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ADVANCES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM ALIPHATIC NITRO DERIVATIVES. A REVIEW

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The literature on the synthesis of heterocyclic compounds from aliphatic nitro derivatives in the past decade has been summarized.

INTRODUCTION

Aliphatic nitro compounds are common starting materials for the synthesis of various types of organic compounds. This was stated in 1979 by Seebach et al. [1] in a review entitled "Aliphatic nitro compounds – ideal intermediates." Aliphatic nitro compounds play an extremely significant role in the synthesis of various heterocyclic systems.

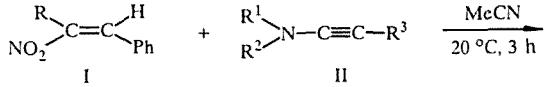
In our previous review [2], data were summarized on the synthesis of heterocyclic products from aliphatic nitro compounds published up to 1982 inclusively. Tartakovskii [8] has examined the principles for the construction of heterocyclic systems from nitronic acid esters and unsaturated compounds and presented a bibliography up to 1982.

In the present review, data on the synthesis of heterocyclic compounds from aliphatic nitro compounds published in the past decade have been summarized. In light of the appearance of a review pertaining to heterocyclic synthesis by 1,3-dipolar cycloaddition involving nitroalkenes in 1990 [4], only those studies on this reaction published after 1989 are given in the present work.

1. SYNTHESIS OF NITROGEN HETEROCYCLES

There is no information in the literature on the synthesis of three-membered ring nitrogen compounds using nitro compounds.

Only two studies have been published on the preparation of azetines, which are four-membered ring nitrogen compounds, using nitro compounds. Thus, the reaction of nitroalkenes I with acetylene derivatives II gives azetine N-oxides II as diastereomer mixtures in 43-61% yield. Elburg et al. [5] have proposed that the reaction involves formation of intermediates IV:*



I II

*The substituents in the starting compounds and reaction products in the reaction schemes presented in the text are indicated by symbols Alk, Ar, and R. The symbol R is used for compounds, in which there are different substituents (Alk and Ar) and functional groups at the same carbon atoms.

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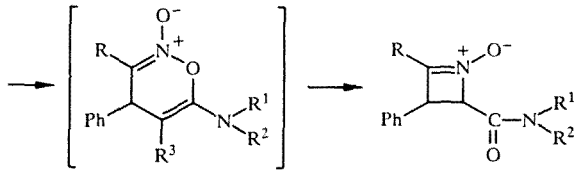


IV III

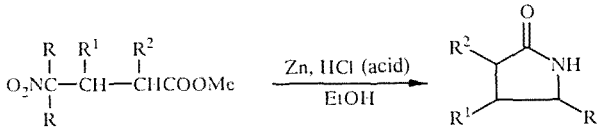
The synthesis of 1-substituted 2-nitromethylenediazetidines by the reaction of the corresponding N-monosubstituted diamines with 1,1-bis(methylthio)-2-nitroethylene, $(MeS)_2C{=}CHNO_2$ (V), has been reported in a Japanese patent [6].

The most interesting and numerous publications are related to the synthesis of various five- and six-membered heterocycles, including compounds with such rings in condensed systems.

1.1 SYNTHESIS OF FIVE-MEMBERED HETEROCYCLES

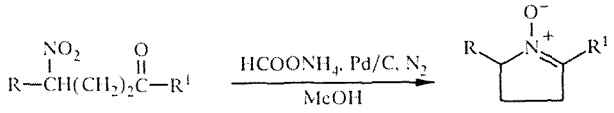
The preparation of five-membered nitrogen heterocyclic compounds has been reported by numerous workers.

The reduction of γ-nitrocarboxylic acids by the action of zinc and hydrochloric acid in ethanol leads to derivatives of α-2-pyrrolidone (VI) [7, 8]:

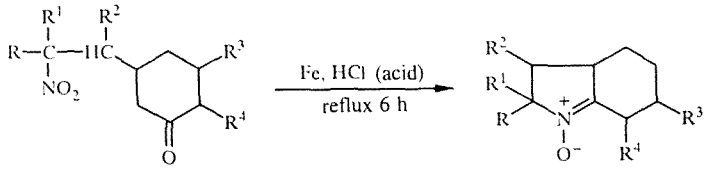


VI

γ- (IX) and σ-Nitroketones (X) give pyrroline N-oxides VII and VII upon the action of ammonium formate in the presence of Pd/C [9, 10] or the action of iron and hydrochloric acid [11] in 36-77% yield:

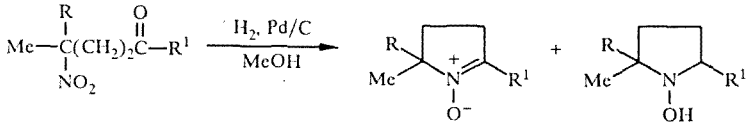


IX VII



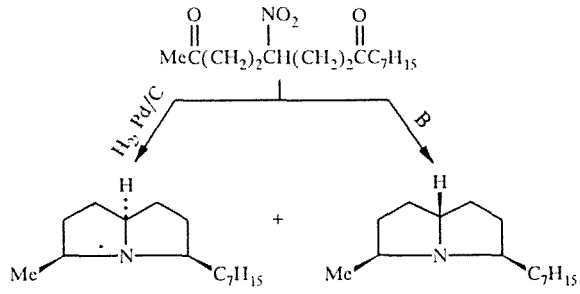
X VIII

The hydrogenation of γ-nitroketones XI in the presence of Pd/C in methanol leads to mixtures of pyrroline N-oxides XII and N-hydroxypyrrolidines XIII (31-75% yields) [12]:



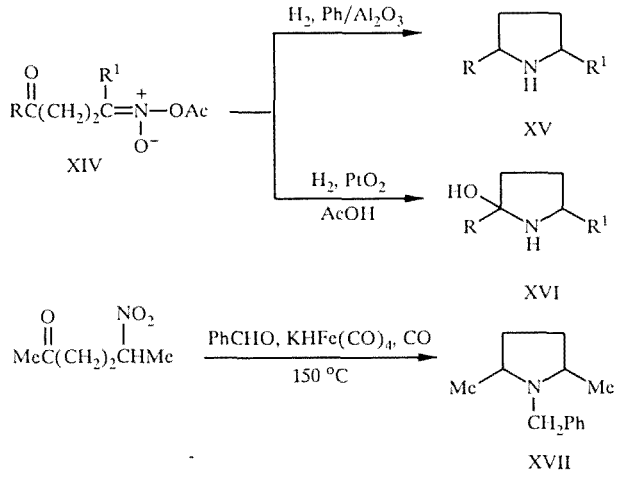
XI XII XIII

5-Nitropentadecane-2,8-diones is converted into a mixture of 5-epixenovenin (65% yield) and xenovenin (5%) upon hydrogenation over Pd/C (A) [13, 14]. Only 85% *cis* isomer is formed in the presence of the $NaBH_3CN-NaBH_4-NH_4AOc-KOH-MeOH$ system (B) [14]:

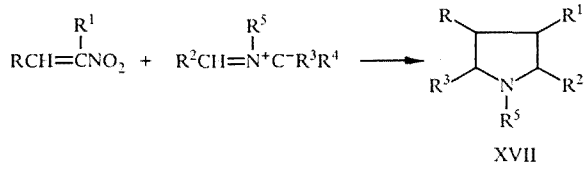


The electrochemical reduction of γ-nitroketones may give derivatives of pyrrolidine, pyrroline, or pyrroline N-oxide [15].

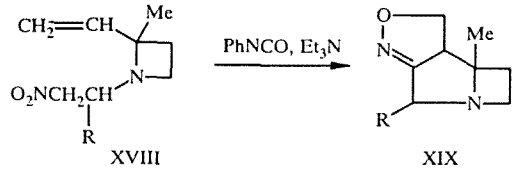
Substituted pyrrolidines XV, XVI, or XVII are formed in 34-68% yield upon the hydrogenation of acetyl derivatives of nitronic acids XIV [16] or the action of $KHFe(CO)_4$ and PhCHO on 5-nitrohexen-2-one [17]:



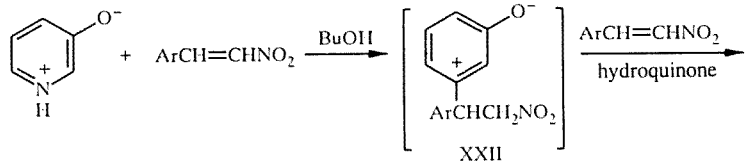
Benhaoua [18, 19], Tischer [20], and Deprez [21] have described the synthesis of derivatives of pyrrolidine XVII by the action of conjugated nitroalkanes with azomethinylids in 19-79% yield:



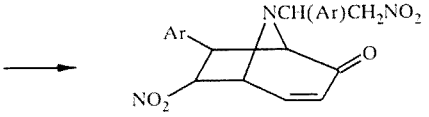
Mixtures of *cis* and *trans* isomers of tricyclic compounds (XIX) containing condensed azetidine, pyrrolidine, and 1,3-isoxazoline systems, were obtained from azetidine derivatives XVIII by an intramolecular 1,3-dipolar cyclocondensation 22]:



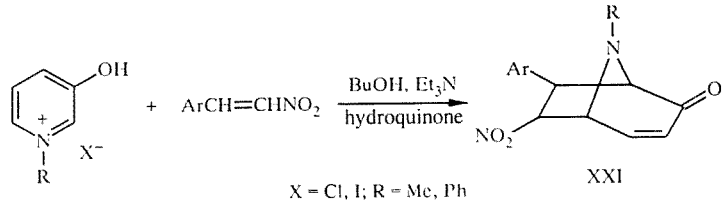
Reactions of conjugated nitroalkenes with 3-hydroxypyridine or with pyridinium salts lead to bicyclic compounds XX and XXI in 45-55% yield. However, the reaction proceeds in two steps when 3-hydroxypyridine is used. 3-Hydroxypyridine initially adds to nitroalkenes through a Michael reaction, while the resultant dipoles XXII react with the starting nitroalkenes to give XX. On the other hand, pyridinium salts undergo a Diels–Alder reaction with one nitroalkene molecule [23]:



XXII



XX

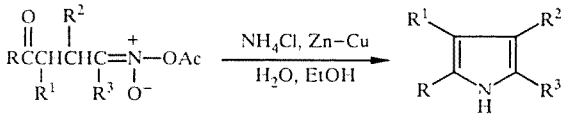


X = Cl, I; R = Me, Ph

XXI

Heating 1-phenyl-2-nitropropene with 1,2-diphenyl-3-methoxycarbonylaziridine in xylene led to 1,2,4-triphenyl-3-methyl-5-methoxycarbonylpyrrole in 44% yield [19].

The action of aqueous NH_4Cl in the presence of Zn–Cu on acetyl derivatives of nitronic acids XXIII leads to substituted pyrroles XXIV in 57-68% yield [24]:



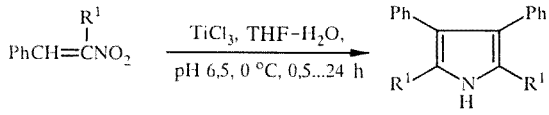
XXIII

XXIV

Boberg et al. [25] used several reduction systems including Zn–Cu/HCl, Zn–ZnCl/HCl, $FeSO_4$/HCl, Na_2S–NH_4OH–NH_4Cl, or $Ph(CH_2)_2SH$ in benzene to convert 1,4-nitroketones into pyrrole derivatives in 36-96% yield.

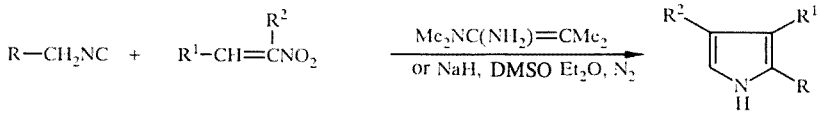
2,3,4-Trisubstituted pyrroles are obtained in 65-85% yield upon treating 1,4-nitroketones $RCH(NO_2)CH(R^1)CH_2C(O)R^2$ with Bu_3P or PhSSPh [26].

Pyrrole derivatives XXV were synthesized by the action of titanium trichloride on nitroalkenes in 3-32% yield [27, 28]:



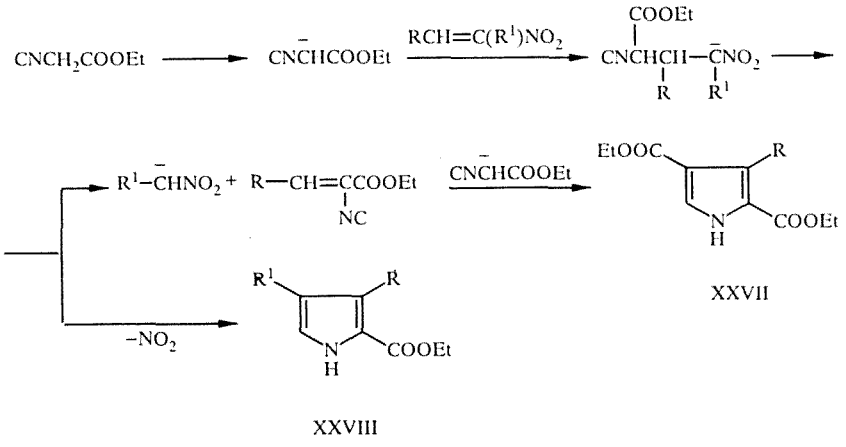
XXV

Conjugated nitroalkenes react with isonitriles in the presence of strong base to give pyrrole derivatives XXVI in 55-97% yield [29, 30]:



XXVI

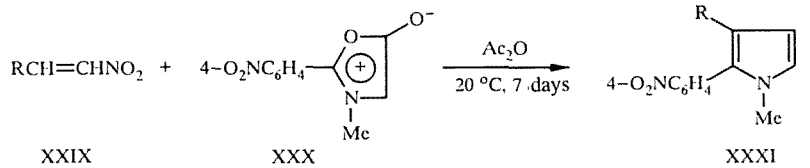
The formation of XXVII in 70-80% yield and XXVIII in 5-8% yield as the result of the reaction of conjugated nitroalkenes with isonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was explained by Ono and Marujama [31] by the following scheme:



XXVII

XXVIII

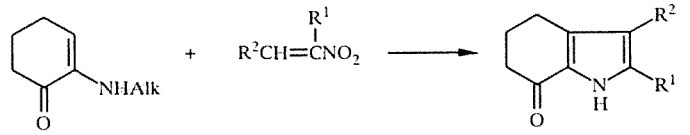
The reaction of nitroalkene XXIX and mesoionic compound XXX gave the corresponding pyrrole derivative XXXI [32]:



XXIX XXX XXXI

$R = [CH(OAc)]_4CH_2OAc$

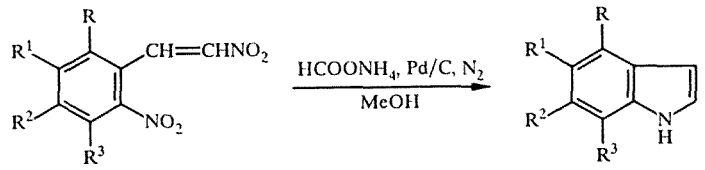
The reaction of aminoketones XXXII with conjugated nitroalkenes in ethanol at reflux or without solvent at 20°C gave XXXIII in 65-80% yield [33]:



XXXII XXXIII

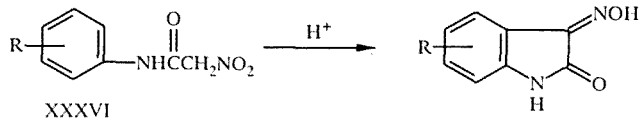
The electrochemical reduction of 2,2'-dinitrostyrene [34] or the action of $TiCl_3$ leads to indole formation in 56% yield [35].

Nitrostyrene derivatives XXXIV are converted to indole derivatives XXXV by the action of ammonium formate in the presence of Pd/C in 52-86% yield [36].



XXXIV XXXV

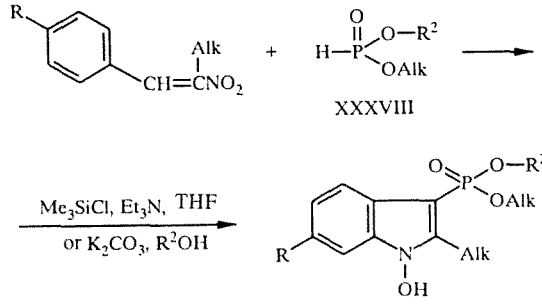
Anilides XXXVI form derivatives of the β-oxime of isatin by the action of F_3CSO_3H or H_2SO_4 in 42-89% yield [37]:



XXXVI

5,6-Dihydroxyindole was synthesized by the hydrogenation of 1-nitro-2-(3,4-dihydroxyphenyl)ethylene in the presence of palladium [38].

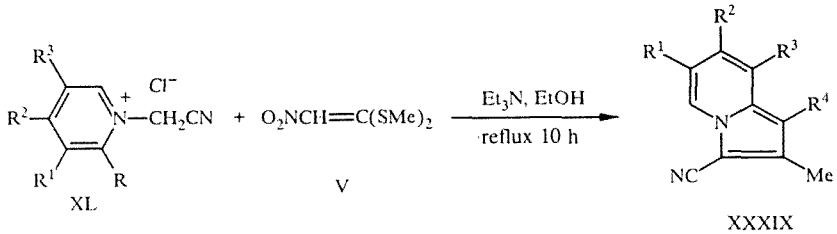
1-Hydroxyindole derivatives (XXXVII) are formed in 50-98% yield in the reaction of nitroalkenes with phosphites and phosphonites (XXVIII) in the presence of base [39, 40]:



XXXVIII

XXXVII

The reaction of pyridinium salts XL with nitroalkene V leads to XXXIX in 47-90% yield [41]:

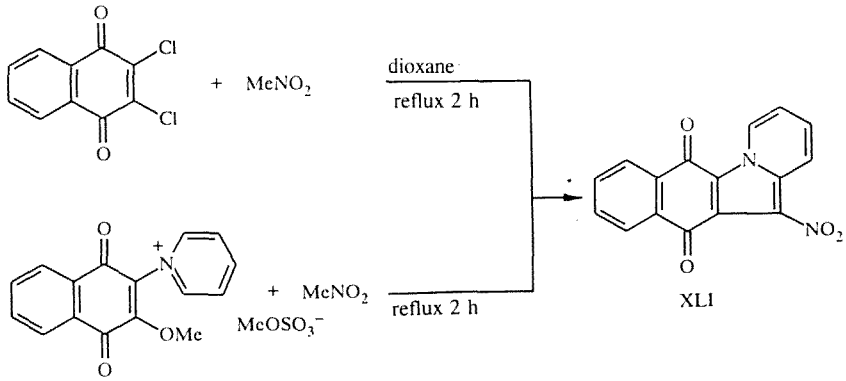


XL

V

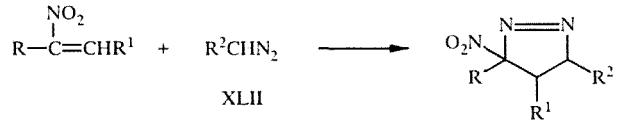
XXXIX

Ayyanger et al. [42] have described two methods for the synthesis of tricyclic compound XLI in 30 and 17% yield:



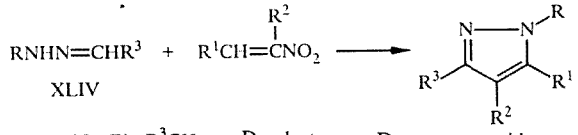
XLI

The reaction between conjugated nitroalkenes and diazo compounds XLII proceeds stereoselectively to give a single regioisomer of XLIII in all cases [43]:



XLII XLIII

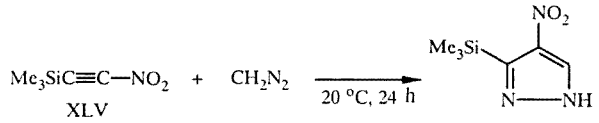
The reaction of D-galactose or D-mannose XLIV with nitroalkenes in DMF proceeds at 20-30°C over several days [44]. If, on the other hand, this reaction is carried out in aqueous DMF, the reaction is completed after only 2-4 h. The yields of the pyrazole derivatives are 9-76% [45]:



XLIV

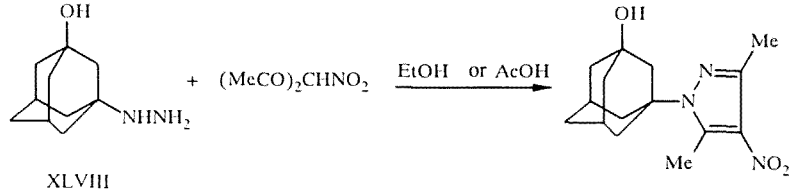
R = Me, Ph; R^3CH = —D-galactose or D-mannose residue

1-Trimethylsilyl-2-nitroacetylene (XLV) was used by Bottaro and Schmidt [46] in the synthesis of various five-membered heterocyclic compounds. Thus, the reaction of acetylene derivative XLV with diazomethane was carried out at 20°C to give 3-(trimethylsilyl)-4-nitropyrazole in 30% yield [46]:

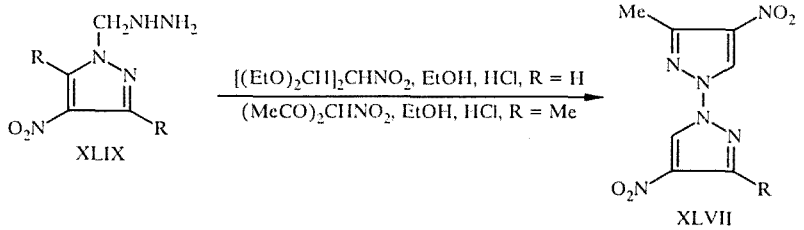


XLV

A patent has been issued for the preparation of pyrazole derivatives XLVI and XLVII in 65-85% yield by the condensation of monosubstituted hydrazines XLVIII or XLIX with 3-nitropentane-2,5-dione or with $[(EtO)_2CH]_2CHNO_2$ [47, 48]:



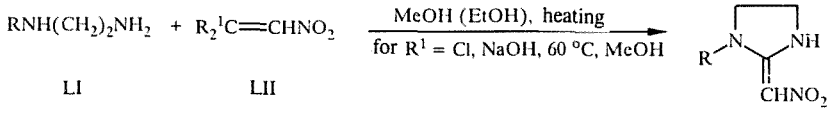
XLVIII XLVI



XLIX XLVII

The treatment of nitroenamine $MeNHCH{=}C(Me)NO_2$ with CF_3COOH at reflux gives the 2,5-dimethyl-3-acetylpyrazole 1-(N-oxide) in 5% yield [49].

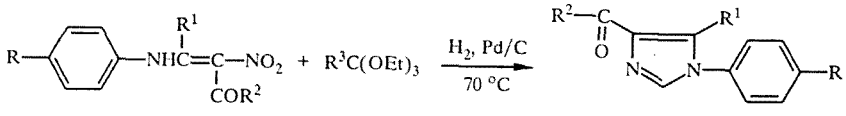
The reaction of diamines LI with 2,2-disubstituted nitroethylene LII was used to obtain imidazolidine derivatives L in 50-85% yield [6, 50-54]:



LI LII L

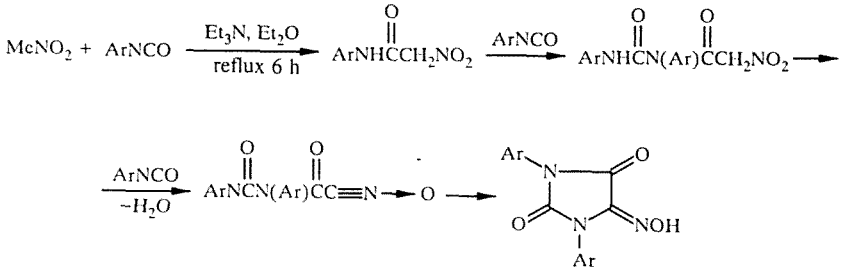
R^1 = SH, S-alkyl Cl

Substituted imidazoles LIII were synthesized in 16-68% yield by the hydrogenation of a mixture of nitroalkenes LIV and orthoesters LV in the presence of Pd/C [55]:



LIV LV LIII

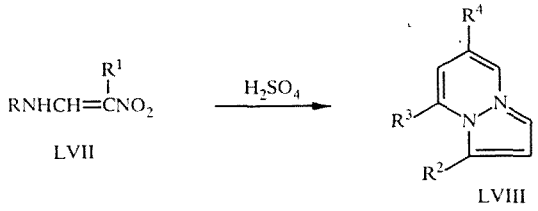
The following scheme was proposed to explain the formation of 1,3-diaryl-5-(hydroxyimino)imidazolidine-2,4-diones (LVI) in 5-32% yield from nitromethane and aryl isocyanates [56]:



LVI

2-Arylbenzimidazole was synthesized by heating a mixture of 2-arylnitroethylenes $ArCH{=}CHNO_2$ with *o*-phenylenediamine in butyl alcohol at reflux [57].

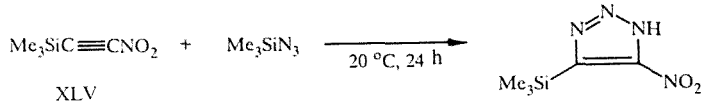
Nitroenamines LVII are converted upon heating with concentrated sulfuric acid or 40% sulfuric acid in methanol at reflux to give imidazopyridines LVIII in 65-70% yield [49, 58]:



LVII LVIII

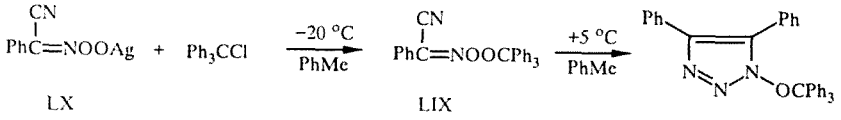
R, R^1, R^2, R^3, R^4 = Me, pyrid-2-yl Me, H, Me; Me, 4-methylpyrid-2-yl 2,4-dimethylpyrid-2-yl, Me, Me [49]; 4-methylpyrid-2-yl, Me, Me, H, Me [58]

1H-4-(Trimethylsilyl)-5-nitro-1,2,3-triazole was formed under mild condition in 21% yield in the reaction of acetylene derivative XLV with trimethylsilyl azide [46]:



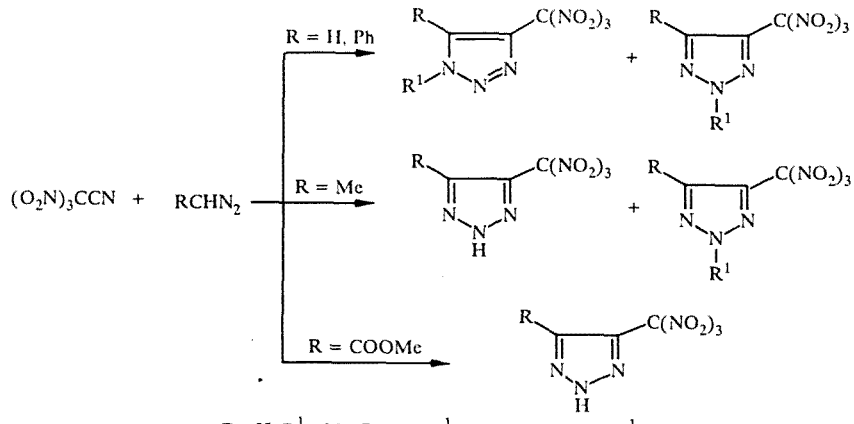
XLV

Nitrile LIX obtained from silver salt LX and Ph_3CCl at −20°C is converted upon warming to +5°C to 1-(triphenylmethyloxy)-4,5-diphenyl-1,2,3-triazole in 24% yield [59]:



LX LIX

The structure of the 1,2,3-triazole derivatives formed in 23-65% yield in the reaction of trinitroacetonitrile with diazo compounds $RCHN_2$ depends on the nature of substituent R in the diazo compound [60]:



5-(2-Nitroethyl)tetrazole was synthesized in 17% yield upon heating 3-nitropropionitrile with AlN_3 (formed *in situ* from NaN_3 and $AlCl_3$) in THF over 8 h [61].

1.2. SYNTHESIS OF SIX-MEMBERED HETEROCYCLES

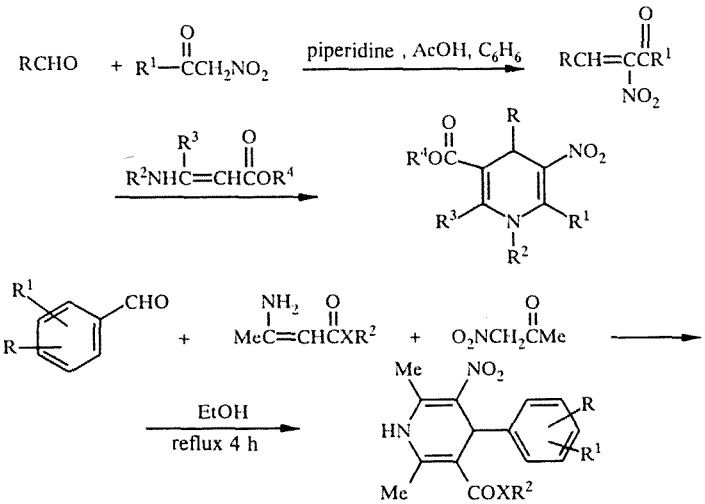
Aliphatic nitro compounds have been frequently used for the synthesis of six-membered nitrogen heterocycles.

The irradiation of nitro compounds $RCH(R^1)NO_2$ in methanol in the presence of ammonia leads to 2,2,6,6-tetrasubstituted piperidines [62].

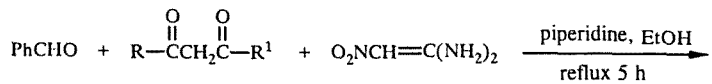
3-Nitro-5-ethyl-6-methyl-2-piperidone was obtained in 80% yield in the reaction of 2-ethyl-3-ketobutyral with nitroacetamide in the presence of piperidine and piperidine acetate in water at 20°C over 22 h [63].

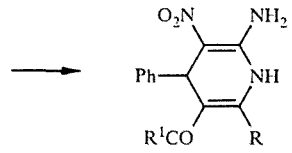
Various methods have been described for the synthesis of 1,4-dihydropyridine derivatives from aliphatic nitro compounds:

a) by the reaction of aromatic aldehydes with nitroketones and derivatives of unsaturated β-amino acids [64, 65]:

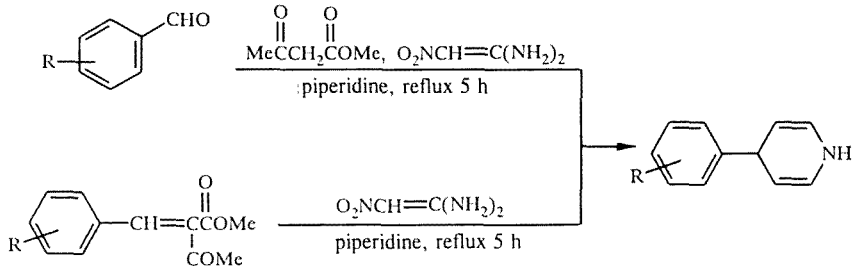


b) by the reaction of aromatic aldehydes with diketones and $O_2NCH\text{-}C(NH_2)_2$ in the presence of piperidine in 39-55% yield [66]:

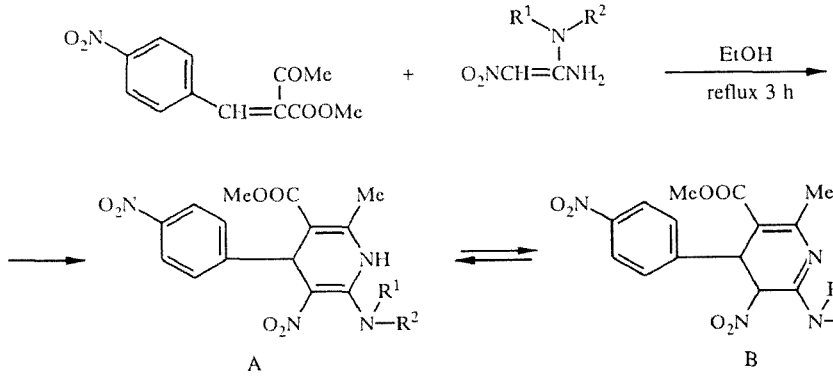




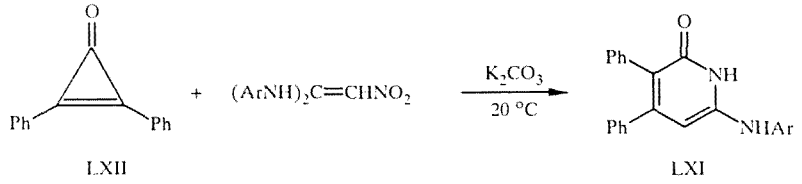
c) by the condensation of aromatic aldehydes with methyl acetoacetate and $O_2NCH{=}C(NH_2)_2$ in the presence of piperidine in 32-56% yield [66] or by the reaction of methyl esters of arylmethylenacetoacetic acids with nitroketenaminal $O_2NCH{=}C(NH_2)_2$ in 47-64% yield [66]:



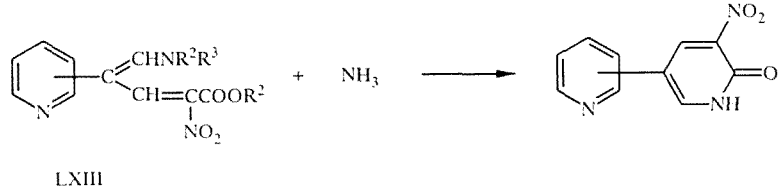
d) by the condensation of methyl esters of arylmethylenacetoacetic acids with asymmetrically substituted nitroketenaminals $O_2NCH{=}C(NH_2)NR^1R^2$ in 60-71% yield to give derivatives existing as isomers A and B:



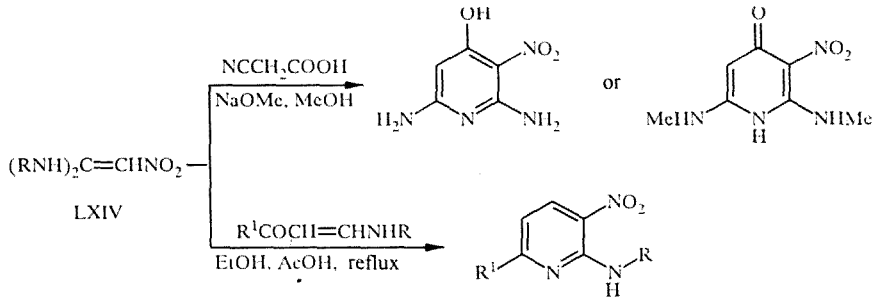
Derivatives of 2-pyridone LXI were synthesized by the reaction of 1,3-diphenyl-1-cyclopropen-2-one with nitroketenaminals LXII in 24-56% yield [67].



Piperidine derivatives are formed by the reaction of LXIII with ammonia [68]:

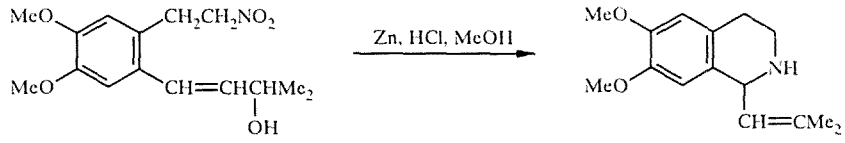


Substituted pyridines may be obtained by the reaction of nitroketenaminals LXIV with cyanoacetic acid in 81-91% yield or with aminoketones in 50-73% yield [69, 70]:



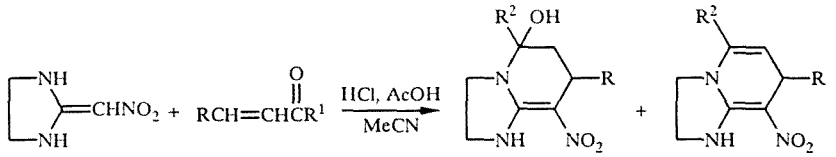
2,4,6-Trinitropyridine was obtained in 80% yield by heating 2,2-dinitroethanol in nitric acid at reflux [71].

Tetrahydroisoquinoline derivative LXV was synthesized by the reduction of LXVI [72]:



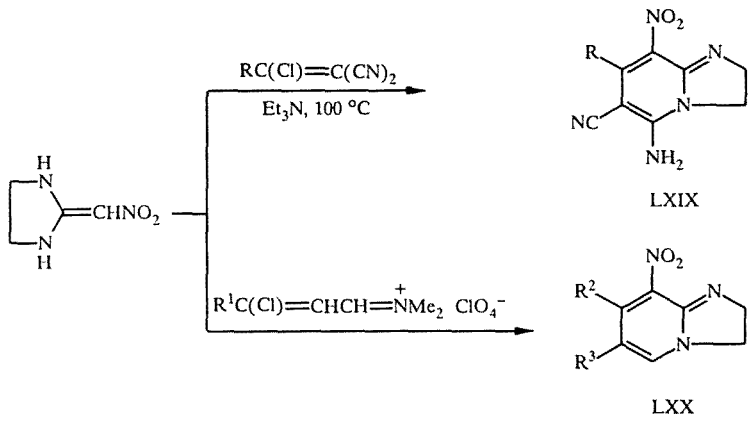
LXVI LXV

2-Nitromethylenimidazoline and 2-nitromethylenebenzimidazoline are converted by treatment with α,β-unsaturated ketones to condensed systems LXVII-LXX in 6-87% yield [73, 74]:



LXVII LXVIII

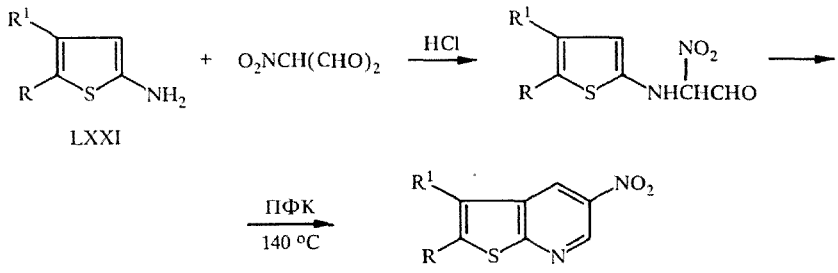
R, R^1, R^2 = H, COMe, Me; H, CHO, H; Me, CHO, H; Ph, CHO, H



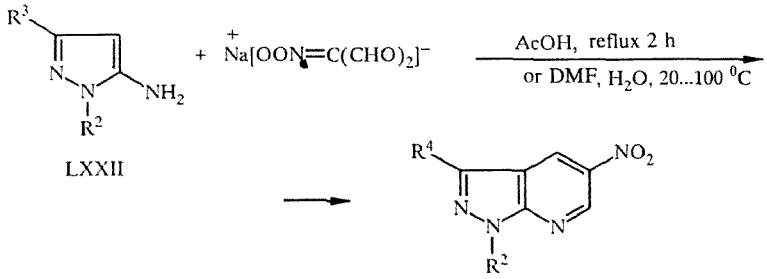
LXIX LXX

R^1, R^2, R^3 = $Me_2NCH{=}N{-}$, NH_2, $CONH_2$; Ph, Ph, H; 4-$R^4C_6H_4$, 4-$R^4C_6H_4$ (R^4 = Me, NO_2), H

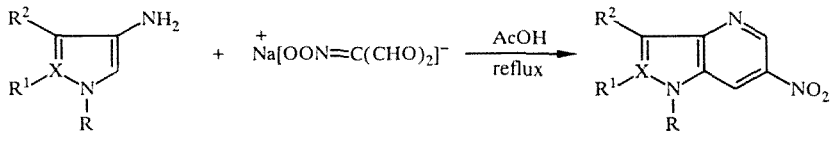
Heterocyclic amines LXXI-LXXIII and nitromalonaldehyde or its sodium salt also give bicyclic compounds in 80-95% yield [75, 76]:



LXXI



LXXII

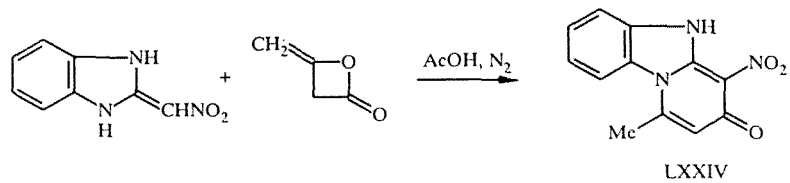


R^2, R^3, R^4 = Ph, CH_2NO_2, CHO; Me, Ph, Ph; H, Me, Me

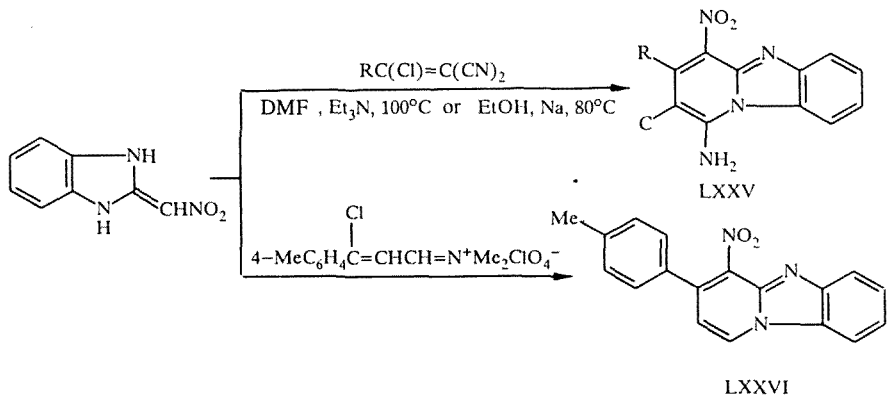
LXXIII

X=N, C

Tricyclic derivatives LXXIV-LXXVIII were synthesized in 45-97% yield using various unsaturated nitro compounds [54, 74, 77, 78]:

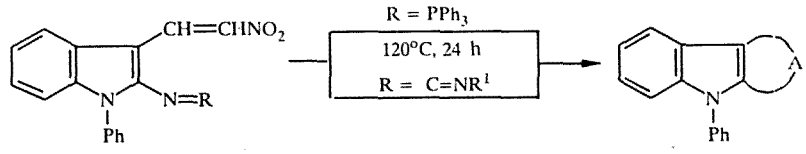


LXXIV

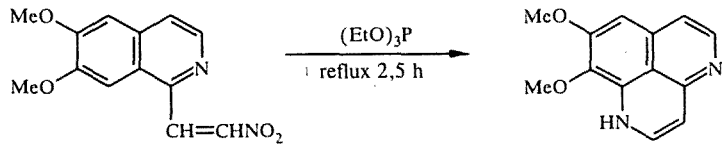


LXXV

LXXVI



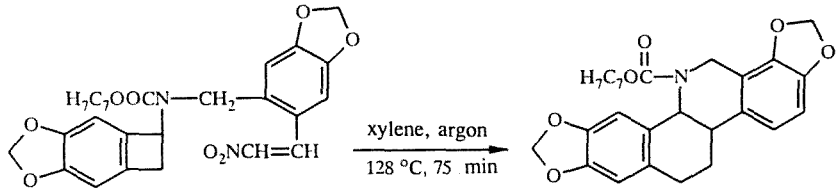
LXXVII



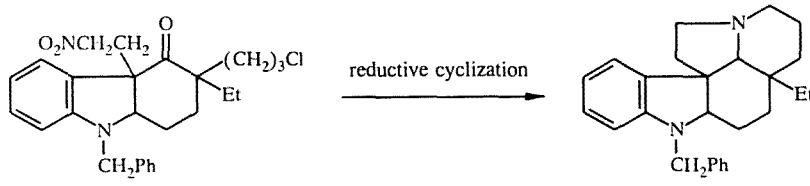
LXXVIII

R = PPh_3, A = —CH–C(NO_2)C(O)NH—; R = PPh_3, A = —CCH–C(NO_2)C(NHR^1)–N—

Oppolzer [79] and Benchekroun–Mouniz [80] have described the cyclization of nitro compounds LXXIX (92% yield) and LXXX, during which a six-membered nitrogen ring and an additional six-membered carbon ring or condensed five-membered and six-membered rings (including systems with fusion at the nitrogen atom) are formed simultaneously:

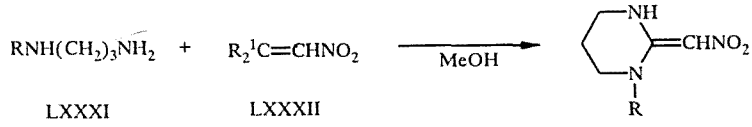


LXXIX



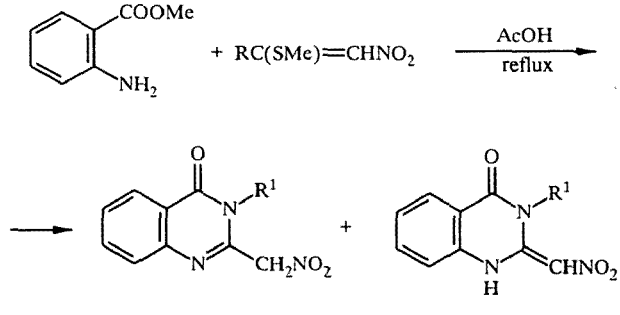
LXXX

N-Monosubstituted 1,3-diaminopropanes (LXXXI) readily react with nitroalkenes LXXXII to give compounds with a hydrogenated pyrimidine system LXXXIII [50-53, 81, 82]:



LXXXI LXXXII LXXXIII

The reaction of nitroalkenes RC(SMe)-$CHNO_2$ with the methyl ester of anthranilic acid gives 4-quinazolone derivatives (LXXXIV and LXXXV) [83]:

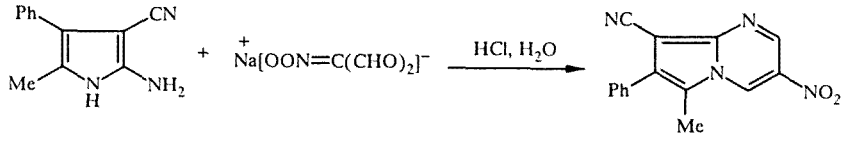


LXXXIV LXXXV

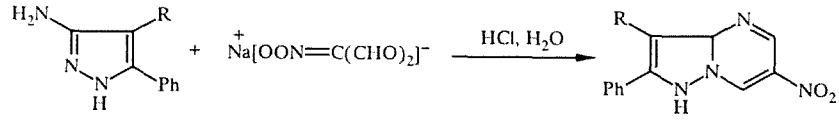
R, R^1=PhNH, Ph; SMe, 2-$MeOCOC_6H_4$ (2 moles 2-$MeOCOC_6H_4NH_2$ taken)

The reaction of 2-isocyanatobenzoyl chloride with nitromethane in benzene in the presence of Na_2CO_3 at 20°C over 20 h gave 5H,12H-quinazolino[3,2-*a*][3,1]benzoxazine-5,12-dione [84] in 90% yield.

The condensation of the sodium salt of nitromalonaldehyde with pyrrolic (LXXXVI) or pyrazolic amines (LXXXVII) gave the corresponding bicyclic derivatives (LXXXVIII or LXXXIX) [75]:

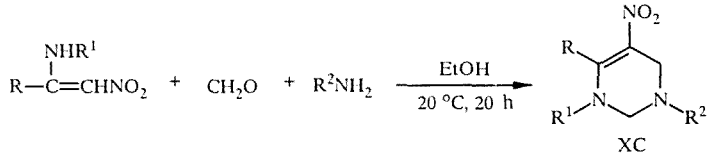


LXXXVI LXXXVIII

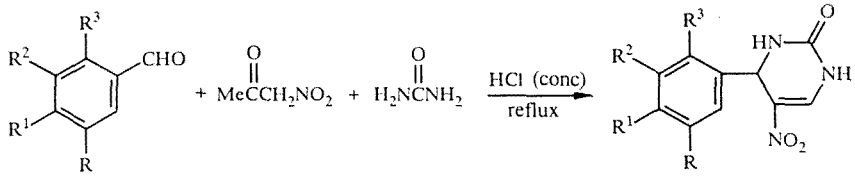


LXXXVII LXXXIX

Tetrahydropyrimidine derivatives (XC or XCI) are formed in the reaction of three-component systems, containing compounds with aldehyde, nitro, and amino groups. The yields are 34-68% [85, 86]:

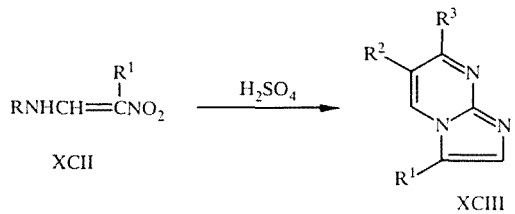


XC



XCI

The treatment of nitroenamines XCII with sulfuric acid gave imidazopyrimidine derivatives XCIII in 86-90% yield [49, 58]:



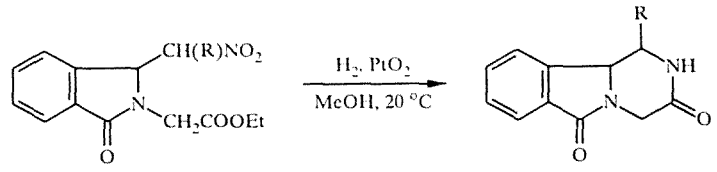
XCII XCIII

R, R^1, R^2, R^3 = pyrimidin-2-yl Me, Me; Me, 4,6-dimethylpyrimidin-2-yl Me, Me [49]; pyrimidin-2-yl Me, H, H [58].

2-R-Substituted 1-methyl-5-nitro-6-methylaminopyrimidine-4-thiones were synthesized in ≤81% yield by the reaction of $(MeNH)_2C{=}C(NO_2)C(S)NHC(O)R$ with methyl iodide [87].

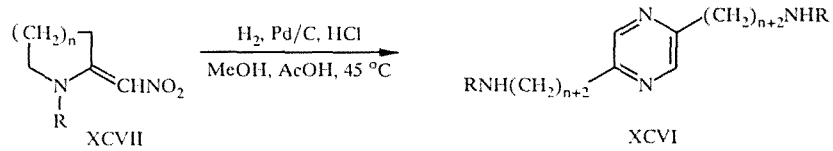
The treatment of nitroenamines $RNHCH{=}C(R^1)NO_2$ with concentrated sulfuric acid at 0-20°C leads to 2-R^1-7-R-quinoxazolines 1-N-oxides in 10 and 30% yield [49, 58].

The hydrogenation of XCIV in the presence of platinum oxide leads to intramolecular cyclocondensation and derivatives containing a hydrogenated pyrazine ring (XCV) [88]:



XCIV XCV

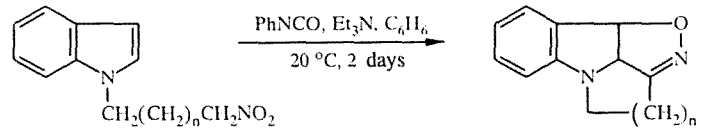
2,5-Disubstituted pyrazines (XCVI) were obtained by the hydrogenation of XCVII over Pd/C in the presence of hydrogen chloride [89]:



XCVII XCVI

R, n, yield (%): H, 1, 26; H, 2, 8,0; H, 3, 60; H, 4,70; Me, 3,10

N-Nitroalkylindoles (XCVIII) are converted upon treatment with phenyl isocyanate in the presence of triethylamine into tricyclic compounds (XCIX) containing three condensed heterocyclic rings. This reaction proceeds through the formation of a nitrile N-oxide (as a result of conversion of the CH_2NO_2 group into a $C\equiv N\rightarrow O$ group), which undergoes intramolecular 1,3-dipolar cycloaddition with the double bond of the pyrrole ring [90]:



XCVIII XCIX

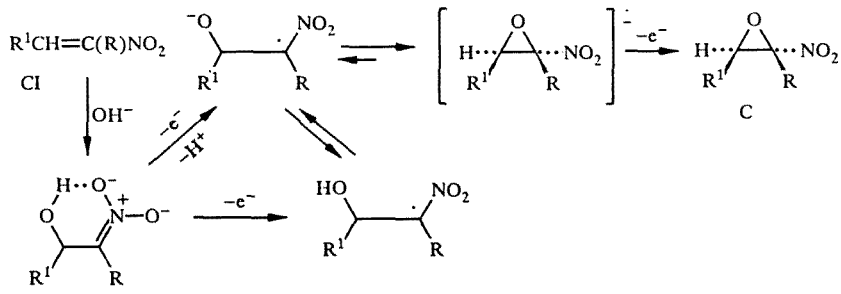
N-Substituted hexahydro-1,3-diazepins were synthesized by the condensation of N-monosubstituted 1,4-diaminobutanes with $(MeS)_2C=CHNO_2$ [50, 51, 53].

These results show that the nitrogen atom in the nitro group of aliphatic nitro compounds may virtually in all cases serve as a source for the nitrogen atom in nitrogen heterocyclic systems.

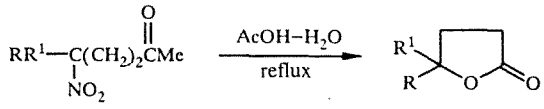
2. SYNTHESIS OF HETEROCYCLES CONTAINING OXYGEN ATOMS

There has been much less work on the synthesis of oxygen-containing heterocycles from aliphatic nitro compounds than work on the synthesis of nitrogen heterocycles from such derivatives.

Epoxides (C) are formed in 5-55% yield upon the action of $K_3Fe(CN)_6$ in the presence of KOH in DMF or $CH_2Cl_2-H_2O$ on nitroalkenes (CI) [91]. Bowman et al. [91] proposed the following reaction scheme:

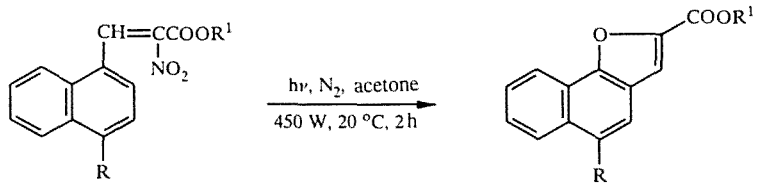


2-Dihydrofuranone derivatives (CIII) are obtained in 62-75% yield upon heating nitroketones (CII) in aqueous acetic acid at reflux [92]:



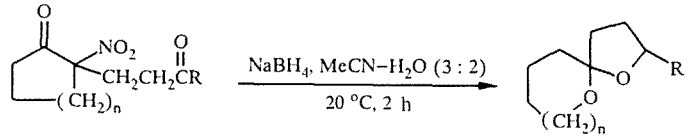
CII CIII

A furan ring is obtained upon irradiating esters of β-substituted acrylic acids CIV using a high-pressure mercury lamp in 2.2-10% yield [93]:



CIV

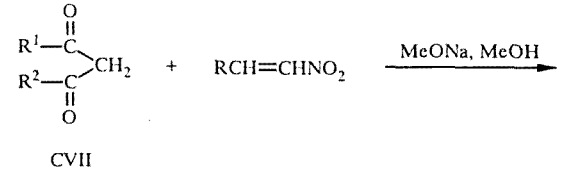
Nitrodiketones (CV) are converted by the action of $NaBH_4$ into a mixture of the *E* and *Z* isomers of spiro derivatives CVI containing a five-membered ring with an oxygen atom and a six- or seven-membered oxygen-containing ring in 65-75% yield [94]:



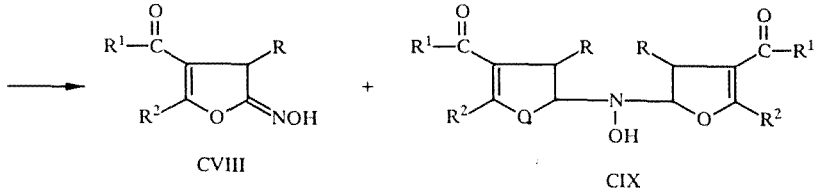
CV CVI

n = 1, 2

1,3-Dicarbonyl compounds CVII undergo cyclocondensation with nitroalkenes in the presence of sodium methylate to give CVIII and CIX in 25-75% yield [95, 96]:



CVII

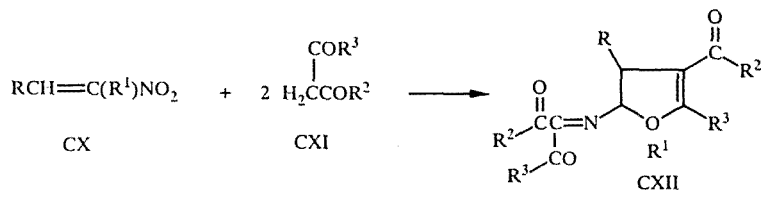


CVIII CIX

if $R^1 = R^2 =$ Me in CVII, analogous compounds containing a $-N{=}C(COMe)_2$ moiety instead of the $=NOH$ group are obtained in addition to CVIII [96].

The reaction of nitroalkenes $RCH{=}CHNO_2$ (where R are fully acetylated residues of D-glucose, D-galactose, or D-xylose) with aminoester $MeC(NH_2){=}CHCOOMe$ in the presence of MeONa in methanol also gives CVIII (in 18% yield) and CIX (in 15% yield) where R^1 = OMe and R^2 = Me [97].

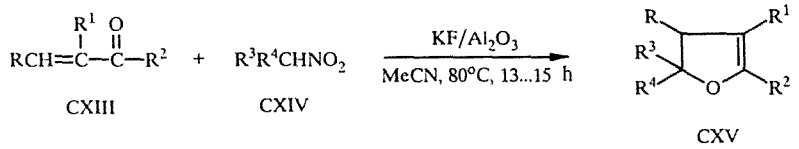
The reaction of conjugated nitroalkenes (CX) with 1,3-diketones or with esters of malonic or acetoacetic acids (CXI) in the presence of $PhCH_2NBu_3^+Cl^-$ and KOH [98] or Na and KOH [99, 100] gave 2,3-dihydrofuran derivatives CXII in 3-78% yield:



CX CXI CXII

R = Me, Ar; R^1 = Me, Ph; R^2 = Me, Ph, O-alkyl; R^3 = Me, Ph, O-alkyl

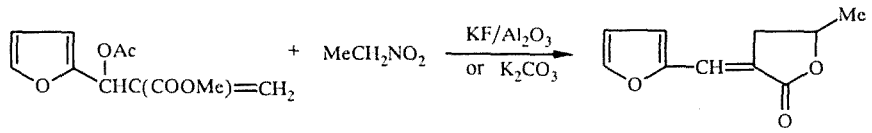
Unsaturated ketones (CXIII) and nitroalkanes (CXIV) react in the presence of KF/Al_2O_3 to give 2,3-dihydrofuran derivatives (CXV) in 45-98% yield [101, 102]:



CXIII CXIV CXV

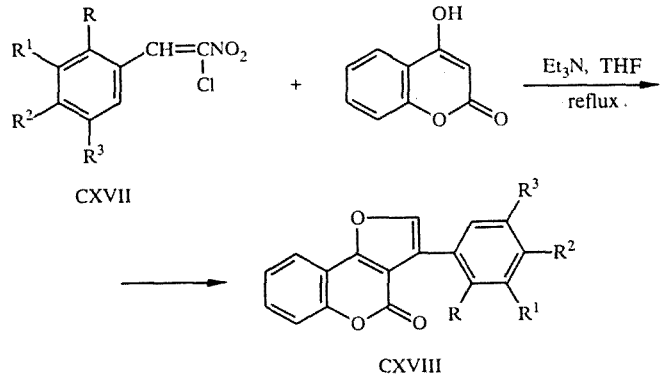
R = alkyl, aryl; R^1 = CN, COMe, COPh, CO_2-alkyl, SO_2Ar; R^2 = Me, Ph; R^3 = H, Me, Et; R^4 = Me, Et

If R = H, R^1 = CH(OAc)fur-2-yl, and R^2 = OMe in CXIII, the reaction with nitroethane gives CXVI [102]:



CXVI

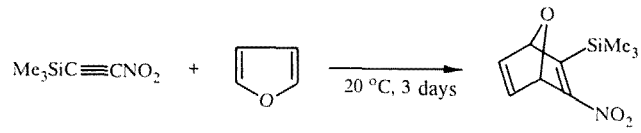
2-Aryl-1-chloronitroethylenes (CXVII) condense with 4-hydroxycoumarin in the presence of triethylamine to give tricyclic products CXVIII in 35-90% yield [103]:



CXVII CXVIII

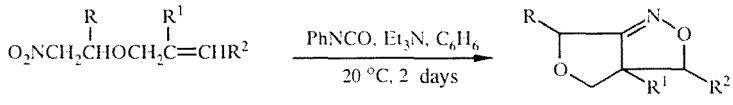
Heating these reagents in the presence of KF in $MeOCH_2CH_2OMe$ at reflux gives analogous products with a dihydrofuran ring, containing a nitro group at $C_{(2)}$ [103].

The reaction of nitroacetylene derivative XLV with furan leads to the Diels–Alder product CXIX in 21% yield [46]:



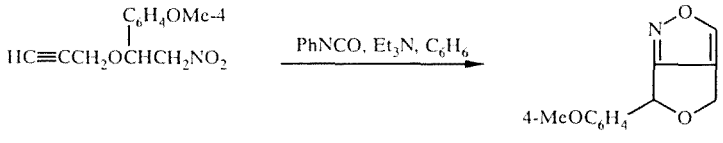
XLV CXIX

The $-CH_2NO_2$ group in ethers CXX containing a double bond is converted to a $-C\equiv\rightarrow O$ group upon the action of phenyl isocyanate in the presence of triethylamine. The N-oxide group and double bond in the product formed undergoes 1,3-dipolar cycloaddition to give *cis* and *trans* isomers of CXXI in 75-90% yield [90, 104, 105]:



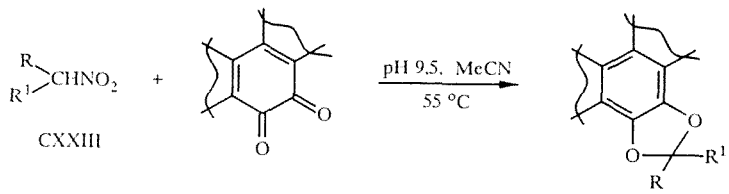
CXX CXXI

In the case of ether CXX, which contains a carbon–carbon triple bond instead of a double bond, product CXXII with fused isoxazoline and tetrahydrofuran rings was obtained in 85% yield [105]:



CXXII

The condensation of nitroalkanes CXXIII with orthoquinones in the presence of carbonate buffer excluding contact with the atmosphere leads to CXXIV (53-88% yield), containing a five-membered ring with two oxygen atoms [106]:



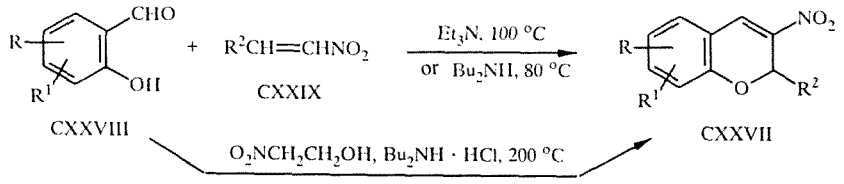
CXXIII CXXIV

Aliphatic nitro compounds are used rather rarely in the synthesis of six-membered oxygen-containing heterocycles.

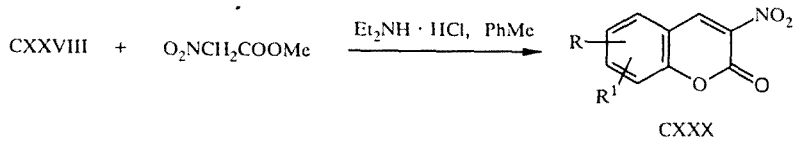
Substituted benzoic acids CXXV were converted into isocoumarin derivatives CXXVI in 79-85% yield by a three-step procedure involving a Neff reaction, cyclization, and dehydration [107]:

CXXV CXXVI

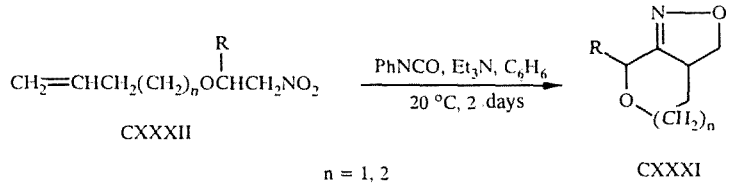
Benzopyran derivatives CXXVII are formed in the reaction of substituted salicylaldehydes CXXVIII with conjugated nitroalkenes CXXIX in the presence of triethylamine in 30-35% yield [108, 109] or dibutyl amine in 50-85% yield [110]. Analogous compounds were obtained in 45-67% yield in the reaction of aldehydes CXXVIII with nitroethanol in the presence of dibutylamine hydrochloride [111]:



Coumarin derivatives CXXX are obtained in 29-85% yield in the reaction of aldehydes CXXVIII with methyl nitroacetate in the presence of hydrochloride salts of secondary amines [112]:



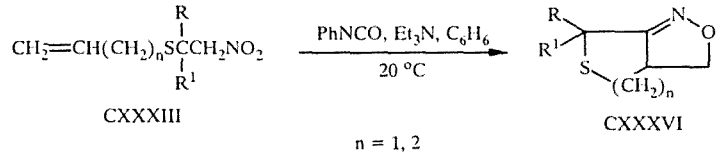
Bicyclic products CXXXI containing an isoxazoline ring fused to a six- or seven-membered ring containing a ring oxygen were obtained in 72-95% yield from unsaturated nitro compounds CXXXII upon reaction with phenyl isocyanate in the presence of triethylamine [104, 105]:

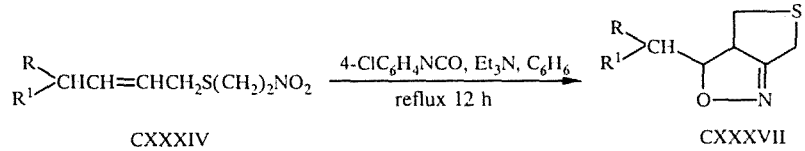


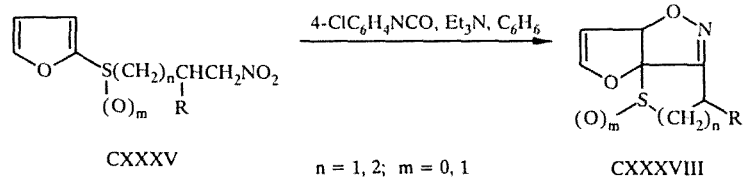
3. SYNTHESIS OF SULFUR HETEROCYCLES

There have been only seven reports in the literature on the use of aliphatic nitro compounds to obtain sulfur heterocycles. The synthesis of a six-membered sulfur heterocycle was noted in one report.

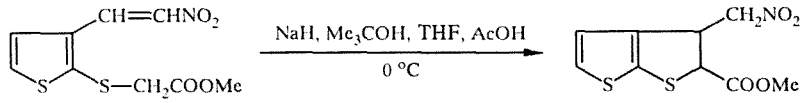
The $-CH_2NO_2$ group is converted to a $-C{\equiv}N{\rightarrow}O$ moiety upon the action of aryl isocyanates on unconjugated nitroalkenes (CXXXIII, CXXXIV, or CXXXV) in the presence of triethylamine followed by intramolecular 1,3-dipolar cycloaddition to give a mixture of *cis* and *trans* isomers of CXXXVI [104, 114], CXXXVII [115], or CXXXVIII [113] in 60-90% yield:





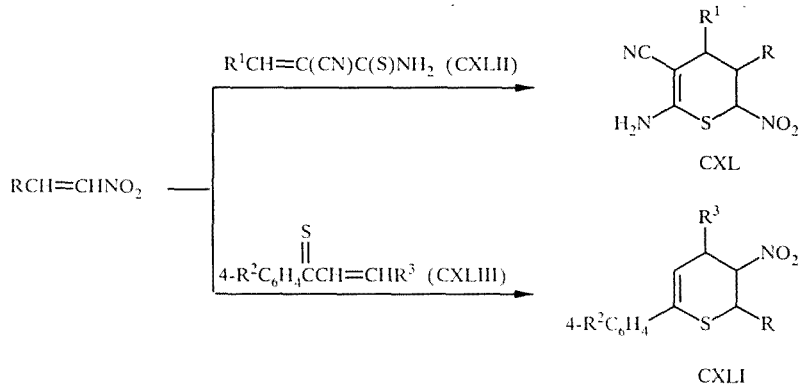


The action of sodium hydride on CXXXIX results in quantitative intramolecular cyclization and formation of a 2,3-dihydrothiophene ring [116]:



CXXXIX

Derivatives of 2,3-dihydro-(4H)-thiine (CXL or CXLI) were synthesized by the Diels–Alder reaction of conjugated nitroalkenes with unsaturated thioamides CXLII [117] or thioketones CXLIII in 70-90% yield [118]:

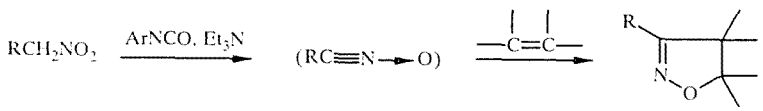


4. SYNTHESIS OF HETEROCYCLES CONTAINING NITROGEN AND OXYGEN ATOMS

There have been no reports in the literature on the preparation of products containing both nitrogen and oxygen atoms in three- or four-membered rings from aliphatic nitro compounds.

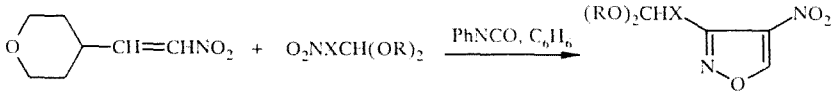
The most common method for the synthesis of derivatives of isoxazoline or isoxazole from aliphatic nitro compounds involves the 1,3-dipolar cycloaddition of nitrile N-oxides generated from compounds with a $-CH_2NO_2$ group to compounds containing carbon–carbon multiple bonds. Two variants of this method have been proposed. In the first variant, an N-oxide is first obtained from a primary nitro compound and the reaction of this product (sometimes *in situ*) with an unsaturated nitro compound is carried out. Intramolecular 1,3-dipolar cycloaddition then occurs with formation of the heterocycle. There have been no reports of use of the second variant for preparing heterocyclic compounds with oxygen or sulfur atoms containing a fused isoxazoline or isoxazole ring.

Quite a few studies have been devoted to the synthesis of isoxazoline derivatives using the first variant [8, 119-124]:



Baranski et al. [125] studied the effect of substituents on the regio- and stereoselectivity of the reaction of *trans*-$RCH=CHNO_2$ with $4\text{-}O_2NC_6H_4C\equiv N\rightarrow O$.

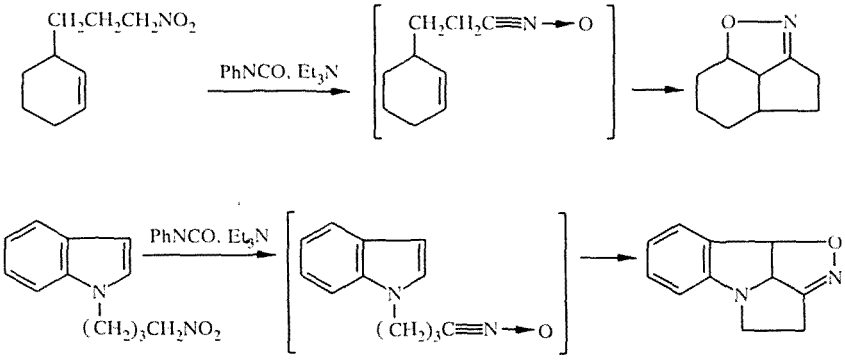
We should note that isoxazole derivatives CXLIV were obtained [126] by the reaction of 2-(4-tetrahydropyranyl)nitroethylene with nitro derivatives CXLV upon treatment with phenyl isocyanate in benzene without triethylamine:



CXLV CXLIV

X, R = CH_2, Me; bond, Et

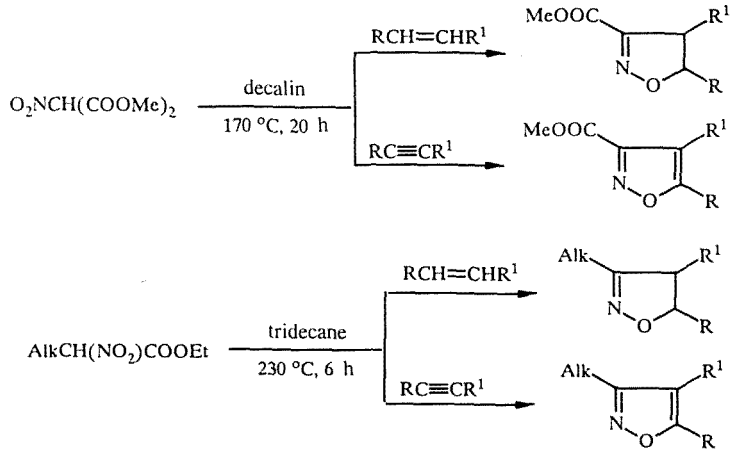
Not only bicyclic compounds [104, 105, 114, 115, 127] but also tricyclic (3-97% yield) [41, 90, 113, 114, 127-129] or tetracyclic compounds (20-70% yield) [90, 128] may be obtained when the reaction is carried out according to the second variant involving intramolecular cycloaddition, for example:



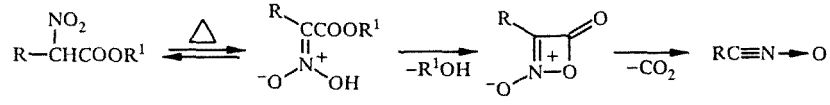
The following reagents were used to generate nitrile N-oxides in the preparation of isoxazolines and isoxazoles from primary nitro compounds and unsaturated compounds in addition to aryl isocyanates: $4\text{-}MeC_6H_4SO_3H\cdot H_2O$ in mesitylene at reflux [130], anhydrides of dibasic acids in the presence of base [131, 132], Ph_3PCl_2 (generated *in situ* from PPh_3 and C_2Cl_6) in the presence of triethylamine [133, 134], and Ce(III) ammonium nitrate [135].

Coutouli–Argypopoulou [136] proposed that nitrile N-oxides $4\text{-}RC_6H_4C{\equiv}N{\rightarrow}O$ are formed as intermediates in the preparation of 3-aryl-5-methoxycarbonylisoxazolines in the reaction of nitro compounds $RC_6H_4CH(Br)NO_2$ (R = H, Me, Cl) with methyl acrylate in the presence of PPh_3.

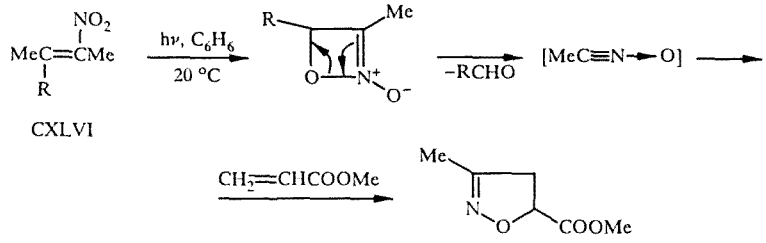
Shimizu et al. [137, 138] developed two original methods for the synthesis of isoxazoline or isoxazole derivatives in 14-100% yield involving an unusual preparation of nitrile N-oxides:



These workers proposed the following scheme for the nitrile N-oxide formation.



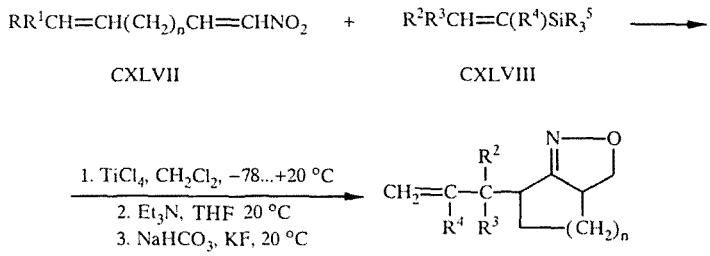
An analogous scheme for the preparation of nitrile N-oxides was presented in a description of the synthesis of 3-methyl-5-methoxycarbonylisoxazoline (in 17.5 and 19.7% yield) by irradiation of a mixture of a nitroalkene (CXLVI) and methyl acrylate in benzene [139]:



CXLVI

R = Me, Ph

Treatment of the products of the reaction of nitrodienes CXLVII and an alkene CXLVIII in the presence of $TiCl_4$ with triethylamine and then, KF and $NaHCO_3$ leads to bicyclic derivatives CXLIX in 8-92% yield [140]:

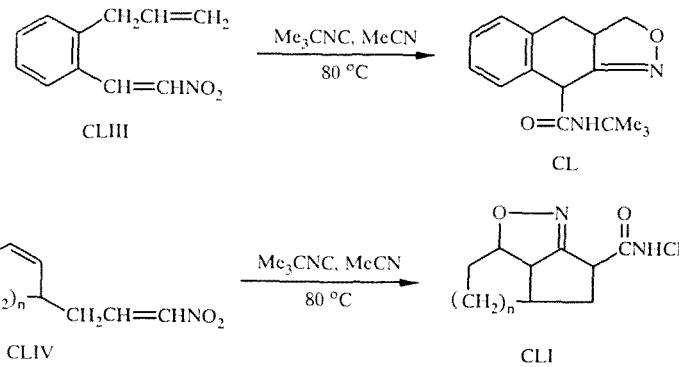


CXLVII CXLVIII

CXLIX

n = 2, 3

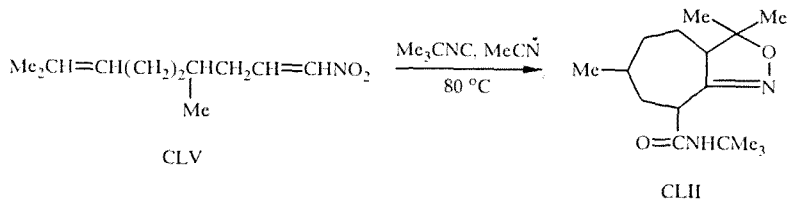
The synthesis of CL, CLI, or CLII (in 14-88% yield) was carried out by the reaction of nitroalkenes CLIII, CLIV, or CLV, respectively, with Me_3CNC in acetonitrile at reflux [141]:



CLIII CL

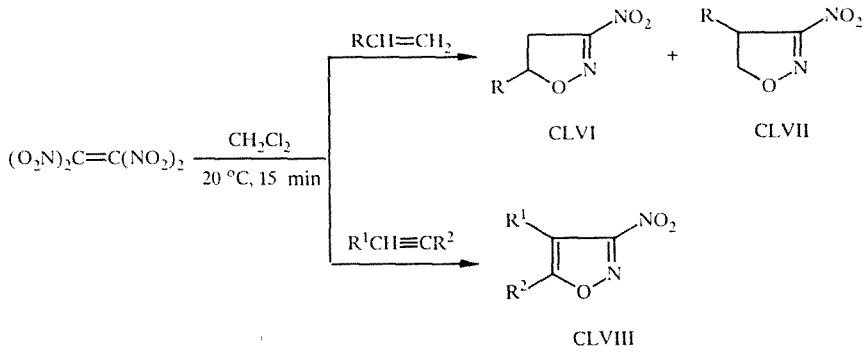
CLIV CLI

n, yield (%): 1,36; 2,88



CLV CLII

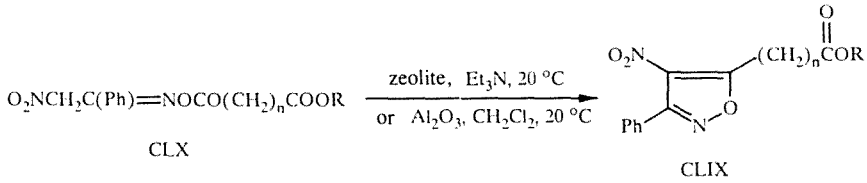
Tetranitroethylene reacts readily with alkenes or alkynes to give 3-nitroisoxazolines (CLVI and CLVII) or 3-nitroisoxazoles (CLVIII) in 23-27% yield [142]:



CLVI CLVII CLVIII

R, compound, yield (%): H, CLVI, 32; Me_3C, CLVI, 20; Me, CLVI + CLVII, 12

Isoxazole derivatives (CLIX) were obtained in high yield in the cyclization of CLX in the presence of zeolite and Et_3N or Al_2O_3 [143]:

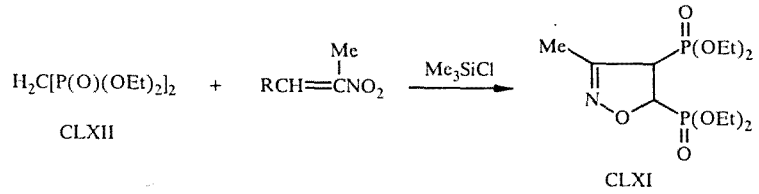


CLX CLIX

n, R, yield (%): 0, Et, 99,6; 1, Me, 87,7; 2, Me, 89; 3, Me, 87,8

Heating 2-(2-furyl)nitroethylene in concentrated hydrochloric acid gives 3-(3-chloro-5-isoxazolyl)propionic acid [144] in 60% yield.

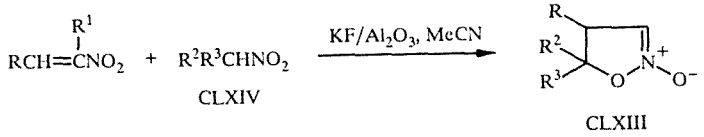
High yields (90-99%) of phosphorus derivatives of isoxazoline CLXI were obtained in the reaction of methylene diphosphate CLXII with conjugated nitroalkenes in the presence of trimethylchlorosilane [145]:



CLXII CLXI

The reaction of $XC(NO_2)_2CN$ (X is a halogen) with diazomethane in ether at 0-5°C gave 3-cyanoisoxazoline N-oxide in 41% yield [146].

A series of isoxazoline N-oxide derivatives (CLXIII) was synthesized in 45-98% yield by the reaction of conjugated nitroalkenes and nitro compounds (CLXIV) in the presence of KF/Al_2O_3 [101]:

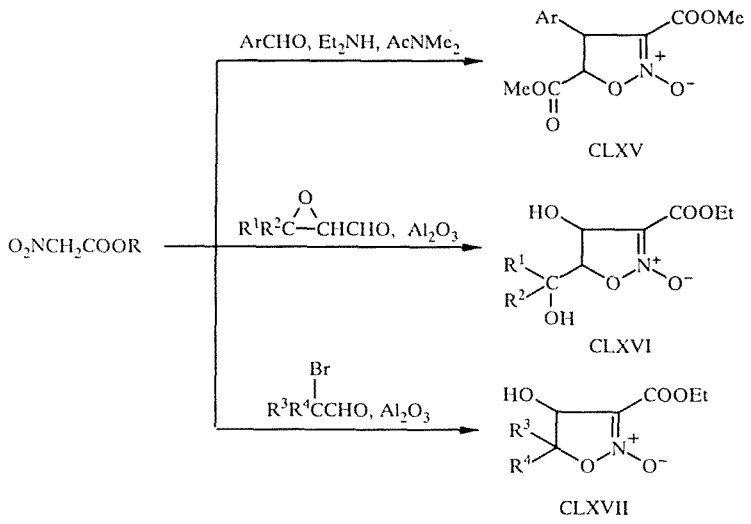


CLXIV CLXIII

R = aryl, 2-furyl R^1 = COOMe; R^2 = Me; R^3 = Me, Et

Irradiation of a mixture of $Me_2CNO_2^-Na^+$ and $ClCH_2CH{=}C(Me)NO_2$ in DMF gives 3-methyl-4-(2-nitro-2-propyl)isoxazoline [147].

Nitroacetate esters react with aromatic aldehydes in the presence of diethylamine [148, 149], with substituted glycidyl aldehydes [150], and with α-bromoaldehydes in the presence of alumina [151] to give isoxazoline N-oxides (CLXV, CLXVI) in 65-99% yield (racemates are formed when R, R^1 = Me, H; Pr, H; $PhCOCH_2$, H; H, H) or a mixture of diastereomers (CLXVII) in 44-79% yield, respectively:



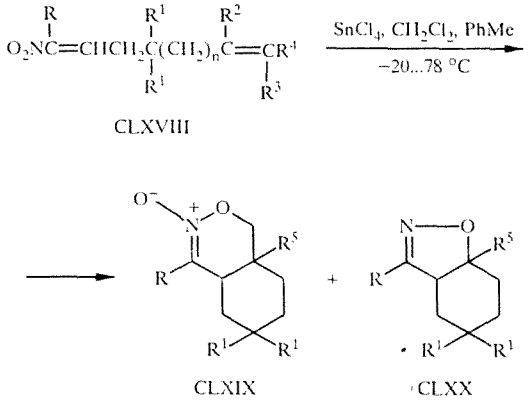
3-Cyano-4,4,5,5-tetramethylisoxazoline N-oxide is obtained in 45% yield in the reaction of O_2NCBr_2CN with 2,3-dimethyl-2-butene in CH_2Cl_2 at 25°C [152].

4-Aryl-3,5-bis(alkoxycarbonyl)isoxazoline N-oxides were prepared by the condensation of ArCHO with two moles of $O_2NCH_2COOAlk$ in the presence of Me_2CHNH_2 in ROH–Et_2O in 41-82% yield [153].

Heating a mixture of $(MeS)_2C{=}CHNO_2$ with $PhCH(OH)CH(Me)NH_2$ in tertiary butyl alcohol at reflux gave 4-methyl-2-nitromethylene-5-phenylisoxazolidine [70].

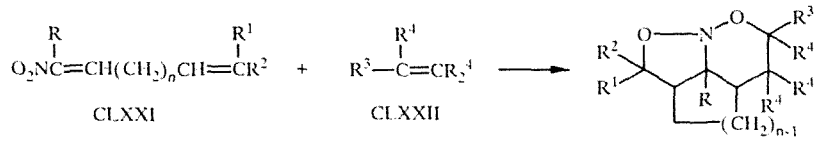
Denmark et al. [154-156] carried out interesting and extensive work on the cyclization of nitrodienes to give bicyclic and tricyclic compounds. The effect of the substituents in the nitrodiene on the regio- and stereoselectivity of the cyclization was studied.

The cyclization of nitrodienes (CLXVIII) in the presence of $SnCl_4$ gave bicyclic compounds (CLXIX and/or CLXX) in 59-95% yield. These products contain an 1,2-oxazoline or isoxazoline ring fused to a cyclohexane ring [154, 155]:



When n = 2, R = H, Me, $R^1 = R^2$ = H, R^3 = Me, H, and R^4 = H, Me, the major product is CLXIX (R^5 = Me). When n = 2, R = R^3 = Me, $R^2 = R^4$ = H, about 11% CLXX (R^5 = Et) is formed. When n = 2, R = $R^1 = R^2$ = H, Me, R^3 = Me, and R^4 = H, Me, the reaction product is only the *trans* isomer of CLXX (R^5 = Me). When n = 1, R = R^3 = Me, and $R^1 = R^2 = R^3$ = H, only 11% CLXX is formed (R^5 = Me). When n = 1, R = R^4 = Me and $R^1 = R^2 = R^3$ = H, 70% CLXX is formed (R^5 = Me) [154].

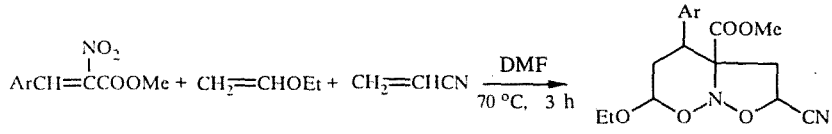
The double [4+2]−[3+2] cycloaddition of nitrodienes (CLXXI) to unsaturated compounds (CLXXII) in the presence of $SnCl_4$ [156] or complex catalysts [156-158] to give tricyclic products (CLXXIII or CLXXIV) without the isolation of intermediates has been described:



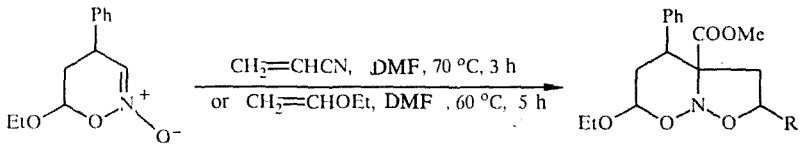
CLXXI, n = 2, 3 CLXXII CLXXIII, n = 2; CLXXIV, n = 3

Denmark et al. [156] have also reported the consecutive [4+2] and [3+2] cycloadditions of nitrodiene CLXXI (n = 3, R = Me, R^1 = COOMe, R^2 = H) to CLXXII (R^3 = OBu, R^4 = H) [156].

Derivatives of 2,9-dioxa-1-azabicyclo[4.3.0]nonane (CLXXV or CLXXVI) were synthesized by the reaction of $ArCH=C(NO_2)COOMe$ with ethyl vinyl ether and acrylonitrile in 57% or by the reaction of N-oxide (CLXXVII) with acrylonitrile in 87% yield or ethyl vinyl ether in 83% yield [159]:

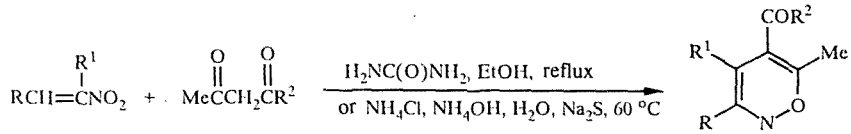


Ar = 4-$O_2NC_6H_4$ CLXXV



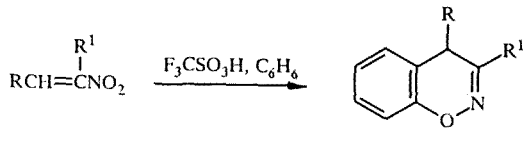
CLXXVII CLXXVI R = CN, OEt

Substituted 1,2-oxazines (CLXXVIII) were obtained in the three-component condensation of nitroalkenes with $MeCOCH_2COR^2$ and H_2NCONH_2 or NH_4Cl [160]:



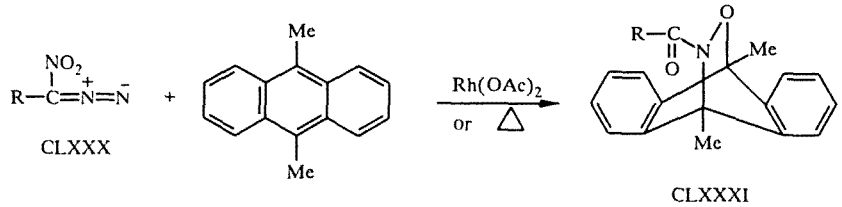
CLXXVIII

1,2-Benzoxazine derivatives (CLXXIX) were synthesized by heating conjugated nitroalkenes in the presence of F_3CSO_3H [161]:



CLXXIX

Diazo compound (CLXXX) reacts with 9,10-dimethylanthracene in the presence or $Rh(OAc)_2$ or simply upon heating to give CLXXXI in 25-67% yield [162]:

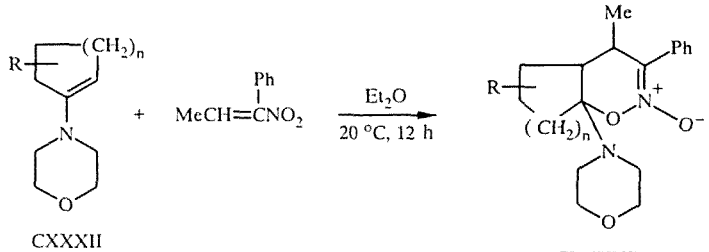


CLXXX CLXXXI

R = H, COOEt, CF_3

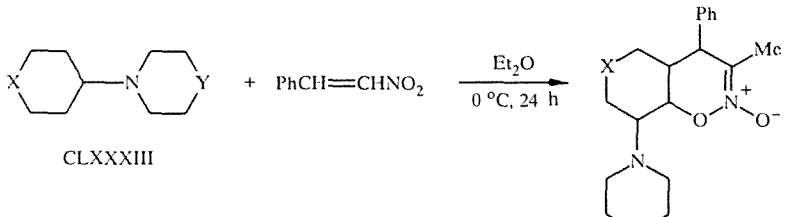
The product of the condensation of 3-(N-piperidyl)-5,5-dimethyl-2-cyclohexenone with two molecules of β-nitrostyrene upon heating in benzene at reflux in a nitrogen atmosphere is 7,7-dimethyl-8-(2-nitro-1-phenylethyl)-4-phenyl-6,7-dihydro-1,2-benzoxazin-5-one in 33% yield [163].

The enamine reaction (CLXXXII or CLXXXIII) with conjugation of nitroalkenamine produces N-oxide (CLXXXIV or CLXXXV) (yield 80-85%) [164, 165]:



CXXXII CLXXXIV

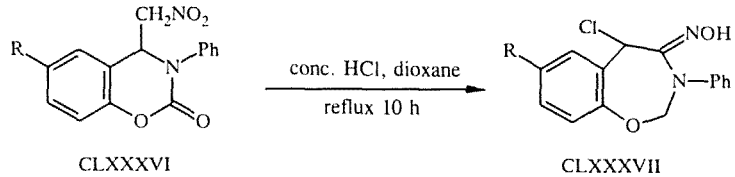
R, n: H, 1; H, 2; 4-Me_3C, 2; 1-oxo, 2



CLXXXIII CLXXXV

X, Y = NMe, O; NMe, CH_2; O, CH_2; S, CH_2

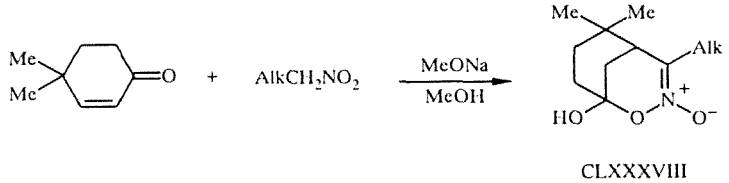
Heating CLXXVI with concentrated hydrochloric acid in dioxane leads to expansion of the heterocycle and formation of derivatives of tetrahydro-1,3-benzoxazepin-2-one (CLXXXVII) [166]:



CLXXXVI CLXXXVII

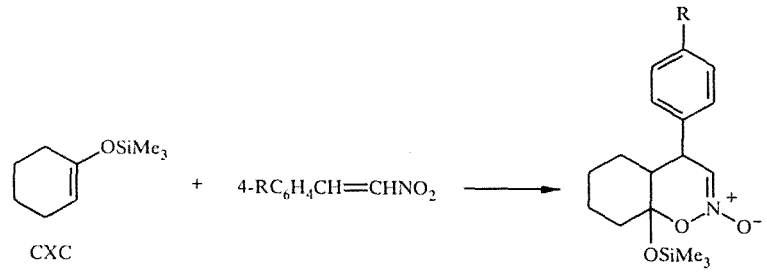
R = H, Cl

Bicyclic derivatives CLXXXVIII were obtained in 32-54% yield upon the condensation of nitroalkanes with 4,4-dimethyl-2-cyclohexenone in the presence of sodium methylate [167]:



CLXXXVIII

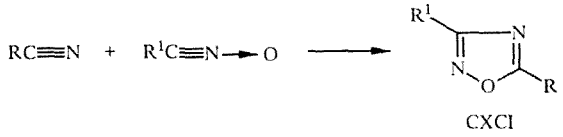
N-Oxides CLXXXIX were synthesized by the cyclocondensation of trimethylsilyl ether (CXC) with nitroalkenes (CXCI) in the presence of $(Me_2CHO)_4Ti$ and $TiCl_4$. The reaction products are formed as stereoisomer mixtures in 55-81% yield [168]:



CXC CLXXXIX

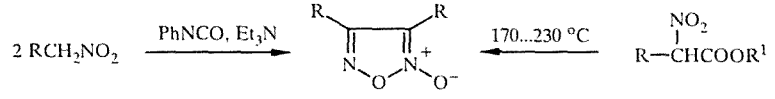
Treatment of LIX with phenyl isocyanate at −20°C leads to 3,4-diphenyl-1,2,4-oxadiazol-5-one in 14% yield [59].

The reaction of nitriles with nitrile N-oxides prepared *in situ* [136] or separately prepared and isolated as pure compounds [169] gives 1,2,4-oxadiazole derivatives (CXCI) in 70-90% yield:

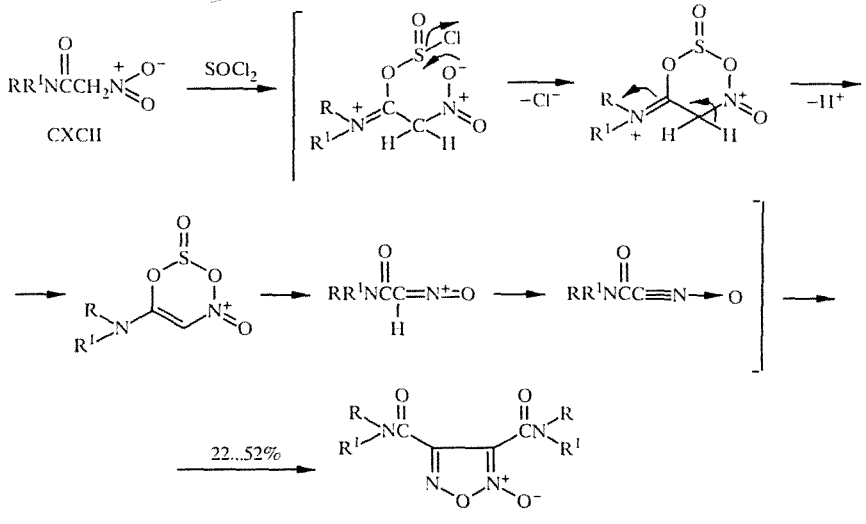


CXCI

Furoxane derivatives (1,2,5-oxadiazole N-oxides) are mainly formed in the preparation of nitrile N-oxides in the absence of dipolarophiles due to the reaction of two nitrile N-oxide molecules. The product yield is 22-25% [90, 130, 137]:

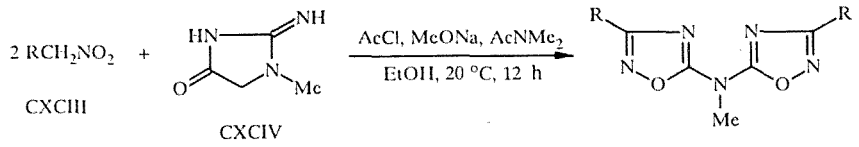


Furoxane derivatives may be synthesized by the action of thionyl chloride on CXCII, which contains a $-CH_2NO_2$ group. The following scheme was proposed for the transformation of CXCII [170]:



Dinitroacetate esters $H(NO_2)_2CCOOR$ (R = Me, Et, Me_2CH) are unstable under ordinary conditions and are converted over several days into 3,4-bis(alkoxycarbonyl)furoxanes in 92-96% yield [171].

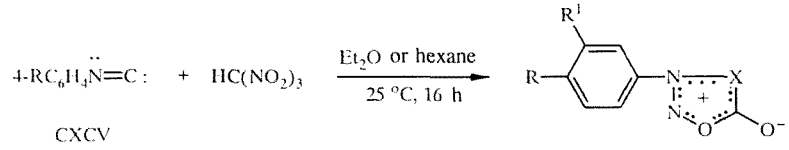
A remarkable transformation was observed by Zen et al. [172], who treated nitro compound (CXCIII) and creatinine (CXCIV) with acetyl chloride in the presence of sodium methylate. The product yield is 60-63%:



CXCIII CXCIV

R = Me, Et, Ph, 4-MeC_6H_4

The reaction of isonitriles (CXCV) with trinitromethane gives mesionic compounds (CXCVI), containing two nitrogen atoms and an oxygen atom or three nitrogen atoms and an oxygen atom in the five-membered ring. The product yield is 6-48% [173]:



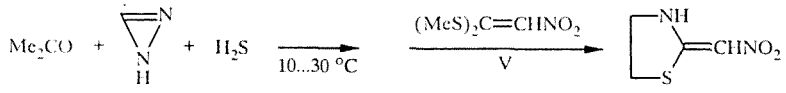
CXCV CXCVI

R, R^1, X = NO_2, H, CH; NO_2, H, N; Me, NO_2, N

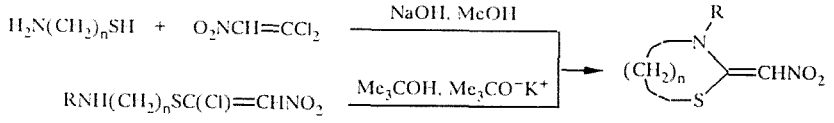
5. SYNTHESIS OF COMPOUNDS CONTAINING NITROGEN AND SULFUR ATOMS

There has been only sparse information on the use of aliphatic nitro compounds in the preparation of heterocycles containing nitrogen and sulfur atoms in the heterocyclic system.

2-Nitromethylene-1,3-thiazolidine was obtained by the condensation of 1,1-bis(methylthio)-2-nitroethylene V with $H_2N(CH_2)_3SH$ at 20-30°C in a nitrogen atmosphere [174] or with $HCl \cdot H_2N(CH_2)_2SH$ in toluene–water in the presence of KOH and $Bu_4N^+Br^-$ at 80°C (82.2% product yield) [175]. The same compound was obtained in 80.5% yield by the reaction of acetone with 1H-diazirine with H_2S and subsequent treatment of the reaction mixture with nitroalkene V [176]:



Two methods have been described for the synthesis of thiazolidine derivatives CXCVII (n = 2), tetrahydro-1,3-thiazine CXCVII (n = 3), and tetrahydro-1,3-thiazetidine CXCVII (n = 4). These methods involve the cyclocondensation of 2-aminoethanethiol with 2,2-dichloronitroethylene [177] or cyclization of CXCVIII [178, 179]:

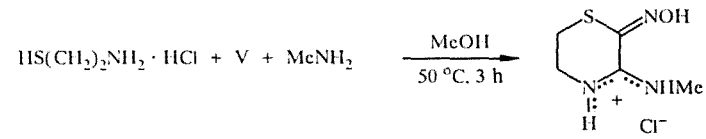


CXCVIII CXCVII

n = 2...4

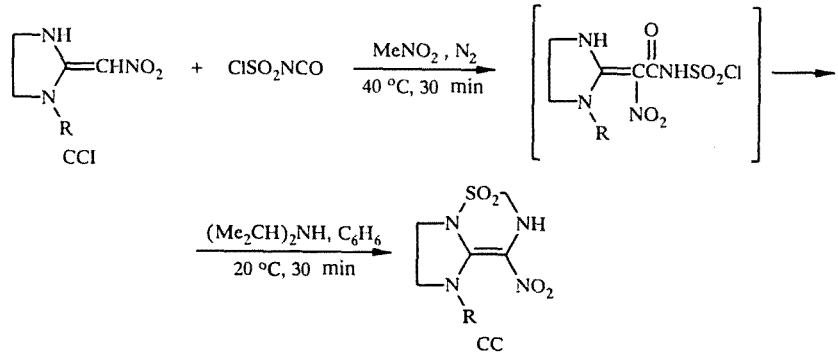
Analogous products CXCVII (R = H, n = 2, 3) are obtained in the reaction of the salt $O_2NCH=C(SMe)S^-K^+$ with amines $H_2N(CH_2)_nOSO_3H$ in dichloroethane at pH 7.3-7.7 [180].

The reaction of hydrochloride salt $HCl \cdot H_2N(CH_2)_2SH$ with nitroalkene V in the presence of methylamine gave CXCIX [181]:



CXCIX

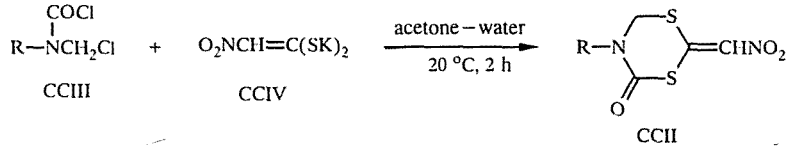
Bicyclic derivatives (CC) containing a five-membered ring with two nitrogen atoms fused to a six-membered ring with two nitrogen atoms and a sulfur atom were obtained in 53-68% yield by the reaction of 2-(nitromethylene)imidazolidine or its N-monosubstituted derivatives (CCI) with chlorosulfonyl isocyanate and subsequent treatment of the reaction product with diisopropylamine [182]:



CCI

R = H, Me, Et, Me_2CH, Ph

The synthesis of CCII was carried out by the reaction of acid chloride CCIII with nitro derivative CCIV in 32-52% [183]:



CCIII CCIV CCII

Thus, analysis of the literature indicates that aliphatic nitro compounds are convenient and available starting reagents for the synthesis of various heterocyclic compounds, including complex condensed heterocyclic systems.

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