NITRILE OXIDES, NITRONES, AND NITRONATES IN ORGANIC SYNTHESIS

Novel Strategies in Synthesis

Second Edition

Edited by

Henry Feuer

WILEY-INTERSCIENCE

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CONTENTS

SERIES FOREWORD

The beginning of aliphatic nitro chemistry goes back to 1872 when V. Meyer and O. Stueber achieved the synthesis of 1-nitropentane by reacting 1-iodopentane with silver nitrite. This report led to an impetus of research in the field, resulting in numerous publications.

Another important development in the field was the discovery of the vapor-phase nitration in the 1930s by H. Hass and his students at Purdue University. It led in 1940 to the commercial production of lower molecular weight nitroalkanes [C1 to C4] at a pilot plant of the Commercial Solvents Corporation in Peoria, Illinois. In the organic nitro chemistry era of the fifties and early sixties, a great emphasis of the research was directed towards the synthesis of new compounds that would be useful as potential ingredients in explosives and propellants.

In recent years, the emphasis of research has been directed more and more toward utilizing nitro compounds as reactive intermediates in organic synthesis. The activating effect of the nitro group is exploited in carrying out many organic reactions, and its facile transformation into various functional groups has broadened the importance of nitro compounds in the synthesis of complex molecules.

It is the purpose of the series to review the field of organic nitro chemistry in its broadest sense by including structurally related classes of compounds such as nitroamines, nitrates, nitrones and nitrile oxides. It is intended that the contributors, who are active investigators in various facets of the field, will provide a concise presentation of recent advances that have generated a renaissance in nitro chemistry research.

In this multi-authored volume are presented the important topics of nitronates, nitrones and nitrile oxides. Their significance in synthesis as starting materials and as reactive intermediates has grown considerably since 1988 in which year Dr. Torssell's monograph was published by Wiley-VCH.

Henry Feuer
Purdue University

LIST OF ABBREVIATIONS

AIBN	2,2’-azo-bis-iso-butyronitrile
AN	aliphatic nitro
AR	aminyl radical
ASIS	aromatic solvent induced shift
BIGN	*N*-benzyl-2,3-o-isopropylidene-D-glyceraldehyde nitrone
BINOL	2,2’-dihydroxy-1,1’-binaphthyl
Boc	*tert*-butyldimethylsilyl
BOX	bisoxazoline
BSTFA	N,O-bis(trimethylsilyl)trifluoroacetamide
CAN	cerium ammonium nitrate
Cbz	carbobenzyloxy
CIPE	complex Induced Proximity Effect
CRP	controlled radical polymerization
CVA	cyclic voltammogram
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DFT	density functional theory
DIBALH	diisobutylaluminium hydride
DIPT	diisopropyl (*R,R*)-tartrate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMD	dimethyldioxiran
DMF	dimethylformamide
DMPO	5,5-dimethylpyrroline *N*-oxide
DMSO	dimethylsufoxide
EDTA	ethylenediaminetetraacetic acid
EO	electrochemical oxidation
EPR	electron paramagnetic resonance
ES	embryonic stem
ESR	electron spin resonance
EWG	electron-withdrawing groups
FAB	fast atom bombardment
FMO	frontier molecular orbital
Fmoc	*N*-fluorenylmethoxycarbonyl
FSPE	fluorous solid phase extraction
HFI	hyperfine interaction
HIV	human immunodeficiency virus
HMDN	α-(2-hydroxy-4-methacryloyloxyphenyl)(2,6-dimethylphenyl)nitrone

HMPA	hexamethylphosphoramide
HMPN	α-(2-hydroxy-4-methacryloyloxyphenyl)-*N*-phenylnitrone
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
INAC	intramolecular nitrone-alkene cycloaddition
INEPT	insensitive nuclei enhanced by polarization transfer
INOC	intramolecular nitrile oxide cycloaddition
INR	iminonitroxyl radical
LA	Lewis acids
LDA	lithium diisopropylamine
LUMO	lowest unoccupied molecular orbital
MAD	methyl acetylenedicarboxylate
m-CPBA	*meta*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MIP	2-methoxyisopropyl
MMA	methyl methacrylate
MOMO	methoxymethoxy
Ms	mesyl
MTO	methyltrioxorhenium
MWD	molecular-weight distribution
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NDMA	*N*-methyl-D-aspartic acid
NIS	*N*-iodosuccinimide
NMO	methylmorpholine *N*-oxide
NMP	nitroxide-mediated polymerization
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NR	nitroxyl radical
OLED	organic light emitting diode
Oxone	potassium peroxymonosulfate
PBN	α-phenyl-*N*-*tert*-butylnitrone
PCWP	peroxotungstophosphate
PDC	pyridinium dichromate
PDT	photodynamic therapy
PEDC	1-phenyl-2-[(S)-1-aminoethyl]-*N,N*-diethylcyclopropanecarboxamide
PEG	polyethylene glycol
PET	photosensitive electron transfer
PMIO	1,2,2,5,5-pentamethyl-3-imidazoline-3-oxide
PPAR	peroxisome proliferator-activated receptor
PPC	polyperoxo complex
PSPO	2-phenylsulfonyl-3-phenyloxaziridine
PTK	protein tyrosine kinase
QSAR	quantitative structure-activity relationship
RA	radical anion

RC	radical cation
SA	spin adduct
SENA	silyl esters of nitronic acid
SET	single electron transfer
SMEAH	sodium bis(2-methoxyethoxy)aluminium hydride
ST	spin trap
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosiliconate
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylethylenediamine
TMINO	isoindoline nitrone 1,1,3-trimethylisoindole *N*-oxide
TMIO	isoindoline nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxy
TMPO	2,2,5,5-tetramethylpyrroline *N*-oxide
TMS	trimethylsilyl
TMSOTf	trimethylsilyltriflate
TOX	trioxazoline
TPAP	tetrapropylammonium perruthenate
TPS	*tert*-butyldiphenylsilyl
UHP	urea hydrogen peroxide

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 Torssell (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, RNCO, are derivatives of fulminic acid ($R = H$). 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 C–N and N–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 $N^{+}{-}X^{-}$ 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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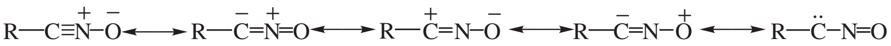


$$R{-}C{\equiv}\overset{+}{N}{-}\overset{-}{O} \longleftrightarrow R{-}\overset{-}{C}{=}\overset{+}{N}{=}O \longleftrightarrow R{-}\overset{+}{C}{=}N{-}\overset{-}{O} \longleftrightarrow R{-}\overset{-}{C}{=}N{-}\overset{+}{O} \longleftrightarrow R{-}\ddot{C}{-}N{=}O$$

Scheme 1.1

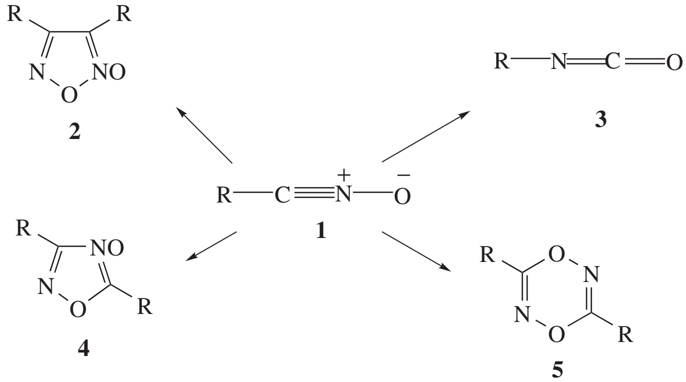
Unstable nitrile oxides XCNO, X = ONC, NC, Cl, Br, and Me, were generated and studied in the gas phase by He I photoelectron spectra (10) and by other methods, such as low resolution mid-IR, high-resolution IR, and microwave spectroscopy (11, 12). In particular, the unstable BrCNO molecule and its stable 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_3CNO 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-thiophenecarbonitrile oxide (21), β,β-diphenylacrylonitrile oxide (22), and (dimorpholinophosphoryl) 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 triphenylacetonitrile 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

$$\text{R-CH=NOH} \xrightarrow[\text{NaOH}]{\text{NaOHal}} [\text{R-C(Hal)=NOH}] \longrightarrow \text{R-CNO}$$

$$\text{Hal} = \text{Cl, Br}$$

Scheme 1.3

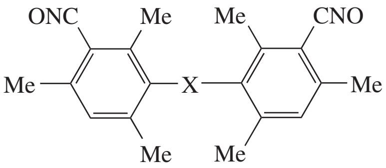
allowed one to hydrolyse the mentioned organosilicon nitrile oxide (27) and to introduce fulminic acid generated in some reactions (28). Nevertheless, because of the explosive nature of metal fulminates, their synthetic use is very limited and no data on their application for generation or formation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

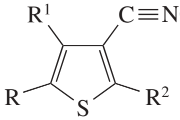
The latter procedure was used in syntheses of stable nitrile oxides such as β,β-diphenylacrylonitrile oxide and 2,6-diphenylbenzonitrile oxide (22), a series of functionally substituted 2,6-dimethylbenzonitrile oxides (29), as well as 2,4,6-triethylbenzene-1,3-dicarbonitrile oxide (29), stable bis(nitrile 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).



6

X = $(CH_2)_n$, where $n = 0, 1, 2, 6$; S; C=CH_2; C=CHEt

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).



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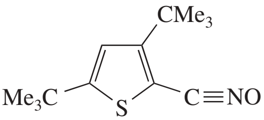


8

$R = R^2 = Me, R^1 = H, Alk;$
$R = H, Me, MeO, MeSO_2, R^2 = H, Br, R^1 = SMe, SO_2Me, OMe$

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 BrCNO was generated in the gas phase from dibromoformaldoxime by pyrolysis or by a chemical reaction with HgO(s) or NH_3(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-isoxazoledicarboxylic 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 RCCl=NOH (R = Ar, 5-nitro-2-furyl, PhCO, *t*-Bu) as precursors of nitrile oxides. However, most useful for both two-step and one-step (usually in the presence of Et_3N) 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 $(SnBu_3)_2O$ or $SnPh_4$ (48, 49). The reaction proceeds under mild conditions, O-stannylated aldoximes like $RCH{=}NOSnBu_3$ 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).

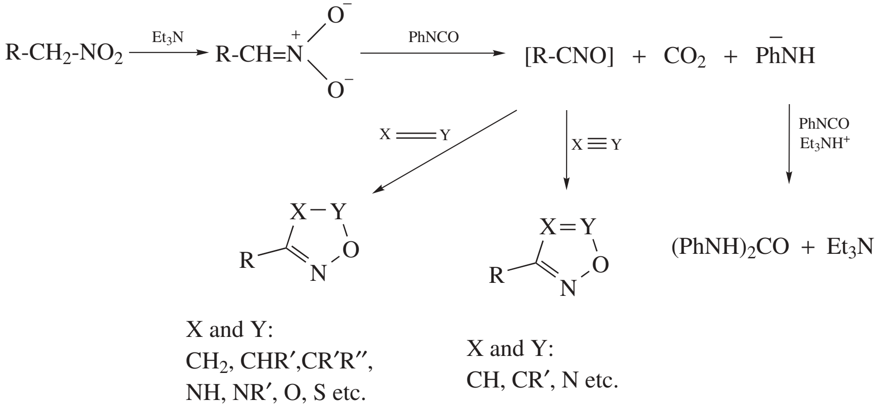
Direct oxidation of oximes is prospective promising procedure for the generation of nitrile oxides. Mercury(II) acetate (54), dimethyldioxirane (55), ceric ammonium nitrate (56), and hypervalent iodine compounds, such as iodobenzene dichloride (57), iodosylbenzene (58), diacetoxy iodobenzene (59) were 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 Et_3N 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 Et_3N, 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 $POCl_3$, AcCl, Ac_2O, BzCl, and $MeSO_2Cl$ (64). A rather "exotic" *p*-toluenesulfonyl chloride – K_2CO_3 – 18-crown-6 system was used in the synthesis of annulated Δ^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

nitrates 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 β-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_2O mixture in the presence of a catalytic amount of strong mineral acid, for example, H_2SO_4, 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).

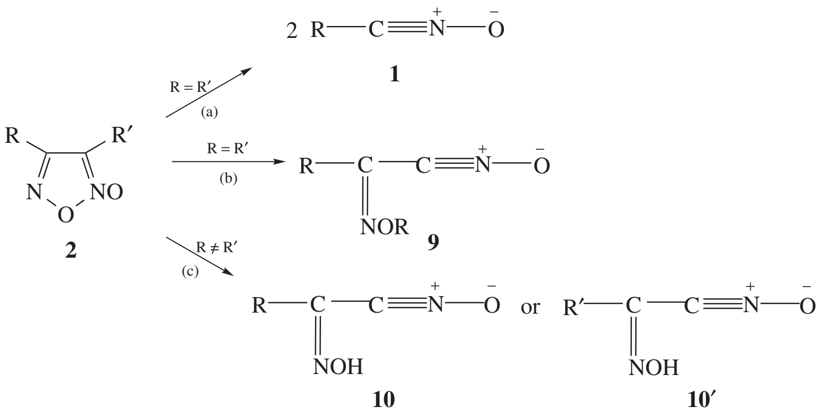
Generation of nitrile oxides can also proceed by the action of “neutral” or basic reagents, for example, *tert*-butyl carbonate (72) or 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, both in the presence of a catalytic amount of 4-(dimethylamino)pyridine (73), the latter with microwave 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).

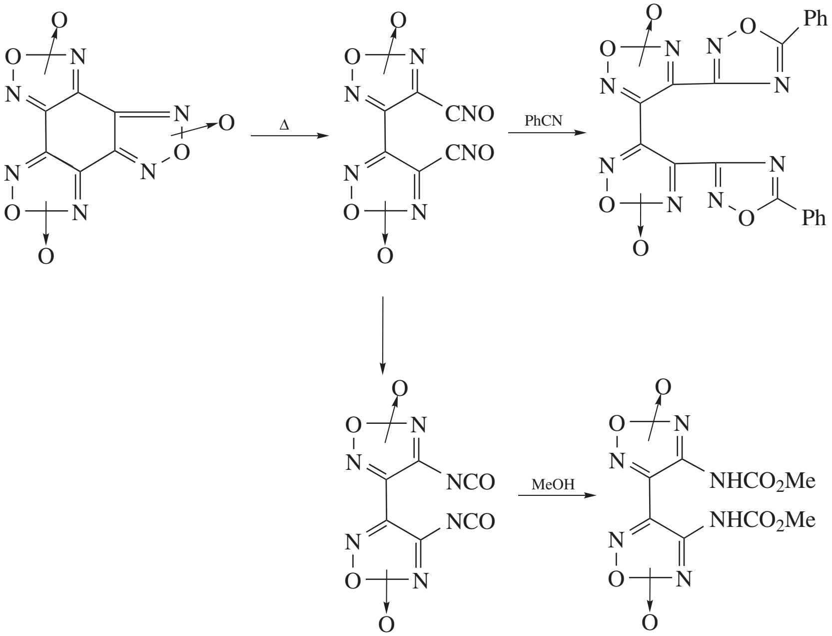
1.2.3. Formation by Cycloreversion

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 α-acyloximinonitrile oxides **9** as well as fragmentation [route (c)] leading to a mixture of α-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).

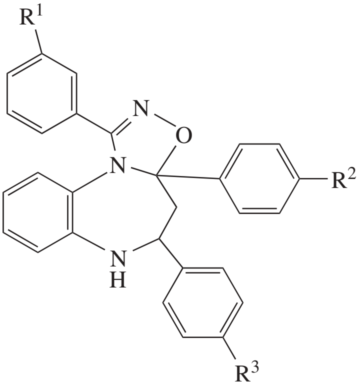


Scheme 1.5



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).



11

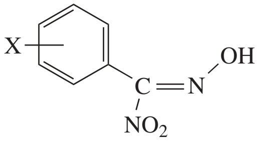
(R^1 = H, Br; R^2= H, OMe; R^3 = H, OMe)

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 $RC(NO_2)=NO_2K$ [R = Ph, $3\text{-}O_2NC_6H_4$, $3,5\text{-}(O_2N)_2C_6H_3$, $4\text{-MeO-}3,5\text{-}(O_2N)_2C_6H_2$, EtO_2C, Me, MeO_2C] was carried out in the generation of nitrile oxides RCNO (84, 85). Using ^1H, ^{13}C and ^{14}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.

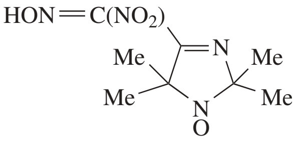
Z-Acetonitrolic acid rapidly loses NO_2^- to form unstable acetonitrile oxide, which could be detected by monitoring its subsequent reactions (86). Arylnitrolic acids **12** (X = *p*-Cl, *m*-NO_2, *o*-NO_2) exist in the *E*-configuration and undergo slow loss of NO_2^- to give nitrile oxides. Subsequently it was shown (87) that nitrolic acids are converted to nitrile oxides in practically quantitative yields under neutral conditions (heating in THF).



12

(X = *p*-Cl, *m*-NO_2, *o*-NO_2)

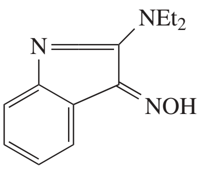
Thermolysis of a stable radical 4-[(hydroxyimino)nitromethyl]-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl **13** gives the corresponding spin-labeled nitrile oxide. It was also identified in isoxazolines formed in cycloadditions with olefins (88).



13

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

Nitro(imidoyl)ketene $PhN{=}C(NEt_2)C(NO_2){=}CO$ eliminates CO_2 on heating and rearranges to 2-diethylamino-3-hydroximino-3*H*-indole **14**, presumably via nitrile oxide $PhN{=}C(NEt_2)C{-}N^+O^-$(90).

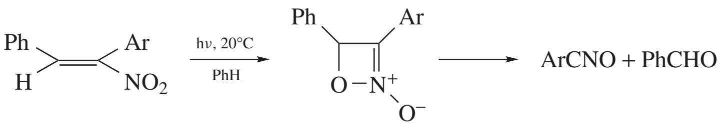


14

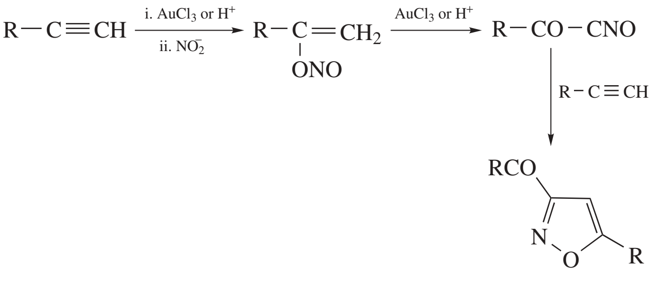
In alkali solutions, 5-nitro-2-furaldehyde forms an anion of (5-nitrofuran-2-yl)methanediol, which undergoes an irreversible redox ring-opening reaction to give mono(nitrile oxide) of α-ketoglutaconic acid $HO_2CCOCH{=}CH{-}CNO$,°o the latter was identified as furoxan (91).

Very interesting transformations were reported in terminal alkynes RC≡CH (R = 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 ($AuCl_3$ or H^+) and of a nucleophile ($NO_2{}^-$) 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 N_2O_4 (94).



Scheme 1.7



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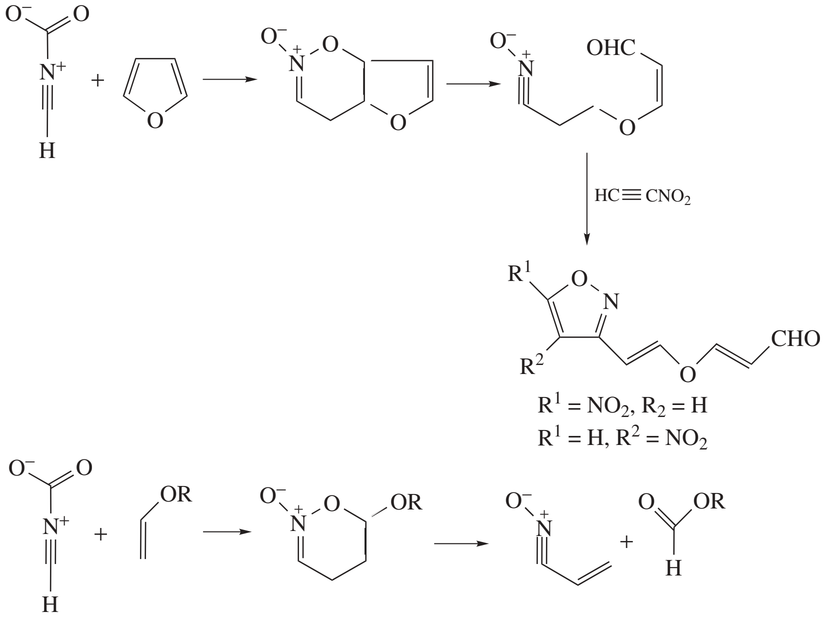
Scheme 1.8



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 β-elimination of methanol from *E*-N-methoxy-N-(methoxycarbonylmethylene)amine N-oxide, $MeO_2CCH{=}N(OMe)O$, in the presence of a catalytic amount of boron trifluoride etherate (96).

Phosphorylated and thiophosphorylated diazo compounds, $i\text{-}Pr_2P(X)C(N_2)SiMe_3$ ($X = O, S$) react with nitrosyl chloride to give α-nitroso-diazo derivatives which rapidly eliminate nitrogen to form i-$Pr_2(X)CNO$ (97). Similarly phosphorylated nitrile oxide, $R_2P(O)CNO$ (R = morpholino) was prepared by treatment of $R_2P(O)CHXCHO$ (R = morpholino; X = Cl, Br) with HNO_2 in 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).

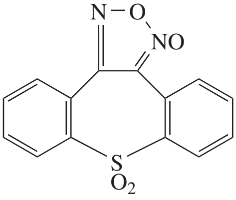
1.3. REACTIONS OF NITRILE OXIDES

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** (R = H, Me) at reflux in benzene (102).



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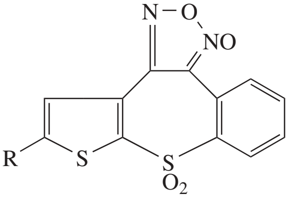
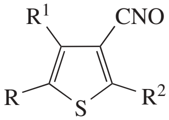


17

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** ($R = R^1 = R^2 = Me$; $R = R^2 = Me$, $R^1 = i$-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 $R^2 = SO_2Me$, Br) dimerized to form furoxans **19**.



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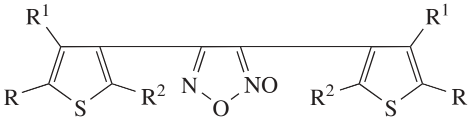
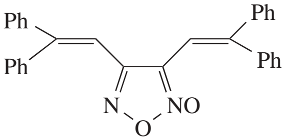


19

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



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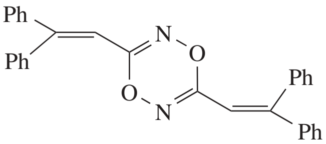
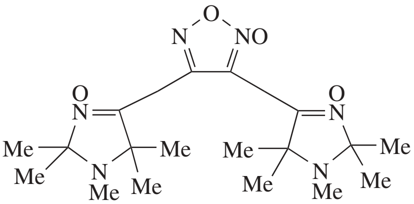


21

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.



22

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 $(4\text{-}BrC_6H_4)_3N^+\ SbCl_6^-$ (109).

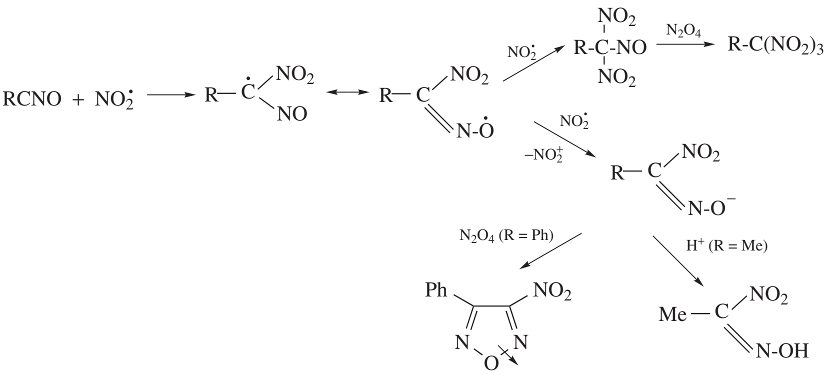
1.3.2. Deoxygenation

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 furoxannitrolic 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).

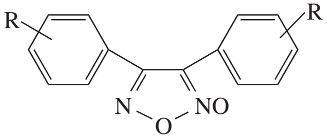
Deoxygenation by NO proceeds rather slowly, and nitrile oxides take part simultaneously in two other reactions: (a) dimerization to furoxans **23** and (b) interaction with NO_2 which is formed in the reaction, to give aryltrinitromethanes. The most unstable of the known arenecarbonitrile oxides, benzonitrile 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

$$ArCNO + NO^{\bullet} \longrightarrow [Ar\text{-}\dot{C}{=}N\text{-}N{=}O] \longrightarrow ArCN + NO_2^{\bullet}$$

Scheme 1.11

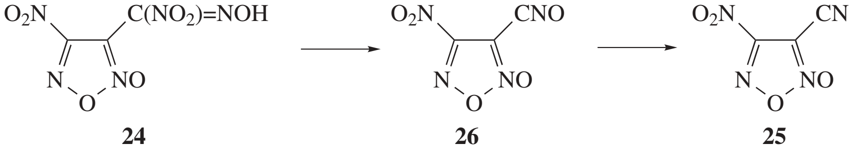


23 (R = H, 2-, 3-, 4-O_2N)

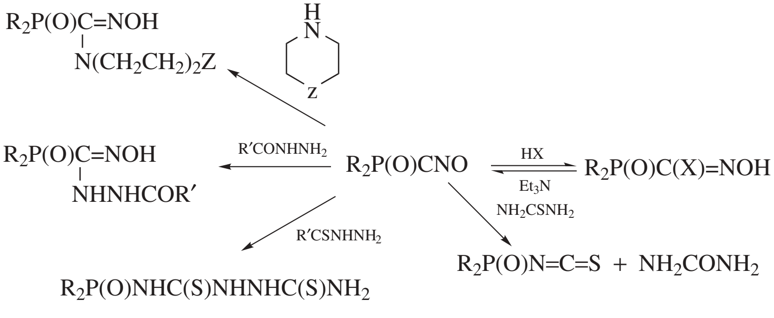
Investigation of the reaction of furoxannitrolic acids with nitrogen tetroxide (113) showed that the first step is the formation of the corresponding intermediate nitrile oxides followed by their transformations. Thus, treating nitrolic acid **24** with N_2O_4 in $CHCl_3$ resulted in furoxancarbonitrile **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 Tranformations

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



X = Cl, I; Z = O, CH_2
R = morpholino; R′ = Ph, NH_2

Scheme 1.13

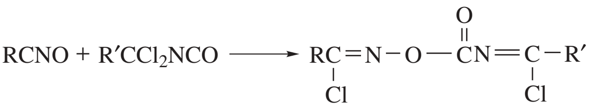
of the nucleophile (by an anion as a limiting case), while its positively polarized or charged part (proton in the simplest case) adds to the oxygen atom of the fulminate moiety. 1,3-Addition reactions proceed with halogen, N-, O-, S-, C-, and other nucleophiles. The adducts formed might undergo further 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-aminoantipyryne 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 $(i\text{-PrO})_2P(O)C(:NOH)OMe$, which is formed as a 1:1 mixture of *E* and *Z* isomers.

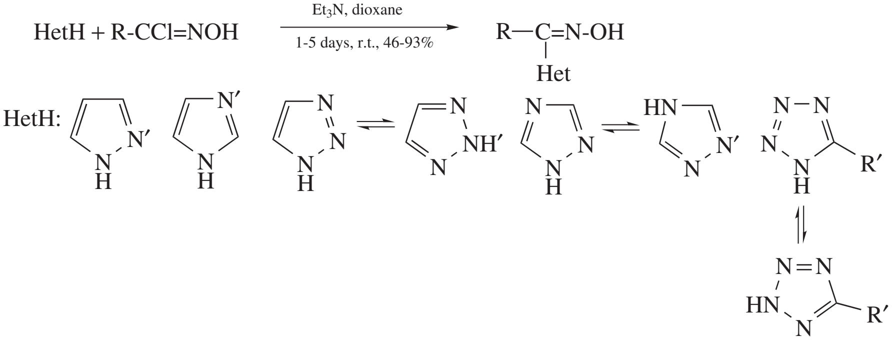
3-Arylsydnone-4-carbonitrile oxides add hydrogen chloride to give the corresponding hydroximoyl chlorides on treatment with HCl/EtOH (115). Reactions of nitrile oxides, RC−NO (R = mesityl, duryl, p-$O_2NC_6H_4$, PhCO) with 1,1-dichloroalkyl isocyanates, $R'CCl_2NCO$ ($R' = CCl_3$, CF_3) in benzene containing Et_3N lead by [2 + 3] cycloaddition (116) to the corresponding O-acylated chloro-oximes $RCCl{=}NO_2CN{=}CClR$ 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



$$RCNO + R'CCl_2NCO \longrightarrow \underset{Cl}{RC}=N-O-\overset{O}{\overset{\|}{C}}N=\underset{Cl}{C}-R'$$

Scheme 1.14



R = t-Bu,Ph$_2$CH, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2,4,6-Me$_3$C$_6$H$_2$, 2-pyridyl

R′ = H, Me, Et, i-Pr, Ph, 2-O$_2$NC$_6$H$_4$, PhH$_2$, MeO, MeS, EtS, Me$_2$NH, PhNH, NH$_2$

Scheme 1.15

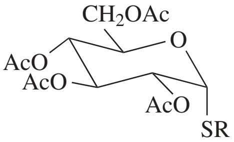
1,2,4-triazoles or tetrazoles and its 5-substituted derivatives give hydroximoylazoles (Scheme 1.15) on addition to nitrile oxides, which are generated from the corresponding hydroximoyl chlorides (117).

The 1,3-dipoles were generated by the addition of Et$_3$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]mesitylenecarboamidoxime (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).

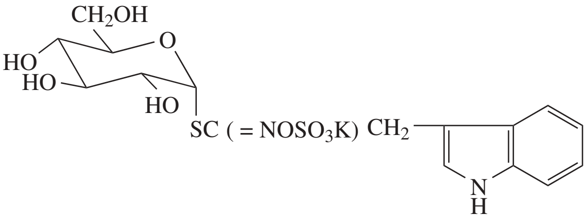
Addition of ammonia as a model nucleophile to nitrile oxides was studied by a semiempirical MNDO method, for fulminic acid and acetonitrile oxide (121). The reaction is exothermic and proceeds in two steps. The first (and rate-determining) step is the formation of a zwitterionic structure as intermediate. 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 α-glucosinolates **27** ($R = CR^1{=}NOH$; R^1 = Ph, CH_2Ph, CH_2CH_2Ph, (*E*)-CH=CHPh, 3-indolylmethyl) was prepared by addition reactions of thiol **27** (R = H) with nitrile oxides (123). The indolyl-substituted glucosinolate was then converted to α-glucobrassicin **28**.



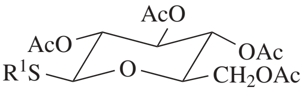
27

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



28

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

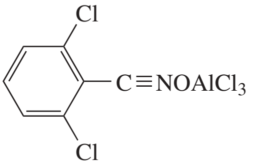


29

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 phenylacetonitrile 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_2Zn catalyzed by $BF_3.OEt_2$ afford ketoximes ArC(:NOH)R (Ar = 2,6-$Cl_2C_6H_3$, 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 $EtO_2CC{\equiv}NO$ 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-$Cl_2C_6H_3CCl{=}NOH$ with $AlCl_3$ gives the nitrile oxide–Lewis acid complex **30**, which reacts with benzene to afford oxime **31** in 70% yield (127).



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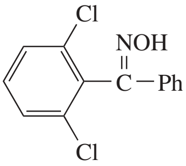


31

Nitrile oxide–BF_3 complexes can also be used as electrophilic moieties with aromatic systems. Introducing BF_3 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:$NNMe_2$ (R = 4-$O_2NC_6H_4$, MeCO, MeC (:NOH)). The reaction is performed on treatment of oximes with CH_2:$NNMe_2$ in the presence of Et_3N 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 isoxazolines 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 isoxazolines via a 1,3-dipolar cycloadditions is elaborated. Poly(ethylene glycol)-supported alkyne or alkene react with nitrile oxides, generated *in situ* from aldoximes 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 isoxazolines 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

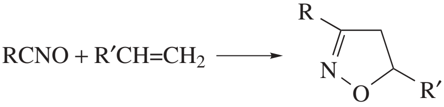
4-chlorobenzhydroximoyl chloride with dimethyl 2-butenedioate and dimethyl acetylenedicarboxylate. Cycloadditions of mesitonitrile oxide to various dipolarophiles in supercritical carbon dioxide were studied. The magnesium bromide-mediated cycloaddition to pent-1-en-3-ol gave higher stereoselectivity 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, ω (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 α,β-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



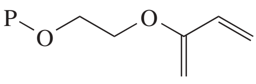
Scheme 1.16

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 Unsubsituted 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 (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 subsituent 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 N,N’-dioxide (generated from *N*,*N*’-dihydroxy-1,4-benzenedicarboximidoyl dichloride) to polyethylene glycol-supported 2-propenoic acid 2-hydroxyethyl ester **32** (**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.



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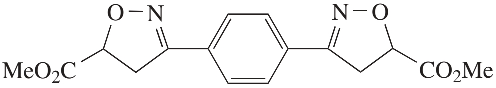
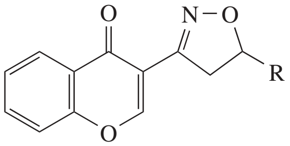


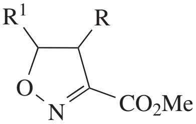
33

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).



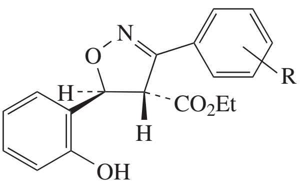
34 (R = CN, Ph, *p*-Tol, CH_2Br, Ac)

Reaction of methoxycarbonylformonitrile oxide (generated from $MeO_2CCCl{=}NOH$ in the presence of Et_3N in Et_2O) with methyl undec-10-enoate gave 90% of isoxazoline **35** [$R = (CH_2)_8CO_2Me$, $R^1 = H$] whereas a similar reaction with methyl oleate gave a 40% isomeric mixture of **35** [R = 1-octyl, $R^1 = (CH_2)_7CO_2Me$ and $R = (CH_2)_7CO_2Me$, R^1 = 1-octyl] (176).

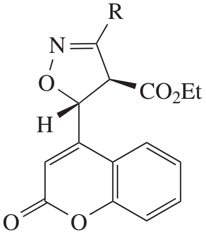


35

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** ($R = 4\text{-}MeOC_6H_4$) (85%) (179).



36 (R = H, 4-Me, 2,4,6-Me_3)



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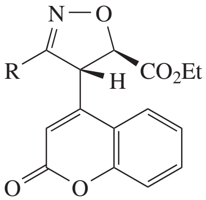
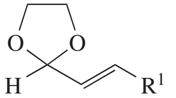


38

1,3-Dioxolanes **39** derived from α,β-unsaturated aldehydes react with nitrile oxides R^2CNO 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 cycloadditon reactions of nitrile oxides and α,β-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).



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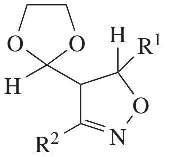
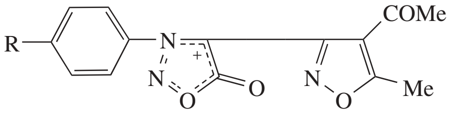


40

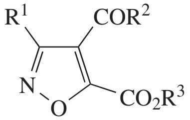
R^1 = Ph, Me, Pr; R^2 = Ph, CO_2Et, Et

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-carbohydroximic acid chlorides react with acetylacetone in the presence of Et_3N to give arylisoxazolyl sydnones **41** (182). Cycloaddition of nitrile oxides R^1CNO with β-acylpyruvates, $R^2COCH{=}C(OH)CO_2R^3$, results in izoxazole derivatives **42** (183). β-Acylpyruvates, unlike ordinary β-diketones, show high dipolarophilic reactivity toward nitrile oxides in the absence of base.



41

R = H, Me, EtO

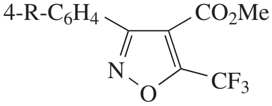


42

R' = CF_3, Ac, CO_2Et, Bz, Ph, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 2,5-$Cl(O_2N)C_6H_3$, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$, $R^2 = R^3$ = Me; R^1 = 2,6-$Cl_2C_6H_3$, R^2 = Ph, Et, R^3 = Me

Other compounds, with C=C bond activated by an electron-withdrawing group and bearing a good leaving group in the β-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 β-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 β-bromo-β-trifluoromethylacrylate, (*Z*)-$F_3CCBr=CHCO_2Me$, was used in the solid-phase synthesis of trifluoromethylated isoxazolecarboxylates using aromatic nitrile oxides generated *in situ* from hydroxymoyl chlorides ($4\text{-}RC_6H_4C(Cl)=NOH$) and Et_3N, followed by removing the resin with trifluoroacetic acid. Methylation of the free acid with diazomethane in diethyl ether gave aryltrifluoromethylisoxazolecarboxylates **43** as major products in 21% to 48% yields and in 8:1–14:1 regioselectivities (186).



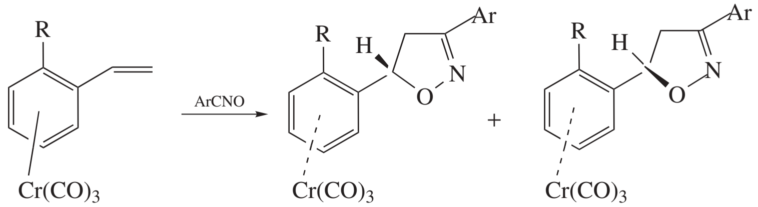
43

R = MeO, EtO, Me, H, Cl, PhO, $PhCH_2O$

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 $MgBr_2$ (188, 189), achiral alkenes with Lewis acid complexes with chiral ligands, the role of Lewis acid being played by $MgBr_2$ (190), Et_2Zn (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_2-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 γ-oxygenated-α,β-unsaturated phenyl sulfones (206), chiral (α-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



44 **45**

Ar = 3,5-$Cl_2C_6Me_3$

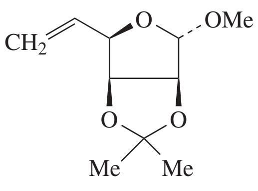
	44		45
R = MeO	80	:	20
Me	98	:	2
Cl	96	:	4

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 tricarbonylchromium 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 π face opposite to $Cr(CO)_3$ and the reactive rotamer of the dipolarophile is transoid (213).

π-Facial selectivity occurs in regio- and diastereoselective cycloaddition reactions of benzonitrile oxide and ethoxycarbonylformonitrile oxide to α-methyl dideoxy-D-lyxo-hexenofuranoside **46** giving isoxazolines **47** (R = Ph, CO_2Et), respectively (214).



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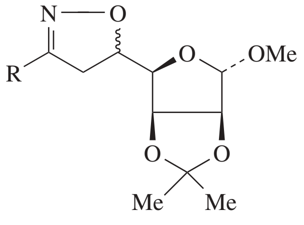

47

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.