoisomers lead to unambiguous assignments of relative and absolute stereochemistry (494).



447

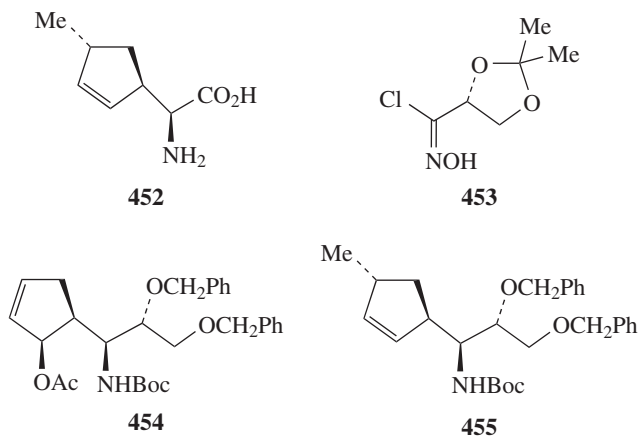
The 1,3-dipolar cycloaddition of nitrile oxides and 2-methylfuran provides suitable precursors for  $\alpha$ -amino acids such as L-furanomycin **448** that contains a dihydrofuran ring (495). By using a chiral nitrile oxide derived from mannitol bis(acetonide), the enantiomerically pure furoisoxazoline **449** has been obtained. Hydroboration–oxidation of the latter leads to the hydroxy-substituted annulated THF derivative **450**, which is converted via dihydrofuran **451** to furanomycin **448** in enantiomerically pure form (Scheme 1.55).

A concise and efficient asymmetric synthesis of L-(+)-carbafuranomycin **452**, a novel analog of L-(+)-furanomycin, which is an unusual antibiotic amino acid of great interest, due to its activity as an isoleucine antagonist, has been reported (496). The synthesis starts with the 1,3-dipolar cycloaddition of a chiral nitrile oxide (obtained *in situ* from hydroximinoyl chloride **453** via slow addition of  $\text{NEt}_3$ ) with cyclopentadiene. Then methylation of cyclopentenyl acetate **454**,



Scheme 1.55

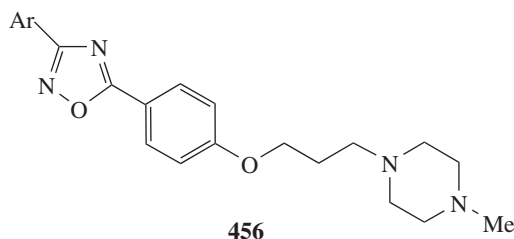
using MeMgBr with CuCN in Et<sub>2</sub>O, affords stereo- and regioselective addition of the Me group to the cyclopentene ring of cyclopentenyl(dibenzoyloxy)propylamine **455**, a precursor to **452**.



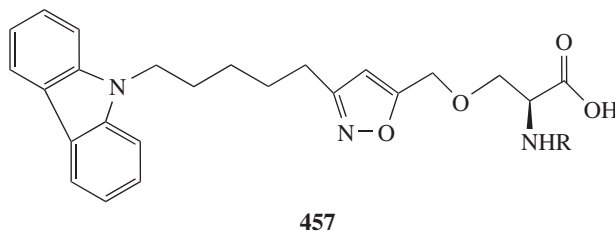
**1.4.1.4. Synthetic Biologically Active Compounds** Silyl- and carbonyl-substituted isoxazoles have been prepared and screened for their cytotoxic activity (497). Some exhibited moderate cytotoxicity toward the HT-1080 and MG-22A cell lines. The highest activity level has been displayed by 3-methyl-5-diphenyl-methylsilylisoxazole.

A series of 3,5-diarylisoxazole and 3,5-diaryl-1,2,4-oxadiazole derivatives, novel classes of small molecule interleukin-8 (IL-8) receptor antagonists, **456** (Ar = 4-FC<sub>6</sub>H<sub>4</sub>), have been identified as IL-8 inhibitors. These compounds exhibit activity in an IL-8 binding assay as well as in a functional assay of IL-8 induced

elastase release from neutrophils. In addition, one of the compounds exhibited oral activity in a rat adjuvant arthritis test (498).



Peroxisome proliferator-activated receptors (PPARs), important molecular targets for developing drugs for the treatment of human metabolic diseases, inflammation, and cancer, are known to be activated by a variety of structurally diverse compounds. Using a structure-based drug design approach, a series of novel isoxazolyl-serine-based PPAR ligands **457** [R = Boc, Cbz, *o*-Cl-Cbz, H, Ph(CH<sub>2</sub>)<sub>3</sub>, CO(CH<sub>2</sub>)<sub>4</sub>Me], possessing moderate binding affinities to the three PPAR subtypes, has been synthesized (499). Some of the new PPAR ligands stimulate cardiomyocyte differentiation from murine embryonic stem (ES) cells. Ligand **457** (R = Boc) is the most active one tested at concentrations between 1.25 to 20  $\mu$ M between 2 and 6d. This is the period when mesodermal cells become cardiomyocytes.



#### 1.4.2. Nitrile Oxides in Polymer Chemistry and Technology

The ability of nitrile oxides to undergo addition and cycloaddition reactions makes it possible to use them in polymer chemistry and technology. Major trends might be synthesis, modification, cross-linking of polymers, addition of nucleophiles, and 1,3-dipolar cycloaddition of nitrile oxides. Taking into account the scarcity of reviews devoted to this topic, not only recent but also previous references will be cited in this subsection.

**1.4.2.1. Synthesis and Modification of Polymers** Unstable bis(nitrile oxide), generated by dichloroglyoxime dehydrochlorination, polymerizes in solution to give poly(furoxan) or (in the presence of 1,3-dienes) gives rise to their being cross-linked (500). Polymerization of terephthalonitrile dioxide and its

co-polymerization with bis-unsaturated compounds, for example, *p*-diethynylbenzene, is also described (501). Interaction of bis(nitrile oxides) with ketene dimer leads to polymers (502).

Efficient generation of aliphatic bis(nitrile oxides) has been investigated for preparing novel polymers with a polymethylene backbone. Conventional methods, using  $\alpha,\omega$ -dinitroalkanes and phenylisocyanate, give the corresponding bisisoxazoline compounds in poor yields, presumably because of the intramolecular reaction of terminal groups. The reaction of aliphatic dialdehydes with *N*-chlorosuccinimide, followed by thermal and/or base catalyzed reactions gives fair yields. Polycycloaddition reactions of bis(nitrile oxides) with diene compounds have also been studied (503).

Important for both the synthesis and modification of polymers is also the elongation of polymer chains. Bisnitrile oxides have been claimed as reagents for chain elongation of polyimides containing terminal groups with C=C, C $\equiv$ C, C $\equiv$ N, C=O, and C=N bonds (504).

Modification of *cis*-poly(butadiene) and *cis*-poly(isoprene) has been attained on heating in boiling toluene, in the presence of mononitrile oxides: 35%–55% of C=C bonds have been replaced by isoxazoline fragments. The process also demands the presence of a base because the nitrile oxides have been generated from hydroximoyl chlorides (505).

Unsaturation of hydroxy-containing compounds are reduced on reaction with nitrile oxides such as tetramethyl terephthalonitrile *N,N'*-dioxide (506) or 1,3,5-triethylbenzene-2,6-dicarbonitrile oxide (507). The reaction of a nitrile oxide with terminal unsaturation, associated with the preparation of a poly-ol from propylene oxide, reduces the mono-ol content of the poly-ol composition. Thus, stirring a solution of an ethylene oxide–propylene oxide copolymer with an OH content of 2.39% and vinyl unsaturation of 3.58% in THF with 1,3,5-triethylbenzene-2,6-dicarbonitrile oxide for 1 min results in an effective removal of the terminal unsaturation.

**1.4.2.2. Cross-linking of Polymers** Among applications of nitrile oxides, cross-linking of polymers is of main importance. Both nucleophilic addition and 1,3-dipolar cycloaddition are the pertinent reactions.

Cross-linking of mercapto group-containing polymers using thiol nucleophilic addition to nitrile oxide has been reported (508). Several aromatic bis(nitrile oxides) have been prepared as potential curing agents for elastomeric sealants, produced from thiol-terminated liquid polysulfides (509). All have been obtained by dehydrohalogenation of  $\alpha$ -halo oximes, and the requisite aldehydes have been synthesized from the dimethyl derivatives or the chloromethylated hydrocarbons. The direct chloromethylation of naphthalene, which offers a convenient route to the naphthalene-1,4- and -1,5-bis(carbonitrile oxides), is used. Naphthalene-2,6-bis(carbonitrile oxide), anthracene-9,10-bis(carbonitrile oxide), and 4,4'-sulfonylbisbenzonitrile dioxide have also been prepared.

Efficient addition between various nitrile oxides and both, short (C<sub>2</sub>) and long-chain (C<sub>16</sub>) alkyl thiols, aliphatic dithiols and aryl thiols occurs rapidly at

ambient temperature with the formation of thiohydroxamic acid derivatives (510). Competitive experiments with bis(nitrile oxides) shows that for terephthalonitrile oxide the second addition proceeds more readily than the first, whereas with anthracene-9,10-bis(carbonitrile oxide) elevated temperatures are needed to obtain the diadduct. The reaction between prop-2-ene-1-thiol and *p*-nitrobenzonitrile oxide affords products resulting from both cycloaddition and 1,3-addition with the latter predominating. The polysulfide prepolymer LP-2 has been vulcanized effectively at ambient temperatures by both, terephthalonitrile oxide and 4,4'-sulfonylbisbenzonitrile dioxide, at CNO to SH ratios of 1.5 and higher. Unreinforced sealants produced in this manner are firm elastomers. The naphthalenebis(carbonitrile oxides) afford softer products, while anthracene-9,10-bis(carbonitrile oxide) is ineffective. Formulations involving *in situ* generation of nitrile oxide from hydroximoyl chlorides and Ba(OH)<sub>2</sub> (formed by action of water vapor on BaO) have been also carried out.

Sealants obtained by curing polysulfide liquid polymers with aryl bis(nitrile oxides) possess structural feature of thiohydroxamic acid ester. These materials exhibit poor thermal stability; when heated at 60°C they soften within days and liquefy in 3 weeks. Products obtained with excess nitrile oxide degrade faster than those produced with equimolar amounts of reagents. Spectroscopic studies demonstrate that, after an initial rapid addition between nitrile oxide and thiol, a second slower reaction occurs which consumes additional nitrile oxide. Thiohydroxamic acid derivatives have been shown to react with nitrile oxides at ambient temperature to form 1,2,4-oxadiazole 4-oxides and alkyl thiol. In the case of a polysulfide sealant, the rupture of a C–S bond to form the thiol involves cleavage of the polymer backbone. Continuation of the process leads to degradation of the sealant. These observations have been supported by thermal analysis studies on the polysulfide sealants and model polymers (511).

It is evident that reactions of unsaturated polymers with bisnitrile oxides lead to cross-linking. Such a procedure has been patented for curing poly(butadiene), butadiene–styrene copolymer, as well as some unsaturated polyethers and polyesters (512–514). Bisnitrile oxides are usually generated in the presence of unsaturated polymers by dehydrochlorination of hydroximoyl chlorides. Cross-linking of ethylene–propylene–diene co-polymers with stable bisnitrile oxides has been studied (515, 516). The rate of the process has been shown to reduce in record with the sequence 2-chloroterephthalonitrile oxide > terephthalonitrile oxide > 2,5-dimethylterephthalonitrile oxide > 2,3,5,6-tetramethylterephthalonitrile oxide > anthracene-9,10-dicarbonitrile oxide (515).

Bis(nitrile oxides) obtained from dialkylbenzenes have been claimed as low-temperature rubber vulcanization agents (517). Curing of poly(butadiene-co-acrylonitrile) with 2,4,6-trimethylisophthalodinitrile N-oxide produces rubbery material of good quality, however, curing of (polybutadiene) was unsuccessful (518). The solubility of dinitrile oxides and stability of their ketone solutions has been studied for their application as vulcanizing agents in the production of rubberized materials (519).

Anthracene-9,10-dicarbonitrile oxide has been used for cross-linking of cyano group-containing poly(arylene sulfides) (520). Acrylic polymers containing nitrile groups do not possess typical curing sites such as double bonds. Addition of stable bis(nitrile oxide) to the acrylic polymer, causes cross-linking at a low-temperature. Heat-resistant thermoplastic vulcanizates with high resistance to solvents and increased compression resistance are formed (521).

Nitrile oxides have been used as reagents for heat activated cross-linking of polymers having appropriate functionality, such as alkenes, alkynes, nitriles, and isocyanates. The use of nitrile oxide compounds are in filled or unfilled applications such as pressure sensitive adhesives, reactive hot melts, polyurethane dispersions, thermosetting adhesives, thermoplastic adhesives and coatings (522, 523). Formulations containing stable nitrile oxide reagents have been developed for coatings, composites, and moldings (524).

Aqueous polynitrile oxide curing compositions, with good storage stability, have been patented (525). The compositions comprise aqueous dispersions containing nitrile oxides and are useful for coating systems that are cured at room temperature without the release of byproducts. Latexes are cured by mixing a polymer latex with a stable polynitrile oxide, for example, 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide, and removing water from the mixture.

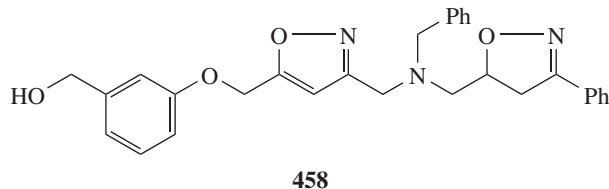
Foam compositions, including a latex and a polynitrile oxide such as 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide, or a latex and an epoxy silane, or a latex and a mixture of the two crosslinkers have been prepared (526). The compositions may also contain additional components, including fillers, surfactants, cell detackifiers, froth stabilizers, froth boosters, viscosity reducers, and compounds to improve resilience, and antioxidants. The compositions are particularly useful in the manufacture of flooring, wall covering, shoe lining and nonwoven materials.

Nitrile oxide precursors have been prepared by the reaction of an isocyanate and an alkyl nitroacetate. These precursors release alkanol and carbon dioxide when heated, to liberate the highly reactive nitrile oxide species. An improved synthetic procedure has been developed to afford novel cross-linking agents based on difunctional, trifunctional and aliphatic precursors. Application of these agents to polymer cross-linking has been demonstrated (527).

Although bisnitrile oxides are generated *in situ* in the presence of a polymer, the use of stable bisnitrile oxides prepared beforehand is more attractive owing to the absence of byproducts. Therefore, special attention has been paid to the development of syntheses of stable bisnitrile oxides (29–32, 102, 509, 517, 518, 522, 528).

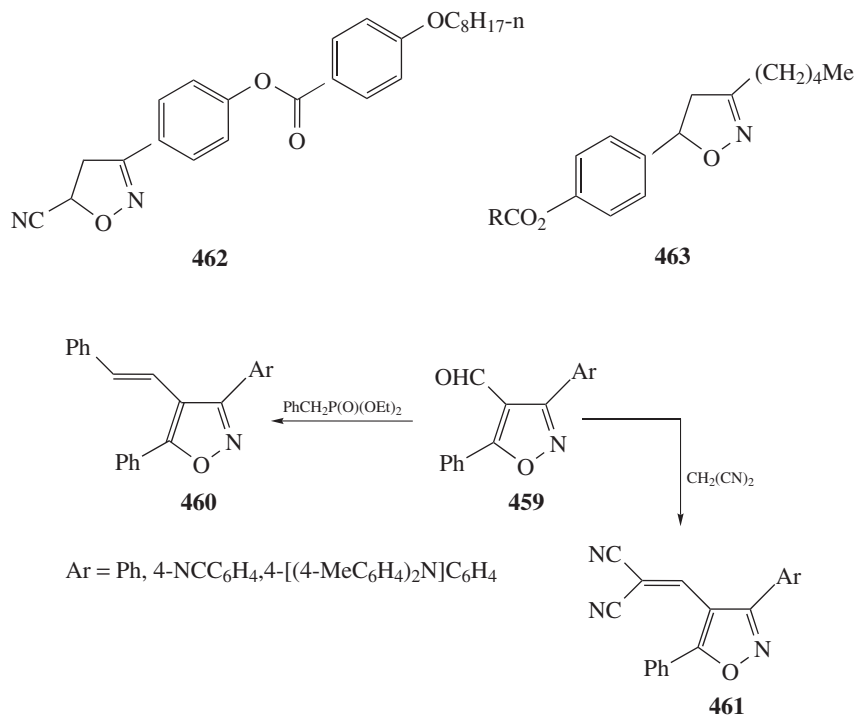
#### 1.4.3. Other Applications of Nitrile Oxides

Using nitrile oxides, various compounds and materials possessing valuable properties have been prepared. Among them are thin-film resistors useful for a thermal head and comprising a nitrile oxide, ruthenium and oxygen, a method for manufacturing the resistor by coating or deposition (529), isoxazole and/or isoxazoline polyheterocyclic systems like **458**, which are useful for development of a new class of ionophores (530).



Transformations of nitrile oxides are very useful in the synthesis of isoxazole, isoxazoline, and oxadiazole compounds, possessing interesting optical properties. Thus, 1,3-dipolar cycloaddition of nitrile oxides, derived from corresponding oximes with phenylpropargyl aldehyde, give aldehydes **459**, subsequent Wittig–Horner reactions with  $\text{PhCH}_2\text{P}(\text{O})(\text{OEt})_2$  or Knoevenagel condensation with malononitrile afford isoxazoles **460** and **461** (Scheme 1.56). These compounds have both high electron acceptability and electron-transfer character, and are useful for organic light emitting diode (OLED) in a plane panel display (531).

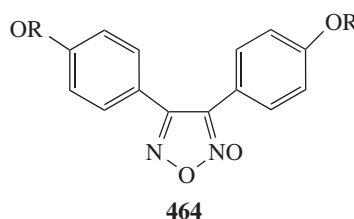
3-Aryl-5-cyano-2-isoxazolines, possessing liquid crystal properties (smectic phases A or E) have been synthesized, 1,3-dipolar cycloaddition of nitrile oxides to acrylonitrile being the key step (532). For example, nitrile **462** has been obtained in 66% yield from substituted benzaldoxime and acrylonitrile *via in situ* generated nitrile oxides.



Scheme 1.56

Several 4-(3-alkyl-2-isoxazolin-5-yl)phenol derivatives that possess liquid crystal properties have also been obtained (533–535). In particular, target compounds such as **463** (R = pentyl, nonyl) have been prepared by the reaction of 4-acetoxystyrene with the nitrile oxide derived from hexanal oxime, followed by alkaline hydrolysis of the acetate and esterification (535). A homologous series of 3-[4-alkoxyphenyl]-5-[3,4-methylenedioxybenzyl]-2-isoxazolines, having chiral properties has been synthesized by the reaction of nitrile oxides, from the dehydrogenation of 4-alkoxybenzaldoximes. These compounds exhibit cholesteric phase or chiral nematic phase (N\*), smectic A (S<sub>A</sub>), and chiral smectic phases (S<sub>C</sub>\*), some at or just above room temperature (536).

Liquid-crystalline 3,4-disubstituted furoxans such as **464** (R = 4-alkoxybenzoyl, Ph) have been prepared by cyclodimerization of 4-AcOC<sub>6</sub>H<sub>4</sub>CNO, followed by hydrolysis to **464** (R = H) and acylation. The products form a nematic mesophase (537).



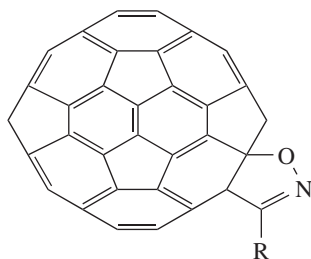
Many papers and patents are devoted to the use of nitrile oxides for the preparation of fullerene derivatives with practically attractive properties.

Electroactive 3-(N-phenylpyrazolyl)fullereno[1,2-*d*]isoxazolines have been synthesized by using 1,3-dipolar cycloaddition of pyrazole nitrile oxides, generated *in situ*, to C<sub>60</sub> at elevated temperature or microwave irradiation. The cyclic voltammetry measurements show a strong donor pyrazole ring, and a better acceptor ability of the fullerene moiety than the parent C<sub>60</sub> (538). Treating fullerene C<sub>60</sub> with mesitonitrile oxide in toluene gives fullerene–nitrile oxide adduct, which is supposed to be useful for electrical and optical components (539).

The methodology required for the construction of fullerene-based nanostructures including fullerenes and rigid spacers has been investigated. Such assemblies require the ability to control the regiochemistry of multiple addition of fullerenes. The kinetic and thermodynamic isomer distribution of nitrile oxide dipolar additions to C<sub>60</sub>, as well as the separation and characterization of the major species have been reported (540, 541). The structures of such fullerene isoxazolines, as nano-scale connectors, have been optimized by using the semiempirical PM3 calculations. Also the regiochemistry of the second addition of a nitrile oxide to a fullerene isoxazoline has been considered. The results indicate that fullerene isoxazoline derivatives are useful nano-scale connectors with the possibility of attaching spacer units in a specific angular arrangement (542, 543).

Novel C<sub>60</sub> and C<sub>70</sub> adducts have been synthesized by [2 + 3] cycloadditions of the appropriate nitrile oxides. Variations in the distance and geometry of the donor

and acceptor substituents have been shown to have an influence on the redox behavior of the fullerene adducts in cyclic voltammetry experiments (544). Thus, 3-R-substituted fullereno[1,2-d]isoxazolines **465** (R = 2,4,6-trimethoxyphenyl, 2,4,6-trimethoxystyryl, 2-(2-thienyl)phenyl) shows shifts of about 30mV or 40mV to more negative values as compared with the reference compound (R = H). Strong acceptor properties have been detected in the compounds with R = CH=C(CO<sub>2</sub>Me)<sub>2</sub>, which show a positive shift of 30mV relative to R = H.

**465**

The data demonstrate that the electron-transfer rate in donor-substituted fullerenes can be controlled by the electron-releasing property of the substituent as well as by the electronic structure and/or length of the spacer used.

The synthesis of C<sub>60</sub>-based dyads in which the C<sub>60</sub> core is covalently attached to a strong electron acceptor moiety, has been carried out by 1,3-dipolar cycloaddition of *in situ* generated nitrile oxides with C<sub>60</sub>. As expected, the obtained adducts show reduction waves of the fullerene core that are anodically shifted in comparison with the parent C<sub>60</sub>. This indicates that they are remarkably stronger acceptors than C<sub>60</sub>. The electron acceptor organic addend also undergoes an anodic shift due to the electronic interaction with the C<sub>60</sub> moiety (545).

Properties of FeC<sub>60</sub> solid samples have been studied by X-ray diffraction, <sup>57</sup>Fe Mossbauer spectroscopy and magnetic measurements to stimulate the interaction of Fe with fullerene. FeC<sub>60</sub> samples have been prepared by decomposition of the 1,3-dipolar cycloadduct of the fullerene and ferrocene nitrile oxide. The components exhibit super paramagnetic properties originating from an interaction between FeC<sub>60</sub> complexes within the nano-particles. Each nano-particle consists of hundreds to thousands complexes (546).

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