Tandem *in situ* generation and 1,5-electrocyclization of N-hetaryl nitrilimines. A facile methodology for synthesis of annulated 1,2,4-triazoles and their acyclo C-nucleosides

Ahmad Sami Shawali

*Department of Chemistry, Faculty of Science, University of Cairo, Egypt*

*E-mail: as_shawali@mail.com*

**Abstract**

This review summarizes results of literature reports concerning tandem *in situ* generation and 1,5-electrocyclization of N-hetaryl nitrilimines reported by us and other research groups from 1960 to mid 2009. It outlines the utility of such reactions as facile synthetic strategy for synthesis of annulated triazoles and their acyclo C-nucleosides.

**Keywords**: Nitrilimines, 1.5-electrocyclization, heterocycles, acyclo C-nucleosides

**Contents**

1. Introduction
2. Fused Azolo-triazoles
   2.1. Pyrazolo[5,1-c][1,2,4]triazoles
   2.2. Imidazo[2,1-c][1,2,4]triazoles
   2.3. Thiazolo[2,3-c][1,2,4]triazoles
   2.4. 1,2,4-Triazolo[5,1-c][1,2,4]triazoles
   2.5. 1,2,4-Triazolo[3,4-b][1,3,4]oxadiazoles
   2.6. 1,2,4-Triazolo[4,3-d]tetrazoles
3. Fused triazolo-azines
   3.1. 1,2,4-Triazolo[4,3-a]pyridines
   3.2. [1,2,4]Triazolo[1,5-a]pyridines
4. Fused triazolo-diazipines
   4.1. [1,2,4]Triazolo[4,3-b]pyridazines
   4.2. [1,2,4]Triazolo[4,3-a]pyrimidines
   4.3. [1,2,4]Triazolo[1,5-a]pyrimidines
   4.4. [1,2,4]Triazolo[4,3-a][1,2,4]pyrazines
5. Fused triazolo-triazipines
5.1. [1,2,4]Triazolo[4,3-\(a\)][1,3,5]triazines
5.2. [1,2,4]Triazolo[4,3-\(b\)][1,2,4]triazines
5.3. Acenaphtho[1,2-\(e\)][1,2,4]triazolo[3,4-c][1,2,4]triazines
6. Fused triazolo-benzoazoles
6.1. [1,2,4]Triazolo[4,3-\(a\)]benzoimidzoles
6.2. [1,2,4]Triazolo[3,4-\(b\)]-1,3-benzothiazoles
7. Fused triazolo-azolo-diazines
7.1. Pyrazolo[4,3-\(e\)][1,2,4]triazolo[4,3-\(c\)]pyrimidines
7.2. [1,2,4]Triazolo[4,3-\(e\)]purines
7.3. [1,2,4]Triazolo[3,4-\(f\)]purines
8. Fused triazolo-azolo-triazines
8.1. Pyrazolo[3,4-\(e\)][1,2,4]triazolo[3,4-\(c\)][1,2,4]triazines
8.2. Bis(1,2,4-triazolo)[4,3-\(b\) : 4,3-\(d\)][1,2,4]triazines
9. Fused triazolo-benzoazines
9.1. [1,2,4]Triazolo[4,3-\(a\)]quinolines
9.2. [1,2,4]Triazolo[4,3-\(a\)]isoquinolines
10. Fused triazolo-benzodiazines
10.1. [1,2,4]Triazolo[3,4-\(a\)]phthalazines
10.2. [1,2,4]Triazolo[4,3-\(a\)]quinazolines
10.3. [1,2,4]Triazolo[4,3-\(c\)]quinazolines
10.4. 1,2,4-Triazolo[4,3-\(a\)]quinoxalines
10.5. Pyrido[3,2-\(e\)][1,2,4]triazolo[4,3-\(a\)]pyrimidines
11. Fused triazolo-azolo-triazines
11.1. Tris-[1,2,4-triazolo][4,3-\(a\) : 4,3-\(c\) : 4,3-\(e\)][1,3,5]triazines
11.2. [1,2,4]Triazolo[4',3':2,3][1,2,4]-triazino[5,6-\(b\)]indoles
12. Fused triazolo-azolo-diazines
12.1. [1,2,4]Triazolo[4,3-\(a\)]tetrazolo[5,1-\(c\)]quinoxalines
13. Fused triazolo-thieno-diazines
13.1. Thieno[3,2-\(e\)][1,2,4]triazolo[4,3-\(a\)]pyrimidines
13.2. Thieno[2,3-\(e\)][1,2,4]triazolo[3,4-\(b\)]pyrimidines
13.3. Cyclohexathiено[3,2-\(e\)][1,2,4]triazolo[1,5-\(c\)]pyrimidines
13.4. Cycloheptathiено[3,2-\(e\)][1,2,4]triazolo[3,3-\(b\)]pyridines
13.5. Naphtho[1',2':4,5]thienо[3,2-\(e\)][1,2,4]triazolo[4,3-\(c\)]pyrimidines
14. Fused triazolo-thieno-azino-diazines
14.1. Pyrido[3',2',4,5]thieno[2,3-\(e\)][1,2,4]triazolo[4,3-\(c\)]pyrimidines
14.2. Quinolino[3',2':4,5]thienо[2,3-\(e\)][1,2,4]triazolo[1,5-\(c\)]pyrimidines
15. Conclusions
16. References
1. Introduction

Basically a nitrilimine \(1\) is a flexible system of three atoms over which four pi-electrons are distributed. Although one can write seven possible resonance structures for such a system, the 1,3-dipolar sextet structure \(1A\) with its complementary nucleophilic and electrophilic centers will be used throughout this article, although theoretical calculations have indicated that all the octet zwitterionic structure \(1B\) is the most stable contributor to the resonance hybrid.

\[
\begin{align*}
1A & \quad \text{R-C} \quad + \quad \text{N-N-R'} \\
1B & \quad \text{R-C} \quad \equiv \quad \text{N-N-R'}
\end{align*}
\]

As very authoritative reviews\(^1\)\textsuperscript{-10} of the chemistry of the precursors of nitrilimines exist, brief sketches will be given here for the various methods of the generation of nitrilimines as depicted below. The various methods used for generation of nitrilimines include:

1. Thermal\(^11\)\textsuperscript{-13} and photochemical\(^14\)\textsuperscript{-17} extrusion of nitrogen from tetrazoles.
2. Thermal extrusion of carbon dioxide from 1,3,4-oxadiazol-5-ones.\(^18\)\textsuperscript{-20}
3. Thermal extrusion of sulfur dioxide from 1,2,3,4-oxathiadiazol-2-oxide.\(^21\)\textsuperscript{-22}
4. Base induced elimination of hydrogen halide from hydrazonoyl halides.\(^23\)\textsuperscript{-28} The mechanism of this 1,3-elimination reaction has been studied.\(^26\)\textsuperscript{-32} Dehydrohalogenation reaction of the hydrazonyl halides can also be effected by silver nitrate.\(^28\), \(^33\), \(^34\)
5. Oxidation of aldehyde N-acyl or N-heteroaryl-substituted hydrazones with lead tetra-acetate,\(^35\)\textsuperscript{-38} iron(III) chloride,\(^39\) bromine in acetic acid in the presence of sodium acetate,\(^36\), \(^40\)\textsuperscript{-42} trifluoroboron-etherate solution in acetic acid.\(^43\) Also, nitrilimines can be generated electrolytically by anodic oxidation of aldehyde N-substituted hydrazones,\(^37\), \(^44\)\textsuperscript{-47} heating them with sulfur,\(^38\) nitrobenzene\(^39\), \(^48\) or stirring with HNO\(_3\) in DMF.\(^49\)
6. Thermolysis of sodium salt of \(\alpha\)-nitrohydrazones.\(^50\), \(^51\)
7. Photolysis of sydnones.\(^52\)\textsuperscript{-59}
8. Thermal decomposition of 5-aryl-4-arylaiozoisoxazoles.\(^60\), \(^61\)

Nitrilimines having a double bond at the N-terminus are prone towards the 1,5-electrocyclization as depicted in equation 1. If the double bond is a part of the heterocyclic moiety, such 1,5-electrocyclization will lead to fused ring system as shown in equation 2. Nitrilimines having both \(\alpha,\beta\)- and \(\gamma,\delta\)-double bonds are also susceptible to 1,7-electrocyclization of the 8-pi electron system to give the respective triazepine, oxadiazepine or thiadiazepine derivatives according to the nature of \(Z\) as shown in equation 3.
2. Fused azolo-triazoles

2.1. Pyrazolo[5,1-c][1,2,4]triazoles
1H-3-Substituted-aryl-6-methyl-7-ethoxycarbonyl-pyrazolo[5,1-c][1,2,4]-triazoles 2 were obtained by the action of lead tetraacetate or bromine in acetic acid on 1H-2-methyl-3-ethoxycarbonyl-4-arylidenehydrazinopyrazole 1.62, 63 Hydrolysis of 2 and decarboxylation of the resulting carboxylic acids gave the corresponding 1H-3-substituted-aryl-pyrazolo-[5,1-c][1,2,4]triazoles 3.63
Other pyrazolo[5,1-c][1,2,4]triazoles 5(7) were prepared by either treatment of the hydrazone 4 with bromine in acetic acid in presence of sodium acetate or by treatment of the hydrazonoyl chloride 6 with triethylamine.
2.2. Imidazo[2,1-c][1,2,4]triazoles

Imidazo[2,1-c][1,2,4]triazoles 9 were prepared by Scott et al.\textsuperscript{65, 66} via heating the hydrazonoyl chloride 8 in aqueous dioxane containing catalytic amount of triethylamine.

\[
\text{R = OC}_2\text{H}_5; \text{Me; COMe; NH}(p\text{-MeOC}_6\text{H}_4) \\
\text{R}'' = \text{H; COOEt} \\
\text{R}' = \text{H; Me}
\]

2.3. Thiazolo[2,3-c][1,2,4]triazoles

Treatment of the acid hydrazide 10 with POCl\textsubscript{3} gives the hydrazonoyl chloride 11A. The latter was reported to undergo, upon treatment with a base, \textit{in situ} tandem dehydrochlorination and 1,5-electrocyclization of the resulting nitrilimine to yield the corresponding thiazolo[2,3-
c][1,2,4]triazoles 12. Also, bromination of the hydrazone 13 afforded the hydrazonoyl bromide 11B which underwent in situ dehydrobromination to yield the respective thiazolo[2,3-c][1,2,4]triazoles 14.

\[
\text{R} = \text{CH}_3; \text{Ph}
\]

### 2.4. 1,2,4-Triazolo[5,1-c][1,2,4]triazoles

Treatment of aldehyde N-(1,2,4-triazol-3-yl)hydrazones 15 with lead tetraacetate gave a mixture of 3-aryl-6-phenyl-1,2,4-triazolo[5,1-c][1,2,4]triazoles 17 and the N-acetylated hydrazide 16.\(^{35,70-71}\)
Treatment of the hyrazonoyl bromide 18 with bases was reported to give a mixture of 3-aryl-6-phenyl-1,2,4-triazolo[5,1-c][1,2,4]triazoles 19 and 3-aryl-5-phenyl-1,2,4-triazolo[3,4-c][1,2,4]triazoles 20 with the former being predominant products.\textsuperscript{72} However, treatment of 18 with sodium acetate in acetic acid yielded mainly 19 as end products.\textsuperscript{73}
Similiar treatment of 21 with a base forces the cyclization to take place at the less nucleophilic N-4 to give 1,2,4-triazolo[4,3-c][1,2,4]triazoles 22.\(^{74}\)

\[
\begin{align*}
\text{R} & = \text{H; CH}_3 \\
\text{Ar} & = \text{Ph; } p\text{-ClC}_6\text{H}_4; \text{ m}-\text{BrC}_6\text{H}_4; \text{ p}-\text{BrC}_6\text{H}_4; \text{ p}-\text{NO}_2\text{C}_6\text{H}_4
\end{align*}
\]

2.5. 1,2,4-Triazolo[3,4-b][1,3,4]oxadiazoles

1,2,4-Triazolo[3,4-b][1,3,4]oxadiazoles 25 have been prepared by treatment of the hydrazonoyl bromides 23 with triethylamine.\(^{75, 76}\) The same products were also obtained by oxidative cyclization of the parent hydrazones 24 by heating them in nitrobenzene.\(^{48}\)

\[
\begin{align*}
\text{Ar} & = \text{Ph; } p\text{-ClC}_6\text{H}_4; \text{ m}-\text{BrC}_6\text{H}_4; \text{ p}-\text{BrC}_6\text{H}_4; \text{ p}-\text{NO}_2\text{C}_6\text{H}_4
\end{align*}
\]
2.6. 1,2,4-Triazolo[4,3-d]tetrazoles

Treatment of N-(tetrazol-5-yl)hydrazones \(26\) with bromine in acetic acid in the presence of sodium acetate afforded the respective 1,2,4-triazolo[4,3-d]tetrazole derivatives \(28\) via in situ 1,5-electrocyclization of the respective nitrilimines generated from dehydrohalogenation of the hydrazonoyl bromide \(27\). Attempts to prepare \(28\) by oxidative cyclization of the hydrazone \(26\) with lead tetraacetate gave a mixture of \(28\) and the N-acetyl derivatives \(30\) of the parent hydrazones.\(^{77-81}\)

\[
\begin{align*}
\text{Pb(OAc)}_4 & \quad \text{Br}_2/\text{AcOH} \\
\begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{CHAr} & \\
\end{array} & \quad \begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{C(Br)HAr} & \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{C(Br)HAr} & \\
\end{array} & + 28 \\
\begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{CHAr} & \\
\end{array} & + 28
\end{align*}
\]

\[
\begin{align*}
\text{NaOAc} & \\
\begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{CHAr} & \\
\end{array} & + \begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Me} & \text{NN} = \text{CHAr} & \\
\end{array}
\]
\]

\[\text{Ar} = \text{Ph}; \; p-\text{ClC}_6\text{H}_4; \; p-\text{BrC}_6\text{H}_4; \; 2\text{-thienyl}\]

3. Fused triazolo-azines

3.1. 1,2,4-Triazolo[4,3-a]pyridines

Aldehyde N-(pyrid-2-yl)hydrazones \(31\) have been cyclized into the respective 1,2,4-triazolo[4,3-a]pyridine derivatives \(32\) upon chemical oxidation with either lead tetraacetate,\(^{35,38,82,83}\) ferric chloride,\(^{39,83}\) iodobenzene-diacetate (IBD),\(^{84}\) CuCl\(_2\)\(^{85}\) or mercuric acetate.\(^{86}\) Also treatment of \(31\) with either bromine in acetic acid in presence of sodium acetate,\(^{40,83}\) sulfur\(^{38}\) or with boron trifluoride etherate in acetic acid\(^{43}\) gave the respective \(32\). An evidence was presented to indicate that such conversion proceeds via the initial formation of nitrilimines as intermediate which then undergo 1,5-electrocyclization to give \(32\) as end products.\(^{22,87,88}\) The latter products were also
obtained by either anodic oxidation of the parent hydrazones 31 or by refluxing them in nitrobenzene.\textsuperscript{39, 44}

\[
\begin{align*}
\text{31} & \quad \text{i} \quad \text{32} \\
\text{N} & \quad \text{NHN=CHR} \\
& \quad \text{R}
\end{align*}
\]

\( \text{i} = \text{Pb(OAc)}_4; \; \text{IBD} / \text{CH}_2\text{Cl}_2; \; \text{FeCl}_3; \; \text{Br}_2 / \text{AcOH} / \text{AcONa}; \; \text{CuCl}_2 \) or BF\(_3\)-etherate.

\( \text{R} = \text{Ph}; \; 4\text{-MeC}_6\text{H}_4; \; 2\text{-MeOC}_6\text{H}_4; \; 4\text{-MeOC}_6\text{H}_4; \; 3\text{-NO}_2\text{C}_6\text{H}_4; \; 4\text{-NO}_2\text{C}_6\text{H}_4; \; 4\text{-BrC}_6\text{H}_4; \; 4\text{-ClC}_6\text{H}_4; \; 2\text{-ClC}_6\text{H}_4; \; 2,4\text{-Dichlorophenyl}; \; 3,4\text{-Methylenedioxyphenyl}; \; 2\text{-Carboxyphenyl}; \; 2\text{-Hydroxyphenyl}; \; \text{Furyl.}
\)

Nitrilimines generated by thermolysis of 3-(2-pyridyl)tetrazole 33 yielded 1,2,4-triazolo-[4,3-\(a\)]pyridine 34.\textsuperscript{89}

\[
\begin{align*}
\text{33} & \quad \text{heat} \quad \text{34} \\
& \quad \text{O}_2\text{N} \\
& \quad \text{N} \\
& \quad \text{Ph} \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{Ph}
\end{align*}
\]

Recently, it was reported that treatment of aldose N-(2-pyridyl)hydrazones 35 with bromine in methanol resulted in the formation of the respective 3-(polyhydroxyalkyl)-1,2,4-triazolo-[4,3-\(a\)]pyridine derivatives 36.\textsuperscript{90} Acetylation of the latter acyclo C-nucleosides afforded the acetylated derivatives 37.\textsuperscript{90}
3.2. [1,2,4]Triazolo[1,5-α]pyridines

Reaction of 5-(β-D-ribofuranosyl)tetrazols 39 with 2-chloro-3-nitropyridine 38 gave a mixture of 1,2,4-triazolo[4,3-α]pyridin-3-yl 41 and 1,2,4-triazolo[1,5-α]pyridin-2-yl 42 C-nucleosides. The product 41 is formed via in situ 1,5-electrocyclization of the initially formed nitrilimines, whereas the product 42 resulted from thermally induced Dimroth like rearrangement of 41.91 Treatment of each of 41 and 42 with sodium methoxide in methanol resulted in deprotection of the sugar residue and the formation of C-nucleoside 41b and 42b respectively.91 The acyclic C-nucleoside 41 and 42 were also obtained by thermolysis of the respective acyclonucleosides 40.91
4. Fused triazolo-diazines

4.1. 1,2,4-Triazolo[4,3-b]pyridazines
Aldehyde N-(pyridazin-3-yl) hydrazones 43 yielded the respective 1,2,4-triazolo[4,3-b]pyridazines 44 upon treatment with bromine in acetic acid\(^{92-93}\) or lead tetraacetate (LTA).\(^{92}\) The latter products were formed via in situ 1,5-electrocyclization of the corresponding
nitrilimines. It is interesting to find that similar oxidative cyclization of the hydrazones 45 with lead tetraacetate afforded 6-azido-1,2,4-triazolo[4,3-b]pyridazines 46.94

\[
\begin{align*}
\text{NHN=CHR} & \quad [O] \\
\text{NHN=CHR} & \quad [O] \\
43a & \quad 44a \\
45 & \quad 46
\end{align*}
\]

\[R = \text{Me; Ph}\]

When a solution of each of the hydrazones 43b was refluxed with CuCl\(_2\) in dimethylformamide (DMF), the respective 6-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazines 44b were produced in 62-70% yields.95 In addition, it was reported that aldehyde N-(pyridazin-3-yl)hydrazones 43c have been cyclized upon treating with any of the oxidizing agents including: Pb(OAc)\(_4\), Br\(_2\) / Na\(_2\)CO\(_3\), FeCl\(_3\), NaOCl or Pd / C.96,97
Also, treatment of the hydrazones 43d(43e) with bromine in methanol afforded the corresponding (2R,3S)-3-(6-chloro-1,2,4-triazolo[4,3-b]pyridazine-3-yl)-2,3-diacetoxypropanoic acid methyl ester 44d(e) and (2R,3S)-3-(6-phenyl-1,2,4-triazolo[4,3-b]pyridazine-3-yl)-2,3-diacetoxypropanoic acid methyl ester 44e.²⁹

Treatment of aldose N-(pyridazin-3-yl)hydrazones of the cyclic sugars 45 with bromine in methanol in the presence of sodium acetate at room temperature yielded the respective 1,2,4-triazolo[4,3-b]pyridazines 46, respectively.²⁹ Oxidative cyclization of the hydrazone 45 with lead tetraacetate (LTA) in methylene chloride at room temperature afforded also the C-nucleoside 46.²⁹
4.2. 1,2,4-Triazolo[4,3-a]pyrimidines

Aldehyde N-(4,6-dimethyl-2-pyrimidinyl)hydrazones 47 gave, upon treatment with lead tetraacetate\textsuperscript{100, 101} or with iodobenzene diacetate in dichloromethane\textsuperscript{102} the respective 3-aryl-5,7-dimethyl-1,2,4-triazolo[4,3-a]pyrimidines 48. In addition, 3-aryl-[1,2,4]triazolo[4,3-a]pyrimidines 48b were formed by refluxing the parent hydrazones 47b with CuCl\textsubscript{2} in DMF.\textsuperscript{85}
Treatment of 2-phenylidenehydrazino-6-methylpyrimidine-4(1H)-one \(49\) with lead tetraacetate may theoretically afford 3-phenyl-7-methyl-1,2,4-triazolo[4,3-\(a\)]pyrimidin-5-one \(50\) and / or 3-phenyl-5-methyl-1,2,4-triazolo[4,3-\(a\)]pyrimidin-7-one \(51\). Practically, however, the reaction furnished one product which was assigned structure \(50\) by Bower and Doyle\(^3\) and \(51\) by Allen et al.\(^{103}\) The latter authors rationalized their conclusion on the basis of obtaining \(51\) also from the reaction of 3-amino-5-phenyl-1,2,4-triazole \(52\) with ethyl acetoacetate. Evidently, this rationale is irrelevant since the last reaction may also yield \(50\).\(^{103}\)

Oxidative cyclization of 2-(arylidenehyrazino)-6-methylpyrimidin-4-one \(53\) with bromine in acetic acid took place with concomitant bromination of pyrimidine ring to form the respective 1,2,4-triazolo[4,3-\(a\)]pyrimidin-5-one \(54\).\(^{104}\)
Refluxing the hydrazones \(55\) with lead tetraacetate in AcOH yielded the corresponding [1,2,4]triazolo[4,3-\(a\)]pyrimidines \(56\).\(^{105}\)

Oxidative cyclization of \(57\) with FeCl\(_3\) gave \(58\). When the cyclization of \(57\) was carried out with Br\(_2\) in acetic acid, it gave \(59\) as a major product in addition to \(58\) as minor product. The product \(59\) resulted from Dimroth rearrangement of the initially formed \(58\). The latter was also converted into \(59\) by heating with KOH in ethanol.\(^{106}\)
However, similar treatment of the hydrazones 60 with Br₂/AcOH was reported to give the Dimroth rearrangement products 62 directly as end product. On the other hand, the cyclization of 60 with thionyl chloride gave 61 as the major isolated products. Partial Dimroth rearrangement has taken place during this cyclization, where 62 were formed as by products.

\[
\text{NC} \begin{array}{c}
\text{O} \\
\text{Ph} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{H} \\
\text{NHN=CHAr} \\
\end{array} \begin{array}{c}
\text{R} \\
\text{Ph} \\
\end{array}
\text{Br}_2 / \text{AcOH}
\]

\[
\text{NC} \begin{array}{c}
\text{O} \\
\text{Ph} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{H} \\
\text{NHN=CHAr} \\
\end{array} \begin{array}{c}
\text{R} \\
\text{Ph} \\
\end{array}
\text{SOCl}_2
\]

\[
\text{NC} \begin{array}{c}
\text{O} \\
\text{Ph} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{H} \\
\text{NHN=CHAr} \\
\end{array} \begin{array}{c}
\text{R} \\
\text{Ph} \\
\end{array}
\text{Br}_2 / \text{AcOH}
\]

\[
\text{NC} \begin{array}{c}
\text{O} \\
\text{Ph} \\
\end{array} \begin{array}{c}
\text{N} \\
\text{H} \\
\text{NHN=CHAr} \\
\end{array} \begin{array}{c}
\text{R} \\
\text{Ph} \\
\end{array}
\text{SOCl}_2
\]

\[
\text{R} = \text{Me}; n-\text{Bu} \\
\text{Ar} = \text{XC}_6\text{H}_4 \\
\text{X} = \text{H; 4-NH}_2
\]
Also, oxidative cyclization of the hydrazones 57 with ferric chloride gave 59 as end product via Dimroth rearrangement of the initially formed 1,2,4-triazolo[4,3-α]pyrimidine derivative 58. Methylation of 59 with MeI gave the product 63 which was found different from the product 62 which was produced by oxidation of 57b. Similar oxidation of 64 with FeCl₃ afforded 66 via Dimroth rearrangement of the initially formed product 65. In this latter case the reaction seems to proceed via intramolecular addition of NH to the C=N double bond, followed by oxidation of the initially formed adduct.
Oxidative cyclization of the hydrazones 67 with FeCl₃ in ethanol gave the corresponding 68.

\[
\begin{align*}
\text{NHN=CHAr} & \quad \text{FeCl}_3 \\
\text{Me} & \quad \text{NHN=CHAr} \\
\text{NHPh} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = 4-X\text{C}_6\text{H}_4; \quad X = \text{Cl; MeO}
\end{align*}
\]

Attempts to cyclize the hydrazones 69 via treatment with an excess of Br₂ in AcOH in presence of NaOAc gave the corresponding 8-bromo-1,2,4-triazolo[4,3-c]pyrimidines 70.

\[
\begin{align*}
\text{NHN=CHAr} & \quad \text{Br}_2 \quad \text{AcOH} \\
\text{Br} & \quad \text{NHN=C(Br)Ar} \\
\text{Me} & \quad \text{Br} \\
\text{SMe} & \quad \text{Me} \\
\text{SMe} & \quad \text{SMe} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} = 4-X\text{C}_6\text{H}_4; \quad X = \text{Cl; NO}_2
\end{align*}
\]

Bitha et al. reported that pyrimidino[1,2-b][1,2,4,5]tetrazin-6-ones 71 underwent acid catalyzed ring contraction via 1,5-electrocyclization of the generated nitrilimines to give 1,2,4-triazolo[4,3-a]pyrimidin-7-ones 72.
A number of 3-(alditol-1-yl)-5-methyl-7-oxo[1,2,4]triazolo[4,3-a]pyrimidines 74 were synthesized by oxidative cyclization of the respective aldose (pyrimidin-2-yl)hydrazones 73 with bromine in water. The other regioisomeric structure was eliminated based on finding that acetylation of 74 afforded the same acetylated acyclo C-nucleoside 76 as those obtained by oxidative cyclization of the hydrazones 75. Treatment of 76 with methanolic ammonia resulted in deprotection of the sugar residue and the formation of 77. It was possible to avoid nuclear bromination of 73 and 75 by performing the reaction in the absence of light.
Similarly, it was indicated that poly-O-acetyl-adehydo sugar (3-acetyl)4-oxo-6-phenyl-pyrimidin-2-yl)hydrazones 75A undergo oxidative cyclization with bromine in acetic acid in the presence of sodium acetate to give the respective 8-acetyl-3-(poly-O-acetyl-alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidines 76A.\textsuperscript{111} Deacetylation of the latter 76A with ammonium hydroxide in methanol gave the corresponding 3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidines 77A.

\[
\begin{align*}
\text{R} = \text{HOCH}_2-(\text{CHOH})_n & \quad \text{R'} = \text{AcOCH}_2-(\text{CHOAc})_n \\
n = 3, 4
\end{align*}
\]

Also, it was indicated that adehydo-sugar 4-oxo-6-phenyl-pyrimidin-2-yl)hydrazones 75B undergo oxidative cyclization with bromine in water to give the respective 3-(alditol-1-yl)-7-oxo-5-substituted-1,2,4-triazolo[4,3-a]pyrimidines 76B.\textsuperscript{112} Similar treatment of 75B with bromine in acetic acid in the presence of sodium acetate followed by acetic anhydride gave the polyacetyl derivative 76B whose deacetylation with ammonium hydroxide in methanol gave the corresponding 3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidines 77B.\textsuperscript{112}
Thermolysis of tetrazole derivative 79, prepared from 2-chloro-4,6-disubstituted-pyrimidine 78 and 5-(2,3,5-tri-O-benzoyl-B-D-ribofuranosyl)-tetrazole 5, afforded the respective 1,2,4-triazolo[4,3-a]pyrimidine C-nucleoside 80.\(^{113}\)
Hydrazones 81, derived from aldose monosaccharides and 2-hydrazinopyrimidine gave, upon oxidative cyclization with bromine in methanol, the corresponding 3-(alditol-1-yl)-1,2,4-triazolo[4,3-a]pyrimidines 82.\textsuperscript{98}

\[ \text{81} \xrightarrow{\text{Br}_2 / \text{MeOH}} \text{82} \]

\[ R = \text{HOCH}_2\text{-(CHOH)}_4 \]

4.3. [1,2,4]Triazolo[1,5-a]pyrimidines
Treatment of the aldose hydrazones 83 with ferric chloride in ethanol was reported to give the acyclo C-nucleosides 85 and not the isomeric nucleosides 86. It seems in this case the initially formed 1,2,4-triazolo[4,3-a]pyrimidines 84 underwent \textit{in situ} Dimroth rearrangement to give 85 as end products. Periodate oxidation of 83 afforded the aldehydes 87.\textsuperscript{114, 115}
4.4. 1,2,4-Triazolo[4,3-a][1,2,4]pyrazines

Nitrilimines, generated in situ by oxidation of aldehydes N-(pyrazin-2-yl)hydrazones 88 with lead tetra-acetate or dehydrohalogenation of the hydrazonyl chlorides 89, underwent 1,5-electrocyclization to afford the respective 1,2,4-triazolo[4,3-a][1,2-4]pyrazines 90.116
5. Fused triazolo-triazines

5.1. 1,2,4-Triazolo[4,3-a][1,3,5]triazines

Nitrilimines derived from oxidative dehydrogenation of aldehyde N-(4,6-disubstituted-1,3,5-triazin-2-yl)hydrazones 91a with lead tetraacetate gave only 92a because of the symmetry of 91a. Also, treatment of aldehyde N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)hydrazones 91b with lead tetraacetate gave 92b only as a result of cyclization with the more nucleophilic nitrogen adjacent to the more electron-releasing methoxy group.
The hydrazone 91c underwent cyclization upon treatment with lead tetraacetate in CH$_2$Cl$_2$ to yield [1,2,4]triazolo[4,3-a][1,3,5]triazine 92c. The latter product underwent Dimroth rearrangement upon heating in MeOH-NaOH to give 1,2,4-triazolo[1,5-a][1,3,5]triazine 93 in 95% yield.\textsuperscript{119}

5.2. 1,2,4-Triazolo[4,3-b][1,2,4]triazines

Oxidative cyclization of the hydrazone derivatives of the aldose monosaccharides 94 and concurrent acetylation was reported to occur upon treatment with bromine in acetic acid in the presence of sodium acetate and acetic anhydride and yielded products that were assigned the
structure of 6,7-diphenyl-1,2,4-triazolo[4,3-b][1,2,4]triazine acyclo C-nucleosides 95 and not the isomeric structure 97.\textsuperscript{120} Deacetylation of 95 yielded 96.

![Chemical Structure Diagram]

\[\text{R} = (\text{CHOH})_n\text{-CH}_2\text{OH} \]
\[\text{R'} = (\text{CHOAc})_n\text{CH}_2\text{OAc} \]
\[n = 3, 4 \]

5.3. Acenaphtho[1,2-e][1,2,4]triazolo[3,4-c][1,2,4]triazines
Oxidative cyclization of the hydrazone derivatives of aldose monosaccharides 98 was reported to occur upon treatment with ethanolic ferric chloride and provided 1-(alditol-1-yl)acenaphtho[1,2-e][1,2,4]triazolo[3,4-c][1,2,4]triazines 99. The cyclization occurred at N4 rather than N2 of the 1,2,4-triazine ring.\textsuperscript{121}
6. Fused triazolo-benzoazoles

6.1. 1,2,4-Triazolo[4,3-a]benozimidazoles
Treatment of the hydrazonoyl chlorides 100 with a base furnished 3-substituted 1H-1,2,4-triazolo[4,3-a]benozimidazoles 101.\(^{122}\)

6.2 1,2,4-Triazolo[3,4-b]-1,3-benzothiazoles
Bower and Doyle\(^{123}\) reported that treatment of aldehyde N-(benzothiozole-2yl)hydrazones 102 with lead tetraacetate gave 3-aryl-1,2,4-triazolo[3,4-b]-1,3-benzothiazoles 103 via tandem generation and electrocyclization of nitrilimines.\(^{83, 124, 125}\) In addition, the latter conversion has been affected by other reagents such as FeCl\(_3\) in ethanol,\(^{126, 127}\) bromine in acetic acid and bromine in presence of sodium carbonate.\(^{128}\)
The hydrazonoyl chloride 104, prepared by the reaction of POCl$_3$ on the hydrazide in DMF, cyclizes in situ to give the respective 1,2,4-triazolo[4,3-b]-1,2-benzothiazoles derivative.$^{129}$ Also, 3-substituted-1,2,4-triazolo[4,3-b][1,2]benzothiazole-5,5-dioxide 106 (R = Me) was obtained upon thermolysis of 105, prepared by reaction of 3-chloro-1,2-benzothiazole-1,1-dioxide with methyltetrazole in presence of pyridine.$^{130}$ Although no mechanistic rationalization was indicated, the formation of the latter products 106 may result via tandem generation and electrocyclization of the respective nitrilimine.
7. Fused triazolo-azolo-diazenes

7.1. Pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidines

The hydrazones 107 were reported to cyclize upon treatment with 70% nitric acid to afford the corresponding 5-substituted-7H-pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidines 108.49

\[ \text{NHN=CHR} \xrightarrow{70\% \text{HNO}_3} \]

\[ 107 \quad 108 \]

\[ R = \text{Me; } n\text{-C}_7\text{H}_{15}; \text{Ph; } p\text{-FC}_6\text{H}_4; p\text{-ClC}_6\text{H}_4; p\text{-MeC}_6\text{H}_4; p\text{-MeOC}_6\text{H}_4; p\text{-NO}_2\text{C}_6\text{H}_4 \]

Recently Shawali et al prepared a series of pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]-pyrimidines 113 via oxidative cyclization of aldehyde \( N\)-(1,3-diphenylpyrazolo-[3,4-d]pyrimidin-4-yl)hydrazones 112.134 The required aldehyde \( N\)-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazones 112 were prepared by condensation of the appropriate aldehydes 111 with 1,3-diphenyl-4-hydrazino-pyrazolo[3,4-d]-pyrimidine 110. The latter was prepared by Dimroth type rearrangement of 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1\( H\)-pyrazolo[3,4-d]pyrimidine 109 via its treatment with excess hydrazine hydrate at room temperature.134 Dimroth rearrangement of 113 such a series yielded pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines 114.
7.2. 1,2,4-Triazolo[4,3-e]purines

Stirring the hydrazone 115 with either CuCl$_2$ in warm DMF at 100° or bromine in acetic acid yielded 3-substituted-5,7,9-trimethyl-5,9-dihydro[1,2,4]triazolo[4,3-e]purine-6,8-dione 116. $^{95,135}$

\[
\begin{align*}
\text{Reagents:} & \quad \text{i, H$_2$NNH$_2$.H$_2$O / RT; ii, FeCl}_3 / \text{EtOH / RT; iii, MeCOONa / heat; iv, RCOCl, (RCO)$_2$O or RCOOH.} \\
R & = a) \ C_6H_5; \ b) \ 4-\text{MeC}_6H_4; \ d) \ 4-\text{MeOC}_6H_4; \ e) \ 4-\text{O}_2\text{NC}_6H_4; \\
& f) \ 4-\text{Me}_2\text{NC}_6H_4; \ g) \ \text{PhCH}=\text{CH}; \ h) \ 1\text{-Naphthyl; i) \ 2-furyl; j) \ 2-thienyl; k) CH}_3; \ l) \ H. \\
\end{align*}
\]
7.3. 1,2,4-Triazolo[3,4-i]purines

Oxidative cyclization of the hydrazones 117 was accomplished by heating with lead tetraacetate in anhydrous dioxane to afford the corresponding 5-Iodo-7-(2',3',5'-tri-O-acetyl-β-ribofuranosyl)-7H-[1,2,4]triazolo[3,4-i]purine derivatives 118. The latter products were also obtained by refluxing 117 with diethyl azodicarboxylate in acetonitrile.

Heating the hydrazones 119 with diethyl azidicarboxylate (DEAD) in acetonitrile at reflux for 5-10 h afforded the respective 5-iodo-7-(2',3',5'-tri-O-acetyl-B-ribofuranosyl-5-yl)-7H-[1,2,4]triazolo[3,4-i]purines 120. The latter could also be obtained by heating 119 with lead tetraacetate in anhydrous dioxane.
8. Fused triazolo-azolo-triazines

8.1. Pyrazolo[3,4-e][1,2,4]triazolo[3,4-c][1,2,4]triazines
Reaction of aldehyde (7-methyl-5-phenyl-5H-pyrazolo[3,4-e][1,2,4]-triazin-3-yl)hydrazones 121 with SOCl₂ at reflux afforded the corresponding 1-phenyl-8-aryl-1H-pyrazolo[3,4-e][1,2,4]-triazolo[3,4-c][1,2,4]triazines 122.¹³⁸

\[
\text{Me} \quad \text{Ph} \quad \text{NHN}=\text{CHAr} \quad \xrightarrow{\text{SOCl}_2} \quad \text{Me} \quad \text{Ph} \quad \text{Ar} \quad \xrightarrow{-\text{HCl}, - \text{SO}_2} \quad -\text{H}\text{Cl}, - \text{SO}_2
\]

\[\text{Ar} = XC_6\text{H}_4, \quad X = \text{H}; \text{2-Br}; \text{2-HO}; \text{4-MeO}; \text{2-O}_2\text{N}\]

8.2. Bis(1,2,4-triazolo)[4,3-b:4,3-d][1,2,4]triazines
Treatment of aldehyde N-(1,2,4-triazolo[4,3-b]triazin-7-yl)hydrazones 123 with bromine in methanol resulted in oxidative cyclization to give the respective bis(1,2,4-triazolo)- [4,3-b:4,3-d][1,2,4]triazines 124.¹³⁹

\[
\text{R''CH}=\text{NHN} \quad \xrightarrow{\text{Br}_2, \text{MeOH}} \quad \text{R'} \quad \text{R''} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{R'} \quad \text{R''}
\]

\[\text{R''} = 4-XC_6\text{H}_4, \quad X = \text{H}; \text{CH}_3; \text{OCH}_3; \text{Cl}; \text{Br}; \text{NO}_2, \quad \text{R} = \text{H}; \text{CH}_3; \text{Cl}, \quad \text{R'} = \text{CH}_3\]
9. Fused triazolo-benzoazines

9.1. 1,2,4-Triazolo[4,3-a]quinolines
Aldehyde hydrazones 125 underwent oxidative cyclization when treated with lead tetra-acetate in CH₂Cl₂ to give the corresponding 3-aryl-1,2,4-triazolo[4,3-a]quinolines 126. The latter products were also obtained by the reaction of the hydrazones 125 with either Br₂ in CHCl₃ in the presence of Na₂CO₃, ethanolic FeCl₃, NaOCl in dioxane or refluxing in nitrobenzene.³⁹, ⁸³, ⁸⁴

\[
\text{i = LTA / CH}_2\text{Cl}_2 ; \text{ Br}_2 / \text{CHCl}_3 / \text{Na}_2\text{CO}_3 ; \text{FeCl}_3 / \text{EtOH or NaOCl / dioxane}
\]

\[
\begin{array}{c}
\text{Ar} = \text{Ph; } p-\text{MeC}_6\text{H}_4; \text{ } p-\text{ClC}_6\text{H}_4; \text{ } p-\text{MeOC}_6\text{H}_4; \\
5-\text{NO}_2-\text{2-furyl; } 2\text{-thienyl}
\end{array}
\]

Similarly, the acyclo C-nucleosides 128 were produced by oxidation of aldehyde N-(2-quinolinyl)hydrazones 127 with ferric chloride in ethanol.³⁹, ¹⁴⁰
Contrary to the foregoing reports, it was indicated that treatment of the aldose hydrazones 129 with lead tetraacetate in acetic acid afforded the hydrazones 130 and not the expected acyclo C-nucleoside 131.\textsuperscript{141}

Furthermore, it was indicated that treatment of 132 with ferric chloride in ethanol gave tarry material, while its treatment with sodium periodate or bromine in acetic acid afforded the aldehyde 134 and the \textit{N,N}-diacetyl hydrazine derivative 133, respectively.\textsuperscript{141}
9.2. 1,2,4-Triazolo[4,3-a]isoquinolines

Thermolysis of 135 afforded the respective 3-substituted 1,2,4-triazolo[3,4-a]isoquinolines 136 via cyclization of the initially formed nitrilimines.²²
Similarly, nitrilimines, generated by treatment of the hydrazones 137 with ferric chloride\textsuperscript{39, 142} or thermolysis of 1-(2-tetrazolyl)isoquinolines 138\textsuperscript{143} afforded the respective 1,2,4-triazolo[3,4-a]isoquinolines 139.

\[
\text{NHN}=\text{CHR} \quad \xrightarrow{\text{FeCl}_3 / -\text{H}_2} \quad \xrightarrow{\text{heat} / -\text{N}_2} \quad \text{R} = \text{CH}_3; \text{C}_6\text{H}_5; \text{p-O}_2\text{N-C}_6\text{H}_4
\]

10. **Fused triazolo-benzodiazines**

10.1. **1,2,4-Triazolo[3,4-a]phthalazines**

A series of 3-substituted[1,2,4]triazolo[3,4-a]phthalazines 141 were obtained by oxidative cyclization of the respective hydrazones 140 by heating with CuCl\textsubscript{2} in DMF\textsuperscript{95} or heating with Pd / C\textsuperscript{144} or treatment with bromine in acetic acid in the presence of sodium acetate\textsuperscript{145, 146}.

\[
\text{NHN}=\text{CHAr} \quad \xrightarrow{i} \quad \xrightarrow{} \quad \text{Ar} = \text{C}_6\text{H}_5; \text{p-MeC}_6\text{H}_4; \text{p-MeOC}_6\text{H}_4; \text{p-NMe}_2\text{C}_6\text{H}_4; \text{p-ClC}_6\text{H}_4; \text{p-BrC}_6\text{H}_4; \text{p-IC}_6\text{H}_4; \text{p-NO}_2\text{C}_6\text{H}_4
\]

\[
\text{R} = \text{Ph; PhCO}
\]
A number of 3-(alditol-1-yl)-1,2,4-triazolo[3,4-a]phthalazines 143 were synthesized by thermal dehydrogenation of the respective aldose N-(phthalazin-1-yl)hydrazones 142. The formation of the latter was also obtained by catalytic dehydrogenation with palladium on charcoal.\(^{147-152}\) Treatment of the C-acyclonucleosides 143 with sodium metaperiodate in water resulted in the cleavage of the alditol chain and gave the 3-formyl derivative 144.\(^{153}\)

\[
\begin{align*}
&\text{NHN=CHR} \\
\xrightarrow{- \text{H}_2} \\
&\text{N=NCHR} \\
&\text{R'} \\
&\text{R} = (\text{CH}_2\text{OH})_n\text{CH}_2\text{OH}; \quad n = 3, 4 \\
&\text{R'} = \text{Ph, PhCH}_2
\end{align*}
\]

A series of 1,2,4-triazolo[3,4-a]phthalazine C-nucleosides 146 were prepared by thermal dehydrogenative cyclization of the respective hydrazones of lactose, maltose and melibiose 145.\(^{154}\) Acid hydrolysis of 146 yielded 3-\((D\)-gluco-pentahydroxypentyl\()-6\)-phenyl-1,2,4-triazolo[3,4-a]phthalazines 148. Furthermore, acetylation of 146 with acetic anhydride in pyridine gave the respective octa-O-acetyl derivatives 147.\(^{154}\)
Also, oxidative cyclization of aldose hydrazones 149 by action of ferric chloride in ethanol afforded the corresponding 3-(alditol-1-yl)-1,2,4-triazolophthalazines 150.155

\[ R : \text{CHOH-CHOR'}-\text{CHOH-CH}_2\text{OR''} \]

10.2. 1,2,4-Triazolo[4,3-a]quinazolines
Oxidative cyclization of aldehyde N-(2-quinazolinyl)hydrazones 151 with ferric chloride was reported to give the angular 1,2,4-triazolo[4,3-a]quinazolines 152 and not the linear triazolo[3,4-b]quinazolines 153.156 The structure of 152 was confirmed by comparison of its N-ethyl derivatives 155 with an authentic sample prepared by the reaction of 154 with aryl chloride.156
Recently two novel series of aldehyde N-(3-phenyl-4-oxoquinazolin-2-yl)hydrazones 156A and their N-(3-cyclohexyl)-analogs 156B were prepared by condensation of each of the appropriate 2-hydrazino-3-substituted-quinazolin-4(3H)-one with the aldehydes. Treatment of each of the hydrazones 156 with equivalent amount of iron(III) chloride in ethanol gave the respective 1,4-disubstituted-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one 157. Treatment of each of 157 with potassium hydroxide in refluxing ethanol yielded, in each case, one product that was identified as the respective 2,4-disubstituted-1,2,4-triazolo[1,5-a]quinazolin-5(4H)-one 158. This isomerization is similar to Dimroth rearrangement of 1,2,4-triazolo[4,3-a]pyrimidine into 1,2,4-triazolo[1,5-a]pyrimidine.159
Also, it was recently reported that treatment of each of the aldose N-(3-phenyl-4-oxoquinazolin-2-yl)hydrazones 159A and aldose N-(3-cyclohexyl-4-oxoquinazolin-2-yl)hydrazones 159B with equivalent amount of iron(III) chloride in refluxing ethanol was reported to afford the respective 1,4-disubstituted-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones 160A and 160B, respectively. In contrast to the behaviour of 159Aa-c and 159Ba-c, when each of the hydrazones 159Ad and 159Ae was subjected to oxidative cyclization following the same procedure, both hydrazones were found to give, one and the same product that was identified as 4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one 161. Similarly, oxidative cyclization of the hydrazones 159Bd and 159Be following the same procedure above gave also one and same compound that was identified 4-cyclohexyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one 161. The structures of the unexpected products 161A and 161B were further evidenced by comparison with authentic samples prepared by refluxing each of 2-hydrazino-3-phenylquinazolin-4(3H)-one and its 3-cyclohexyl analog with ethyl orthoformate or formic acid.
Recently, it was reported that aldose hydrazones 162 were prepared by condensation of 3-substituted-2-hydrazinoquinazolin-4(3H)-one with equimolar amount of appropriate D-aldose in aqueous ethanolic solution in presence of catalytic amount of acetic acid. Treatment of each of such aldose hydrazones 163 with hot ethanolic ferric chloride resulted in an oxidative cyclization to afford the angularly annelated 1-(alditol-1-yl)-4-substituted-1,2,4-triazolo[4,3-a]quinazolin-5(4H)ones 163 rather than to the linearly annulated regioisomers 164.\textsuperscript{161}
10.3. 1,2,4-Triazolo[4,3-c]quinazolines

Nitrilimine generated *in situ* from either aldehyde N-(4-quinazolinyl)hydrazone 166, N-quinazolinyl acid hydrazide 167, or 4-(5-substituted-tetrazol-3-yl)quinazoline 165 underwent 1,5-electrocyclization to give the corresponding 3-substituted 1,2,4-triazolo[4,3-c]quinazoline 168.
10.4. 1,2,4-Triazolo[4,3-α]quinoxalines

Aldehyde N-(quinoxalin-2-yl)hydrazones 169 were reported to afford, upon heating with ferric chloride, or lead tetra-acetate in CH₂Cl₂ or refluxing in nitrobenzene the corresponding 1,2,4-triazolo[4,3-α]quinoxalines 170.¹⁶³⁻¹⁶⁵

\[
\begin{align*}
\text{i} &= \text{FeCl}_3 / \text{EtOH} ; \text{or LTA / CH}_2\text{Cl}_2 \\
R' &= \text{Ph} ; 4-\text{MeC}_6\text{H}_4 ; 4-\text{MeOC}_6\text{H}_4 ; 2-\text{MeOC}_6\text{H}_4 ; 4-\text{NO}_2\text{C}_6\text{H}_4 ; \\
&\quad 4-\text{ClC}_6\text{H}_4 ; 3-\text{CH}_3\text{O}-4-\text{HOC}_6\text{H}_3 ; 4-\text{FC6H4} ; 4-\text{Biphenyl} ; 3\text{HO,4-EtC}_6\text{H}_3
\end{align*}
\]

Aldehyde N-(quinoxalin-2-yl)hydrazones 171 afforded the respective 3-substituted-1,2,4-triazolo[4,3-α]quinoxalines 172 in 61-84% yield upon treatment with CuCl₂ in DMF.⁹⁵

\[
\begin{align*}
\text{R} &= p-\text{ClC}_6\text{H}_4 ; 3,4-(\text{MeO})_2\text{C}_6\text{H}_3
\end{align*}
\]

In another report it was indicated that heating the hydrazones 173 in ethylene glycol and DMSO for 5-8 h afforded 174.¹⁶⁶
10.5. Pyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrimidines

The hydrazones 175 were reported to cyclize easily on treatment with excess thionyl chloride to give 9-aryl-2,4,6-triphenylpyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrimidin-5(6H)-ones 176.167

11. Fused triazo-lo-azo-lo-triazines

11.1. Tris-[1,2,4-triazolo][4,3-a:4,3-c:4,3-e][1,3,5]triazines

Reactions of 2,4,6-trichloro-1,3,5-triazine 177 with three equivalents of 5-substituted tetrazoles 178 led to the formation of the title heterocyclic system 180.89 In this case, the initially formed substitution intermediate 179 underwent nitrogen elimination to give the respective tri-nitrilimine which cyclized in situ to give 180 as end product.
11.2. 1,2,4-Triazolo[4',3':2,3][1,2,4]-triazino[5,6-b]indoles

Cyclodehydrogenation of 181 with ethanolic FeCl₃ was reported to give 182 and not 183. Unequivocal synthesis of 183 by condensing diaminotriazole 185 with 5-methylisatin 184. The isolated product was found different from 182 (R = Me).¹⁶⁸
Similarly, oxidative cyclization of \( \text{186} \) with \( \text{FeCl}_3 \) in ethanol or with \( \text{Pd} / \text{on-charcoal} \) was reported to give \( \text{187} \) and not \( \text{188} \). The distinction between \( \text{187} \) and \( \text{188} \) was based on alternate synthesis of \( \text{188} \) by either the reaction of \( \text{189} \) with acetic acid or the reaction of isatin \( \text{190} \) with diaminotriazole \( \text{191} \).\(^{169}\)

\[
\begin{align*}
\text{186} & \xrightarrow{\text{FeCl}_3 \text{ or Pd/C}} \text{187} \\
\text{189} & \xrightarrow{\text{CH}_3\text{COOH}} \text{188} \\
\text{190} & + \text{191} \xrightarrow{- \text{H}_2\text{O}} \text{188}
\end{align*}
\]

However when the hydrazones \( \text{192} \) were treated with bromine in acetic acid in presence of sodium acetate, they yielded 1,2,4-trizolo[3′,4′:2,3][1,2,4]triazino[5,6-\( b \)]indoles \( \text{193} \).\(^{170}\)
Oxidative cyclization of the aldose hydrazones 194a-d, derived from 3-hydrazino-5H-1,2,4-triazino[5,6-indole and aldehydes as well as aldose monosaccharides produced the 3-substituted derivatives 197a-c and the acyclo C-nucleosides 197d, respectively. Oxidative cyclization of the hydrazones 194d with bromine in acetic acid in the presence of sodium acetate and acetic anhydride was reported to afford 196d with concurrent acetylation of the sugar residue. Treatment of each of the latter with ammonium hydroxide solution in methanol resulted in deprotection of the sugar residue and the formation of C-nucleoside 197d. 168-170
Later, it was reported that oxidative cyclization of both poly-O-acetyl derivatives of aldose (5-methyl-1,2,4-triazino[5,6-b]indol-3-yl)hydrazones 198A and aldose (5-ethyl-1,2,4-triazino[5,6-b]indol-3-yl)hydrazones 198B with bromine in acetic acid in the presence of sodium acetate afforded the respective linearly annelated 3-(polyacetoxyalkyl)-10-alkyl-1,2,4-triazolo[4',3':2,3][1,2,4]-triazino-[5,6-b]indoles 199A and 199B, respectively rather than the their sterically unfavourable angularly annelated isomers 200A and 200B. Treatment of the latter products 199 with ammonia in methanol resulted in their deacetylation and the formation of the respective acyclo C-nucleosides 201. The regiospecific outcome of this oxidative cyclization is discussed in terms of electronic and steric factors and the assignment of structures 199A and 199B have been based on the basis of chemical as well as spectroscopic evidences.
12. Fused triazolo-azolo-diazines

12.1. 1,2,4-Triazolo[4,3-a]tetrazolo[5,1-c]quinoxalines
Several derivatives of the title ring system 203 were prepared by thermolysis of 202, prepared by reaction of 4-chloro-1,2,3,4-tetrazolo[1,5-a]quinoxaline with 5-substituted tetrazoles in presence of triethylamine.\textsuperscript{176}
13. **Fused triazolo-thieno-diazines**

13.1. **Thieno[3,2-\(e\)][1,2,4]triazolo[4,3-\(a\)]pyrimidines**

Treatment of the hydrazone 204 with excess \(\text{Br}_2\) in \(\text{AcOH}\) in the presence of \(\text{NaOAc}\) afforded thieno[3,2-\(e\)][1,2,4]triazolo[4,3-\(a\)]pyrimidin-5-one derivatives 205.\(^{131}\)
13.2. Thieno[3,2-e][1,2,4]triazolo[3,4-b]pyrimidines

3-Aryl-6-methyl-7-phenyl-5H,9H-thieno[3,2-e][1,2,4]triazolo[3,4-b]pyrimidine-5-ones 207 were obtained by treatment of the respective hydrazones 206 with Br₂ in AcOH in presence of NaOAc.¹³²

\[
\text{Ar} = \text{Ph; } p-\text{MeC}_6\text{H}_4
\]

Reaction of aldehyde hydrazones 208 and 209 with ferric chloride in ethanol gave the triazolopyrimidine acyclo C-nucleosides 210 and 211 respectively.¹³³

When 210 (R = R' = Me) was treated with potassium hydroxide in ethanol, it underwent Dimroth type rearrangement to give 212.

\[
208 (210) \text{ R' = R'' = CH}_3 ; \quad 209 (211): \text{ R', R'' = (CH}_2)_4 \quad R = (\text{CHOH})_n-\text{CH}_2\text{OH} \quad n = 3,4
\]

13.3. Cyclohexathieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines

Treatment of the hydrazones 213 with Br₂ in AcOH at 45°C was reported to give a mixture of 214 and its rearrangement product 215. The latter product was the sole isolated product of the
reaction of the hydrazone when reacted with Br₂ in AcOH at reflux temperature. It appears that when acetic acid is used for crystallization at reflux temperature the initial product 214 undergoes Dimroth type rearrangement to the thermodynamically more stable [1,5-c] isomer 215.\(^{177}\)

\[
\begin{align*}
\text{NHN=CHR'} & \quad \text{Br₂ / AcOH} \\
\text{213} & \quad \text{214} \\
R = & \quad \text{H; CH₃} \\
R' = & \quad \text{Ph; } o-C\text{ClC}_6\text{H}_4; m\text{-CIC}_6\text{H}_4; p\text{-CIC}_6\text{H}_4; o\text{-BrC}_6\text{H}_4
\end{align*}
\]

13.4. Cycloheptathieno[3,2-e][1,2,4]triazolo[3,4-b]pyrimidin-5-ones

Recently it was reported that stirring of the sugar hydrazone 216 at room temperature in acetic anhydride–pyridine (1:1) mixture afforded the respective 3-(2',3',4',5'-O-tetraacetyl-glycosyl)-6,7,8,9,10-pentahydrocycloheptathieno[3,2-e][1,2,4]triazolo[3,4-b]pyrimidin-5-one 217.\(^{178}\) Deprotection of the protected acyclo-nucleosides 217 to give 3-glycosyl-6,7,8,9,10-pentahydrocycloheptathieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one 218 was achieved by treatment with methanolic ammonia solution (25%) at room temperature for 24 h.\(^{178}\)

Oxidative cyclization of the hydrazones 219 using bromine in acetic acid afforded the O-acetylated cyclic C-nucleosides 220. Deprotection of 220 using ammonium hydroxide solution in methanol gave the target free acyclic C-nucleosides 221.\(^{179}\)
14. Fused triazolo-thieno-azino-diazines

The reaction of 222 with SOCl₂ was reported to yield 3-aryl-5,7,9-trimethyl-pyrido[3',2':4,5]thieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidines 223.¹⁸⁰

\[ \text{Ar} = \text{XC}_6\text{H}_4 \quad \text{X} = \text{H}; 4-\text{MeO}; 4-\text{O}_2\text{N} \]

14.2. Quinolino[3',2':4,5]thieno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidines
The hydrazones 224 were reported to be easily cyclized upon treatment with SOCl₂ to give 2-aryl-7-(p-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3',2':4,5]thieno[2,3-e][1,2,4]-triazolo[1,5-c]pyrimidines 226. The formation of the latter products seems to result via Dimroth rearrangement of the initially formed fused triazoles 225.¹⁸¹
15. Conclusions

The present review has outlined the importance of tandem \textit{in situ} generation and 1,5-electrocyclization of N-hetaryl nitrilimines as a convenient methodology for synthesis of numerous fused 1,2,4-triazoles and some of their acyclo C-nucleosides. It is hoped that it will further stimulate the interest of more chemists to explore the utility of such strategy for synthesis of other heterocycles of industrial and biological potentials.
16. References

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Biographical Sketch

Prof. Ahmad Sami Shawali is presently Emeritus Professor of Physical Organic Chemistry, Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt. He graduated with B.Sc. from the University of Cairo in 1958. He received his M.Sc. and Ph.D. degrees in 1962 and 1966, respectively, from Lowell Technological Institute, presently the University of

Lowell, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from the university of Cairo after recommendation from a British committee from the Royal Chemical Society in 1995. Prof. Shawali has been the recipient of the state award and Egypt State Medal of Science and Arts in 1977. He holds several national and international certificates of merit for his distinguished services. He was appointed Vice-Dean for student affairs in 1989 and he was elected Dean of the Faculty of Science in 1991. He was visiting professor at the university of Texas at El Paso, Texas, USA from 1979 to 1980, University of Kuwait from 1973 to 1977 and King Abdulaziz University, Jeddah, Saudi Arabia from 1982 to 1988. He has published 223 scientific papers including 10 review articles, all in international journals. At present there are more than 1800 citations of his work from 1970 until mid 2006 (i.e about 50 citations / year or 8 citations / paper). He supervised till now 45 M.Sc. and 15 Ph.D. graduate theses. He was invited to present plenary lectures at 29 conferences. His research interests are in the fields of reaction mechanisms, applications of LFERS, chemistry of hydrazonoic acid derivatives, 1,3-dipolar cycloadditions and 1,5-electrocyclizations.