The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis
Abdel-Sattar S Hamad Elgazwy* and Mahmoud R Mahmoud Refaee
Department of Chemistry Faculty of Science, Ain Shams University, Abbassia 11566, Cairo, Egypt

Abstract
This review deals with the synthesis involving alkenyl nitriles of heterocyclic systems arranged by increasing ring size and the heteroatoms. Reagents containing alkenyl nitriles and aryl nitriles centers are very important in organic synthesis since they can be versatile and effective species for the efficient construction of rather complex structures from relatively simple starting materials. These reagents have proven to be valuable tools in the synthesis of a wide variety of molecular heterocyclic systems. Their importance stems from the facile bond formation at cyanide centers which can react selectively under suitable conditions. The aim of this review is the analysis and comparison of the various models having evolved on the basis of alkenyl nitriles and their application toward stereoselective synthesis.

Keywords: Alkenyl Nitriles; Annelated heterocycles; Oxygen nucleophile; Nitrogen nucleophile; Sulfur nucleophile; Carbon nucleophile

Introduction
The first compound of the homolog row of nitriles, the nitrile of formic acid, hydrogen cyanide was first synthesized by C.W. Scheele in 1782 [1]. In 1811 J. L. Gay-Lussac was able to prepare the very toxic and volatile pure acid. The nitrile of benzoic acids was first prepared by Friedrich Wohler and Justus von Liebig, but due to minimal yield of the synthesis neither physical nor chemical properties were determined or a structure suggested. Théophile-Jules Pelouze synthesized propionitrile in 1834 suggesting it to be ether of propionic alcohol and hydrocyanic acid [2]. The synthesis of benzonitrile by Hermann Fehling in 1844, by heating ammonium benzoate, was the first method yielding enough of the substance for chemical research. He determined the structure by comparing it to the already known synthesis of hydrogen cyanide by heating ammonium formate to his results. He coined the name nitrile for the new found substance, which became the name for the compound group [3].

Nitriles occur naturally in a diverse set of plant and animal sources with over 120 naturally occurring nitriles being isolated from terrestrial and marine sources. Nitriles are most commonly encountered in fruit pits, especially almonds, and during cooking of Brassica crops (such as cabbage, brussel sprouts, and cauliflower) which lead to nitriles being released through hydrolysis. Mandelonitrile, a cyanoaldrin produced by ingesting almonds or some fruit pits, releases cyanide as the main degradation pathway and is responsible for the toxicity of cyanogenic glycosides [4].

Historically over 30 nitrile-containing pharmaceuticals are currently marketed for a diverse variety of medicinal indications with more than 20 additional nitrile-containing leads in clinical development. The nitrile group is quite robust and, in most cases, is not readily metabolized but passes through the body unchanged. The types of pharmaceuticals containing nitriles are diverse, from Vildagliptin a recently released anti-diabetic drug to Anastrozole which is the gold standard in treating breast cancer. In many instances the nitrile mimics functionality present in the natural enzyme substrate while in other cases the nitrile increases water solubility or decreases susceptibility to oxidative metabolism in the liver [5].

Alkenyl nitrile is one of the most versatile reagents in Organic Chemistry. It has been used as a precursor for producing nucleotides and for synthesising a wide variety of heterocyclic compounds [6] including purines [7,8], pyrimidines [9], pyrazines [10] (some which are widely employed in the fluorescent dye industry [11]), imidazoles [12], biphenylenes [13], porphyrines (which have great potential in optical sensor technology) [14] and daimines that are used as catalysts [15]. This review highlights the alkenyl nitrile chemistry with the focus on the utility of heterocyclic compounds. The synthesis and chemistry of the highly strained aryl nitrile is also briefly reviewed [16].

Heterocycles are ubiquitous in all kind of compounds of interest, and among all the possible synthetic methods of achieving their introduction into a structure, probably the use of a alkenyl nitrile analogue is the most direct one. The present review deals with the generation and synthetic uses of alkenyl nitriles and aryl nitriles formed in heterocyclic synthesis, and can be considered as an update of our revision published in 2007 on this topical [17]. Therefore, only references published from the second quarter of 2003 until the third quarter of 2010 are included, and the same restrictions to the literature coverage applied. Thus, only heterocycles compounds which are found applicability are considered. As previously, the present review is organized by the type of ring members and subdivided by the type of heterocycles fused compounds, including methods for their preparation and their synthetic uses. New developments in the utilities of some alkenyl nitriles in heterocyclic synthesis are reviewed. General synthetic routes based on the utilization of alkenyl nitriles of active imines are discussed. The major methods and modifications are analyzed [18-21].

In this review, which covers the literature up to date, we describe the new and improved methods for the construction of the skeletons, with a particular emphasis on the four, five and six membered ring of heterocyclic compouns. Some of these procedures have clear technical advantages over older methods in terms of yield and versatility, but do not employ new chemistry in the construction of the ring systems. The

*Corresponding author: Abdel-Sattar S. Hamad Elgazwy, Department of Chemistry Faculty of Science, Ain Shams University, Abbassia 11566, Cairo, Egypt, E-mail: elgazwy@sci.asu.edu.eg

Received April 26, 2013; Accepted June 25, 2013; Published June 28, 2013

Citation: Elgazwy ASSH, Refaee MRM (2013) The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis. Organic Chem Curr Res 2: 117. doi:10.4172/2161-0401.1000117

Copyright: © 2013 Elgazwy ASSH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
use of combinatorial synthesis, microwave enhanced processes and new catalytic methodologies in the preparation of these heterocycles is a clear indication that significant advancement has been made in recent years. The syntheses of both on the four, five and six membered ring of fused and polyheterocyclic compounds will be classified into the following five categories, based on the substitution patterns of the ring system: New approaches for synthesis of different mono and polyheterocyclic derivatives arranged by increasing ring size and the heteroatoms utilizing activated nitriles are surveyed. Activated nitriles are very important in organic synthesis since they can be used as effective species for efficient construction of rather complex structures from relatively simple starting materials. The scope and limitation of the most important of these approaches are demonstrated.

Preparation of Alkenyl Nitrile and Aryl Nitrile Derivatives

Industrially, the main methods for producing nitriles 2 are ammonoxidation and hydrocyanation. Both routes are green in the sense that they do not generate stoichiometric amounts of salts. In ammonoxidation, a hydrocarbon is partially oxidized in the presence of ammonia. This conversion is practiced on a large scale for acrylonitrile, as shown below [22].

\[
\begin{align*}
\text{C}_2\text{H}_4 + & 3\text{O}_2 + \text{H}_2\text{O} & & \text{C}_2\text{H}_3\text{CN}
\end{align*}
\]

An example of hydrocyanation is the production of adiponitrile 4 from 1,3-butadiene 3, as outlined below.

\[
\begin{align*}
\text{C}_2\text{H}_4 & + 2\text{HCN} \quad \text{NC} \quad \text{CN} \quad \text{C}_2\text{H}_4 \quad \text{NC} \quad \text{CN}
\end{align*}
\]

Usually for more specialty applications in organic synthesis, nitriles can be prepared by a wide variety of other methods: Dehydration of primary amides. Many reagents are available, the combination of ethyl dichlorophosphate and DBU just one of them in this conversion of benzoamide to benzonitrile [23]. Two intermediates in this reaction are amide tautomer A and their phosphate adducts B, as summarized diagrammatically in Scheme 1.

Scheme 1

In one study an aromatic or aliphatic aldehyde is reacted with hydroxylamine and anhydrous sodium sulfate in a dry media reaction for a very small amount of time under microwave irradiation through an intermediate ald oxime [24], as shwon in Scheme 2. A commercial source for the cyanide group is diethylaluminum cyanide Et\textsubscript{2}AlCN [25], which can be prepared from triethylaluminum and HCN, it has been used as nucleophilic addition into ketones [26].

Scheme 2

For an example of its use Kuwajima Taxol total synthesis of cyanide ions facilitate the coupling of dibromides. Reaction of α,β-dibromo adipic acid with sodium cyanide in ethanol yields the cyano cyclobutane [27], as shown in Scheme 3.

\[
\begin{align*}
\text{HOOC}-\text{CH} \quad \text{CH} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \quad \text{COO} \quad \text{Et} \quad \text{NaCN} \quad \text{EtOH} \quad \text{99%}
\end{align*}
\]

Scheme 3

In the so-called Franchimont Reaction (A. P. N. Franchimont, 1872) α-bromocarboxylic acid is dimerized after hydrolysis of the cyan group and decarboxylation. Aromatic nitriles can be prepared from base hydrolysis of trichloromethyl aryl ketimines (RC(CCl\textsubscript{3})=NH) in the Houben-Fischer synthesis [28-31]. In reductive decyanation the nitrile group is replaced by a proton [32]. An effective decyanation is by a dissolving metal reduction with HMPCA and potassium metal in tert-butanol. α-Amino nitriles can be decyanated with lithium aluminum hydride. Nitriles self-react in presence of base in the Thorpe reaction in a nucleophilic addition. In organometallic chemistry nitriles are known to add to alkynes in carbo cyanation, as summarized diagrammatically in Scheme 4 [33].

![Scheme 4](image)

Synthesis

Four membered rings

Organic cyanocompounds are versatile reagents, which have been extensively utilized in heterocyclic synthesis. Alkenyl nitriles behaves as a typical stable organic molecule, the stability of alkenyl nitriles and aryl nitriles arises from the fact that it has an aromatic delocalized π-electron system. Enormous number of reports [34-43], on the utility of these compounds in synthesis of heterocycles has been reported. It is our intention in this review, therefore, to fill the gaps and report on the utilities of α-β-unsaturated nitriles. Such as aryldiene malononitrile 13 which successfully used to prepare 4-Aryl-2-iminothietane-3-carbonitrile 14 in a moderate yield via the reaction [44] of with ammonium benzydithio-carbamate 15, as outlined in Scheme 5.

Scheme 5

Five membered rings

Five membered ring with one heteroatom:

Synthesis of thiophene and fused thiophene derivatives: The α-β-unsaturated nitriles with active methylene group at β-carbon 16 could react with elemental sulphur to yield an intermediate mercapto derivative 17, which cyclizes into the most isolable stable aminothiophene derivative 18, as outlined in scheme 6 [45-49].

![Scheme 6](image)
the presence of a basic catalyst.

\[
\begin{align*}
\text{Scheme 7} \\
\text{Formation of thiophenes 22 from the reaction of } \alpha-\beta\text{-unsaturated nitriles with thioglycollic acid has been reported [50-53].}
\end{align*}
\]

\[
\begin{align*}
\text{(21a-c)} \\
\text{a) } X = \text{CN} \\
\text{b) } X = \text{CO}_2\text{Et} \\
\text{c) } X = \text{CO}_2\text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 8} \\
\text{Tetracyanoethylene 23 has been reported to react with hydrogen sulphide [54,55] to produce the thiophene derivative 24 in moderate yields 68%}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 9} \\
\text{Another similar synthesis that affords thiophene derivatives 26 utilizing thioanilides of the type as starting component is the reaction of 25 with active methylene reagents [56].}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 10} \\
\text{Formation of thiophenes via the reaction of arylidene derivatives of 3-oxoalkanenitriles has been reported by El-Nagdy et al. [51,52,56-58]. For example, the thiophene derivatives 28 were formed from the reaction of 27 with ethyl thioglycollate. On the other hand, the thiophene derivative 29 was isolated on using thioglycollic acid together with Michael adduct 30, as outlined in Scheme 11.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 11} \\
\text{Synthesis of furan derivatives: To be considered as an update of our revision published in 1998 on this topic such as photochemical transformations of 2(SH) furanones [59]. In the last decade, it was reported by Aran and Soto [60] for the formation of furan derivatives 31 by heating 2-benzoyl-3-phenyl-acrylonitrile 27 with cyanide ion.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 12} \\
\text{Synthesis of pyrrole and condensed pyrrole derivatives: Several synthesis of pyrrole derivatives utilizing organic cyano compounds as starting components were reported [60-68]. The most interesting results of that are demonstrated in Scheme 13 [68-73].}
\end{align*}
\]
Heating pyrrole-2-carbodithionates \( S_x \) with anions of C-H acids generated from malononitrile or cyanoacetamide in KOH/DMSO (room temperature, 0.5 h). Interaction of the resulting enethiolates \( S_x \) with haloacetylenes \( 54 \) afforded the pyrrolothiazolidines \( 55 \), as outlined in Scheme 18 [86-91].

Scheme 18

**Five membered rings with two heteroatoms:**

**Synthesis of 1,2-oxazole derivatives:** The \( \alpha-\beta \)-Unsaturated nitriles are extensively utilized for the syntheses of 1,2-oxazoles [92-95]. For example, the dimer of ethyl cyanoacetate \( 56 \) reacted with hydroxylamine hydrochloride to yield \( 57 \). In Scheme 19.

Scheme 19

Other examples for the syntheses of amino-1,2-oxazole are shown in Scheme 20 [96-98].

Scheme 20

**Synthesis of thiazole derivatives:** The chemistry of thiazoles has been reviewed by one of us [105] and the thiazole derivatives \( 72 \) was produced by treatment of the dimercaptomethylenemalononitrile salt \( 69 \) with elemental sulfur in refluxing methanol, in a good yield. The existence of intermediates \( 70 \) and \( 71 \) has been envisioned. The former arises from nucleophilic attack by mercaptoide anion on sulfur, whereas the latter involves a second nucleophilic attack on the nitrile with expulsion of the sulfur moiety by the nitrogen. Another example of this reaction involving the mononitrile derivative \( 73 \) has been described, which presumably proceeds through the same path, leading to the isothiazole derivative \( 74 \) [106], as outlined in Scheme 23.

Scheme 23

**Synthesis of isothiazole derivatives:** The chemistry of isothiazoles has been reviewed by one of us [105] and the isothiazole derivatives \( 66 \) was allowed to react with different arylidenenitriles in the presence of triethylamine and yielded spirolbenzodiazepine isoxazole derivatives \( 67 \) and \( 68 \), as outlined in Scheme 23 [104].

Scheme 24

**Synthesis of thiazole derivatives:** An investigation was undertaken to explore the potential utility of the reaction of some activated nitriles with mercaptoacetic acid as a route for the synthesis of thiazoles, thus, cinnamononitriles \( 63 \) react with mercaptoacetic acid to give the thiazole derivatives \( 75 \) [107,108], as outlined in Scheme 25.

Scheme 25

**Synthesis of pyrazole and fused pyrazole derivatives:** Scission of the double bond in the arylidine derivatives of 3-oxoalkanenitriles \( 27 \) was reported to take place by the action of hydrazines in basic media, whereas the formation of 3,5-diaryl-3-pyrazolines \( 76 \) was reported to take place in acidic media [109-111]. The intermediate phenylhydrazone derivative \( 77 \) was isolated together with \( 78 \) on reaction of \( 27 \) (\( 27 \) = p-O,N-C,H) with phenylhydrazine. El-Nagdy et al. [112-114] have reported that \( 27 \) (\( 27 \) = p-Me,N-C,H) reacts with \( \beta \)-cyano-ethylhydrazine to yield the hydrazone \( 79 \), which was cyclized to yield either \( 80 \) or \( 81 \) depending on the applied reaction conditions as shown in Scheme 26.

Scheme 26
Cusmano and Sprio [109,110,115,116] have shown that the double bond in compound 82 functions as a ylidenic bond even toward the action of semicarbazide hydrochloride, thus heating benzylidene-ω-cyanoacetophenone 27 with semicarbazide hydrochloride in an ethanolic solution of sodium carbonate results in the formation of benzaldehyde semicarbazone and ω-cyanoacetophenone. However, when the reaction mixture was left for several days, compound 82 (formulated by Cusmano and Sprio as R1 = H, R2 = Ph, R3 = CONH2) was formed in addition to benzaldehyde phenylhydrazono, as described in Scheme 27.

Scheme 27

It has been shown that ethyl β-trichloromethyl-β-aminomethylenecyanocacetate (84, X = CCl3) reacts with hydrazine hydrate to afford the aminopyrazole derivative 86 via intermediate formation of the amidrazone 85 which could be isolated [116,117-119]. This is in contrast to the reported formation of 3-amino-4-cyano-5-trifluoromethylpyrazole 87 on treatment of β-trifluoromethyl-β-aminomethylene-malononitrile (84, X = CF3) with hydrazine hydrate [120]. Synthesis of pyrazoles via similar routes has been reported [107,121], as outlined in Scheme 28.

Scheme 28

Ethoxymethylenemalononitrile 88 reacted with hydrazine hydrate to yield the pyrazole derivatives 89 and 90 [122], as outlined in Scheme 29.

Scheme 29

In an attempt to synthesize 3-amino-4-ethoxycarbonyl-pyrazole 92 via reacting 91 with hydrazine hydrate in a manner similar to that reported for its reaction with phenyl hydrazine which is established to afford pyrazole derivatives, Midorikawa et al. [123,124] have obtained, instead of the expected pyrazole derivative 92, the pyrazolo[1,5-a]pyrimidine derivative 94. The formation of this product is expected to proceed via intermediate formation of 93, as outlined in Scheme 30.

Scheme 30

4-(4-Phenyl-3-pyrazolyl)-4H-1,2,4-triazole 97 was recently prepared by the action of formylhydrazine 96 on α-phenyl-α-cyanoacetophenylhydrazine 95 [125], as depicted in Scheme 31.

Scheme 31

β-Dimethylamino- α-(2-ribosyl) acrylonitrile 98 reacted with hydrazine hydrate to yield the aminopyrazole derivative 99. This reaction opened a new route for the synthesis of formycone and formycone analogues [126], as shown in Scheme 32.

Scheme 32

A variety of new pyrazole derivatives 101-104 have been synthesized utilizing the same idea of reacting α-β-unsaturated nitriles 100a-c with hydrazine or acylated hydrazines [99,127-149]. Examples for the most interesting of these syntheses are shown in Scheme 33.
derivatives of 2,3-dioxo-3-phenylpropionitrile reacted with ethyl formylacetate to yield the imidazo[1,2-b]pyrazole derivative 116 in excellent yield. Attempted cyclization of 111 by action of 3% NaOH has afforded the carboxylic acid derivatives 113. On the other hand the hydrochloride 114 was obtained on attempted cyclization of 112 by the action of conc. HCl [113], as shown in Scheme 37.

Scheme 36

Furthermore, compound 108 reacted with the dimer of malononitrile 111 to afford 112 in excellent yield. Attempted cyclization of 111 by action of 3% NaOH has afforded the carboxylic acid derivatives 113. On the other hand the hydrochloride 114 was obtained on attempted cyclization of 112 by the action of conc. HCl [113], as shown in Scheme 37.

Scheme 37

Similar to the behaviour of 77, phenyl hydrazonomalononitrile 115 reacted with 108 to yield the imidazo[1,2-b]pyrazole derivative 116 is depicted in Scheme 38.

Scheme 38

The behaviour of the ethoxymethylene derivatives of cyanoacetic acid 117 has also been investigated [113]. It has been found that 117 react with 108 to yield the aminopyrazole derivatives 118 are depicted in Scheme 39.

Scheme 39

The nitrile 119 reacted with 4-bromo-3-methylpyrazol-5-one 120 in ethanol in the presence of catalytic amount of triethylamine to give the corresponding pyrano[2,3-c]pyrazole derivatives 121 [150] are depicted in Scheme 40.

Scheme 40

Treatment of activated nitrile 122 under the above conditions gave the acyclic pyrazolone derivative 123 which could not be cyclized.
were formed from pyranopyrazoles 126d-i, as depicted in Scheme 43.

Scheme 43

The structure of the products of the reaction of 124 with 125b has been recently shown [157] to be 133 formed most likely via decomposition of the initially formed Michael adduct 131 into 132 and addition of one molecule of 125b to this decomposition product affording arylidene-bis-pyrazolones that react with piperidine present in the reaction mixture to yield 133, as depicted in Scheme 44 [158].

Scheme 44

Girgis et al. [150] have reported that compound 129g,h was formed via reacting 124g,h with 125b. However, Abdelrazik et al. [151] have later reported that the product of the reaction of 125b with 124g is 129. Similar to the behaviour of 125a, compound 125c reacted with 124a to yield 134 [159]. Similar results were obtained with 125d, as depicted in Scheme 45 [160-162].

Scheme 45

El-Torgoman et al. [162] reported the formation of 137 from 125 and p-anisylidene thiocyanoacetamide 135 via elimination of hydrogen sulphide from the intermediate Michael adduct 136, as shown Scheme 46.

Scheme 46

Mahmoud et al. [163] reported that equimolar amounts of 1-phenyl-3-methylpyrazolin-5-one 125 and α-cyano-3,4,5-trimethoxyoxanilidone 138 were refluxed in absolute ethanol in the presence of piperidine as a catalytic base. After 15 minutes an insoluble fraction was isolated as colorless crystals (13%) and detected to be the oxinobispyrazole 139 and the reaction was completed for 3h. Removal of most of the solvent and acidification with dilute acetic acid afforded the 1:1 adduct 140a or 140b as pale yellow crystals (44% and 46% yield, respectively), as outlined in Scheme 47.

Scheme 47

Spiropyranopyrazoles 142 have been obtained through reacting substituted cyanomethylideneindolinones 141 with 125a,b. It is of value to report that these products were earlier believed to be the quinoline derivatives 143. 13C-NMR spectra have been utilized to discriminate between the two structures (Scheme 48) [159,164].

Scheme 48

Pyranopyrazoles 145 were formed via reacting 144a,b with 125a [100]. However, the reaction of 144c with 125a led to the formation

under the applied conditions in contrast to the previous case [150], the product is depicted in Scheme 41.

Scheme 41

The arylidene malononitrile 124a-c has been reacted with 3-methyl-2-pyrazolin-5-one 125a to yield the pyranopyrazoles 126a-c, which were also obtained from the reaction of arylidene pyrazolones 127a-c with malononitrile [100] and this reaction proved to be a general one. Thus, pyranopyrazoles 126d-i were formed from 125a and 124d-i in yield (66-99%) [151-156] and the products are depicted in Scheme 42.

Scheme 42

However, attempts to extend this approach in order to enable synthesis of 128 failed. Abdo et al. [100] reinvestigated reaction of 125 with 124a,b and obtained a product the structure of which was assigned as 129 since they proved that 128a,b were obtained via addition of malononitrile to 100a,b [100,140] as depicted in Scheme 43.

Scheme 43

The structure of the products of the reaction of 124 with 125b has been recently shown [157] to be 133 formed most likely via decomposition of the initially formed Michael adduct 131 into 132 and addition of one molecule of 125b to this decomposition product affording arylidene-bis-pyrazolones that react with piperidine present in the reaction mixture to yield 133, as depicted in Scheme 44 [158].

Scheme 44

Girgis et al. [150] have reported that compound 129g,h was formed via reacting 124g,h with 125b. However, Abdelrazik et al. [151] have later reported that the product of the reaction of 125b with 124g is 129. Similar to the behaviour of 125a, compound 125c reacted with 124a to yield 134 [159]. Similar results were obtained with 125d, as depicted in Scheme 45 [160-162].

Scheme 45

El-Torgoman et al. [162] reported the formation of 137 from 125 and p-anisylidene thiocyanoacetamide 135 via elimination of hydrogen sulphide from the intermediate Michael adduct 136, as shown Scheme 46.

Scheme 46

Mahmoud et al. [163] reported that equimolar amounts of 1-phenyl-3-methylpyrazolin-5-one 125 and α-cyano-3,4,5-trimethoxyoxanilidone 138 were refluxed in absolute ethanol in the presence of piperidine as a catalytic base. After 15 minutes an insoluble fraction was isolated as colorless crystals (13%) and detected to be the oxinobispyrazole 139 and the reaction was completed for 3h. Removal of most of the solvent and acidification with dilute acetic acid afforded the 1:1 adduct 140a or 140b as pale yellow crystals (44% and 46% yield, respectively), as outlined in Scheme 47.

Scheme 47

Spiropyranopyrazoles 142 have been obtained through reacting substituted cyanomethylideneindolinones 141 with 125a,b. It is of value to report that these products were earlier believed to be the quinoline derivatives 143. 13C-NMR spectra have been utilized to discriminate between the two structures (Scheme 48) [159,164].

Scheme 48

Pyranopyrazoles 145 were formed via reacting 144a,b with 125a [100]. However, the reaction of 144c with 125a led to the formation
of 126 [151]. Similar results have been reported on treatment of 125 derivatives with 144, as depicted in Scheme 49 [160].

Scheme 49

The reaction of chalcones 146a with 125a yields the corresponding Michael adducts 147 [165-168]. These could be cyclized by the action of polyphosphoric acid into 148. The reaction of α-cyanochalcone 146b with 125a resulted in the direct formation of 148b (X = CN), as outlined in Scheme 50.

Scheme 50

Excellent yield of pyranopyrazole derivatives 149 were obtained upon treatment of nitrile 27 with 125 [169], and is depicted in Scheme 51.

Scheme 51

1-Phenyl-pyrazolin-3,5-dione 150 reacts with activated nitrile derivatives to yield several pyrazol[2,3-c]pyrazoles [161] 151, 152. Similarly, 1,3-diphenylthio-hydantoin, thiazolidinethiones and isorhodanine react with cinnamonic nitriles to yield the corresponding pyrazolo-3,5-dione derivatives, however in some cases, ylidene group exchange took place and the compound is depicted in Scheme 52 [161].

Scheme 52

During the course of our investigations on the use of DAMN in heterocyclic synthesis, we designed new approaches to 4-cyano-1,3-diylhydro-2-oxo-2H-imidazole-5-(N1-tosyl)carboxamide as a reactive precursor thiopurine [170]. In some of these cases, new DAMN derivatives, N-[(Z)-2-amino-1,2-dicyanovinyl]amino|carbonyl]-4-methylbenzenesulfonamide, were used as the key intermediates. Since until now the preparation and characterization of the above stated sulfonamides have been mentioned only briefly, we give herein a report on these compounds in more detail [170]. Tetracyanoethylene 23 reacted with 123 to yield product of condensation by the elimination of hydrogen cyanide, which is formulated as 124 depicted in Scheme 53 [171].

Scheme 53

Madkour et al. [171] has reported that hydrazinolysis of 3-(4-methoxyphenyl) and 3-(2'-thienyl)-2-cyano-2-propenoyl chlorides 155a [172-176] and 155b at 0ºC afforded the pyrazolone derivatives 156, bishydrazine 157 and anisylidenediazene 158, while, treatment of 155a with benzylohydroxyamine afforded the pyrazolone 159, as outlined in Scheme 54.

Scheme 54

Furthermore, the electrophilicity of the lactonic carbonyl functionality of benoxazinone 160 has been investigated [172] via its reaction with some nitrogen and oxygen nucleophiles. Thus, stirring 160 with hydrazine hydrate at 0ºC in dioxane gave the pyrazolone5,1-b]- (N, S-acetals) [178] to give pyrazolino-1,3-oxazine derivatives, as outlined in Scheme 55.

Scheme 55

4-Arylidene-1-phenyl-3,5-pyrazolinediones 164 [177] reacted with activated nitriles 165 (N, S-acetals) [178] to give pyrazolino-1,3-oxazine derivatives 166, as outlined in Scheme 56.

Scheme 56

On refluxing compound 167 with cycloalkylidenedicyanoacetamide 168 in dioxane in the presence of triethylamine, the corresponding pyrazolopyridinethione derivatives 169 were obtained [179], as outlined in Scheme 57.
Treatment of 170 [179] with benzylidene malononitrile furnished the corresponding spiroazaheterocyclic derivatives 171 and are depicted in Scheme 58 [180].

![Scheme 58]

The synthesis of various pyrazolo[1,5-a]pyrimidines as unique phosphodiesterase inhibitors from easily available starting materials has been the subject of several publications [181-183]. In spite of enormous literature reported for the synthesis of pyrazolo[1,5-a]pyrimidines using 5-aminoalkyl derivatives as educts, very few reports have appeared describing the utility of aminopyrazoles as starting components for the synthesis of condensed pyrazoles. In conjunction to previous work, compound 172 was reacted with cinnamoyl chloride to yield the pyrazolo[1,5-a]imidazole derivative 173 depicted in Scheme 59 [184].

![Scheme 59]

New spiro heterocyclic systems attached by coumarin nucleus were synthesized by the reaction of 2-coumarylidene malononitrile 174 with some active methylene or bidentate such as hydrazine hydrate to afford 175 and 176, respectively [179], as outlined in Scheme 60.

![Scheme 60]

**Synthesis of imidazoles and condensed imidazoles derivatives:** A New Synthesis of 4-Cyano-1,3-dihydro-2-oxo-2H-imidazole-5-(1H)-carboxamide: A Reactive Precursor for Thio Purine Analogs 
Hamad et al. [169]. 2,3-Diaminomaleonitrile 177 has been recently utilized for the synthesis of imidazole derivatives. Thus, 177 reacted with formamidine to yield 2,3-diaminomaleonitrile 178 which could be cyclized under different conditions to yield different imidazole derivatives 179-182, and the product is depicted in Scheme 61 [149,185-188].

![Scheme 61]

Aziz et al. [102] found that the activated nitriles 184 react with 3-phenyl-2-thiohydantoin 185 to yield 1:1 adducts 186 together with the 5-benzylidene-2-thiohydantoin derivatives 187. The same products were obtained when 187 were treated with malononitrile, as shown in Scheme 62.

![Scheme 62]

In contrast to the behaviour of compound 185 towards 184a-d, the 2-thiohydantoin derivatives 185b,c reacted with 184a,b to yield 5-arylidenec derivative 187ab, 187bb and 187ac, respectively, as the sole isolable products and were recovered almost unaffected after treatment with 184c under the same experimental conditions, as outlined in Scheme 63.

![Scheme 63]

**Synthesis of imidazoles and condensed imidazoles derivatives:** A New Synthesis of 4-Cyano-1,3-dihydro-2-oxo-2H-imidazole-5-(1H)-carboxamide: A Reactive Precursor for Thio Purine Analogs 
Hamad et al. [169]. 2,3-Diaminomaleonitrile 177 has been recently utilized for the synthesis of imidazole derivatives. Thus, 177 reacted with formamidine to yield 2,3-diaminomaleonitrile 178 which could be cyclized under different conditions to yield different imidazole derivatives 179-182, and the product is depicted in Scheme 61 [149,185-188].

![Scheme 61]

Aziz et al. [102] found that the activated nitriles 184 react with 3-phenyl-2-thiohydantoin 185 to yield 1:1 adducts 186 together with the 5-benzylidene-2-thiohydantoin derivatives 187. The same products were obtained when 187 were treated with malononitrile, as shown in Scheme 62.
In contrast to the behaviour of compound 184a-c toward 185, ethylbenzylidene cyanoacetate 152f reacted with imidazolidines 185a-c to give the benzylidene derivatives 187aa, 187ab and 155ac, respectively. The reaction of thiodydantoin 185b with 27 has been, however, shown to yield either pyrano[2,3-d]imidazoles 191 or pyrrolo[1,2-c]imidazoles 192 depending on the nature of substituents on the thiodydantoin and is depicted in Scheme 65 [102].

Scheme 65

Synthesis of five membered rings with three heteroatoms

The synthetic potentials of 2-arylhydrazinonitriles have recently been reviewed [189]. El-Mousawi et al. have reported that 2-phenylhydrazono-3-oxo-butanenitrile 191 reacted with hydroxylamine hydrochloride in ethanolic sodium acetate to yield amidoxime 193 that could cyclize to 1,2,4-oxadiazoles [194] on reaction with hydroxylamine and the product depicted in Scheme 66.

13C-NMR of the reaction product indicated that this is not the case, as it indicated the absence of the carbonyl carbon in the range δ = 180-200 ppm. Therefore, the formation of isomeric oxazole II was considered as the correct structure which can take place only via intermediacy of the initial product of condensation of the ketocarbonyl 193 with hydroxylamine yielding intermediate I that could cyclize to isomeric oxazole II. Intermediate isomeric oxazole II when heated in DMF in the presence of piperidine it rearranged readily to 195 [191], as outlined in Scheme 67.

Scheme 67

Tetracyanoethylene 23 reacts with ethyldiazoacetate to yield 1,2,3-triazoles 196 is depicted in Scheme 68 [186,192]

Scheme 68

Cyanamide derivatives 197 have been extensively utilized for the synthesis of 1,2,4-triazoles [193-195]. The one interesting example for the utility of these reactions in synthesis of triazole derivatives 198 and 199 is shown below in the following Scheme 69.

Scheme 69

Cyanamide derivatives have been utilized for the synthesis of oxadiazoles [196]. For example, benzoyldicyandiamide 200 afforded a mixture of the urido-1,2,4-oxadiazole derivatives 201 and 202 on treatment with hydroxylamine, the first was predominating, as the product depicted in Scheme 70 [194,196].

Scheme 70

Similarly, the iminoether 203 afforded the amino-oxadiazole derivative 204 on reaction with hydroxylamine and the product depicted in Scheme 71 [197].

Scheme 71

Also, the cyanamide 205 reacted with hydroxylamine to yield 1,2,4-oxadiazole derivative 206 is depicted in Scheme 72 [198].

Scheme 72

1-Substituted-3-cyano-isothioureas 207, gave mixture of the 5-amino-3-substituted-amino-1,2,4-oxadiazoles 208 and the isomeric 3-amino-5-substituted-amino-1,2,4-oxadiazoles 209 on reaction with hydroxylamine, the compound 208 usually predominated and is depicted in Scheme 73 [199].

Scheme 73

Six-membered heterocycles

Six membered heterocycles with one heteroatom

Synthesis of pyridine and condensed pyridine derivatives:

Several pyridine syntheses, utilizing nitriles as starting components have been reported [37-41]. Although a number of papers have been
published concerning the synthesis of 2-oxopyridine derivatives [200-212] no preparations using 2-cyano acrylates, cycloalkanones and ammonium acetate as starting materials have been reported. Some 2-oxopyridine derivatives such as 4-aryl-3-cyano-2-oxo-7-(substituted benzylidene)-2,5,6,7-tetrahydro-1H-pyridines (38-57% yield) 212 were synthesized from ethyl 2-cyanoacrylates 210, cycloalkanones 211 and ammonium acetate in refluxing ethanol [213], as shown in Scheme 74.

![Scheme 74](image)

An analogous reaction between ethyl 2-cyanoacrylates (R = Me, Et) 213, cyclopentanone and ammonium acetate gave, as products, ethyl-2-cyclopentylidene-2-cyanoacetate (major product) and the 4-alkyl-3-cyano-2-oxo-2,5,6,7-tetrahydro-1H-pyridines 214 instead of the expected 7-alkylidene derivatives and the product depicted in Scheme 75.

![Scheme 75](image)

The reaction of 210a-d with 215b gave the 4-aryl-3-cyano-2-oxo-1,2,3,4,4a,5,6,7-octahydroquinolines 216 and/or the 4-aryl-3-cyano-2-oxo-1,2,5,6,7,8-hexahydroquinoline 217, the product depicted in Scheme 76.

![Scheme 76](image)

The 2-iminopyridine derivatives 220 obtained in fairly good yield from the condensation of arylidene malononitrile 218 with alkyl ketones 219 in the presence of excess ammonium acetate with boiling benzene and the product depicted in Scheme 77 [214].

![Scheme 77](image)

The reaction of β-alkylarylidenemalononitrile 50 with phenylisocyanate or phenylisothiocyanate under PTC conditions (MeCN/K2CO3/TBAB) yielded pyridinone and pyridine-2-thione derivatives 221 [105,215], as shown in Scheme 78.

![Scheme 78](image)

However, treatment of arylidene malononitrile with some reactive halo compounds under PTC afforded the N-aminopyridine derivative 222, [105,215]. Where with hydrazine hydrate yielded the pyridine derivatives 223 and 224 in moderate to good yields, as shown in Scheme 79.

![Scheme 79](image)

The cinnamonitriles 63 react with cyanoacetic acid hydrazide 226 to afford N-aminopyridines. Soto et al. [215] reported the direct formation of 226 as sole reaction product on heating 63 with 225 for 5 min. However, El-Moghayar et al. [216] have reported that the product previously identified as 226 is really 227 which rearranged on refluxing in aqueous ethanolic triethylamine solutions into 228, as shown in Scheme 80. Evidence afforded on this problem are not conclusive and further investigation seem to be mandatory.

![Scheme 80](image)

The reaction of the dimers 111 and 56 with cinnamonitriles in ethanolic triethylamine solutions afforded the pyridine derivatives 229, 230 are depicted in Scheme 81 [217-219].
Recently, this approach has been explored for the synthesis of several pyridine derivatives 231-236, as outlined in Scheme 82 [220-223].

Scheme 82

Daboun et al. [223] have found that a solution of equimolar amounts of 2-amino-1,1,3-tricyanoprop-1-ene 111 and acetylacetone in ethanol was refluxed for 2 hr in the presence of piperidine as a catalyst to yield a product of molecular formula C_{11}H_{8}N_{4}. Two possible structures, 3-cyano-2-dicyanomethylene-4,6-dimethyl-1,2-dihydropyridine 237 and the isomeric 238, were considered. Structure 237 was established by the results of IR and 1H-NMR spectra. The obtained products bear several functional substituents and appear promising for further chemical transformations, as outlined in Scheme 83.

Scheme 83

The activated nitrile 240 and 241 was synthesized by El-Nagdy et al. [224] through the reaction of phenacylthiocyanate 239 with malononitrile, as outlined in Scheme 84.

Scheme 84

The structure 241 was ruled out on the basis of IR and 1H-NMR spectra. Reaction of trichloroacetanilide with 240 in refluxing toluene in the presence of a catalytic amount of piperidine yield a 1:1 gave adduct 241 which cyclized into product 243 which was suggested based on spectroscopies. The compound 240 also might be gave 242 and then cyclized to give 244, as outlined in Scheme 85.

Scheme 85

Conflicting results have been reported for the reaction of cinnamnonitrile 63 with cyanothioacetamide 215. Thus, Daboun and Riad [225] reported that the dihydropyridines 246a,b were isolated from the reaction of 63 with 245. On the other hand, Sato et al. [226] reported that the pyridines 246a,b were the isolable products from the reaction of 63 and 245 [227,228]. Recently, it has been shown that the thiopyrans 247 are the products of the kinetically controlled reactions of 63 with 245 (via chemical routes and inspection of the high resolution 1H-NMR and 13C-NMR). These products rearrange on heating in aqueous ethanol into the thermodynamically stable dihydropyridines 248. Observed [100,101,151] dependency of the products of reactions of active methylene reagents with cinnamnonitrile derivatives on the nature of reactants and reaction conditions has been reported [134,226-236], as outlined in Scheme 86.

Scheme 86

Pyridine derivatives 250, 251, 252, 253 and 255 were successfully synthesized via condensation of cyanothioacetamide 245 with the cinnamnonitrile derivatives 249 or the acrylonitrile derivatives 253, as outlined in Scheme 87 [237].
Gewald et al. [237] have shown that the product of reaction of 56 and 111 with trichloroacetonitrile are really the pyridine derivatives 256 and 257, respectively. Convincing evidence from 13C-NMR for the proposed structures were reported, as outlined in Scheme 88.

Scheme 88

A route for the synthesis of 6-[5-amino-pyrrrol-4-yl]pyridines 253 and their conversion into 3-[pyridine-6-yl]pyrazolo[1,5-a]pyrimidines 263 has been reported [238]. Thus, 1-phenylethylidene malononitrile 258 was refluxed in pyridine solution with enamionitriles 253a-c to yield products via chloroform elimination. Structure 230 or its cyclized product 261 may undergo cyclization into 261 under the reaction conditions. Compound 261 reacted with hydrazine hydrate affording 261, which condensed readily with acetyclonitrene affording the required pyrazolo[1,5-a]pyrimidines 263, as outlined in Scheme 89.

Scheme 89

El-Nagdy et al. [239] reported that 3-amino-2-cyano-4-ethoxycarbonyl crotononitrile 234 reacted with trichloroacetonitrile in refluxing ethanol in presence of triethyamine to give 235 which resemble the formation of pyridine derivative from the reaction of 2-amino-1,1,3-tricyanopropene with trichloroacetonitrile. Compound 235 reacted with hydrazine hydrate to yield hydrazine derivatives 236 which successfully cyclized into 261, as outlined in Scheme 90.

Scheme 90

It was reported that when indan-1,3-dione or 1-phenylimino-indan-3-one 268a,b were heated with arylidenecyanothalactamide in refluxed ethanol in the presence of a catalytic amount of piperidine, 4-aryl-3-cyano-5-oxo- or (phenylimino)-inden-1,2-b)pyrimide-2[1H]thiones [240] 269a-c were obtaine, as outlined in Scheme 91.

Scheme 91

When 269 was subjected to react with NaN₃ in DMF in the presence of NH₄Cl to synthesize mercaptotetrazolylindeno pyridine 271 as reported [241,242] the aminodindeno pyridine derivative 270 was obtained instead of 271, as depicted in Scheme 92.

Scheme 92

1-Dicyanomethylene-3-indanone 272 was prepared by the reaction of indandione and malononitrile in ethanolic sodium ethoxide solution [243,244]. Compound 272 reacted with carbon disulphide to give the dithiocarboxylic acid derivative 273, which in turn was alkylated with methyl iodide and ethyl chloroacetate to give 274 and 275. Indeno[2,1-c]pyridines 276 were prepared through the reaction of 272 with phenyl (benzoyl) isothiocyanate. Compound 272 with malononitrile and aromatic aldehyde afforded 277, which reacted with acetic acid to give 278. Bromination of 272 with N-bromosuccinimide afforded 2-bromo derivative 279 which reacted with aniline, methylthioglycolate, and ethylglycinate to give indeno[2,1-b]pyroles 280, 281 [245], indeno[2,1-b]thiopyrane 282, 283 and 284, as outlined in Scheme 93.

Scheme 93

Piperidyliden malononitrile 285 reacts with benzaldehyde to...
Compounds in a similar way to that reported for other related structures [247, 248].

Scheme 94, as outlined in Scheme 97.

obtained using a 2:1 molar ratio of cinnamonitrile derivative and by El-Nagdy et al. [101] and Kambe et al. [249]. Better yields were isolated, as depicted in Scheme 98.

pyridines and 6-substituted-7H-2,3-dihydro-5-amino-8-cyano-3-oxo-2-(3,4,6-thiazolo[3,2-a] pyridines (ethanol soluble fraction, major yield) can be obtained from the reaction of two fold of 2-amino crotononitrile with aromatic nitriles are already available in literature; a very old example is the reaction of 4-acetyloxazoles into pyridine derivatives 306 via reaction with malononitrile has been reported. The reaction proceeds via formation of the ylidenemalononitrile derivative 304 and then cyclized into 305 [254], as outlined in Scheme 102.

Scheme 98

Several other pyridine syntheses from activated α,β-unsaturated nitriles are already available in literature; a very old example is the reaction of two fold of 2-amino crotononitrile with aromatic

E-Z-assignment of compounds containing exocyclic C=C double bonds throughout the present work were elucidated and proven by 1H-NMR calculations [251]. Unexpectedly, it has been found that the product 299 from the reaction of 292 with 2-oxo-3-dicyanomethyliden-2,3-dihydroindole 297a. 2-oxo-3-cyanoethoxy carbonylmethyliden-2,3-dihydroindole 297b and with isatin under the same experimental conditions was one and the same product 298 [252], as outlined in Scheme 99.

It was believed that the reaction product was found via additions of 292 to the activated double bond in 297a,b to form the corresponding intermediate Michael adducts, which then loses either malononitrile or ethyl cyanoacetate to yield the final isolable product 298. Junek [253] has reported that salicylaldehyde 299 reacts with 2-amino-1,1,3-tricyanophrop-1-ene 111 to yield the benzopyrano[3,4-c]pyridine 300 is depicted in Scheme 100.

Scheme 100

Midorikawa et al. [249] have shown that the reaction of substituted amines with ylidenemalononitriles affords pyridine derivatives 301 and 302, as outlined in Scheme 101.

Scheme 101

Conversion of 4-acetyloxazoles 303 into pyridine derivatives 306 via reaction with malononitrile has been reported. The reaction proceeds via formation of the ylidenemalononitrile derivative 304 and then cyclized into 305 [254], as outlined in Scheme 102.

Scheme 102

Several other pyridine syntheses from activated α,β-unsaturated nitriles are already available in literature; a very old example is the reaction of two fold of 2-amino crotononitrile with aromatic

give 286, which underwent an addition reaction with malononitrile to give 287, which was also obtained by reacting 288 with one mole of benzaldehyde and two moles of malononitrile [246], as outlined in Scheme 94.

Scheme 94 & 95

Synthesis of novel 1,4,5,6,7,8-hexahydroquinoline 291 bearing amino and cyano groups on C4 and C6 has been carried out by refluxing equimolar amounts of the corresponding aryldiene malononitrile 289, dimedone 290 and excess of ammonium acetate in acetic acid as solvent in a similar way to that reported for other related structures [247,248]. Compounds 291 are obtained as crystalline solids in 55-75% yields, as outlined in Scheme 96.

Scheme 96

A route for the synthesis of thiazolo[2,3-a]pyridine 293 from the reaction of 2-functionally substituted 2-thiazoline-4-one 292 with cinnamonitrile has been reported simultaneously and independently by El-Nagdy et al. [101] and Kambe et al. [249]. Better yields were obtained using a 2:1 molar ratio of cinnamonitrile derivative and 292, as outlined in Scheme 97.

Scheme 97

In our laboratories [250] it has been found that the reaction of 292 with cinnamonitrile 294a,b in absolute ethanol in presence of piperidine afforded a semisolid product from which 6-substituted-7H-2,3-dihydro-5-amino-8-cyano-3-oxo-7-(3,4,5-trimethoxyphenyl)-thiazolo[3,2-a] pyridines 295a,b (ethanol soluble fraction, major yield) and 6-substituted-7H-2,3-dihydro-5-amino-8-cyano-3-oxo-2-(3,4,6-trimethoxybenzylidene)-7-(3,4,5-trimethoxyphenyl)-thiazolo [3,2-a] pyridines 296a,b (ethanol-insoluble fraction, minor yield) can be isolated, as depicted in Scheme 98.

Scheme 98
aldehyde 307 to yield a pyridine derivative 308 is depicted in Scheme 103 [255].

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 103

Other interesting examples, 2-amino-1,1,3-tricyano-prop-1-ene 111 has been reported to react with benzalmalononitrile to yield pyridine derivative [256] 309. Similarly, diethyl-3-amino-2-cyanopent-2-ene-1,5-dicarboxylate 56 has been reported to yield pyridines 310 utilizing almost the same idea [218], as outlined in Scheme 104.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 104

2-Amino-1,1,3-tricyano-prop-1-ene 111 has been reported to condense with β-diketones 311 and β-aminoenones 312 to yield pyridine derivatives 313, 314 respectively [40,257], as outlined in Scheme 105.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 105

The reaction of 3-aminoacrylonitriles derivative 315 with ethoxymethylene malononitrile in chloroform or dichloromethane at temperature below 0°C and 5°C for 24 hours, leads to dienaminonitriles 316 in good yields [257]. These adducts 316 are transformed into the pyridine derivatives 317 in almost quantitative yields. The reaction of compound 317 with formamide lead to pyrido[2,3-d]pyrimidine derivatives 318 in 65-98% yields as outlined in Scheme 106.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 106

The synthesis of pyridine derivatives 320 is best accomplished by cyclization of the new dienaminoster 319 in refluxing DMSO and as depicted in Scheme 107 [258].

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 107

5.3.1.2. Synthesis of quinoline and fused quinolone derivatives:
The ylidene 321 could be cyclized by heating with ethylphosphate at 160-170°C into the corresponding quinoline derivatives 322 is depicted in Scheme 108 [259].

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 108

Several pyrano[3,2-c]quinolines 324 were prepared [231,260] from 4-hydroxy-2(1H)quinolones 323 and ylidene nitriles is depicted in Scheme 109.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 109

Khallh et al. [261] reported that 8-quinolinol 325 reacts with cinnamotriole derivatives in an ethanolic solution in the presence of piperidine to afford 2-amino-4-aryl-4H-pyrano[3,2-h]quinoline-3-carbonitriles 326 or ethyl 2-amino-4-aryl-4H-pyrano[3,2-h]quinoline-3-carboxylates 326 in moderate yields as depicted in Scheme 110.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 110

Mahmoud et al. [262] reported that the same results obtained when α-cyano-3,4,5-trimethoxyphenyl cinnamotriole 327a and/or ethyl α-cyano-3,4,5-trimethoxyphenylcinnamotriole 327b been reacted with 325. Thus, 2-amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4H-pyrano[3,2-h]quinoline 328a and ethyl 2-amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4H-pyrano[3,2-h]quinoline-3-carboxylate 328b were synthesized from 325 and 327a,b, as depicted in Scheme 111.

```
\begin{center}
\includegraphics[width=0.8\textwidth]{scheme.png}
\end{center}
```

Scheme 111

The reaction of acetyl and benzoylmethyl pyridine 329 with ethoxymethylene malononitrile in DMSO in the presence of potassium carbonate gave acetycyaninmoquinolines 330 with yields 70-96%, respectively, as depicted in Scheme 112 [263].
Ortho-ito-benzaldehyde 307 reacted with 2-amino-1,1,3-tricyano-prop-1-ene 111 to yield the condensation product 331 which could be readily cyclized into 332 as depicted in Scheme 113 [254].

High yielding syntheses of polyfunctional benzo[a]quino-lizines are well-documented [264]. Abdallah et al. [265] reported a new and general one-step route affording polyfunctional substituted benzo[a]quino-lizines in good yield from readily available inexpensive starting materials using isoquinoline derivatives. Thus, treatment of 1-methylquinolizines in boiling methanol with active methylene reagents and as depicted in Scheme 116.

Ortho-into-benzaldehyde 307 reacted with 2-amino-1,1,3-tricyano-prop-1-ene 111 to yield the condensation product 331 which could be readily cyclized into 332 as depicted in Scheme 113 [254].

High yielding syntheses of polyfunctional benzo[a]quino-lizines are well-documented [264]. Abdallah et al. [265] reported a new and general one-step route affording polyfunctional substituted benzo[a]quino-lizines in good yield from readily available inexpensive starting materials using isoquinoline derivatives. Thus, treatment of 1-methylisoquinoline 334 with aryldeneisoufromonitriles 333 in boiling acetonitrile in the presence of an equimolar amount of piperidine leads, in each case, to the formation of only one product 337 and 338, as indicated by TLC and 1H-NMR analysis. The formation of 338 out in the presence of excess piperidine (2 moles) then the product 337 was carried through the cyclization and dehydrogenation of 340, which could be achieved from the reaction of cinnamonitrile derivative 343 with active methylene reagents and as depicted in Scheme 116.

The reaction of arylidene malononitrile 45 to α-cyanochalcones with active methylene nitriles and active methylene ketones. Thus, benzyldiene derivatives, aminomethylene and mercaptomethylene derivatives has been reported [170,235,236] to react with active methylene reagents to yield pyran derivatives [266-272].

The development of new method [273] for asymmetric synthesis of highly functionalized 2-amino-4-aryl-4H-pyrans 347 was achieved via Michael addition reaction of β-ketoesters 346 to arylidene malononitriles 218, as depicted in Scheme 117 in the presence of piperidine as a base.

4-Alkyl-2-amino-4H-pyran 349 was synthesized via Michael addition reaction of benzoyl acetonitrile to α-cyanoacrylates 348 is depicted in (Scheme 118) using piperidine as a catalyst [274].

Asymmetric Michael addition of cyanoacettes 45 to α-benzylocinnamoni-trile 27 in the presence of piperidine as catalyst has been studied, the resulting 3-alkoxy carbonyl-2-amino-5-cyano-4,6-diphenyl-4H-pyran 350 have been obtained in good yield, , as depicted in Scheme 119 [275].

The reaction of arylidene malononitrile 63 with some reactive halo compounds under phase transfer conditions (PTC) afforded the pyran derivative 351, as depicted in Scheme 120.
Several new benzo[b]pyrans 352, naphtho[1,2-b:6,5-b]dipyrans 353, naphtho[1,2-b]pyrans 354 and naphtho[2,1-b]pyrans 355 have been prepared by the reaction of cinnaminitriles 63 with resorcinol, 1,5-naphthalenediol, 1-naphthol and 2-naphthol, respectively [276,277], as outlined in Scheme 121.

Scheme 121

It was reported [254] that salicylaldehyde reacted with diethyl 3-amino-2-cyano-pent-2-ene-1,5-dicarboxylate 111 to yield the coumarin derivative 356. The same compound has been claimed to be obtained directly from the reaction of salicylaldehyde with ethylcyanooacetate [278], as shown in Scheme 122.

Scheme 122

Similarly, substituted salicyaldehyde have been reported [254] to afford the iminocoumarin derivative 357 when reacted with 2-amino-1,1,3-tricyanopropan-1-one, as depicted in Scheme 123.

Scheme 123

3-Phenyl-7-hydroxy-3,4-dihydrocoumarin 358 [279,280] has been reported from the reaction of resorcinol with activated nitrile in catalytic amount of zinc chloride, as depicted in Scheme 124.

Scheme 124

Cycloaddition of substituted phenols with the nitrile derivative gave the 3-cyanocoumarin derivatives 359 is depicted in Scheme 125 [281,282].

Scheme 125

Condensation of 4-hydroxycoumarin 358 has also been successful with unsaturated nitriles 210 using pyridine [283] and yielded the pyrano[3,2-c]coumarin derivatives 360 is depicted in Scheme 126.

Scheme 126

4-Phenylcoumarin-3,4-dihydro-a-pyrene 362 (m.p. 183–4°C) was obtained by condensation of 4-hydroxy coumarin 358 with benzylidene malononitriles 63b in pyridine and the resulting intermediate 361 was subsequently hydrolyzed with HCl/AcOH and finally cyclized with Ac2O [284], as outlined in Scheme 127.

Scheme 127

Recently [285], it was reported that annulations reactions of 4-hydroxycoumarin 358 with p-anisylidene ethylcyanooacetate or p-anisylidene malononitrile 210 yielded the corresponding 2-amino-3-carbomethoxy(cyano)-4′-methoxyphenyl)-5H-1-benzo pyrano-[4,3-b]-pyran-5-ones 363a,b, as depicted in Scheme 128.

Scheme 128

It was reported that [286] thermal Michael addition reaction takes place when 6,7-dimethoxy isochromanone 334 was treated with benzylidene malononitrile 21 at 190°C to afford 364 which underwent elimination of malononitrile producing 365, as shown in Scheme 129.

Scheme 129

New spiro pyran systems attached to coumarin nucleus 366 and 367 were synthesized by the reaction of 2-coumarylidenemalononitriles with some active methylene compounds in the presence of triethylamine [189], as shown in Scheme 130.

Scheme 130

Six membered rings with two heteroatoms

Synthesis of pyridazine and condensed pyridazine derivatives: An interesting approach for synthesis of pyridazines 368 has been achieved by cyclization of the intermediated of the reaction of cinnaminitrile derivatives 63 with arylidiazonium chloride [287]. This
synthetic approach is summarized below in the following Scheme 131.

\[
\begin{align*}
\text{Scheme 131} & \\
\text{El-Nagdy et al. [239] reported that 3-amino-2-cyano-4-ethoxy carbonyl but-2- enonitrile coupled with aromatic diazonium chlorides to yield 369 which converted to 370 on refluxing in acetic acid / HCl mixture, as outlined in Scheme 132.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 132} & \\
\text{Coupling of 2-amino-1,1,3-tricyanoprop-1-ene with aryldiazonium salts and subsequent cyclization of the coupling products yielded the pyrazidine derivative 349. The same pyrazidine derivatives 373 could be alternatively synthesized via treatment of aryhydrazonemalononitrile derivatives 371 with malononitrile, a reaction that proceeds almost certainly via the intermediacy of the hydrazone 372 [288], as outlined in Scheme 133.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 133} & \\
\text{Similar synthesis of pyrazidine derivatives utilizing diethyl 3-amino-2-cyanopent-2-ene-1,5-dicarboxylate has been reported [287]. Acenaphthoquinones readily condense with malononitrile to yield the corresponding yildenemalononitrile 374, which reacts readily with hydrazine hydrate to yield aminopyrazidine derivatives 375 [41], as depicted in Scheme 134.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 134} & \\
\text{Cinnoline derivatives were also reported utilizing α-hydrazononitrile as starting components. Thus, heating phenylhydrazonomalononitrile 371 with anhydrous aluminum chloride affords 4-amino-3-cyanocinnoline 376 is depicted in Scheme 135 [289].}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 135} & \\
\text{Synthesis of pyrimidine and fused pyrimidine derivatives: α,β-unsaturated nitriles have been extensively utilized for the synthesis of pyrimidines. Tylor et al. [290,291] have summarized all literature in this area in more than one reference. One of the interesting examples of the utility of α,β-unsaturated nitriles for pyrimidine synthesis is the reported reaction of 2-aminomethylene malononitrile 377 with acetamidine 378 to yield pyrimidines 379 and 380 and cyclized into fused pyrimidine derivative 381, as outlined in Scheme 136 [291].}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 136} & \\
\text{Cya}oethylithylen [292] of cyanoguanidine in presence of lithium hydride has been reported to yield pyrimidines 382-385 in good to moderate yields, as outlined in Scheme 137.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 137} & \\
\text{4-Oxo-2-thioxopyrimidine derivative 386 [293] was obtained by the reaction of ethyl α-cyano-β-methoxy-cinnamate with thiourea in the presence of potassium carbonate, as depicted in Scheme 138.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 138} & \\
\text{The reaction of ethoxymethylene derivatives 388 with urea derivatives 387 were shown to yield carbethoxy pyrimidines [294-296]. The behaviour of 363 with thiourea [297] was demonstrated and gave the pyrimidine derivatives 389-393, as outlined in Scheme 139.}
\end{align*}
\]
A direct one-step synthesis of pyrimidines has been reported utilizing 3-oxoalkanenitriles as starting materials, thus, 2-aryl-3-oxoalkanenitriles 394 reacts with formamide and phosphoryl chloride to yield pyrimidines 395, as depicted in Scheme 140 [297].

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

as depicted in Scheme 140

The isolation of several other side products, depending on the nature of the oxoalkanenitrile, has been reported [298-301]. Several other synthetic approaches for pyrimidines utilizing 3-oxoalkanenitriles as starting material have been reported and surveyed [301,302].

Compound 396 reacted with either phenylisothiocyanate or benzoylisothiocyanate in refluxing dioxane to yield the pyrimidine derivative 397 is depicted in Scheme 141 [240].

Scheme 141

The reaction of barbituric acid, thiobarbituric acid and 4-bromo-3-methyl pyrazolin-5-one with acrylonitriles was reported by Abdel-Latif [303], thus, the compound 398 reacted with either phenylisothiocyanate or benzyloisothiocyanate in refluxing dioxane to yield the pyrano[3,2-d]pyrimidines 399a-c. The alternative structure 400a-c resulted in the formation of ylidene derivatives 400d-e. On the contrary, attempts to bring about addition of 399b to 399b,c (Ar = 2-furyl, 2-thienyl) failed and the reactions were recovered unchanged after being refluxed in ethanolic triethylamine. Thus, it can be concluded that the introductions of a π-deficient heterocycles at β-position of the acrylonitrile increases the reactivity of the double bond towards Michael type addition reaction and the methylene reagents has been observed earlier in several reactions [101,250], as shown in Scheme 142.

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

Scheme 142

Mahmoud et al. [163] found that when compound 374a,b was submitted to react with the cinnamionitrile derivatives 63 in refluxing pyridine afforded the arylidene derivative 378 as the sole product, as depicted in Scheme 143.

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

Scheme 143

A variety of pyrimidine synthesis, utilizing nitriles as starting components has been reported [291,292,304-308]. Enaminonitriles 403 and 404 react with trichloro-acetonitrile to yield the corresponding pyrimidine derivatives 405 and 406, respectively [106,229,309], as shown in Scheme 144.

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

Scheme 144

Another reported pyrimidine synthesis is summarized below as depicted in Scheme 1145 [310].

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

Scheme 145

Fawzy et al. [310] reported that hydrazopyrimidine 407 was reacted with cinnamionitriles afforded the corresponding arylhydrazopyrimidine 408 is depicted in Scheme 146.

\[
\begin{align*}
\text{HN} & \text{CN} \\
\text{R} & \text{R} \\
\text{NH} & \text{NH}
\end{align*}
\]

Scheme 146

Geies [311] has been reported that 6-aminouracil and 6-aminothioauracil 409 were reacted with benzylidenemalononitrile in ethanol in the presence of piperidine to afford 410a,b, respectively. The reaction was assumed to proceed via Michael addition of the pyrimidine nucleus to the α,β-unsaturated nitriles and subsequent cyclization through nucleophilic addition of the amino group to one of the two cyano groups [312], as shown in Scheme 147.
The structure of compound 410a,b was established as pyridopyrimidine rather than pyranopyrimidine 411 on the basis of 1H-NMR and IR spectra. On the other hand, the reaction of 409a,b with benzylidenecycloacetacte under the same conditions results in a mixture of compound 412a,b and/or 413a,b, respectively. Aminopyrazole and aminoisoxazole derivatives have also been reported to react with acrylonitrile to yield either fused pyrimidines or ring N-cyanoethylated products, which readily cyclized to fused pyrimidines 414-416 [46,111,309,313-324], as outlined in Scheme 148.

A recent interesting pyrimidine synthesis has been reported and is summarized in Scheme 149. The utility of the resulting cyanopyrimidines for building up fused heterocycles has also been reported [106].

The enaminonitrile 31 was utilized for synthesis of several new fused pyrimidine derivatives 422-427, as described in Scheme 150.

Scheme 150

Synthesis of several new ring system derived from pyrazolo[1,5-a] pyrimidines 429 and 1,2,4-triazolo[3,4-a]pyrimidines 430 has been recently reported via the reaction of enaminonitrile 428 with cyclic amidines. The mechanism of the reaction involved was discussed, as depicted in Scheme 151 [320].

Scheme 151

Other syntheses of fused pyrimidines 431-433 from enaminonitriles are shown below [320-324], as outlined in Scheme 152.

Scheme 152

Synthesis of pyrazine derivatives: Only few examples for synthesis of pyrazines 434, 435 utilizing nitriles as starting materials have been reported. A demonstrated example for this synthesis approach is shown below [325,326], as outlined in Scheme 153.

Scheme 153

Synthesis of thiazine derivatives: Several new pyrrolidino[1,2-a]-3,1-thiazine-5,6-dione derivative 436 was synthesized via the reaction of 4-cyano-2,3-dioxo-5-thienopyrroline 437 with a variety of activated nitriles, as depicted in Scheme 154 [327].
Treatment of coumarinylmalononitrile 438 with bidentates, namely, guanidine hydrochloride, thiourea, thiosemicarbazide, thioacetamide and phenyl isothiocyanate in the presence of acetylacetone under phase transfer conditions gave the corresponding spiro coumarinyl-1,3-thiazine 439 and 440 [178], as outlined in Scheme 155.

Scheme 155

Six-membered rings with three heteroatoms: Several triazine syntheses starting from α,β-unsaturated nitriles have appeared in some literature [41,287,288]. An interesting example of these syntheses is shown in Scheme 156 [328,329].

Scheme 156

Synthesis of Other Heterocyclic Compounds

The recent wide applications of 2-propenoylamides, esters and 2-propenoyl chlorides in the synthesis of biologically and pharmacologically active compounds [330-340] and beside their uses in the synthesis of industrial products make them worthy to be synthesized to obtain new structures of anticipated enhanced potency. Madkour et al. reported the reaction and uses of 3-(4'-methoxyphenyl)-3-(2'-thienyl)-2-cyano-2-propenoyl chloride in heterocyclic synthesis, as described in Scheme 157.

Scheme 157

Conclusion

Alkenyl nitriles have proved to be a rich source of various heterocyclic compounds, and the discovery of potential biologically active heterocyclic compounds has become increasingly probable. Starting from alkenyl nitriles, our current work is focussed on synthesising novel heterocycles with or without sulphur that have biological activities against different diseases. The search for cheaper and simpler methods to synthesis such new compounds are continuing.

This review has summarised some of the achievements in the field of heterocyclic compounds derived from alkenyl nitriles. Our knowledge of the chemistry and reactions of alkenyl nitriles remains shallow, however, and this field needs to be explored in more detail. Further studies and investigations by us or other workers should continue to provide a strong background in the chemistry and reactions of alkenyl nitriles.

References

1. MOWRY DT (1948) The preparation of nitriles. Chem Rev 42: 189-283.
2. Pelouze J (1834) Notiz über einen neuen Cyanäther. Annalen der Pharmacie 10: 249.
3. Fehling H (1844) Uber die Zersetzung des benzoësauren Ammoniaks durch die Wärme. Justus Liebigs Annalen der Chemie 49: 91–97.
4. Fraser S Flemming (1999) Nitrile-containing natural products. Nat Prod Rep 16: 597-606.
5. Fleming FF, Yao L, Ravikumar PC, Funk L, Shock BC (2010) Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore. J Med Chem 53: 7902-7917.
6. Al-Azmi A, Ellassar AZA, Booth BL (2003) The chemistry of diaminomaleonitrile and its utility in heterocyclic synthesis. Tetrahedron 59: 2749-2763.
7. Alves MJ, Booth BL, Proença MF (1990) Synthesis of 5-amino-4-(cyanoformimidoyl)-1H-imidazole: a reactive intermediate for the synthesis of 6-carbamoyl-1,2-dihydropurines and 6-carbamoylpurinines. J Chem Soc Perkin Trans 2: 1705-1712.
8. Booth BL, Dias AM, Proença MF, Zaki ME (2001) The reactions of diaminomaleonitrile with isocyanates and either aldehydes or ketones revisited. J Org Chem 66: 8436-8441.
9. Ohtsuka Y (1978) Chemistry of diaminomaleonitrile. 3. Reaction with isocyanate: a novel pyrimidine synthesis. J Org Chem 43: 3231-3234.
10. Ohtsuka Y (1979) Chemistry of diaminomaleonitrile. 4. Nitrile hydration of the Schiff bases. J Org Chem 44: 827-830.
11. Shirai K, Matsuoka M, Fukushima K (2000) New syntheses and solid state fluorescence of azomethine dyes derived from diaminomaleonitrile and 2,5-diamino-3,8-dioyanopyrazine. Dyes Pigm 47: 107-115.
12. Begland RW, Hartter DR, Jones FN, Saw DJ, Sheppard WA, et al. (1974) Hydrogen cyanide chemistry. VIII. New chemistry of diaminomaleonitrile. Heterocyclic synthesis. J Org Chem 39: 2341-2350.
13. Barton JW, Goodland MC, Gould KJ, McOmie JF, Jourdren WR (1979) Biphenylenes-xxxi: Condensation of benzylocyclobutene-1,2-dione with aliphatic and heterocyclic 1,2-diamines and the synthesis of cis-2-cyano-3-(2'-cyanovinyl)-1,4-diaz. Tetrahedron 35: 241-247.
14. Beall LS, Mani NS, White AJ, Williams DJ, Barrett AG, et al. (1998) Porphyrazines and Nonheterocyclics Bearing Nitrogen Donor Pockets: Metal Sensor Properties. J Org Chem 63: 5806-5817.
15. Woehrlé D, Buttner P (1985) Polymeric Schiff’s base chelates and their precursors 8a, some cobalt chelates as catalysts for the isomerization of quadryclocyclane to norbornadiene. Polyrm Bull 13: 57-64.
16. Zwanenburg B, Peter ten H (2001) The synthetic potential of three-membered ring aza-heterocycles. Topics in Current Chemistry 216: 93-124.
17. Madkour HMF, Elgazwy ASH (2007) Utilises of some carbon nucleophiles in heterocyclic synthesis. Current Organic Chemistry 11: 853-908.
18. Ayman Wahba (1993) The chemistry of beta-aminonitrinilines as versatile reagents in heterocyclic synthesis. Eriam Chem Rev 93: 1991-2005.
19. Zil’berman EN (1962) Reactions of nitriles with hydrogen halides and nucleophilic reagents. Russ Chem Rev 31: 615.
20. Zil’berman EN (1960) Some reactions of nitriles with the formation of a new nitrogen–carbon bond. Russ Chem Rev 29: 331.
21. Keller CL, Dalessandro JD, Hotz RP, Pinhas AR (2008) Reactions in water: alkyl nitrile coupling reactions using Fenton’s reagent. J Org Chem 73: 3616-3618.
22. Peter Pollak, Gérard Romeder, Ferdinand Hagedorn, Heinz-Peter Gelbke “Nitriles”.
23. Kuo CW, Zhu JL, Wu JD, Chu CM, Yao CF, et al. (2007) A convenient new procedure for converting primary amides into nitriles. Chem Commun (Camb): 301-303.
24. Sharwan K, Dewan, Ravinder Singh, Anil Kumar (2006) One pot synthesis of nitriles from aldehydes and hydroxylamine hydrochloride using sodium sulfate (anhyd) and sodium bicarbonate in dry media under microwave irradiation. Arkivoc 2: 41-44.
Elazawy ASSH, Refaee MRM (2013) The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis. Organic Chem Curr Res 2: 117. doi:10.4172/2161-0401.1000117
Heterocycles 16: 2177-2180.

Sadek KU (1977) M.Sc. Thesis, Cairo University.

El-Nagdy MH (1974) J Org Chem 40: 2604.

Bauer L, Nambury CNV (1961) J Org Chem 26: 4917.

Citation:

ISSN: 2161-0401 OCCR, an open access journal

El-Nagdi MH (1975) J Org Chem 40: 2604.

Akagi K, Nagahara K, Ueda T (1970) Chem Pharm Bull 18: 2353.

Midorikawa H, Saito K, Hori I, Igarashi M (1974) The reaction of ethyl ethoxymethyleneacetoacetate with its hydrazino derivatives. Bulletin of the Chemical Society of Japan 47: 476-480.

Midorikawa H, Iori I, Saito K (1970) The formation of pyrazol[1,5-aj]-5-azimyridinim derivate. Bulletin of the Chemical Society of Japan 43: 849-855.

Lang SA, Lovell FM, Cohen E (1977) Synthesis of 4-(4-phenyl-3-pyrazolyl)-4H-1,2,4-triazoles. Journal of Heterocyclic Chemistry 14: 65-69.

Tam SYK, Klein RS, Wempen I, Fox J (1979) Nucleosides. 112. Synthesis of some new pyrazol[1,5-aj]-1,3,5-triazines and their C-nucleosides. J Org Chem 44: 4547-4553.

Rudorf WD, Augustin M (1978) Acylyketen-S,-S- und Acylyketen-S,N-acetale as Baustene for Heterocyclen: Pyrazole und Isoxazol. Journal for Praktische Chemie 320: 585-599.

Furukawa M, Yuki T, Hayashi S (1973) A convenient synthesis of pyrazolines from β-carbonylthethylthiosulfates. Chemical & pharmaceutical bulletin 21: 1845-1846.

Ege G, Arnold P (1967) Aminopyrazole; II1, C-Substituted 1-Akyl-3-aminoazopyrazole aus 2-Chloroacetylmbenzonitril bzw. 2,3-Dichloropropionitril und Alkylhydrazinen. Synthesis 1976: 52-53.

Burger K, Schikaneder H, Elguero J (1975) Ein einfacher zugang zum 1-NH-3-pyrazol-system. Tetrahedron Letters 33: 2911-2914.

Peseke K (1975) [Preparation of substitution 5-aminomercaptopyrazoles. 8. Syntheses with 1,3-dithietanes]. Pharmazie 30: 802.

El-Nagdi MH, El-Moghayar MRH, Fleita DH (1974) Reactions of α-Arylhydrozido-β-oxo-β-phenyl-propioninitril. Journal für Praktische Chemie 316: 975-980.

Taylor EC, Pardur WR (1977) Preparation of 3,4,5-trisubstituted pyrazoles from 2,2-dioxoketene-S,S-acetals Heterocycles 6: 1865-1869.

French J, Peseke K, Kristen H, Brünger H (1975) [Preparation of (2-nitrovinyl)-pyrazole derivatives]. Pharmazie 31: 851-855.

Nagahara K, Takagi K, UedaT (1967) Reaction of ethoxyethylideneaminonitroso with hydrazine hydrate. Chemical & pharmaceutical bulletin 24: 2880-2882.

Alcalde E, Mendoza JD, Elguero J, Marino J, Garcia-Marquina JM, et al. (1974) Elude de la réaction du β-aminoacrotinol et du ou formal phenylacrotinol avec l'hydrazine: Synthèse d’azimino-7 pyrazol[1,5-aj]azimidines. Journal of Heterocyclic Chemistry 11: 423-429.

Marsico JW, Joseph JP, Goldmann L (1972) Patent US 3: 760.

Senga K, Robins RK, O’Brien DE (1975) Synthesis of pyrazol[1,5-aj]-1,3,5-triazolo[5,6-aj]benimidazoles. Journal of Heterocyclic Chemistry 12: 899-901.

Breuer H, Treuner UD (1974) Ger Offen 2: 408

Marsico JW, Joseph JP, Goldmann L (1973) US Patent 3: 760.

Kreutzberger A, Burgwitz K (1979) Antibakterielle wirkstoffe. IV. Die nitrosubstitution im system der 5-amino-4-cyanopyrazole. Journal of Heterocyclic Chemistry 17: 265-266.

Kilger P (1973) Ger Offen 2: 141.

Peseke K (1973) Ger (East) Patent 102: 382.

Schmidt R, Klemm K (1975) Ger Offen 2: 426.

Dickinson CL, Williams JK, Mckusick BC (1964) Aminocyanopyrazol. J Org Chem 29: 1915-1919.

Hecht SM, Werner D, Traffante DD, Sundaralingam M, Prusiner P, et al. (1975) Structure determination of the N-methyl isomers of 5-amino-3,4-dicyanopyrazole and certain related pyrazol[4,3-d]pyrimidines. J Org Chem 40: 1815-1822.

Earl RA, Pugmire RJ, Revankar GR, Townsend LB (1975) Chemical and
carbon-13 nuclear magnetic resonance reinvestigation of the N-methyl isomers obtained by direct methylation of 5-amino-3,4-dicyanopyrazole and the synthesis of certain pyrazolo[3,4-d]pyrimidines. J Org Chem 40: 1822-1828.

147. Ege G, Arnold P (1974) A simple synthesis of 3(5)-aminopyrazole. Angewandte Chemie International Edition in English 13: 206-207.

148. Shuman RF, Shearin WE, Tull RJ (1979) Chemistry of hydrocyanic acid. 1. Formation and reactions of N-(aminomethylene)diaminomalononitrile, a hydrocyanic acid pentamer and precursor to adenosine. J Org Chem 44: 4532-4536.

149. Aziz SI, Abd-Allah SO, Ibrahim NS (1984) Reactions with nitriles: a novel synthesis of fur[2,3-c]pyrazoles and pyran[2,3-c]pyrazoles. Heterocycles 22: 2523-2527.

150. Girgis NS, El-Gemei GEH, Nawar GAM, El-Nagdy MH (1983) α, β-Unsaturated Nitriles in Heterocyclic Synthesis: The Reaction of β-(2-Furanyl)- and β-(2-Thienyl)acylonitriles with Active Methylene Reagents. Liebigs Annalen der Chemie 1983: 1498-1475.

151. Abdel-Razek FM, Kandeel ZES, Hilmy KMH, El-Nagdy MH (1985) Substituted acrylonitriles in heterocyclic synthesis. The reaction of α-substituted β-(2-furyl)-acrylonitriles with some active-methylene heterocycles. Synthesis 1985: 432-434.

152. El-Gemei GEH, El-Faham HA, Ibrahim YR, El-Nagdy MH (1989) α, β-Unsaturated nitriles in heterocyclic synthesis: Synthesis of several arylypirdine and arylypirdine derivatives. Archiv der Pharmazie 332: 535-539.

153. Abdel-Gail FM, Abdel-Motaleb RM, El-Nagdy MH (1988) Ann Chim 84: 19.

154. Otto HH (1974) Darstellung einiger 4H-pyran[2,3-c]pyrazolidervate. Archiv der Pharmazie 307: 444-447.

155. Otto HH, Schmelz H (1980) Zur Darstellung von 6-Oxo-2H-pyran[2,3—c]pyrazolen. Monatshefte fur Chemie 111: 53-61.

156. Martin-Leon N, Queuteux M, Seoane C, Soto JL (1990) J Chem Res(s) 156.

157. El-Nagdy MH, Taha NH, Elall FAMA, Abdel-Motaleb FM, Mahmoud FF (1989) Collect-Chem. Chem. Commun., 54, 1082.

158. El-Fahham HA, Abdel-Gail FM, Ibrahim YR, El-Nagdy MH (1983) Activated nitriles in heterocyclic synthesis. A novel synthesis of pyrazolo[1,5-a]pyrimidines and pyrazolo[2,3-c]pyrazoles. Journal of Heterocyclic Chemistry 20: 567-670.

159. El-Gemei GEH, Riad BY, Nawar GA, El-Gamal S (1987) Nitriles in heterocyclic synthesis: Synthesis of new pyrazolo [1,5-a]pyrimidines, pyrano[2,3-c]pyrazoles and pyrazolopyrazoles. Heterocycles 24: 1631-1636.

160. Kandeel ZE, Hilmy KKH, Abdel-Razek FM, El-Nagdy MH (1984) Chem. Ind. (London) 33.

161. Abdel-Hamid AO, Riad BY (1987) Arch Pharm 320: 1010.

162. El-Torgoman AM, El-Kouisy SM, Kandeel ZE, Naturforsh Z (1987) 426: 107.

163. Mahmoud MR, Madkour HMF, Nassar MH, Habashy MM (2000) J Chinese Chem Soc 47: 937-941.

164. Abdel-Galil FM, Ibrahim YR, El-Nagdy MH, Ohta M (1973) Studies on 3,5-pyrazolidinediones. IV. Addition of 4-Aryloyl-3,5-pyrazolidinediones to Ethyl Acrylate. Bulletin of the Chemical Society of Japan 48: 1830.

165. Maquestiau, Van Den Eynde JJ (1984) [C.A. 102, 112645k (1985)] Bull Soc Chim Belg 93: 451.

166. Mityurina KV, Kharchenko VG, Cherkessova LV (1981) Khim Geterotsikl Soedin 40: 112645k (1985) Bull Soc Chim Belg 93: 451.

167. Metylava SA, Younes NS, Nour AM (1986) Synthesis of pyran, thiopyran and pyrrolepyrrole derivatives. Heterocycles 22: 1631-1636.

168. El-Mosawy SM, Moustafa MS, El-Nagdy MH (2007) J Chem Res 9: 515-518.

169. Shaewali AS, Sami M, Sherrif SK, Parkany C (1980) Synthesis of some derivatives of imidazo[1,2-a]pyridine, pyrazolo[1,5-b]imidazole, and 4-(3H) quinazolinone from α-ketohydrazidoyl bromides. J Heterocyclic Chem 17: 877-880.

170. Riad SM, Abde-Hamid IA, Ibrahim HM, Al-Matar HM, El-Nagdy MH (2007) Heterocycles.

171. El-Mousawy SM, Moustafa MS, El-Nagdy MH (2007) J Chem Res 9: 515-518.

172. Bruin P, Bikel AF, Koayman EC (1952) Rec Traw Chem 71: 1152.

173. Heckendorn R, Winkler T (1980) Helv Chem Acta 63: 1.

174. Huffman KR, Schaefer FC (1963) J Org Chem 28: 1816.

175. Gompmer R, Nappel HE, Schaefer H (1963) Angew Chem 75: 918.

176. Mityurina KV, Kharchenko VG, Cherkessova LV (1981) Khim Geterotsikl Soedin 40: 112645k (1985) Bull Soc Chim Belg 93: 451.

177. L.S. Wittenbrook, J. Heterocyclic Chem., 12, 37 (1975).

178. Clapp LB (1976) 1,2,4-Oxadiazoles, in advances in Heterocyclic Chem Ed Ar Katritzky, AJ Bouton, Academic Press, New York, 20, 72.

179. Schneider JP (1967) CR Acad Sci Paris Ser C 265: 638.

180. Person H (1967) CR Acad Sci Paris Ser C 265: 1007.

181. Ziegler E, Wimmer Th (1965) Synthesen von Heterocyclen, 72. Mitt.: 4-Phenyl-3,4-dihydro-carboxystyrol aus α-Cyanométhylacrylat. Monatshefte für Chemie und verwandte Teile anderer Wissenschaften 96: 1252-1260.

182. Coutts RT (1969) Catalysed sodium borohydride reductions of ortho-nitroanilines. J Chem Soc C 713-716.
A Novel Synthesis of Pyridine and Pyridazine Derivatives. Synthesis 1985:
α-oxoketen S,S-diacetals. J Chem Soc Chem Commun 645.

Substituted and fused 3-cyano-4-methylmercapto-2(1H)-pyridones using
Kambe Soto JL, Encinas MJR, Seoane C (1984) Liebigs
and pyridinopyrimidine derivatives. Synthesis 1984: 970-972.

Nitriles in heterocyclic synthesis: a new approach for the synthesis of pyridine
El-Nagdi MH, El-Kashef HS, Saito K, Kishi H, Sakurai A, Midorikawa H (1979) A one-step
of N-Amino-2-pyridones Synthesis 1981: 529-530.

2-Amino-4-aryl-3-cyanopyridines by the Condensation of
Abdel-Razek FM, Ibrahim NS, Kandeel ZES (1984) Activated
malononitrile. J Org Chem 37: 1047-1049.

Activated Nitriles in Heterocyclic Synthesis: A Novel Synthesis of 4-Hydroxy- and
Aminopyrazin[2,3-c]pyrazoles. Heterocycles 19: 1637-1640.

Ghosh AM, Khodairy A (1998) Synthesis of Some New Heterocycles
Technology and Biotechnology 57: 15-19.

N-aryl-3-cyanoazetidin-2,4-diones. A correction.
RF, Unger PL (1974) J Org Chem 37: 3834.

A new antitumor and DNA cross-linking agent, to macromolecules of subcellular
fractions isolated from rat liver and HeLa cells. Biochem Pharmacol 28: 3391-3402.

In vitro binding of metabolically activated [14C]-
edakrin or nitracrine, with DNA and antitumor 1-nitroacridines. II. In vivo enzyme-mediated covalent
binding of a 1-nitroacridine derivative, ledakrin or nitracrine, with DNA and or other macromolecules of mammalian or bacterial cells. Chemico-Biological Interactions 43: 151-173.

El-Kashef HS, Geiss AA, El-Dean AMK, Abdel-Hafez AA (1993) Synthesis of thieno[2,3-c]pyridines and related heterocyclic systems. Journal of Chemical Technology and Biotechnology 57: 15-19.

Citation: Elgazzyw ASSH, Refaee MRM (2013) The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis. Organic Chem Curr Res 2: 117. doi:10.4172/2161-0401.1000117

ISSN: 2161-0401 OCCR, an open access journal

Volume 2 • Issue 2 • 1000117

Organic Chem Curr Res

Page 25 of 27

228.Kandeel ZE, Hilmy KHH, Ismail NS, El-Nagdi MH (1984) J Prakt Chem 326: 248.
229.Corson BB, Stoughton RW (1982) J Amer Chem Soc 50: 2825.
230.Khalifa MAE, Tammm GH, Motaleb RMA, El-Nagdy MH (1983) Synthesis of
alizarin and tolazolicyclic acid derivatives: reactions of 4-araylazo-2-
azolin-5-ones with active methylene compounds. Heterocycles 20: 45-48.
231.El-Gemel GEH, Elecs SA, El-Sakkia I, El-Nagdy MH, Naturforsch Z (1983)
38b: 639.
232.Abdel-Gail FM, Riad BY, Shefri SM, El-Nagdy MH (1982) Chem Lett 1123.
233.Elaal FAEA, Hussein MM, El-Nagdy MH, El-Gemel GEH (1983) Monatsh
Chem 115: 573.
234.Riad BY, Khalifa FA, Abdel-Gail FM, El-Nagdy MH (1982) Activated
Nitriles in Heterocyclic Synthesis: A Novel Synthesis of 4-Hydroxy- and
Aminopyrazin[2,3-c]pyrazoles. Heterocycles 19: 1637-1640.
235.Juergen, Horst H (1974) Ger Offen 106: 831.
236.Werner J, Jachin OH, Horst S (1980) Angew Chem 92: 390.
237.Gewald K, Hain H, Gruner M (1985) Chem Ber 2198.
238.Nadja SI, Mona MH, El-Nagdy MH (1987) Synthesis of New 3-(Pyridin-6-yl)
pyrazol[1,5-a]pyrimidines. Arch Pharm 320: 487-491.
239.El-Nagdy MH, Mona MH, Nadia SS (1987) Heterocycles 26: 4.
240.Geiss AA, Kamal El-DeanAM, Bull Polish (1997) Academy Science Chem 45:
381-390.
241.Ukawa K, Ishiguro T, Wada Y, Nohara A (1986) Heterocycles 24: 1931.
242.Kideki J, Neidlein R (1993) A convenient synthesis of 2-(1H-Tetrazol-5-yl)-2-
cyanoacetate betaines. Synthesis 1993: 873-875.
243.Geiss AA (1997) Synthesis of α-Aminonitriles of Indeno[2,1-b]pyrrole and
Indeno[2,1-c]pyridine. Polish J Chem 71: 774-778.
244.Pawlak JW, Konopa J (1979) In vitro binding of metabolically activated [14C]-
edakrin, or 1-nitro-9-14C-(3'-dimethylamino-N-propylamino) acridine, a new
antitumor and DNA cross-linking agent, to macromolecules of subcellular
fractions isolated from rat liver and HeLa cells. Biochem Pharmacol 28: 3391-
3402.
245.Pawlak JW, Pawlak K, Konopa J (1983) The mode of action of cytotoxic
and antitumor 1-nitroacridines. II. In vivo enzyme-mediated covalent
binding of a 1-nitroacridine derivative, ledakrin or nitracrine, with DNA and or other macromolecules of mammalian or bacterial cells. Chemico-Biological Interactions 43: 151-173.
246.El-Kashef HS, Geiss AA, El-Dean AMK, Abdel-Hafez AA (1993) Synthesis of thieno[2,3-c]pyridines and related heterocyclic systems. Journal of Chemical Technology and Biotechnology 57: 15-19.
247.Martín M, Quintero JL, Segura C, Seoane JL, Solo M, et al. (1991) Ann Chem
287.
248.Suarez Y, Verdecia E, Ochoa N, Martin R, Martinez M, et al. (2000) Synthesis
and structural study of novel 1,4,5,6,7,8-hexahydroquinolines. J Heterocyclic
Chem 37: 735-742.
249.Midorikawa H, Kambe S, Saito K, Sakurai A (1981) Synthetic studies using
α,β-unsaturated nitriles: facile synthesis of pyridine derivatives. Synthesis 1981: 531-533.
250.Madkour HM, Mahmoud MR, Nassar MH, Habashy MM (1998) Sulfur Lett
21: 253-261.
251.Pretsch E, Clerc T, Seibl J, Simon W (1989) Tables of spectral data for
Structura determination of organic compounds (2ndedn), Springer-Verlag,
New York, USA.
252.Hafez EA, Abdel-Gail FM, Shefri SM, El-Nagdy MH (1986) J Heterocyclic
Chem 23: 1375.
253.Junek H (1963) Monatsh Chem 94: 192.
254.Ghosh PB, Tennai B (1972) Reaction of 4- and 5-acetoxyazoles with
malononitrile, J Org Chem 37: 1047-1049.
255.Petrov VA (1948) New syntheses of heterocyclic compounds; 9-amino-6:8-
dimethyl-7:10-diazaphenathrenes. J Chem Soc: 884-888.
pyrido[2,3-d]pyrimidines and pyrido[2,3-d:6,5-d']dipyrimidines. J Chem Res 112-113.

313. El-Nagdy MH, Sallam MMM, Ilas MAM (1975) Helv Chem Acta 58: 1944.

314. El-Nagdy MH, Abd-Allah SO (1973) Reactions with the arylhydrazones of some α-cyanoketones. J Prakt Chem 315: 1009-1016.

315. El-Nagdy MH, Kassab NAL, Fahmy SM, Elall FA (1974) Reactions with 3,5-pyrazolidinediones. III. Cyanoethylation of some 4-arylazo derivatives of 3,5-pyrazolidinediones and 3-amino-2-pyrazolin-5-ones. J Prakt Chem 316: 177-184.

316. El-Nagdy MH, Ohta M (1973) Bull Chem Soc Jpn 46: 3813.

317. El-Nagdy MH, Kandeel EM, El-Moghayar MRH, Naturforsch Z (1977) 32b: 307.

318. Fahmy SM, Kandeel EM, El-Sayed ER, El-Nagdy MH (1978) Reactions with heterocyclic amindes 1. Cyanoethylation of cyclic amindes. J Heterocyclic Chem 15: 1291-1293.

319. El-Nagdy MH, Kandeel EM, Kandil ZE (1978) Pyrimidine derivatives and related compounds. VIII [1]. Routes for the synthesis of 3,5-diaminopyrazolenes, 2-amino pyrazolo[1,5-a]pyrimidines and 5-amino pyrazolo[1,5-a]pyrimidines. J Prakt Chem 320: 533-538.

320. Kagan J, Melnick B (1979) The synthesis and photochemistry of 4-amino-3-cyanopyrazole. J Heterocyclic Chem 16: 1113-1115.

321. Antonini, Cristalli G, Franchetti P, Grifantini M, Martelli S (1980) Synthesis of 2,3,5,6-tetrahydroimidazo[1,2-c]quinazoline derivatives as potential narcotic antagonists. J Heterocyclic Chem 17: 155-157.

322. Papadopoulou EP (1981) Reactions of o-aminonitriles with isocyanates. 2. A facile synthesis of imidazo[1,2-c]quinazoline-2,5-(3H,6H)dione. J Heterocyclic Chem 18: 515-518.

323. Elston SR, Mottson RJ, Sowell JW (1979) Synthesis of substituted pyrrolo[2,3-d]pyrimidine-2,4-diones. J Heterocyclic Chem 16: 929-933.

324. Dave KG, Shishoo CJ, Devani MB, Kalyanaraman R, Ananthan S, et al. (1980) Reactions of nitriles under acidic conditions. Part I. a general method of synthesis of condensed pyrimidines. J Heterocyclic Chem 17: 1497-1500.

325. Fleury JP (1980) Heterocycles 14: 1581.

326. Perchais J, Fleury JP (1972) Tetrahedron 28: 2267.

327. Riad, Abde-Aziz M (1989) Sulfur Lett 9: 75-85.

328. Kandeel EM, Sadek KJ, El-Nagdy MH, Naturforsch Z (1980) 35b: 91.

329. Wenttirnitz P (1978) Helv Chem Acta 61: 1175.

330. Kraemer W, Fischer R, Holmwood G, Hagemann H, Wachendorf-Neumann U, et al. Ger Offen DE 4: 401.

331. Bridges AJ, Denny WA, Dobrusin EM, Doherty AM, Fry DW, et al. (1997) PCT Int App1 Wo 97 38: 983 (C1. C07 D239/94), 23 Oct. (1997), [C.A. 128, 3695c (1998)].

332. Bombrun (1997) PCT Int App1 Wo 97 43: 287 (C1. C07 D471/04), 20 Nov., [C.A. 120, 34753z (1996)].

333. Purohit DM, Shah VH (1997) Heterocycl Commun 3: 437.

334. Mueller K, Wiegrebe W, Gurster D, Peters S (1995) PCT Int App1 Wo 95 03: 266.

335. Isobe Y, Katagiri T, Umerzawa J, Goto Y, Sasaki M, et al. (1996) Can Pat App1 CA 2 154: 293.

336. Courant J, Leblois D, Le Bout G, Venco C, Pancorci E (1993) Eur J Med Chem 28: 821.

337. Haley GJ (1993) US 5, 270, 466.

338. Oozeki M, Kotado S, Yasuda K, Kudo K, Maeda K (1993) Jpn Kokai Tokkyo Koho JP 05, 194, 236.

339. Nishikawa Y, Shindo T, Ishii K, Nakamura H, Kon T, et al. (1989) Chem Pharm Bull 37: 100.

340. Chen Y, Wehrmann R, Koehler B (1996) Ger Offen DE 19: 505, 940 (C1. C07D311/16), 22 Aug. (1996). [C.A. 125, 221585w (1996)].