CHAPTER I

SYNTHESIS OF NITROHETEROCYCLIC COMPOUNDS

Introduction

During the last two decades, more and more nitroheterocycles, with a variety of activities, have found a place in therapy. As a consequence, considerable research efforts have been aimed at the design and synthesis of nitroheterocycles as potential medicinal compounds.

Nitroheterocycles, in general, have been synthesized through the nitration of preformed heterocycles. Thus, 2-methyl-5-nitroimidazole (1) required as the starting material for the synthesis of metronidazole and tinidazole, is obtained by the nitration of 2-methylimidazole.¹

\[ \text{HNO}_3 \quad \text{H}_2\text{SO}_4 \quad \text{N} \quad \text{CH}_3 \]

(1)

Similarly, 5-nitro-2-furaldehyde required for the synthesis of the various 5-nitro-2-furaldehyde derivatives of medicinal...
interest is obtained as a diacetate (2) by the nitration of 2-furaldehyde in acetic anhydride.\(^2\)

\[
\begin{align*}
\text{HO} & \xrightarrow{\text{(CH\(_3\)CO)}_2\text{O}} \text{HNO}_3 \quad \text{CH(OOCOCH\(_3\))}_2 \\
\end{align*}
\]

However, in recent years, an alternate route of heterocyclization of nitroaliphatic compounds to obtain nitroheterocycles has been recognised to have distinct advantages. Nitroheterocycles, with specific substitution pattern, can be obtained directly under mild reaction conditions. Such an approach for the synthesis of nitro heteroaromatic compounds has been the subject of a review by Rajappa and Nair.\(^3\) The authors have classified the reported methods for the synthesis of nitroheterocycles according to the type of heterocycle obtained from nitroaliphatic synthons.

Herein, an attempt has been made to present a review on the synthesis of nitroheterocycles according to the type of nitroaliphatic synthons employed for the heterocyclization. The nitroaliphatic synthons can be classified in two groups according to the fragment which they contribute to the resulting nitroheterocycle: (I) those contributing nitro
bearing carbon chain, and (II) those contributing nitro
bearing carbon chain along with heteroatoms.

**Synthesis of Nitroheterocycles**

(I) From nitroaliphatic synthons contributing
nitrobearing carbon chain

A) **One carbon chain**

a) $O_2N-C$

i) $O_2N-C + C-C-S \rightarrow$ Thiophenes

ii) $O_2N-C + S-C-C \rightarrow$ Thiophenes

iii) $O_2N-C + C-N-C-C \rightarrow$ Pyrroles

b) $O_2N-C-Br$

i) $O_2N-C + S-C-C \rightarrow$ Thiophenes

ii) $O_2N-C + O-C-C \rightarrow$ Furans

iii) $O_2N-C + X-C-C-C \rightarrow$ Selenophenes (X=Se)

iv) $O_2N-C + S-C-N-C \rightarrow$ Tellurophenes (X=Te)

Thiazoles

B) **Two carbon chain**

a) $O_2N-CH = \overset{R}{C-Lg}\ast$

i) $O_2N-C-C + S-C-C \rightarrow$ Thiophenes

ii) $O_2N-C-C + C-S-C \rightarrow$ Thiophenes

iii) $O_2N-C-C + N-C-C \rightarrow$ Pyrroles

\* Lg = Leaving group.
iv) $O_2N-C-C + N-N-C \rightarrow$ Pyrazoles
v) $O_2N-C-C + N-C-N \rightarrow$ Imidazoles
vi) $O_2N-C-C + N-N-N \rightarrow$ Triazoles
vii) $O_2N-C-C + O-N-C \rightarrow$ Isoxazoles
viii) $O_2N-C-C + N-C-C-C \rightarrow$ Pyridines
ix) $O_2N-C-C + N-N-C-C \rightarrow$ Pyridazines
x) $O_2N-C-C + O-C-C-C \rightarrow$ Chromenes
b) $O_2N - C = C-R$

i) $O_2N-C-C + C-N-N \rightarrow$ Pyrazoles
ii) $O_2N-C-C + N-N-N \rightarrow$ Triazoles

Lg H

Lg Lg

c) $O_2N - C = CH$

i) $O_2N-C-C + C-C-O \rightarrow$ Furans
ii) $O_2N-C-C + N-C-C \rightarrow$ Pyrroles
iii) $O_2N-C-C + N-C-Se \rightarrow$ Selenazoles
d) $O_2N-CH=CH-$

i) $O_2N-C-C + C-N-C \rightarrow$ Pyrroles
ii) $O_2N-C-C + N-N-C \rightarrow$ Pyrazoles
iii) $O_2N-C-C + N-N-N \rightarrow$ Triazoles
iv) $O_2N-C-C + C-N-C-C \rightarrow$ Pyridines
C) **Three carbon chain**

\[
\begin{align*}
\text{C-Lg} \\
\text{O}_2\text{N-C} \\
\text{C-Lg}
\end{align*}
\]

\[
\text{NO}_2
\]

i) \[\text{C - C - C + N-C} \rightarrow \text{Pyrroles}\]

\[
\text{NO}_2
\]

ii) \[\text{C-C-C + N-N} \rightarrow \text{Pyrazoles}\]

\[
\text{NO}_2
\]

iii) \[\text{C-C-C + N-O} \rightarrow \text{Isoxazoles}\]

\[
\text{NO}_2
\]

iv) \[\text{C-C-C + N-C-C} \rightarrow \text{Pyridines}\]

\[
\text{NO}_2
\]

v) \[\text{C-C-C + N-C-N} \rightarrow \text{Pyrimidines}\]

vi) \[\text{O}_2\text{N-C-C-C + N-O} \rightarrow \text{Isoxazoles}\]

D) **Four carbon chain**

\[
\text{O}_2\text{N-C-C-C-C}
\]

i) \[\text{O}_2\text{N-C-C-C-C + S} \rightarrow \text{Thiophenes}\]

ii) \[\text{O}_2\text{N-C-C-C-C + N-N} \rightarrow \text{Pyridazines}\]
(II) From nitroaliphatic synthons contributing nitro-bearing carbon chain along with hetero atom(s).

A) Carbon chain and one hetero atom.

\[ O_2N-(CH_2)_nX \]

\[ \text{i)} \quad O_2N-C-S + C-C-C \quad \rightarrow \quad \text{Thiophenes} \]
\[ \text{ii)} \quad O_2N-C-C-S + C-C \quad \rightarrow \quad \text{Thiophenes} \]
\[ \text{iii)} \quad O_2N-C-C-N + C-C \quad \rightarrow \quad \text{Pyrroles} \]
\[ \text{iv)} \quad O_2N-C-C-N + C-S \quad \rightarrow \quad \text{Thiazoles} \]
\[ \text{v)} \quad O_2N-C-C-N + N-N \quad \rightarrow \quad \text{Triazoles} \]
\[ \text{vi)} \quad O_2N-C-C-N + C-C-C \quad \rightarrow \quad \text{Pyridines} \]
\[ \text{vii)} \quad O_2N-C-C-N + C-N-C \quad \rightarrow \quad \text{Pyrimidines} \]
\[ \text{viii)} \quad O_2N-C-C-C-C-O + C \quad \rightarrow \quad \text{γ-pyrones} \]

B) Carbon chain and two hetero atoms.

\[ \text{i)} \quad O_2N-C-N-O + C-C \quad \rightarrow \quad \text{Isoxazoles} \]
\[ \text{ii)} \quad O_2N-C-C-N-N + C-C \quad \rightarrow \quad \text{Pyridazines} \]
\[ \text{iii)} \quad NC-N-C-C-S \quad \rightarrow \quad \text{Isothiazoles} \]
\[ \text{iv)} \quad NC-N-C-C-C \quad \rightarrow \quad \text{Pyrimidines} \]
Synthesis of Nitroheterocycles

I) The nitroaliphatic synthons that contribute nitro bearing carbon chain can be grouped as type A, B, C & D according to their contribution of one, two, three or four carbon atoms to the resultant heterocycle.

Type A: Nitromethane and bromonitromethane have been used extensively in the synthesis of five membered nitroheterocycles, such as thiophenes, selenophenes, tellurophenes, thiazoles, selenazoles, pyrroles, and furans.

a) $O_2N-C$: The nucleophilic activity of nitromethyl anion, generated from nitromethane in the presence of a base, is utilized in the reaction of certain bifunctional or masked bifunctional reagents possessing electrophilic carbon or sulphur atom. Nitrothiophenes and nitropyrrroles have been synthesized by this approach:

i) $O_2N-C + C-C-C-S \rightarrow$ Thiophenes

3-Amino-1,2-dithiolium salts (3) have been reacted with nitromethane in methanol at 20°C in the presence of sodium methoxide to obtain 3-amino-2-nitrothiophenes (4).
ii) $O_2N-C + S-C-C-C \rightarrow $ Thiophenes

Reaction of nitromethane with 2,2'-diformyl diphenyl disulfide (5) in the presence of triethylamine leads to the formation of 2-nitrobenzo(b) thiophene (6) in 29% yield. Addition of benzoyl peroxide (0.5 mol) increases the yield to 77%. Similarly, the reaction of pyrazole (7) with nitromethane gives thieno[3, 2-d] pyrazole (8).
Kiel and Kröhnke have synthesized 3-nitropyroles as well as a variety of annellated 3-nitropyroles by reacting nitromethane with various heterocyclic ylids under basic conditions. Thus, 3-nitropyrole (9) has been obtained by reacting the ylid of N-acetylnbenzthiazolium bromide (10) with nitromethane under basic condition. The free thiol (9) gets oxidised by air to disulphide. The condensation of N-phenacyl or N-acetylnisoquinolinium bromide with nitromethane under basic condition gives the intermediate (12) which on dehydrogenation gives 1-nitropyrole(2,1-α)-isoquinoline (11), while the loss of nitrous acid from the intermediate (12) leads to the formation of the pyrrole (13).
Quinolinium and quinoxalinium ylids when reacted with nitromethane under basic condition gives 3-nitopyrrolo[1,2-a]quinoline (14) and 3-nitro-2-phenylpyrrolo[1,2-a]quinoxaline (15). However, only 3-cyano pyridinium ylid reacts with nitromethane anion to give (16).
b) O₂N-C-Br: Bromonitromethane has been extensively used as one carbon donor in the synthesis of nitroheterocycles. Condensation of bromonitromethane with a suitable nucleophile, such as HZ-C=C-Y, where Z = S, O, Se and Te has yielded a variety of nitroheterocycles, for example thiophenes, selenophenes, tellurophenes, thiazoles, condensed thiophenes and benzofurans. Bromonitromethane initially forms Z-C bond followed by cyclization through the acidic methylene group.

i) O₂N-C + S-C-C-C \rightarrow Thiophenes

Cagiant and co-workers have reacted bromonitromethane with the adduct of β-chloro-α, β-unsaturated aldehydes (17) and sodium sulfide to obtain 2-nitrothiophenes (18).\(^7\)

\[\begin{align*}
\text{Cagiant and co-workers have reacted bromonitromethane with the adduct of } \beta-\text{chloro-} \alpha, \beta-\text{unsaturated aldehydes (17) and sodium sulfide to obtain 2-nitrothiophenes (18).}\]
\[\text{(17)} \quad \text{and } \text{(18)}\]
Multifunctional 2-nitrothiophenes (19) have been obtained by reacting bromonitromethane with enamine-isothiocyanate adduct (20).\(^8\)

\[
\begin{align*}
\text{CH}_2\text{C} = \text{C} - \text{NHR}_3 + \text{BrCH}_2\text{NO}_2 & \rightarrow \text{CH}_3\text{S} = \text{S} + \text{NHR}_3 \\
\text{(20)} & \rightarrow \text{(19)}
\end{align*}
\]

Similarly, morpholide (21) has been reacted with bromonitromethane to give 2-nitrothiophene (22).\(^9\)

\[
\begin{align*}
\text{Ph} & + \text{CHOH} + \text{BrCH}_2\text{NO}_2 \\
\text{(21)} & \rightarrow \text{Ph} + \text{NO}_2
\end{align*}
\]

2,4-Dinitrothiophenes (23) and (24) have been synthesized from the adduct of nitroketeneaminals-isothiocyanate (25)\(^8\) and benzoylnitromethane-isothiocyanate adduct (26)\(^10\) with bromonitromethane.
Phenylnpropionic thioanilide (27) has been reacted with bromo-nitromethane to give 2-nitrothiophene (28).
Similarly, 3-amino-2-nitrobenzo(b)thiophene (29) has been synthesized by reacting o-cyanothiophenol (30) with bromonitromethane in aqueous sodium hydroxide.\textsuperscript{12} The reaction has been extended to the synthesis of pyridothiophene (31).\textsuperscript{13}  

\begin{align*}
\begin{array}{c}
\text{\begin{tikzpicture}[scale=0.5]
\draw (0,0) -- (2,0) -- (2,2) -- (0,2) -- cycle;
\draw (0,1) -- (1,0);
\draw (1,1) -- (2,2);
\draw (0,0) circle (0.15cm);
\draw (2,0) circle (0.15cm);
\draw (0,2) circle (0.15cm);
\draw (2,2) circle (0.15cm);
\end{tikzpicture}}
\end{array}
\quad + \quad \text{\begin{tikzpicture}[scale=0.5]
\draw (0,0) -- (2,0) -- (2,2) -- (0,2) -- cycle;
\draw (0,1) -- (1,0);
\draw (1,1) -- (2,2);
\draw (0,0) circle (0.15cm);
\draw (2,0) circle (0.15cm);
\draw (0,2) circle (0.15cm);
\draw (2,2) circle (0.15cm);
\end{tikzpicture}}
\quad \rightarrow \\
\begin{array}{c}
\text{\begin{tikzpicture}[scale=0.5]
\draw (0,0) -- (2,0) -- (2,2) -- (0,2) -- cycle;
\draw (0,1) -- (1,0);
\draw (1,1) -- (2,2);
\draw (0,0) circle (0.15cm);
\draw (2,0) circle (0.15cm);
\draw (0,2) circle (0.15cm);
\draw (2,2) circle (0.15cm);
\node at (0.5,0.5) {\text{NH}_2};
\node at (2,0.5) {\text{NO}_2};
\end{tikzpicture}}
\end{array}
\end{align*}

(29)

(30)

(31)

ii) $O_2N-C + O-C-C-C \rightarrow $ Furans

Various substituted salicyaldehydes (32) have been condensed with bromonitromethane to give 2-nitrobenzofurans (33).\textsuperscript{14-20} However, the yields of the nitrofurans obtained in this reaction are very low.
Similarly, condensation of (34) with bromonitromethane and potassium fluoride in methanol gives nitrotetrahydronaphthofuran (35).\textsuperscript{21}

\[
\begin{array}{c}
\text{CHO} \\
\text{OH} \\
\text{BrCH}_2\text{NO}_2 \\
\text{OH}
\end{array}
\begin{array}{c}
\text{R} \\
\text{R}_1 \\
\text{R}_2 \\
\text{O}
\end{array}
\begin{array}{c}
\text{NO}_2 \\
\text{R} \\
\text{R}_1 \\
\text{R}_2
\end{array}
\Rightarrow
\begin{array}{c}
\text{CHO} \\
\text{OH} \\
\text{BrCH}_2\text{NO}_2 \\
\text{OH}
\end{array}
\begin{array}{c}
\text{R} \\
\text{R}_1 \\
\text{R}_2 \\
\text{O}
\end{array}
\begin{array}{c}
\text{NO}_2 \\
\text{R} \\
\text{R}_1 \\
\text{R}_2
\end{array}
\begin{array}{c}
(33)
\end{array}

\begin{array}{c}
(34)
\end{array}
\begin{array}{c}
(35)
\end{array}

\text{iii) } \text{O}_2\text{N-}{}^C + \text{X-C-C-C} \quad \Rightarrow \quad \text{Selenophenes } (X = \text{Se}) \\
\quad \quad \quad \quad \text{Tellurophenes } (X = \text{Te})

\text{Cagiant and Co-workers}\textsuperscript{22,23} \text{ have extended the synthesis of 2-nitrothiophenes (18) to prepare 2-nitroselenophenes (36) and 2-nitrotellurophenes (37) by reacting the adduct of } \beta-\text{chloro-}{}^\alpha, \beta-\text{unsaturated aldehyde (38) and}
sodium selenide, or sodium telluride with bromonitromethane.

\[
\begin{align*}
R_1 & \quad \text{CHO} \\
R_2 & \quad \text{Cl}
\end{align*}
\]

(38)

\[
\begin{array}{c}
i) \text{Na}_2X \\
\text{ii} \text{BrCH}_2\text{NO}_2 \\
\end{array}
\]

36) \( X = \text{Se}, \ R_2 = \text{Ph}; \ R = \text{H} \)

37) \( X = \text{Te}, \ R_2 = \text{CMe}_3; \ R_1 = \text{H} \)

\( R_1R_2 = -(\text{CH}_2)_4- \)

iv) \( \text{O}_2\text{N-C} + \text{S-C-N-C} \rightarrow \text{Thiazoles} \)

5-Nitrothiazoles (39) have been synthesized by the condensation of bromonitromethane with the adduct obtained from \( N \)-phenylbenzimidoyl isothiocyanate (40) and a nucleophile in the presence of triethylamine.\(^{24}\)
Similarly, reaction of bromonitromethane with the adduct of amidine-isothiocyanate (41) has yielded the 5-nitrothiazole (42).
A variety of nitroaliphatic synthons of the type $O_2N-C=CH-C-R$ have been employed for the synthesis of nitroheterocycles. Such nitroaliphatic synthons have a leaving group either at $C_1$, $C_2$ or at both $C_1$ and $C_2$. Nitroethylene derivatives have also been used for the synthesis of nitroheterocycles. Various nitroheterocyclic compounds, such as thiophenes, pyrroles, pyrazoles, imidazoles, triazoles, furans, isoxazoles, selenazoles and pyridines have been synthesized from such nitroethylene derivatives.

a) The nitroaliphatic synthons of the type $O_2N-CH=CH-R$ such as nitroketones, aldehydes, enolethers and enamines, nitroacetic acid derivatives, nitroketeneaminals, when condensed with 1-3 dipolar species or reagents possessing appropriately substituted electrophilic-nucleophilic centers result in the formation of various nitroheterocycles, such as thiophenes, pyrroles, pyrazoles, imidazoles, triazoles, isoxazoles, pyridines and condensed pyridines:

i) $O_2N-C-C + S-C-C \rightarrow$ Thiophenes

2-Amino-3-nitrothiophene (43) has been obtained by cyclocondensation of nitroacetonitrile (44) with acetonyl mercaptan (45).
ii) $O_2N\text{-C-C} + C\text{-S-C} \rightarrow \text{Thiophenes}$

The reaction of $\alpha$-haloketone (46) with the adduct of benzoylnitromethane-isothiocyanate (47) gives 3-nitrothiophene (48).\(^{10}\)

iii) $O_2N\text{-C-C} + N\text{-C-C} \rightarrow \text{Pyrroles}$

1,1-Bis(methylmercapto)-2-nitroethylene (49) has been reacted with aminoacetaldehyde diethyl acetal (50) and
the product thus obtained cyclized by dry HCl in ether to give 2-methylmercapto-3-nitropyrrrole (51).\textsuperscript{27}

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{H} & \quad \text{H}_2\text{C}=\text{O} & \quad \text{O}_2\text{C}_2\text{H}_5 & \quad \text{O}_2\text{N} & \quad \text{H}_2\text{C}=\text{O} \\
\text{CH}_3\text{S} & \quad \text{SCH}_3 & \quad & & \quad \text{H}_2\text{N} & \quad \text{CH}_3\text{S} \\
(49) & & & & (50) & & (51)
\end{align*}
\]

iv) \textit{O}_2\textit{N-C-C} + \textit{N-N-C} --------> Pyrazoles

Phenyldiazomethane (52) has been reacted with \textit{O}, \textit{B}-dinitrostyrene (53) to yield 4-nitropyrazole (54).\textsuperscript{28}

\[
\begin{align*}
\text{Ph-C} & = \text{CH-NO}_2 + \text{Ph-CHN}_2 \\
(53) & & (52) & & (54)
\end{align*}
\]

The condensation of 1-morpholino-2-nitroethylene (55) with \textit{O}-chlorohydrazone (56) in the presence of triethylamine gave 4-nitropyrazole (57).\textsuperscript{29}

\[
\begin{align*}
\text{O}_2\text{N-CH=CH-NO}_2 & + \text{Ar-NH-N} = \text{O}_2\text{Cl} \\
(55) & & (56) & & (57)
\end{align*}
\]
A variety of pyrazolopyridines has been synthesized by cyclocondensation of pyridinium N-imines (58) with 1,1-bis-(methylmercapto)-2-nitroethylene (49) to afford 2-methylthio-1-nitropyrazolo[1,5-a]pyridine (59). \[30\]

\[
\begin{array}{c}
\text{(58)} \\
\text{+} \\
\text{(49)} \\
\text{+} \\
\text{(59)} \\
\text{+} \\
\text{(60)}
\end{array}
\]

The intermediate (60) undergoes dehydrogenation instead of losing nitrous acid to give (59). Similarly, 2-methylthio-
1-nitropyrazolo[5,1-a]isoquinoline (61) was obtained from isoquinolinium-N-imine. 30

\[
\text{(61)}
\]

\[\text{v) } \text{O}_2\text{N-C-C} + \text{N-C-N} \rightarrow \text{Imidazoles}\]

Recently, 5-nitroimidazole (62) has been synthesized by the reaction of N-haloamidines (63) and 1-piperidino-2-nitroethylene (64) in carbon tetrachloride in the presence of pyridine. 31

\[\text{(64)}\]

\[\text{(63)}\]

\[\text{(62)}\]

\[\text{vi) } \text{O}_2\text{N-C-C} + \text{N-N-N} \rightarrow \text{Triazoles}\]

Condensation of 1-morpholino-2-nitroethylene (65) with aryl azide and tosyl azide gives 4-nitrotriazole (66)
and (67).²⁹,³²,³³

\[
\begin{align*}
\text{ArN}_3 & \quad \rightarrow \quad \text{ArN}_3
\end{align*}
\]

(66)

\[
\begin{align*}
\text{ArN}_3 & \quad \rightarrow \quad \text{ArN}_3
\end{align*}
\]

(65)

(67)

\[
\begin{align*}
\text{vii) } \text{O}_2\text{N-C-C} + \text{O-N-C} & \quad \rightarrow \quad \text{Isoxazoles}
\end{align*}
\]

1:3 Dipolar cycloaddition reaction of \( \text{R-C≡N}^{+} \) to

nitroketones or nitroacetic acid derivatives has been widely

used for the synthesis of 4-nitroisoxazoles. Nitroketeneaminals (68) have been reacted with nitrile oxide (69) to give

5-amino-4-nitroisoxazoles (70).³⁴

\[
\begin{align*}
\text{R}_2\text{N} & \quad \rightarrow \quad \text{R}_2\text{N}
\end{align*}
\]

(68)

(69)

(70)
A variant in this reaction makes use of hydroxamoyl chloride (71). Nitrile oxide (69) is generated, in situ, from (71) in the presence of a base. Thus, 4-nitroisoxazoles (72) and (73) have been synthesized from hydroxamoyl chloride and the compounds having methylene group activated by nitro on one side and a carbonyl or nitrile on the other side.\textsuperscript{35,36}

\[
\begin{align*}
\text{(71)} & \quad \text{(72)} \\
\text{(73)} & \quad \text{(74)}
\end{align*}
\]

In a one pot reaction, condensation-dehydration of ω-nitroketones (74) at 50-150°C in non-aqueous solvent in the presence of a base catalyst lead to the formation of 3,5-di-substituted-4-nitroisoxazoles (75).\textsuperscript{37} The sequence of the
reaction involves conversion of one molecule of nitroketone to halo aldoxime. Nitrile oxide is formed in situ from halo aldoxime in the presence of a base, followed by its condensation with another molecule of the nitroketone to yield (75).

\[
\begin{align*}
\text{reaction:} & \quad R - C = O \\
\text{KF} & \quad \text{t-C}_{4}H_{9}OH \\
\text{yield:} & \quad R - C = O
\end{align*}
\]

Recently, 4-(2-nitrovinyl)morpholine (55) has been condensed with nitroacetaldehyde diethylacetal (76) in a mixture of benzene-phenyl isocyanate to give 3-substituted-4-nitroisoxazole (77).

\[
\begin{align*}
0_{2}N - \text{CH} - \text{CH}(\text{OC}_{2}H_{5}) \quad + \quad 0_{2}N - \text{CH}_{2} - \text{CH}(\text{OC}_{2}H_{5})_{2} & \quad \rightarrow \quad 0_{2}N - \text{CH}(\text{OC}_{2}H_{5})_{2} \\
(55) & \quad \rightarrow \quad (77)
\end{align*}
\]
A large number of o-amino carbonyl compounds having general structure N-C=C-C-Y when reacted with nitroaldehyde, nitroketones, nitroacetic acid and nitroketene acetal derivatives lead to the formation of nitropyridine and condensed nitropyridine derivatives.

3-Nitropyridones (78) have been obtained by the reaction of enamine-ketones (79) with nitroacetic ester at 60°C.  

\[
R-NH-\text{CH}=\text{CH}-\text{C}-\text{CH}_3 + O_2N-\text{CH}_2-C-\text{OCH}_3 \rightarrow \text{N-CH}_3\text{O}
\]

(79) (78)

1,1-Bis(methylmercapto)-2-nitroethylene (49) has been reacted with 3-bromopropylamine hydrobromide (80) to give the intermediate (81) which cyclizes in the presence of sodium hydride to tetra-hydopyridine (82).
Methazonic acid (83) has been reacted with o-amino ketones (84) to yield 3-nitroquinolines (85). 41-43

Nitromethane reacts with isatin (86) in aqueous potassium hydroxide to give 3-nitrocinchoninic acid (87). 44 The reaction involves in situ formation of methazonic acid from nitromethane, which in turn reacts with the o-amino-phenylglyoxylic acid formed from isatin under basic condition.
Similarly, 2-methyl-3-nitroquinoline (88) has been synthesized by the reaction of nitroacetone (89) with o-aminobenzaldehyde (90).

Nitroacetic acid derivatives have been used extensively for the synthesis of quinolines, thienopyridines and napthyridines. Condensation of 2-aminonicotinaldehyde (91) with nitroacetic ester in the presence of piperidine yield 2-hydroxy-3-nitro-1,8-napthyridines (92).
Reaction of isatoic anhydride (93a) with nitroacetic ester in the presence of sodium hydride gives a series of 4-hydroxy-3-nitroquinolines (94). Under similar condition, 4-hydroxy-3-nitro-1,8-napthyridine (95) was obtained from (93b).

\[
\begin{align*}
(93a) \quad X &= \text{CH} \\
(93b) \quad X &= \text{N}
\end{align*}
\]

A variety of o-aminophenyl ketones (96) has been reacted with 1,1-bis(methylmercapto)-2-nitroethylene (49) in acetic acid to obtain 3-nitroquinolines (97).

\[
\begin{align*}
\text{(96)} &\quad + \quad \text{(49)} \\
\text{(97)} &\quad \text{Ph}
\end{align*}
\]

Thienopyridine (98) has been prepared by reacting 1,1-bis(methylmercapto)-2-nitroethylene (49) with 2-amino-3-benzoylthiophene (99).
2-Amino-3-nitro-4-quinolone derivatives (101) are obtained when anthranilic ester (100) is used in place of o-amino-ketones.  

Condensation of 1-arylamino-1-methylthio-2-nitroethylene (102) with o-aminocarbonyl compounds under acidic condition yields 2-arylamino-3-nitroquinolines (103) and (104).
Nitropyridazinone (105) has been obtained in 45% yield by the condensation of hydrazide (106) with nitroacetic esters in piperidine at 105°C.52
Substituted salicyaldehyde (107) has been reacted with nitroethylene derivatives to afford 3-nitro-2H-chromenes (108, \[ R = \text{NR}_2, \text{OR}, 3,4-\text{RR'} \rightarrow \text{C}_6\text{H}_3 \]). $^{53-55}$

Similarly, the reaction of ethyl nitroacetate with salicyaldehyde yields 3-nitrocoumarins (109). $^{56}$

b) Nitroaliphatic synthons of the type $O_2N-C=CH-R$, such as $\beta$-bromo-$\beta$-nitrostyrene, dinitroethylene when reacted with 1:3 dipolar reactants having electrophilic and nucleophilic centres lead to the formation of nitropyrazoles and nitrotriazoles, respectively.
i) \( \text{O}_2\text{N-C-C} + \text{C-N-N} \rightarrow \text{Pyrazoles} \)

Diazomethane and its derivatives, such as \( \alpha \)-diazoketones (110), have been reacted with \( \beta \)-bromo-\( \beta \)-nitrostyrene (111) and 1,1-dinitroethylene (112) to give 3-nitropyrazoles (113)\(^{57}\) and (114)\(^{58}\) respectively.

\[
\begin{align*}
\text{Ph-CH=C(Br)NO}_2 + \text{CH}_2\text{N}_2 & \rightarrow \text{Ph} \\
(111) & \rightarrow (113)
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2=\text{C(NO}_2\text{)} + \text{R-CO-CH}_2\text{N}_2 & \rightarrow \text{COR} \\
(112) & \rightarrow (110)
\end{align*}
\]

ii) \( \text{O}_2\text{N-C-C} + \text{N-N-N} \rightarrow \text{Triazoles} \)

1:3 Dipolar addition of halogenated nitroethylene (115) derivatives with azides, such as sodium azide and phenyl azide, yields 4-nitro-1,2,3-triazoles (116).\(^{59,60}\)
c) α-Haloketones and 1,2-dihalonitroethylene represent nitroaliphatic synthons of the type \( \text{O}_2\text{N-C}=\text{C-Lg} \) and their condensation with bi-nucleophiles yield nitropyrrroles, nitrofurans, and nitroselenazoles.

i) \( \text{O}_2\text{N-C-C} + \text{C-C-O} \rightharpoonup \text{Furans} \)

Binucleophilic addition of trichloronitroethylene (117) to \( \beta \)-ketoesters leads to the formation of 2-nitrofurans (118). 61-63 Substitution of dimedone for \( \beta \)-ketoesters gives (119).
ii) $O_2N-C-C + N-C-C \rightarrow$ Pyrroles

A series of 2-arylamino-3-nitroindoles (120) have been prepared in high yields (75%) by the condensation of trichloronitroethylene (117) and arylamines.  

\[
\begin{align*}
\text{NH}_2 \\
\text{R} \\
\end{align*}
\]  

\[
\begin{align*}
\text{Cl} = \text{Cl} = \text{Cl} \\
\text{NO}_2 \\
\end{align*}
\]  

(117)  

(120)

iii) $O_2N-C-C + N-C-Se \rightarrow$ Selenazoles

$\alpha$-Bromo-$\alpha$-nitroacetophenone (121) undergoes cyclo-condensation with 1,3-binucleophile, such as $N$-aryl-selenoureas (122) to yield 5-nitroselenazoles (123).

\[
\begin{align*}
\text{Ph} \\
\text{OH} \\
\text{O}_2\text{N} \\
\text{Br} \\
\text{Ph} \\
\text{HSe} \\
\text{NH} \\
\text{NH} \\
\text{Ar} \\
\end{align*}
\]  

(121)  

(122)  

(123)
d) Nitroethylenes, \( \text{O}_2\text{N-CH=CH-} \), have been utilized in the synthesis of some nitroheterocycles.

i) \( \text{O}_2\text{N-C-C} + \text{C-N-C} \rightarrow \text{Pyrroles} \)

3-Nitopyrrole has been obtained by Diels-Alder reaction of nitroethylene with dienophiles. The Diels-Alder adduct obtained from nitroethylene or 1-nitropropene with 5-alkoxy-4-methyloxazole (124) in benzene at \(-3^\circ\text{C}\) followed by acid hydrolysis gives 3-nitopyrrole (125) or 2-acetyl-4-methyl-3-nitopyrrole (126).\(^{66,67}\)

![Chemical structures](image)

(124) \( R = \text{H} \)

(125) \( R = \text{H} \)

(126) \( R = \text{CH}_3 \)
ii) $\text{O}_2\text{N}-\text{C}-\text{C} + \text{N}-\text{N}-\text{C} \rightarrow \text{Pyrazoles}$

Pyrazolopyrazolones (127) have been prepared by treating azomethineimines (128) with nitroethylene derivatives in sodium ethoxide.\textsuperscript{68}

\begin{align*}
(128) & \quad \text{+} \\
& \quad \text{R-CH=CH-NO}_2
\end{align*}

\begin{align*}
\text{(127)} & \quad \text{R} \\
& \quad \text{N}_2\text{O}_2
\end{align*}

iii) $\text{O}_2\text{N}-\text{C}-\text{C} + \text{N}-\text{N}-\text{N} \rightarrow \text{Triazoles}$

Cycloaddition of phenyl azide (129) to $\beta$-nitrostyrene (130) occurs in both the orientations: in one case, the intermediate loses nitrous acid to give 1,4-diphenyl-1,2,3-triazole (131); whereas, the other adduct undergoes dehydrogenation to give 1,5-diphenyl-4-nitro-1,2,3-triazole (132).\textsuperscript{69}
iv) $\text{O}_2\text{N-C-C} + \text{C-N-C-C} \rightarrow \text{Pyridines}$

Diels-Alder reaction of nitropropylene with 5-ethoxyoxazole (133) leads to the formation of 4-nitopyridine (134). 67
Type C: A variety of five and six membered nitro heterocyclic compounds have been synthesized from aliphatic nitro synthons, such as
\[ \text{O}_2\text{N-} \quad \text{C-Lg} \]
which would contribute \[ \text{O}_2\text{N-} \quad \text{C} \]
pattern to the resulting nitroheterocycles. The nitroaliphatic synthons that have been used are nitromalonaldehyde, nitroketones, and nitromalonic ester derivatives. These reagents react with various binucleophiles, such as hydrazines, amidines, hydroxylamine, alkyl- and aryl-amine with an active hydrogen alpha to the amino group to give nitropyrrroles, pyrazoles, isoxazoles, pyridines and pyrimidines.

\[ \text{NO}_2 \]
1) \[ \text{C-C-C + N-C} \quad \text{---------} \quad \text{Pyrroles} \]

Condensation of ethyl glycinate (135) or \( \beta \)-aminopropiophenone (136) with nitromalonaldehyde (137) in the presence of alkali yield 3-nitropyrrrole (138) and (139), respectively. 70-73
3,4-Dinitropyroles (140) have been synthesized from dipotassium salt of trinitropropionaldehyde (141) by reaction with aliphatic aldehydes and primary amines in the presence of little ammonia. 74-76
ii) C-C-C + N-N --------> Pyrazoles

Condensation of nitromalonaldehyde (137) with hydrazine (142a) gives 4-nitropyrazoles derivatives (143a). 77-79

Similarly, the reaction of sodio-nitromalonaldehyde with aminoguanidine (142b) in the presence of acid yields 1-guanyl-4-nitropyrazole (143b). 80,81

\[
\begin{align*}
0_2N-C\overset{\text{CH(OH)}}{\text{CHO}} + R-NH-NH_2 &\rightarrow N\begin{array}{c}
\text{NO}_2 \\
\text{R}
\end{array} \\
(137) &\quad (142a) \quad R = H \\
(142b) &\quad R = C\text{(NH)NH}_2 \\
(143a) &\quad R = H \\
(143b) &\quad R = C\text{(NH)NH}_2
\end{align*}
\]

Reaction of hydrazine and its derivatives with ethyl-\(\beta\) -ethoxy-\(\omega\) -nitroacrylate (144) or crotonate leads to the formation of 4-nitro-3-pyrazolone (145). 82

\[
\begin{align*}
0_2N-C\overset{\text{COOC}_2\text{H}_5}{\text{OC}_2\text{H}_5} + R'-NH-NH-R' &\rightarrow N\begin{array}{c}
\text{NO}_2 \\
\text{R}'
\end{array} \\
(144) &\quad (145)
\end{align*}
\]
Similarly, reaction of hydrazine with 3,3-diamino-2-nitroacrylonitrile (146) or its cyclic analog (147) gives 3,5-diamino-4-nitropyrazoles (148) and (149).  

Nitroketeneaminal-isothiocyanate adduct (150) has been reacted with methyl iodide to give (151) which when condensed with hydrazine yields 4-nitropyrazole (152).
4-Nitroisoxazole (153)\textsuperscript{77,85} and 3,5-diphenyl-4-nitroisoxazole (154) have been synthesized by the condensation of \(\beta\)-diketones, such as nitromalonaldehyde (137) or dibenzoylnitromethane (155) with hydroxylamine.\textsuperscript{35}

\[
\text{C-C-C + N-O} \rightarrow \text{Isoxazoles}
\]

Grundmann and Co-workers have prepared 5-amino-4-nitroisoxazole (156) from sodium salt of nitromalonaldehyde and hydroxylamine.\textsuperscript{86} The initially formed sodium malondialdoxime nitronate (157) is diacetylated and cyclized to the
furazan oxide (158). Acid hydrolysis followed by rearrangement in alkali gives 5-amino-4-nitroisoxazole (156).

\[
\begin{align*}
\text{HO-N=CH-C-CH=N-OH} & \quad \text{ACO-N=CH-C-CH=N-OAC} \\
\Downarrow & \\
\text{(157)} & \\
\end{align*}
\]

\[
\begin{align*}
\begin{array}{ccc}
\text{NO}_2 & \quad \text{CH=N-OH} & \quad \text{CH=N-OAC} \\
\text{NH}_2 & \\
\text{(156)} & & \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{ccc}
\text{NO}_2 & \quad \text{CH=N-OH} & \quad \text{CH=N-OAC} \\
\text{NH}_2 & \\
\text{(158)} & & \\
\end{array}
\end{align*}
\]

iv) C-C-C + N-C-C \rightarrow \text{Pyridines}

4-Hydroxy-3-nitro-2-pyridones (159) have been synthesized by condensing enamino-ketones or esters (160) with nitromalonic esters (161). 87
Nitromalonaldehyde (137) has been reacted with various arylamines to give 3-nitroquinolines (162) in 40 to 77% yields.

The cyclization is best catalyzed by the corresponding amine hydrochloride in acetic acid. The tetracyclic compound (163) has been similarly prepared from 3-amino-napthostyril.
Cyclization of 2-amino-4-cyanopyrrole (164) with nitromalonaldehyde (137) gives pyrrolo[2,3-b]pyridine (165).  

Similarly, nitromalonaldehyde has been reacted with 2,4-diamino-6-hydroxypyrimidine in the presence of a base to give 2-amino-4-hydroxy-6-nitopyrido[2,3-d]pyrimidine (166). Pyridopyrimidine (167) has been obtained by the condensation of (168) with nitromalonaldehyde (137).
1-Carbethoxy-3-nitro-4H-quinolinizin-4-one (169) has been synthesized by the condensation of ethyl 2-pyridylacetate (170) with β-ethoxy-α-nitroacrylate (144). 

\[ \text{C-C-C} + \text{N-C-N} \rightarrow \text{Pyrimidines} \]

A variety of amidines react with nitromalonaldehyde (137) in the presence of Triton B or piperidine to give 5-nitopyrimidines (171). However, acetamidine gives
very poor yield of nitropyrimidine, while formamidine does not yield any isolable product.

\[
\begin{align*}
\text{R-} & \text{C-} + \text{O}_2\text{N-} \text{CH(OH)} \rightarrow \text{O}_2\text{N} \text{N-} \text{R} \\
(137) & \\
(171a) \text{ R} = \text{NH}_2 \\
(171b) \text{ R} = \text{N(CH}_3)_2
\end{align*}
\]

2-Amino-5-nitropyrimidine (171a)\textsuperscript{94,95,99} has been obtained in quantitative yields from guanidine and nitromalonaldehyde. N,N-Dimethylguanidine, similarly, gives 2-dimethylamino-5-nitropyrimidine (171b) in 33% yield.\textsuperscript{100}

2-Aminoimidazole (172), a cyclic guanidine, has been reacted with nitromalonic ester (161) to give imidazo[1,2-a]pyrimidine (173).\textsuperscript{101}

\[
\begin{align*}
\text{O}_2\text{N-CH(COOCH}_2\text{H}_5)_2 + \text{H}_2\text{NN} & \rightarrow \text{O}_2\text{N} \\
(161) & \\
(172) & \\
(173)
\end{align*}
\]
Similarly, cyclocondensation of sodio-nitromalonaldehyde (137) with azoles (174) gives 6-nitroazolopyrimidines (175).  

\[
\begin{align*}
\text{N} &\quad \text{NH} \\
\text{H} &\quad \text{C(OH)} \\
\text{2} &\quad \text{NO}_2
\end{align*}
\]

(174) (137) (175)

Nitropyrimidines have been synthesized by the condensation of thiourea with various nitro-aliphatic synthons contributing \(O_2N - C\equiv C\) to the resulting pyrimidine. Condensation of ethyl ethoxymethylenenitroacetate (144) with thiourea in the presence of a base gives 2-thio-5-nitouracil (176).  

\[
\begin{align*}
\text{C}_{2}\text{H}_5\text{O} &\quad \text{NO}_2 \\
\text{C}_2\text{H}_5\text{COOC}_2\text{H}_5 &\quad \text{CS(NH}_2\text{)}_2
\end{align*}
\]

(144) (176)
2-Thio-5-nitrobarbituric acid (177) has similarly been prepared by the reaction of thiourea with nitromalonic ester. \(^{104}\)

\[
\text{HN} \quad \text{HN}
\]
\[
\text{NO}_2
\]
\[
\text{OH}
\]

(177)

Hale and Brill have condensed thiourea with sodio-nitromalonaldehyde (137) in the presence of piperidine to give thiazine (178). \(^{105}\) Recently, 5-nitro-2-piperidinopyrimidine (179) has been prepared in 15% yield under similar conditions. \(^{106}\)
Reaction of 5-methylisothiouranium sulfate (180) with sodio-nitromalonaldehyde (137) in the presence of 1-ethylpiperidine yields 2-methylthio-5-nitropyrimidine (181). Replacement of 1-ethyl piperidine by piperidine in the above reaction gives (179).

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CHO} \\
& + \quad \text{CH}_3\text{S} - \text{NH} \\
\text{(137)} & \quad \text{NH}_2 \\
\text{(180)} & \quad \text{O}_2\text{N} \\
& \quad \text{N} \\
& \quad \text{SCH}_3 \\
\end{align*}
\]

The intermediate (182) obtained by the condensation of ethyl ethoxymethylene nitroacetate (144) with 2-aminopyridine has been cyclized to 3-nitropyrido[1,2-a]pyrimidine (183) in the presence of polyphosphoric acid.
Reaction of sodium nitrite with substituted propargyl bromide (184) in dimethylformamide gives 3-nitroisoxazole (185). Oxime (186) has been proposed as intermediate in this reaction.109,110,111
Similarly, isoxazole (187) has been obtained by the reaction of substituted propargyl bromide (188) with silver nitrite or sodium nitrite.\textsuperscript{109} Alcohol (189) has been isolated as by product.\textsuperscript{111}

\[
\begin{align*}
\text{Ph-C≡C-C-Br} & \quad \text{MNO}_2 \quad \text{O}_2\text{N} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{Ph} \\
(188) & \quad \text{(187)} \\
& \quad \text{+ Ph-C≡C-CH-OH} \\
& \quad \text{CH}_3 \\
(187) & \quad (189)
\end{align*}
\]

**Type D**: Synthesis employing nitroaliphatic synthons having four carbon chain.

i) \(\text{O}_2\text{N-C-C-C-C} + \text{S} \rightarrow \text{Thiophenes}\)

Recently, 2-amino-5-nitrothiophene (190) has been synthesized by the condensation of 1-dimethylamino-2-nitroethylene (191) with ethyl cyanoacetate and elemental sulfur in dimethylformamide.\textsuperscript{112}
ii) \( \text{O}_2\text{N-C-C-C-C} + \text{N-N} \rightarrow \text{Pyridazines} \)

1-Dimethylamino-2-nitroethylene (191) reacts with diethyl malonate in the presence of alkoxides to yield the nitronate salt (192) of nitroethylidemalonate. This serves as a \( \text{O}_2\text{N-C-C-C-C} \) synthon possessing a nucleophilic carbon (\( C_1 \)) and electrophilic carbon (\( C_4 \)). The salt (192) has been coupled with aryl diazonium salts to yield the hydrazone (193) which on intramolecular cyclization yields 3-nitropyridazines (194). 113
II) From nitroaliphatic synthons contributing nitrobearing carbon chain along with hetero atoms.

Type A: From carbon chain and one hetero atom.

i) $\text{O}_2\text{N-C-S} + \text{C-C-C} \rightarrow \text{Thiophenes}$

Recently, mercaptonitromethane (195) has been used as one sulfur and one carbon atom donor for the synthesis of nitrothiophenes. Condensation of 3-chloroacrylonitrile (196) with mercaptonitromethane gives 3-amino-2-nitrothiophene (197).
3-Nitrothiophenes have been obtained by the reaction of α-haloketones with enethiolate salts derived from the base catalysed condensation of nitromethane with isothiocyanates. For example, sodium salt of 1-anilino-1-mercapto-2-nitroethylene (198) on reaction with α-halocarbonyl compounds yields 2-anilino-3-nitrothiophenes (199).\textsuperscript{115}

\[
\begin{align*}
\text{R}_1 \text{Br} \quad \text{OH} & \quad \text{H} \quad \text{NO}_2 \\
\text{R}_2 & \quad \text{S} \quad \text{NH} \quad \text{Na}^+ \\
\text{Ph} & \quad \text{R}_1 \quad \text{NO}_2 \\
\text{R}_2 & \quad \text{S} \quad \text{NH-Ph}
\end{align*}
\]
\[(198) \quad (199)\]

Similarly, 2-nitroethylene-1,1-dithiolate (200) has been cyclized with α-haloketones to yield 2-mercapto-3-nitrothiophene derivatives. These thiophenes have been isolated either as their di-sulfides (201) or as methylthio derivatives (202).\textsuperscript{116}
Condensation of nitroketeneaminals with aryl or alkyl isothiocyanates gives an intermediate (25) which on reaction with α-haloketones lead to the formation of 5-acyl-3-nitrothiophenes (203). 117, 118
iii) $O_2N-C-C-N + C-C \rightarrow \text{Pyrroles}$

Pyrrolo-$2,1-b$-thiazines (204) and (205) have been obtained by the condensation of nitroenamine (206) with glyoxal or glyoxylic acid. 119,120

\[ \text{(204)} \]
\[ \text{(206)} \]
\[ \text{(205)} \]

iv) $O_2N-C-C-N + C-S \rightarrow \text{Thiazoles}$

5-Nitro-$3H$-$2$-thiazole derivatives (207) have been synthesized by the condensation of chlorothioformyl chloride (208) with 1-anilino-1-methylmercapto-2-nitroethylene (102). 121

\[ \text{(102)} \]
\[ \text{(208)} \]
\[ \text{(207)} \]
v) $\text{O}_2\text{N-C-C-N} + \text{N-N} \rightarrow \text{Triazoles}$

Dehydration of oxime-hydrazone (209), obtained by coupling aromatic diazonium salts with methazonic acid (83), by acid anhydride or acid chloride in alkali, give 4-nitro-2H-1,2,3-triazoles (210).122,123

\[
\text{Ar-N}^+ 
\begin{array}{c}
\text{O}_2\text{N-CH}_2-\text{CH-NOH} \\
(83)
\end{array} \rightarrow
\begin{array}{c}
\text{Ar-N} \\
(210)
\end{array}
\]

vi) $\text{O}_2\text{N-C-C-N} + \text{C-C-C} \rightarrow \text{Pyridines}$

Condensation of 2-nitromethylbenzimidazole (211) with acetylacetone (212) affords 4-nitro-1,3-dimethyl-pyridol[1,2-a]benzimidazole (213).124
The adduct obtained from 2-nitromethylene-hexahydroazepine (214) and benzoyl isothiocyanate on recrystallization from acetic acid gives pyrimido[3,4-\(\beta\)]azepine (215).\(^{125}\)
viii) \( \text{O}_2\text{N-C-C-C-C-0} + \text{C} \rightarrow \gamma \)-pyrones

A series of 3-nitrochromones (216) have been prepared by the cyclization of 2'-hydroxy-2-nitroacetophenone (217) by means of formic-acetic anhydride and sodium formate or acetic anhydride-sulfuric acid.\(^{126,127}\)

\[
\begin{align*}
\text{(217)} & \\
\text{(216)}
\end{align*}
\]

o-Benzyl oxy-2-nitroacetophenone (219) is condensed with appropriate aldehyde to give the chalcone (220). Debenzylation and cyclization of chalcone (220) leads to the formation of 3-nitroflavanone (221).\(^ {128}\) 3-Nitroflavone (218) is obtained by aromatization of 3-nitroflavanone (221) by bromination-dehydrobromination.\(^ {129,130}\)
Type B : From carbon chain and two hetero atoms.

i) $\text{O}_2\text{N-C-N-O} + \text{C-C} \rightarrow \text{Isoxazoles}$

Cyclization of the intermediate obtained from chloro-nitroformoxime (222) with Grignard reagent (223 R=Ph, CH$_2$O-tetrahydropyranyl) leads to the formation of 3-nitro-5-substituted isoxazole (185).$^{131,132}$

\[
\text{R-C=C-MgBr} + \text{Cl-N-O} \rightarrow \text{R-C=C-C-NO}_2
\]

(223) (222) (221)

ii) $\text{O}_2\text{N-C-C-N-N} + \text{C-C} \rightarrow \text{Pyridazines}$

Cyclocondensation of nitro-amidrazones (224) with glyoxal in the presence of a base gives 4-nitropyridazines (225).$^{133}$
The methylmercapto derivative (226), when reacted with pyruvaldehyde gives two isomers (227) and (228) depending on the base employed.¹³³
iii) $\text{N-C-C-C-S} \rightarrow \text{Isothiazoles}$

4-Nitroisothiazoline (229) has been obtained by oxidative cyclization of nitroketeneaminals -isothiocyanate (230) using bromine.¹³⁴

\[
\begin{align*}
\text{CH}_3\text{NH} & \quad \text{NO}_2 \\
\text{CH}_3\text{NH} & \quad \text{G-NH-R} \\
\text{S} & \quad \text{(230)}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{HN} & \quad \text{N-S} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{OH} & \quad \text{(229)}
\end{align*}
\]

iv) $\text{N-C-N-C-C} \rightarrow \text{Pyrimidines}$

Monoureide (231), obtained by reacting urea with nitromalonaldehyde, undergoes ring closure and chlorination with phosphorus oxychloride to give 2-chloro-5-nitropyrimidine (232).¹³⁵
(231) \[ \xrightarrow{POCl_3} \] (232)