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The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis

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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 newfound 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 cyanohydrin 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 antidiabetic drug to Anastrazole 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], porphyrazines (which have great potential in optical sensor technology) [14] and diimines 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 an 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 compounds. 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

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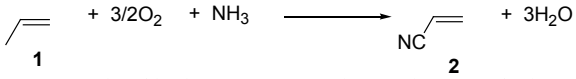
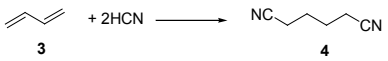
use of combinatorial synthesis, microwave enhanced processes and new catalytic methodologies in the preparation of these heterocycles is a clear indication that significant advancement has been made in recent years. The syntheses of both on the four, five and six membered ring of fused and polyheterocyclic 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 ammoxidation 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].



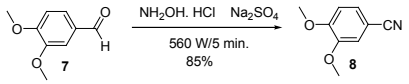
An example of hydrocyanation is the production of adiponitrile **4** from 1,3-butadiene **3**, as outlined below.



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 benzamide to benzonitrile [23]. Two intermediates in this reaction are amide tautomer **A** and their phosphate adducts **B,** as summarized diagrammatically in Scheme 1.

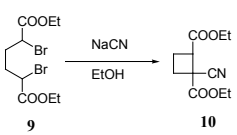
Scheme 1

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 aldoxime [24], as shwon in Scheme 2. A commercial source for the cyanide group is diethylaluminum cyanide Et_2AlCN [25], which can be prepared from triethylaluminium and HCN, it has been used as nucleophilic addition into ketones [26].



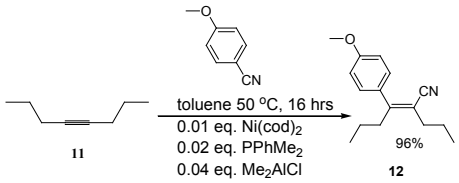
Scheme 2

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



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 ($RC(CCl_3)=NH$) 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 HMPA and potassium metal in *tert*-butanol. α-Amino nitriles can be decyanated with lithium aluminium 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 carbocyanation, as summarized diagrammatically in Scheme 4 [33].

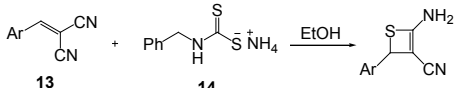


Scheme 4

Synthesis

Four membered rings

Organic cyano compounds 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 $\alpha-\beta-$unsaturated nitriles. Such as arylidene 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 benzyl dithio-carbamate **15,** as outlined in Scheme 5.

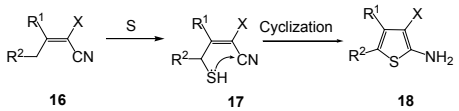


Scheme 5

Five membered rings

Five membered ring with one heteroatom:

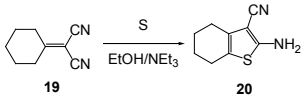
Synthesis of thiophene and fused thiophene derivatives: The $\alpha-\beta$-unsaturated nitriles with active methylene group at β -carbon **16** could react with elemental sulphur to yield an intermediate mercapto derivative **17**, which cyclizes into the most isolable stable aminothiophene derivative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



Scheme 6

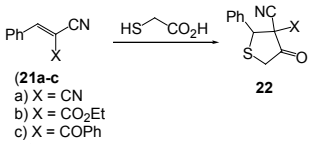
$\alpha-\beta$-unsaturated nitriles were thiolated into thiophene derivatives. For example, the arylidene derivative of cyclohexanone **19** was converted into the enaminothiophene derivative **20** on treatment with elemental sulphur [45]. The enamines can also be formed on heating mixtures of the ketone, the activated nitrile and elemental sulphur in

the presence of a basic catalyst.



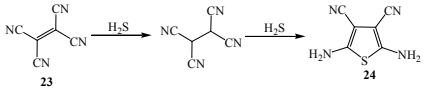
Scheme 7

Formation of thiophenes **22** from the reaction of α–β-unsaturated nitriles with thioglycollic acid has been reported [50-53].



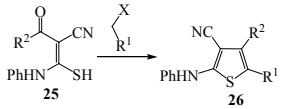
Scheme 8

Tetracyanoethylene **23** has been reported to react with hydrogen sulphide [54,55] to produce the thiophene derivative **24** in moderate yields 68%.



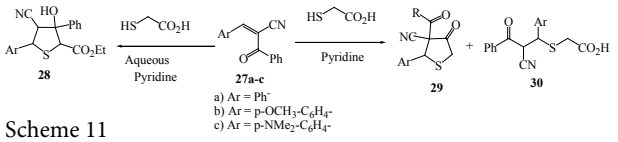
Scheme 9

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].



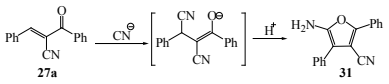
Scheme 10

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.



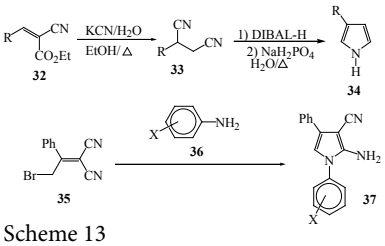
Scheme 11

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(5*H*) 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.



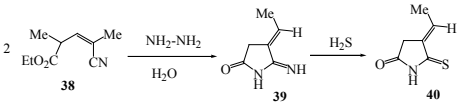
Scheme 12

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].



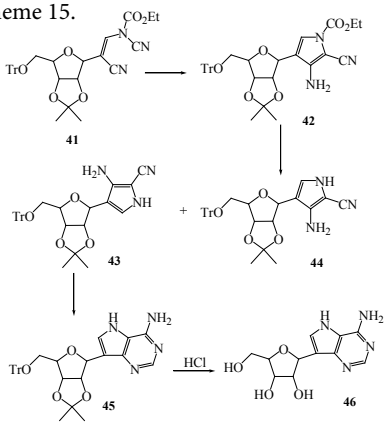
Scheme 13

Hydrazinolysis of *Z* or *E*-2-methyl-3-cyano-4-pentenoate **38** afforded the pyrrole derivatives shown below **39**, **40** [74-76].



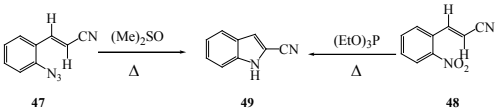
Scheme 14

Nucleosides pyrrole derivatives have also been synthesized utilizing α–β-unsaturated nitriles [77], an interesting example is depicted in Scheme 15.



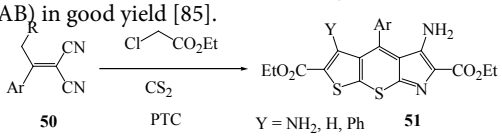
Scheme 15

Several indole syntheses have been reported [78-82]. For example, heating o-azidocinnamonitrile **47** in DMSO at 140°C afforded 2-cyanoindole **49** [83] in good yield. The latter could also be obtained on heating o-nitrocinnamonitrile **48** in triethylorthophosphate at 160°C [84].



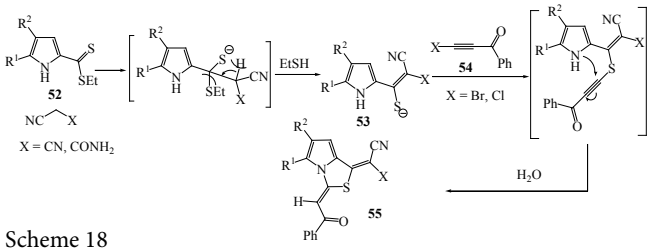
Scheme 16

The 5-Amino-26-diethylcarboxy-3-substituted-4-(4 chlorophenyl)-6-iminothieno[3,2-5,6], thiopyrano[2,3-b]pyrrols **51** were synthesized in a one-pot procedure via the reaction of β-substituted arylidene malononitrile **50** with CS_2 and ethylchloroacetate in 1:1:2 molar ratio under PTC conditions (dioxane/K_2CO_3/tetrabutylammonium bromide TBAB) in good yield [85].



Scheme 17

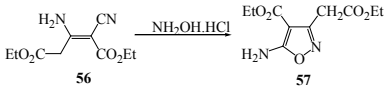
Heating pyrrole-2-carbodithionates **52** with anions of C-H acids generated from malononitrile or cyanoacetamide in KOH/DMSO (room temperature, 0.5 h). Interaction of the resulting enethiolates **53** with haloacetylenes **54** afforded the pyrrolothiazolidines **55,** as outlined in Scheme 18 [86-91].



Scheme 18

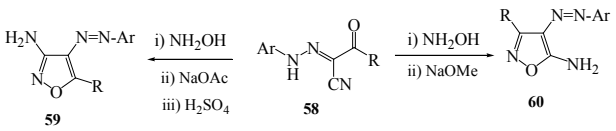
Five membered rings with two heteroatoms:

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**.



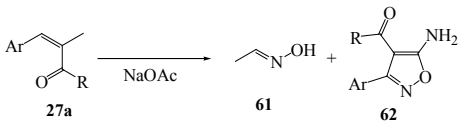
Scheme 19

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



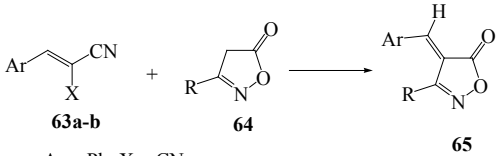
Scheme 20

Compound **27a** was examined against hydroxylamine hydrochloride to yield a mixture of the aldoxime **61** and the aminoisoxazole derivatives **62** [99].



Scheme 21

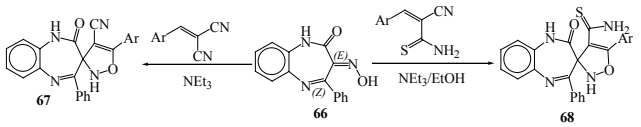
In contrast to the previously reported behaviour of 2-pyrazolin-5-one [100], 2-thiazoline-4-one [101], and 2-thiohydantion derivatives [102], towards the action of arylidenemalononitrile, 3-phenyl-2-isoxazolin-5-one **64** reacted with the cinnamonitrile derivative **63** to yield only the arylidene derivative **65** [103], as shown in Scheme 22.



a, Ar = Ph, X = CN
b, Ar = Ph, X = CO_2Et

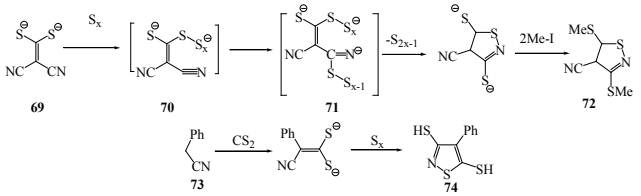
Scheme 22

3-Oxime-4-phenyl-1(H)-1,5-benzodiazepin-2-one **66** was allowed to react with different arylidenenitriles in the presence of triethylamine and yielded spirobenzodia-zepine isoxazole derivatives **67** and **68**, as outlined in Scheme 23 [104].



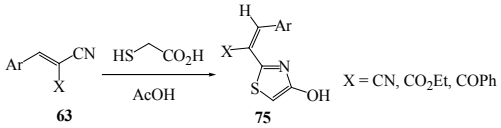
Scheme 23

Synthesis of isothiazole derivatives: The chemistry of isothiazoles has been reviewed by one of us [105] and the isothiazole 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 mercaptide 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 24**.**



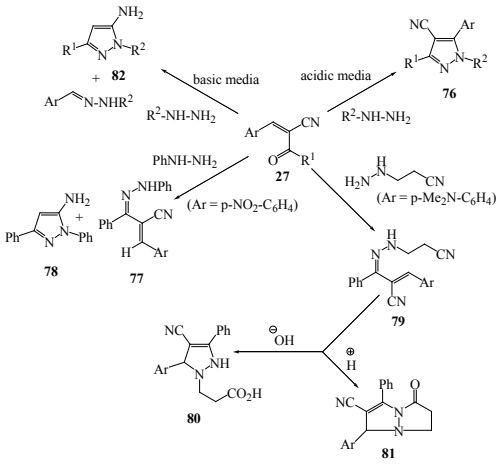
Scheme 24

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, cinnamonitriles **35** react with mercaptoacetic acid to give the thiazole derivatives **75** [107,108], as outlined in Scheme 25**.**



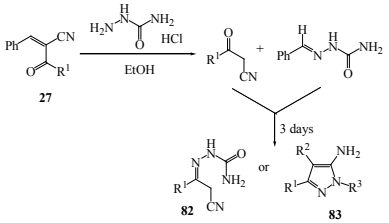
Scheme 25

Synthesis of pyrazole and fused pyrazole derivatives: Scission of the double bond in the arylidene 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** (Ar = p-O_2N-C_6H_4-) with phenylhydrazine. El-Nagdy et al. [112-114] have reported that **27** (Ar = p-Me_2N-C_6H_4-) reacts with β-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.



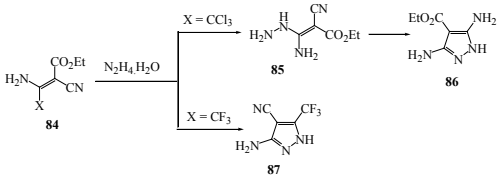
Scheme 26

Cusmano and Sprio [109,110,115,116] have shown that the double bond in compound **27** 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 **83** (R^1 = H, R^2 = Ph, R^3 = $CONH_2$) was formed in addition to benzaldehyde phenylhydrazono, as described in Scheme 27.



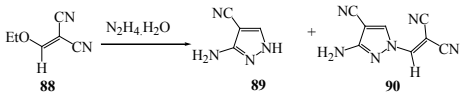
Scheme 27

It has been shown that ethyl β-trichloromethyl-β-aminomethylenecyanoacetate (**84**, X = CCl_3) 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 = CF_3) with hydrazine hydrate [120]. Synthesis of pyrazoles via similar routes has been reported [107,121], as outlined in Scheme 28.



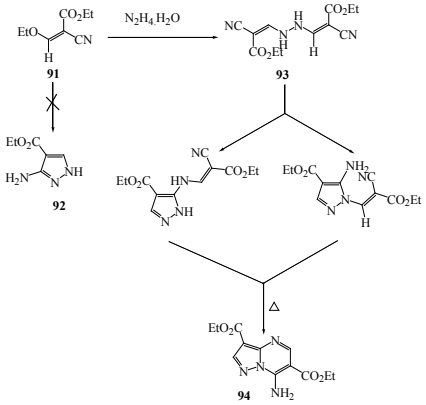
Scheme 28

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



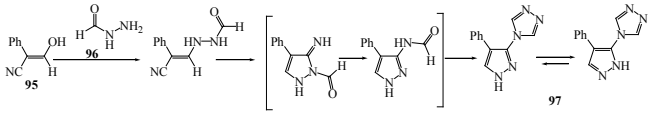
Scheme 29

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.



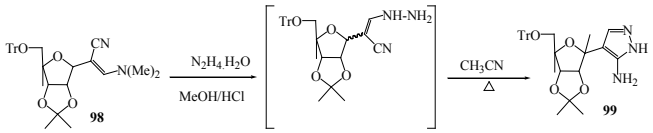
Scheme 30

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



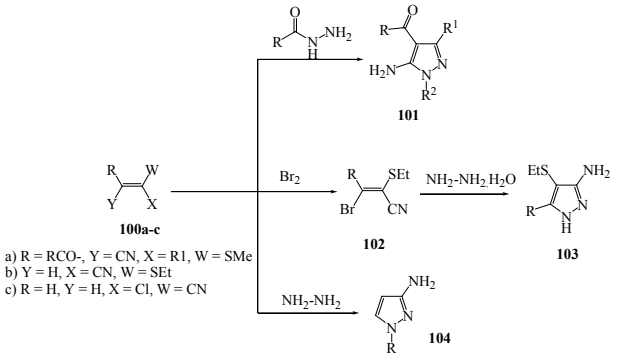
Scheme 31

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 formycine analogues [126], as shown in Scheme 32.



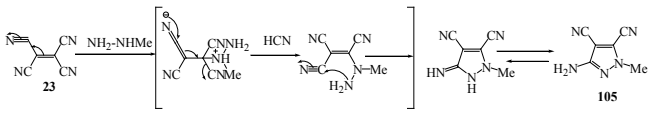
Scheme 32

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.



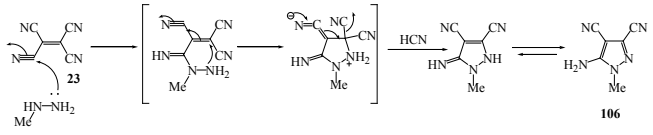
Scheme 33

3,4-Dicyano-5-aminopyrazoles have been synthesized by taking the advantage of the tetracyanoethylene **23** for Michael addition. Thus, aryl and alkyl hydrazones as well as hydrazides, semicarbazides and thiosemicarbazides have been reported to react with tetracyanoethylene to afford 1-substituted-4,5-dicyano-3-aminopyrazoles [145]. The structure assigned for the reaction product of **23** with methylhydrazine was reinvestigated by Hecht et al. [145] and Earl et al. [146] in two separate contributions. It has been shown by Hecht et al. [145] that consideration of the mechanistic routes suggested in literature for this reaction illustrates the source of structural ambiguity in the formation of these products from methylhydrazine and **23**. Thus, one might for example, envision formation of the 1-methyl-4,5-dicyano-3-amino-pyrazole **105** by conjugate addition of the more nucleophilic substituted hydrazine nitrogen of the hydrazine to the cyano group, affording the observed product is depicted in scheme 34.



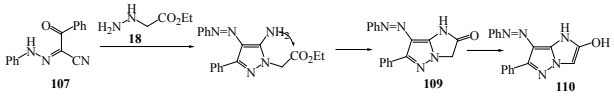
Scheme 34

Alternatively, as has been previously suggested, addition of the substituted nitrogen of methylhydrazine to the cyano group might occur first to give **106** and the reaction then proceeds are depected in Scheme 35.



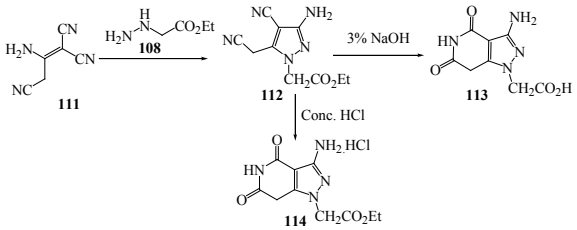
Scheme 35

Both authors on reconducting the above reaction have shown that it affords a mixture of two isomeric pyrazoles (53% and 27%) [146], (47% and 8%) [147]. These author have shown on the basis of chemical evidences as well as spectroscopic data that the major product for which the 3-amino-4,5-dicyano-1-methylpyrazole structure was formally assigned is really 1-methyl-3,4-dicyano-5-aminopyrazole. El-Nagdy et al. [113] reported that the reaction of arylhydrazono derivatives of 2,3-dioxo-3-phenylpropionitrile **107** reacted with ethyl hydrazinoacetate **108** to yield the imidazo[1,2-b]pyrazole derivatives which can be formulated as **109** or **110**. Structure **110** was considered most likely for these products based on spectroscopic data. The formation of **110** in this reaction may be assumed to proceed via the sequence demonstrated in Scheme 36 and attempted to isolate intermediates for this reaction were unsuccessful.



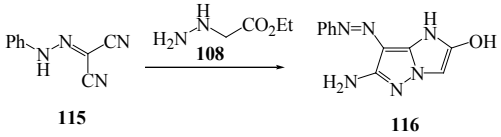
Scheme 36

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.



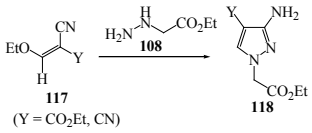
Scheme 37

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.



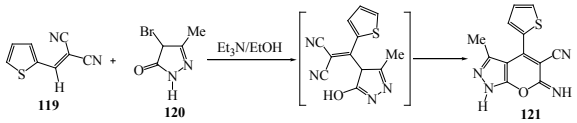
Scheme 38

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

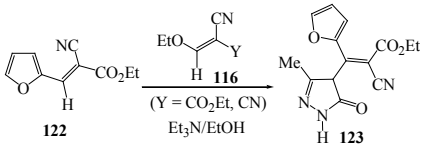
The nitrile **119** reacted with 4-bromo-3-methylpyrazol-5-one **120** in ethanol in the presence of catalytic amount of triethylamine to give the corresponding pyrano[2,3-c]pyrazole derivatives **121** [150] are depicted in Scheme 40.



Scheme 40

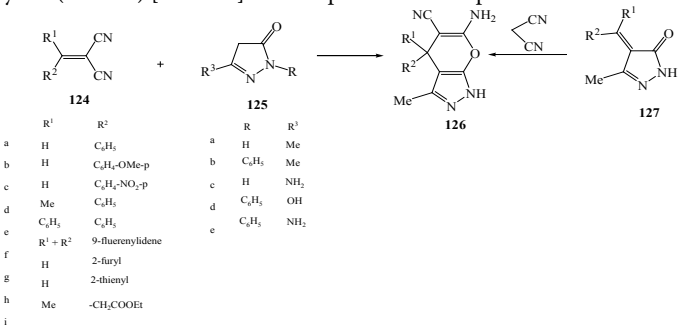
Treatment of activated nitrile **122** under the above conditions gave the acyclic pyrazolone derivative **123** which could not be cyclized

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



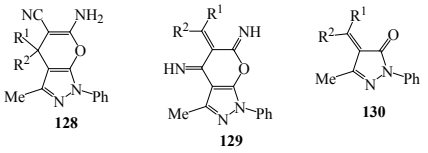
Scheme 41

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.



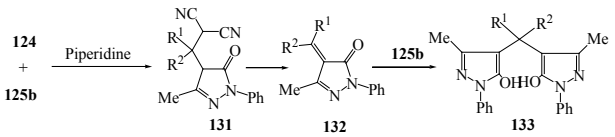
Scheme 42

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.



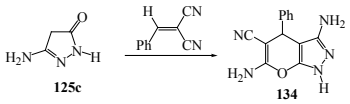
Scheme 43

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].



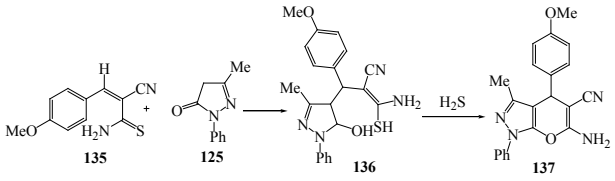
Scheme 44

Girgis et al. [150] have reported that compound **129g,h** were 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].



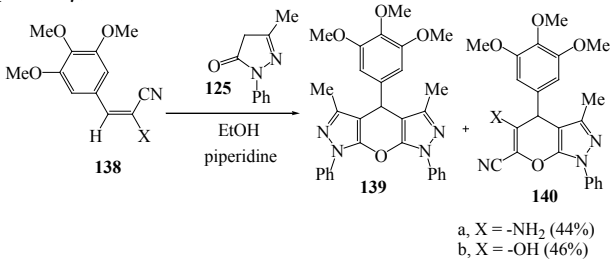
Scheme 45

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.



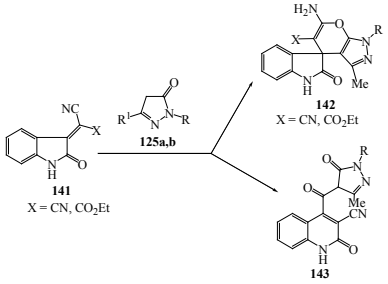
Scheme 46

Mahmoud et al. [163] reported that equimolar amounts of 1-phenyl-3-methylpyrazolin-5-one **125** and α-cyano-3,4,5-trimethoxycinnamonitrile **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

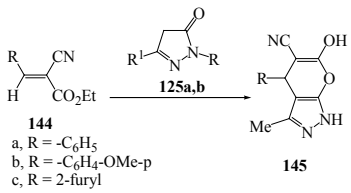
Spiropyranopyrazoles **142** have been obtained through reacting substituted cyanomethylideneindolidinones **141** with **125a,b**. It is of value to report that these products were earlier believed to be the quinoline derivatives **143**. ^{13}C-NMR spectra have been utilized to discriminate between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



Scheme 48

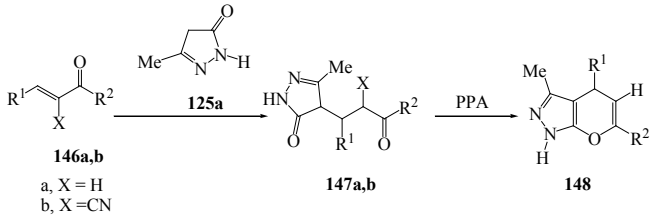
Pyranopyrazoles **145** were formed via reacting **144a,b** with **125a** [100]. However, the reaction of **144c** with **125a** led to the formation

of **126** [151]. Similar results have been reported on treatment of **125** derivatives with **144**, as depicted in Scheme 49 [160].



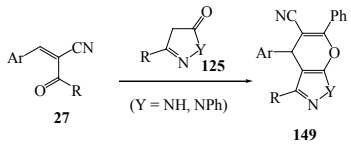
Scheme 49

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.



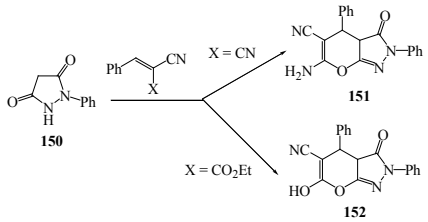
Scheme 50

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



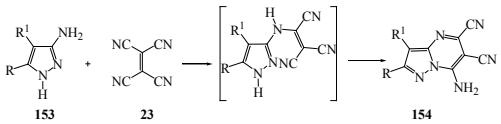
Scheme 51

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



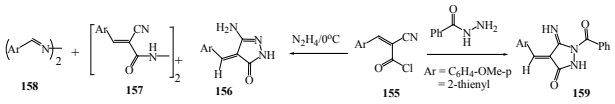
Scheme 52

During the course of our investigations on the use of DAMN in heterocyclic synthesis, we designed new approaches to 4-cyano-1,3-dihydro-2oxo-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].



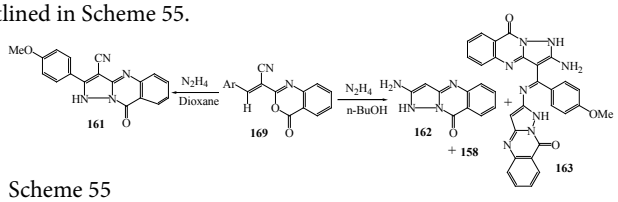
Scheme 53

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 0°C afforded the pyrazolone derivatives **156**, bishydrazine **157** and anisylideneazine **158**, while, treatment of **155a** with benzoylhydrazine afforded the pyrazolone **159**, as outlined in Scheme 54**.**



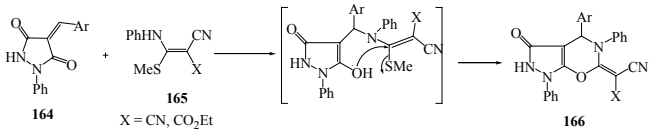
Scheme 54

Furthermore, the electrophilicity of the lactonic carbonyl functionality of benzoxazinone **160** has been investigated [172] *via* its reaction with some nitrogen and oxygen nucleophiles. Thus, stirring **160** with hydrazine hydrate at 0°C in dioxane gave the pyrazolo[5,1-b]-(1H) quinazolinone **161** in moderate yield. On the other hand, addition of hydrazine hydrate to **160** in n-butanol followed by stirring at room temperature or at reflux afforded a mixture of 2-aminopyrazolo [5,1-b] quinazolinone **162** besides the Schiff's base **163** and the azine **158**, as outlined in Scheme 55.



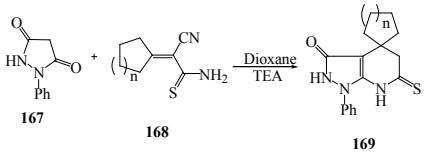
Scheme 55

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.



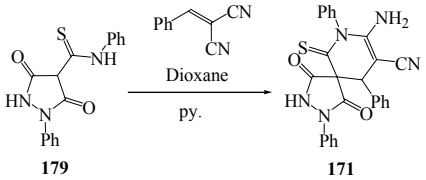
Scheme 56

On refluxing compound **167** with cycloalkylidenecyanoacetamide **168** in dioxane in the presence of triethylamine, the corresponding pyrrazolopyridinethione derivatives **169** were obtained [179], as outlined in Scheme 57.



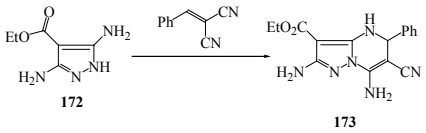
Scheme 57

Treatment of **170** [179] with benzylidenemalononitrile furnished the corresponding spiropyrazolopyridine derivatives **171** and are depicted in Scheme 58 [180].



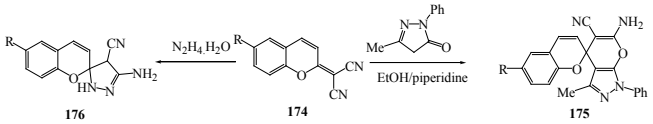
Scheme 58

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



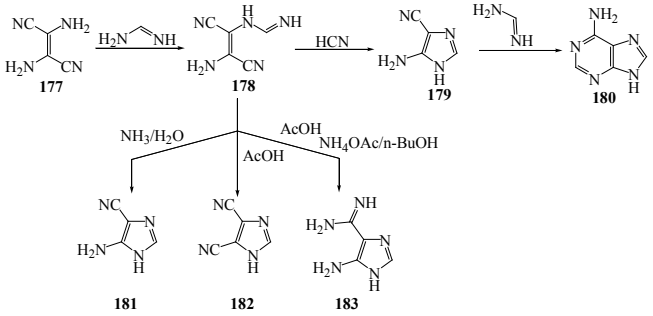
Scheme 59

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



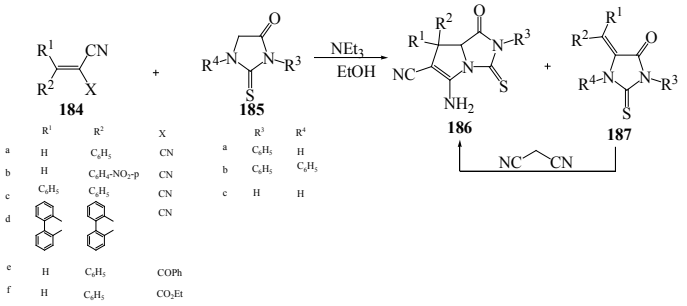
Scheme 60

Synthesis of midazole and condensed imidazole derivatives: A New Synthesis of 4-Cyano-1,3-dihydro-2-oxo-2H-imidazole-5-(*N1*-tosyl) carboxamide: A Reactive Precursor for ThioPurine Analogs Hamad et al. [169]. 2,3-Diaminodinitrile **177** has been recently utilized for the synthesis of imidazole derivatives. Thus, **177** reacted with formamidine to yield 2,3-diaminofumaronitrile **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].



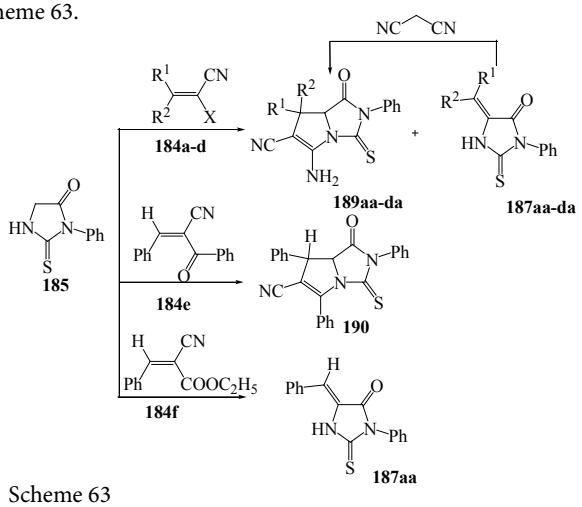
Scheme 61

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.



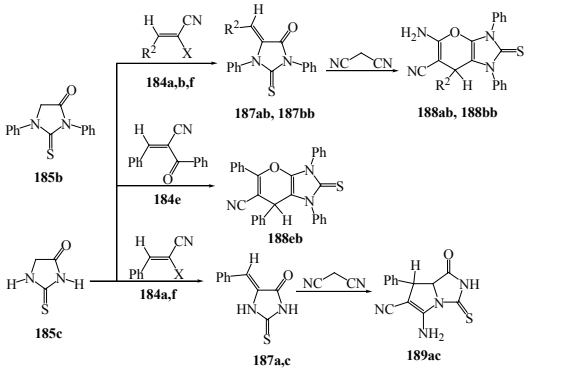
Scheme 62

In contrast to the behaviour of compound **185a** towards **184a-d**, the 2-thiohydantoin derivatives **185b,c** reacted with **184a,b** to yield 5-arylidene 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.



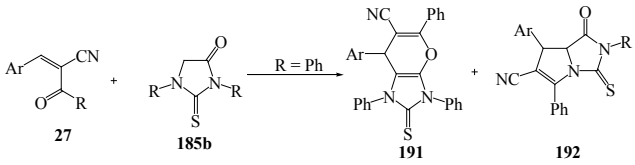
Scheme 63

Treatment of compound **187ab** and **187bb** with malononitrile afforded the pyrano[2,3-d]imidazole derivatives **188ab** and **188bb**, respectively, whereas treatment of **187ac** with malononitrile afforded the pyrrolo[1,2-c]imidazole derivative **189ac,** as outlined in Scheme 52. Compound **184e** reacted with **185a** to yield the pyrrolo[1,2-c] imidazole derivative **190**. On the other hand, the pyrano[2,3-d] imidazole derivative **188eb** was formed from the reaction of **184e** and **185b**, as outlined in Scheme 64.



Scheme 64

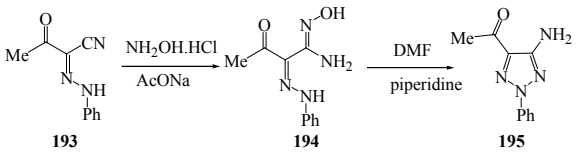
In contrast to the behaviour of compound **184a-c** toward **185**, ethylbenzylidene cyanoacetate **152f** reacted with imidazolidines **185a-c** to give the benzylidene derivatives **187aa**, **187ab** and **155ac**, respectively. The reaction of thiohydantoin **185b** with **27** has been, however, 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 thiohydantoin and is depicted in Scheme 65 [102].



Scheme 65

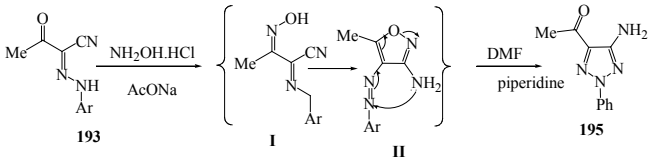
Synthesis of five membered rings with three heteroatoms

The synthetic potentialities of 2-arylhydrazinonitriles have recently been reviewed [189]. El-Mousawi et al. have reported that 2-phenyl-hydrazono-3-oxo-butanenitrile **193** reacted with hydroxylamine hydrochloride in ethanolic sodium acetate to yield amidoxime **194** that cyclized readily into 4-acetyl-2-phenyl-1,2,3-triazol-5-amine **195** upon reflux in DMF in presence of piperidine [190], as outlined in Scheme 66.



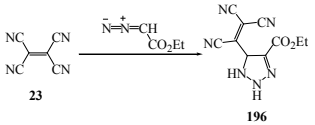
Scheme 66

^{13}C-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 of **193** with hydroxylamine yielding inetrmediate **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.



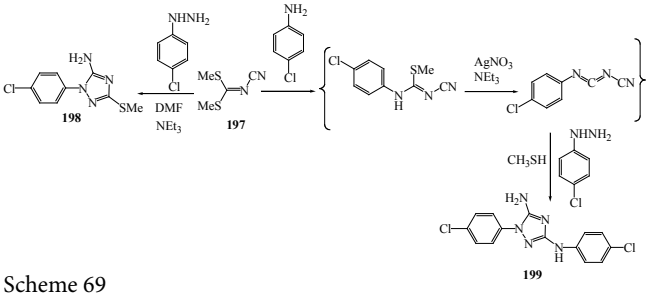
Scheme 67

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



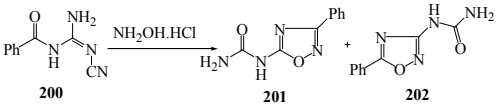
Scheme 68

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.



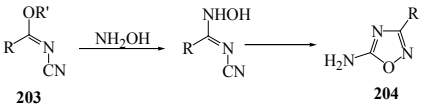
Scheme 69

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].



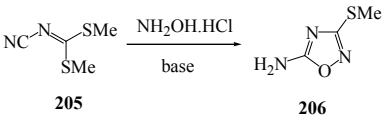
Scheme 70

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



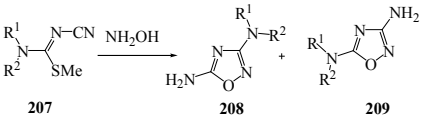
Scheme 71

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].



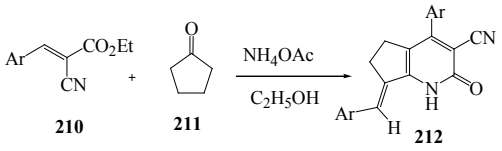
Scheme 73

Six-membered heterocycles

Six membered heterocycles with one heteroatom

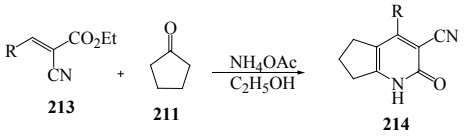
Synthesis of pyridine and condensed pyridine derivatives: Several pyridine syntheses, utilizing nitriles as starting components have been reported [37-41]. Although a number of papers have been

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.



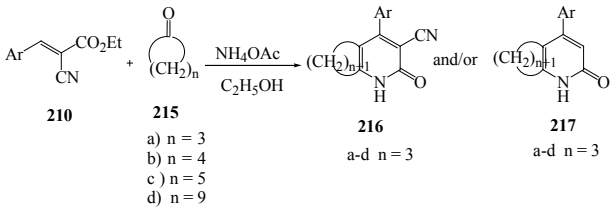
Scheme 74

An analoguous 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-1-pyridines **214** instead of the expected 7-alkylidene derivatives and the product depicted in Scheme 75.



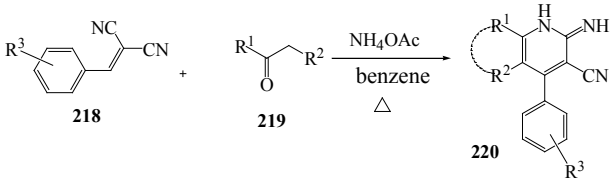
Scheme 75

The reaction of **210a-d** with **215b** gave the 4-aryl-3-cyano-2-oxo-1,2,3,4,5,6,7, 8-(or 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.



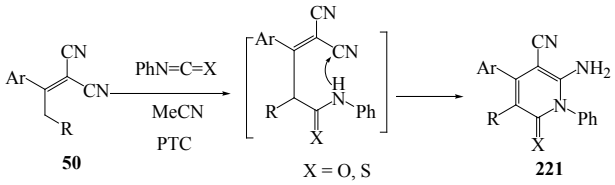
Scheme 76

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].



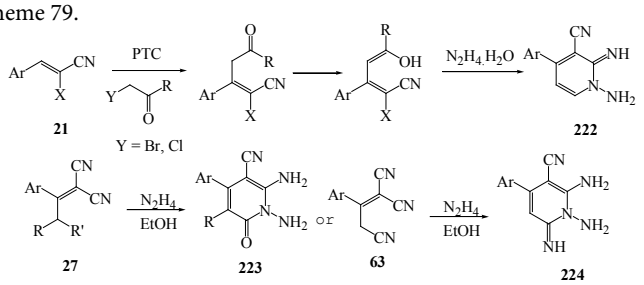
Scheme 77

The reaction of β-alkylarylidenemalononitrile **50** with phenylisocyanate or phenylisothiocyanate under PTC conditions ($MeCN/K_2CO_3$/TBAB) yielded pyridinone and pyridine-2-thione derivatives **221** [105,215], as shown in Scheme 78.



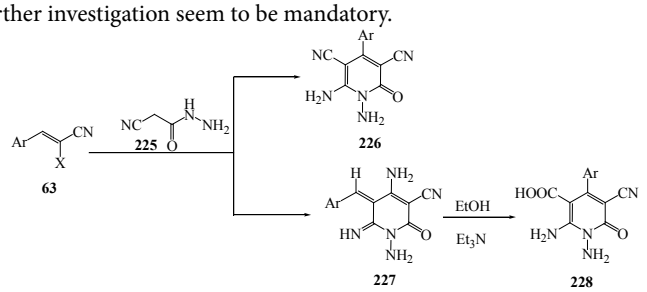
Scheme 78

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.



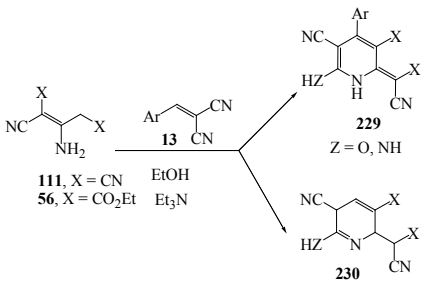
Scheme 79

The cinnamonitriles **63** react with cyanoacetic acid hydrazide **226** to afford N-aminopyridones. 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.



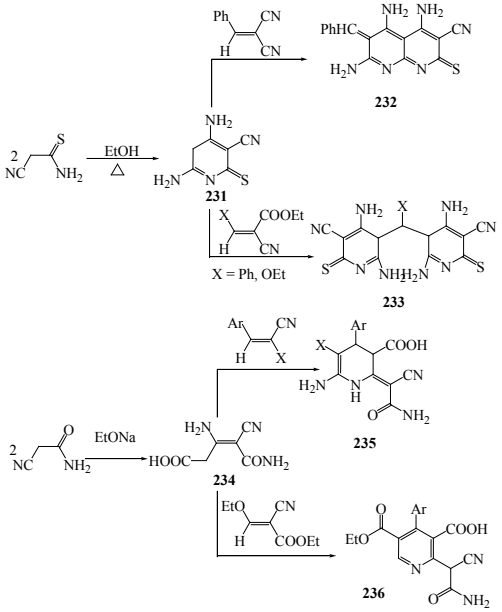
Scheme 80

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].



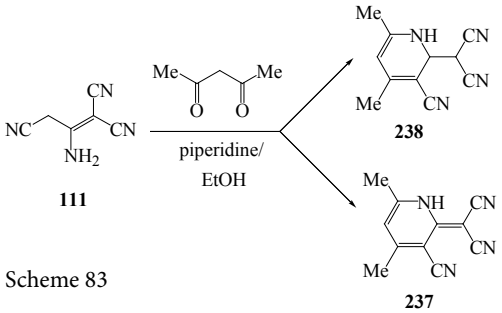
Scheme 81

Recently, this approach has been explored for the synthesis of several pyridine derivatives **231-236**, as outlined in Scheme 82 [220-223].



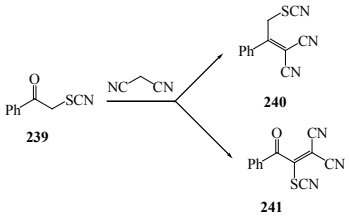
Scheme 82

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 $C_{11}H_8N_4$. 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 ^{1}H-NMR spectra. The obtained products beer several functional substituents and appear promising for further chemical transformations, as outlined in Scheme 83.



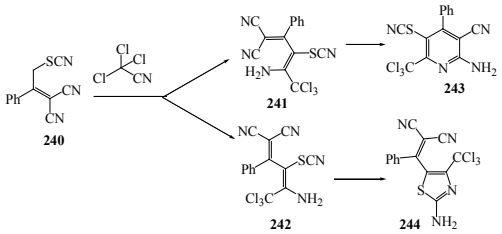
Scheme 83

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



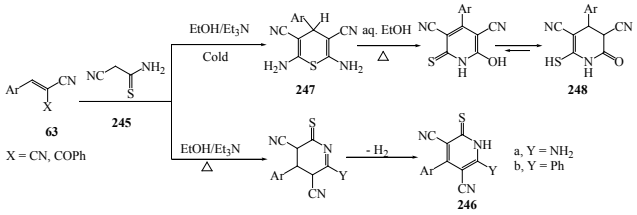
Scheme 84

The structure **241** was ruled out on the basis of IR and ^{1}H-NMR spectra. Reaction of trichloroacetonitrile with **240** in refluxing toluene in the presence of a catalytic amount of piperidine yield a 1:1 gave adduct **241** wich cyclized into produce **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**.**



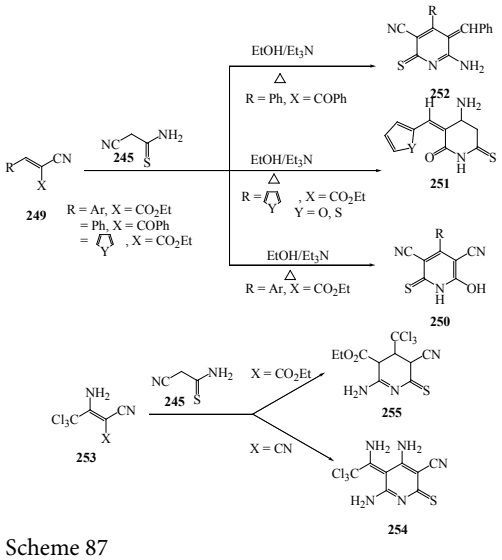
Scheme 85

Conflicting results have been reported for the reaction of cinnamonitrile **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 ^{1}H-NMR and ^{13}C-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 cinnamonitrile derivatives on the nature of reactants and reaction conditions has been reported [134,226-236], as outlined in Scheme 86.



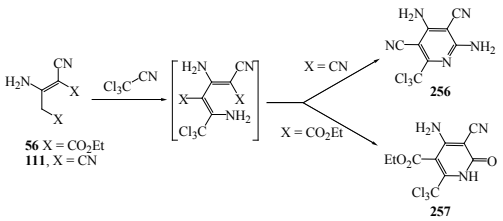
Scheme 86

Pyridine derivatives **250**, **251**, **252**, **253** and **255** were successfully synthesized *via* condensation of cyanothioacetamide **245** with the cinnamonitrile derivatives **249** or the acrylonitrile derivatives **253,** as outlined in Scheme 87 [237].



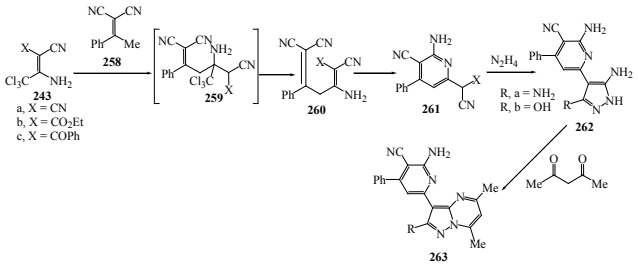
Scheme 87

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.



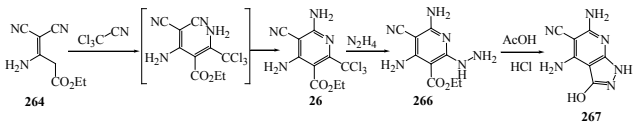
Scheme 88

A route for the synthesis of 6-[5-amino-pyrrol-4-yl]pyridines **253** and their conversion into 3-[pyridine-6-yl]pyrazolo[1,5-a]pyrimidine **263** has been reported [238]. Thus, 1-phenylethylidene malononitrile **258** was refluxed in pyridine solution with enaminonitriles **253a-c** to yield products via chloroform elimination. Structure **230** or its cyclized product **231** seemed possible as **253a-c** were assumed to add **258** affording the intermediate Michael adducts **229** which then lost chloroform to **230**. **230** may undergo cyclization into **261** under the reaction conditions. Compound **261** reacted with hydrazine hydrate affording **261**, which condensed readily with acetylacetone affording the required pyrazolo[1,5-a]pyrimidines **263,** as outlined in Scheme 89.



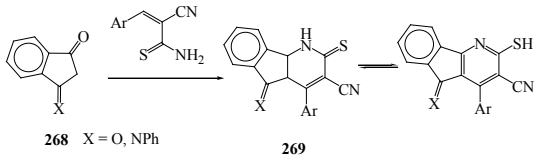
Scheme 89

El-Nagdy et al. [239] reported that 3-amino-2-cyano-4-ethoxycarbonyl crotononitrile **234** reacted with trichloroacetonitrile in refluxing ethanol in presence of triethylamine 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 **237,** as outlined in Scheme 90.



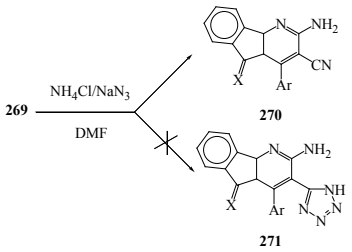
Scheme 90

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



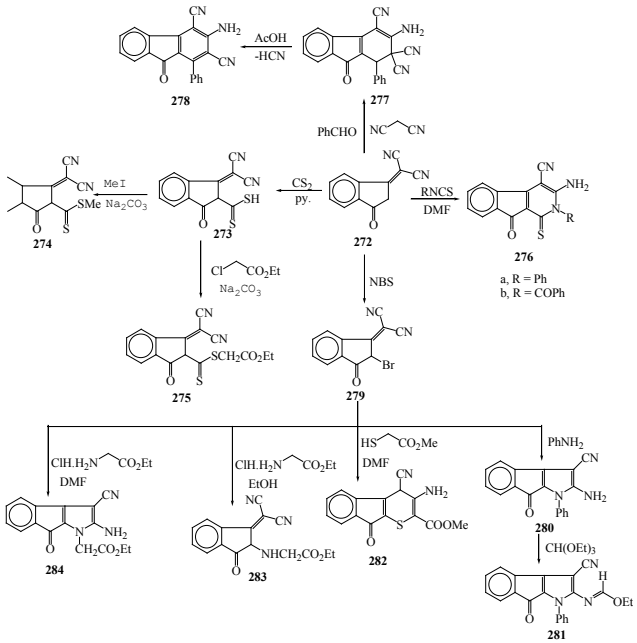
Scheme 91

When **269** was subjected to react with NaN_3 in DMF in the presence of NH_4Cl to synthesize mercaptotetrazolylindeno pyridine **271** as reported [241,242] the aminoindenopyridine derivative **270** was obtained instead of **271**, as depicted in Scheme 92.



Scheme 92

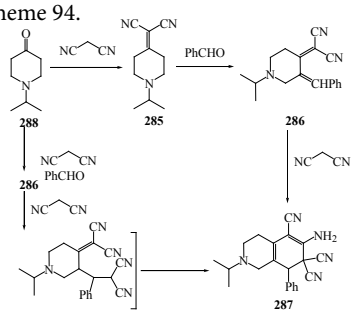
1-Dicyanomethylene-3-indanone **272** was prepared by the reaction of indandione and malononitrile in ethanolic sodium ethoxide solution [243,244]. Compound **272** reacted with carbon disulphide to give the dithiocarboxylic acid derivative **273**, which in turn was alkylated with methyl iodide and 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]pyrroles **280**, **281** [245], indeno[2,1-b]thiopyrane **282**, **283** and **284,** as outlined in Scheme 93.



Scheme 93

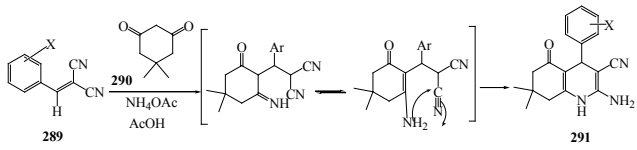
Piperidylidene malononitrile **285** reacts with benzaldehyde to

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.



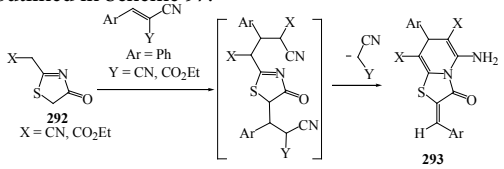
Scheme 94 & 95

Synthesis of novel 1,4,5,6,7,8-hexahydroquinoline **291** bearing amino and cyano groups on C_2 and C_3 has been carried out by refluxing equimolar amounts of the corresponding arylidene 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.



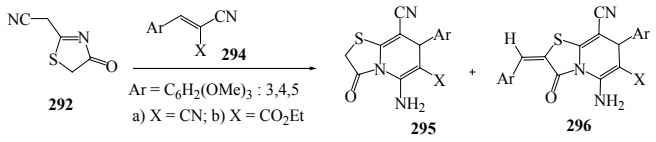
Scheme 96

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.



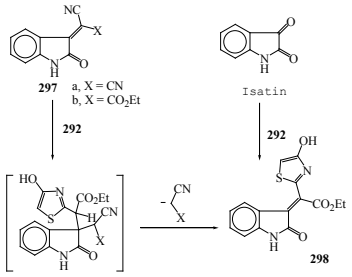
Scheme 97

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.



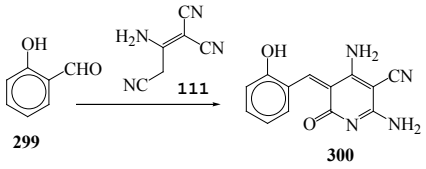
Scheme 98

E-Z-assignement of compounds containing exocyclic C=C double bonds throughout the present work were elucidated and proven by ^{1}H-NMR calculations [251]. Unexpectedly, it has been found that the product **299** from the reaction of **292** with 2-oxo-3-dicyanomethylidene-2,3-dihydroindole **297a**, 2-oxo-3-cyanoethoxy carbonylmethylidene-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.



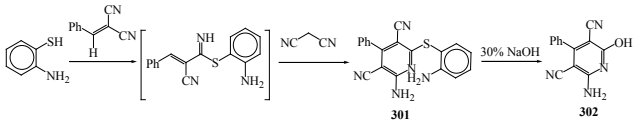
Scheme 99

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-tricyano prop-1-ene **111** to yield the benzopyrano[3,4-c]pyridine **300** is depicted in Scheme 100.



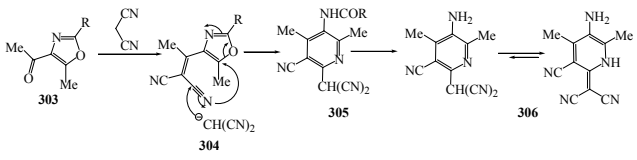
Scheme 100

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

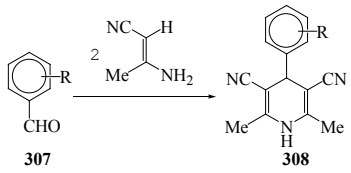
Conversion of 4-acetyloxazoles **303** into pyridine derivatives **306** via reaction with malononitrile has been reported. The reaction proceeds via formation of the ylidenemalononitrile derivative **304** and then cyclized into 305 [254], as outlined in Scheme 102.



Scheme 102

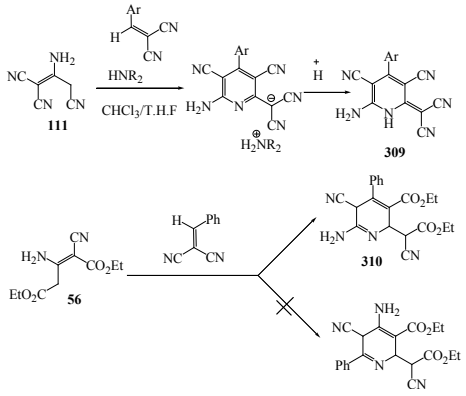
Several other pyridine syntheses from activated α,β-unsaturated nitriles are already available in literature; a very old example is the reaction of two fold of 2-amino crotononitrile with aromatic

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



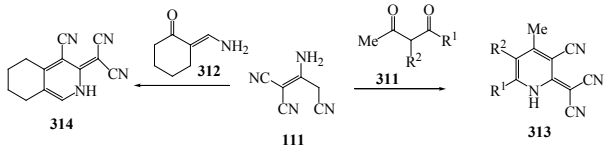
Scheme 103

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.



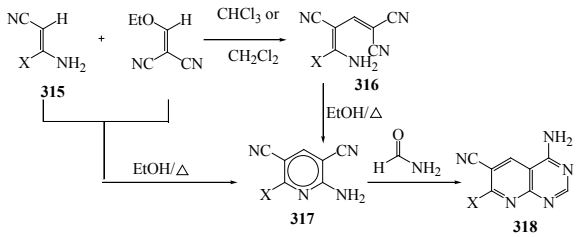
Scheme 104

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.



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.

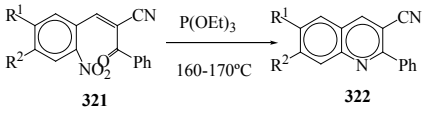


Scheme 106

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

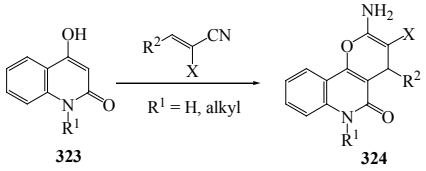
Scheme 107

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



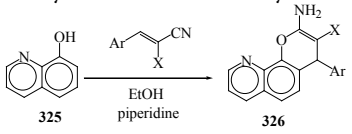
Scheme 108

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



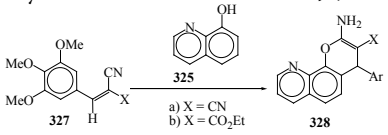
Scheme 109

Khallh et al. [261] reported that 8-quinolinol **325** reacts with cinnamonitrile 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 yield, as depicted in Scheme 110.



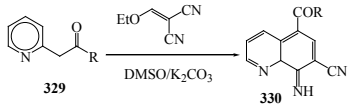
Scheme 110

Mahmoud et al. [262] reported that the same results obtained when α-cyano-3,4,5-trimethoxyphenyl cinnamonitrile **327a** and/or ethyl α-cyano-3,4,5-trimethoxy phenylcinnamate **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.



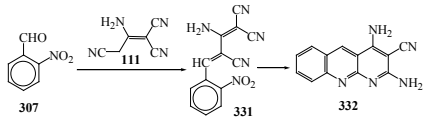
Scheme 111

The reaction of acetyl and benzoylmethyl pyridine **329** with ethoxymethylene malononitrile in DMSO in the presence of potassium carbonate gave acylcyanoimino quinolines **330** with yields 70-96%, respectively, as depicted in Scheme 112 [263].



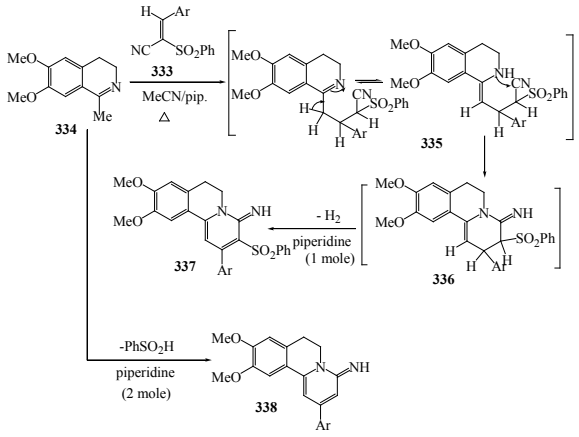
Scheme 112

Ortho-itrobenzaldehyde **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** is depicted in Scheme 113 [254].



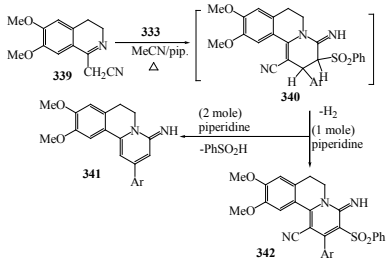
Scheme 113

High yielding syntheses of polyfunctional benzo[a]quinolizines are well-documented [264]. Abdallah et al. [265] reported a new and general one-step route affording polyfunctional substituted benzo[a] quinolizines in good yield from readily available inexpensive starting materials using isoquinoline derivatives. Thus, treatment of 1-methyl isoquinoline **334** with arylidenesulfonylacetonitriles **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 **337** may be explained by cyclization of the initially formed Michael adduct **335** to the unisolated product **336**, subsequent autoxidation of the latter leads to the final product **337**. When the reaction of **334** with **333** was carried out in the presence of excess piperidine (2 moles) then the product **338** were formed directly, as outlined in Scheme 114.



Scheme 114

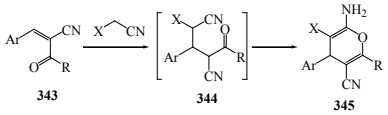
Similarly, isoquinoline-1-yl acetonitrile **339** reacted with **333** to give **341** and **342** through the cyclization and dehydrogenation of **340,** as outlined in Scheme 115.



Scheme 115

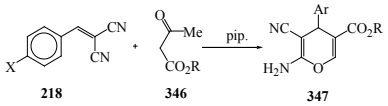
Synthesis of pyran, coumarin and condensed pyran derivatives: Pyrans were readily obtained in good yields on treatment of ylidene derivatives of α-cyanochalcones with active methylene nitriles and active methylene ketones. Thus, benzylidene derivatives, aminomethylene and mercaptomethylene derivatives has been reported [170,235,236] to react with active methylene reagents to yield pyran derivatives [266-272].

The formation of pyrans in these reactions is assumed to proceed via additions of the reagent to the activated double bond and subsequent cyclization to the pyrane derivative, as demonstrated by the formation of **345** from the reaction of cinnamonitrile derivative **343** with active methylene reagents and as depicted in Scheme 116.



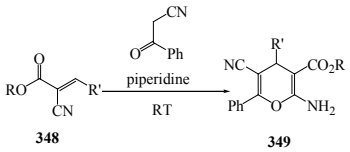
Scheme 116

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.



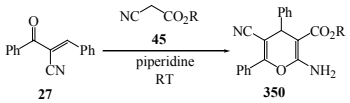
Scheme 117

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].



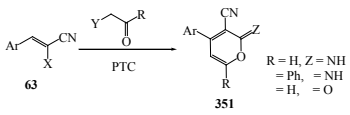
Scheme 118

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



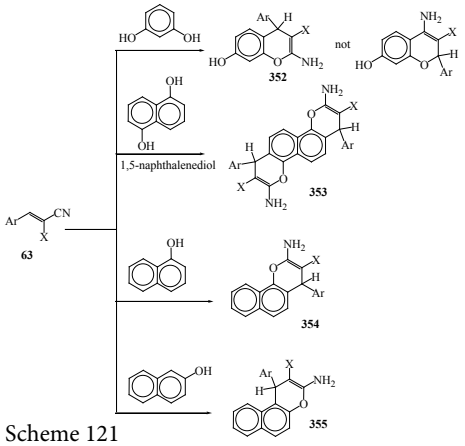
Scheme 119

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.



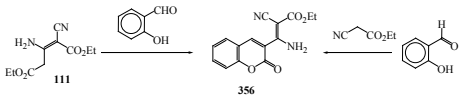
Scheme 120

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 cinnamonitriles **63** with resorcinol, 1,5-naphthalenediol, 1-naphthol and 2-naphthol, respectively [276,277], as outlined in Scheme 121.



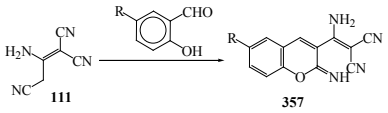
Scheme 121

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 ethylcyanoacetate [278], as shown in Scheme 122.



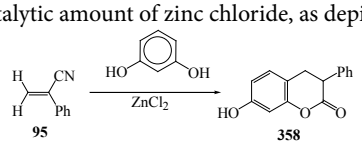
Scheme 122

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



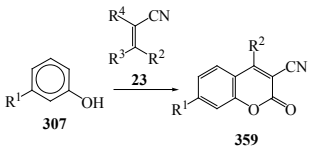
Scheme 123

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.



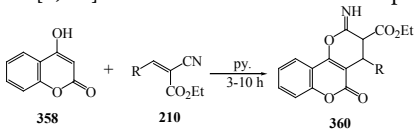
Scheme 124

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



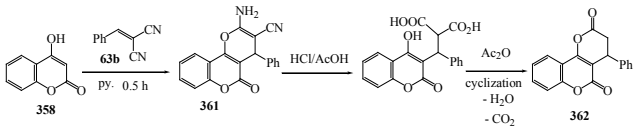
Scheme 125

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.



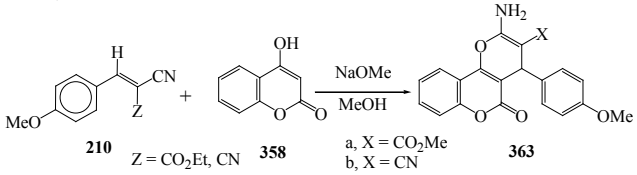
Scheme 126

4-Phenylcoumarin-3,4-dihydro-α-pyrone **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 Ac_2O [284], as outlined in Scheme 127.



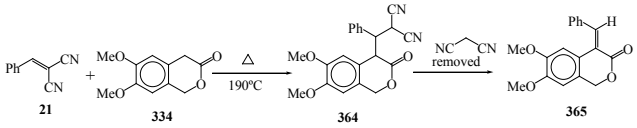
Scheme 127

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



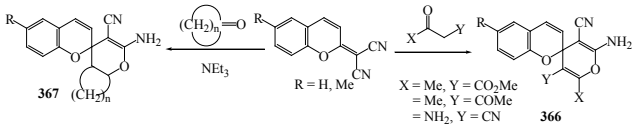
Scheme 128

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 **264** 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.

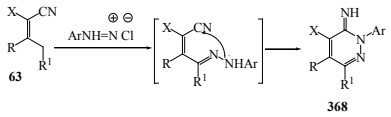


Scheme 130

Six membered rings with two heteroatoms

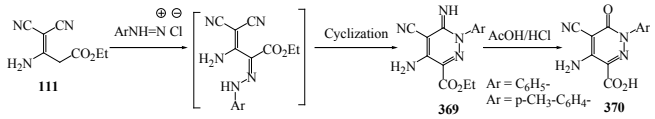
Synthesis of pyridazine and condensed pyridazine derivatives: An interesting approach for synthesis of pyridazines **368** has been achieved by cyclization of the intermediated of the reaction of cinnamonitrile derivatives **63** with aryldiazonium chloride [287]. This

synthetic approach is summarized below in the following Scheme 131.



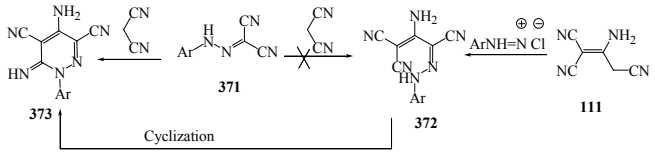
Scheme 131

El-Nagdy et al. [239] reported that 3-amino-2-cyano-4-ethoxycarbonyl 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.



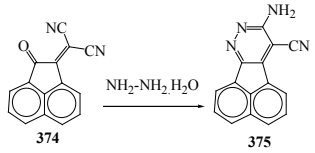
Scheme 132

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



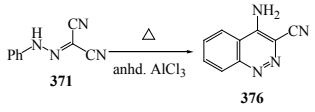
Scheme 133

Similar synthesis of pyridazine derivatives utilizing diethyl 3-amino-2-cyano-pent-2-ene-1,5-dicarboxylate has been reported [287]. Acenaphthenoquinones readily condense with malononitrile to yield the corresponding yildenemalononitrile **374**, which reacts readily with hydrazine hydrate to yield aminopyridazine derivatives **375** [41], as depicted in Scheme 134



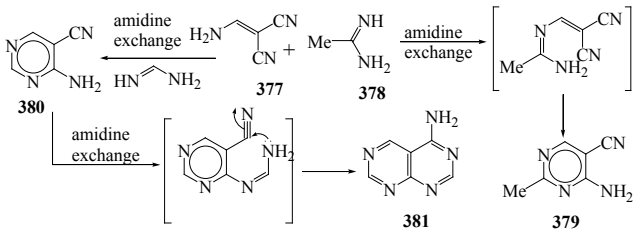
Scheme 134

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].



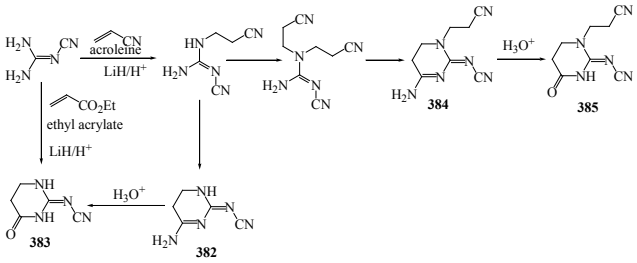
Scheme 135

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].



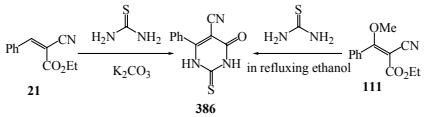
Scheme 136

Cyanoethylation [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.



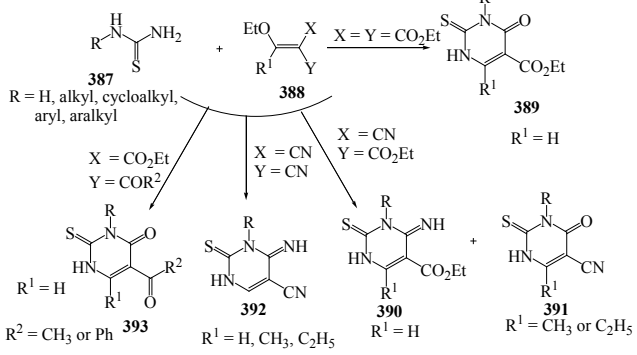
Scheme 137

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.



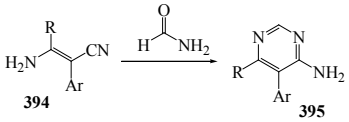
Scheme 138

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.



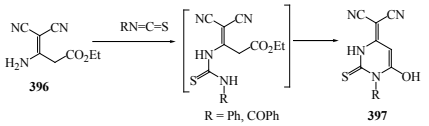
Scheme 139

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].



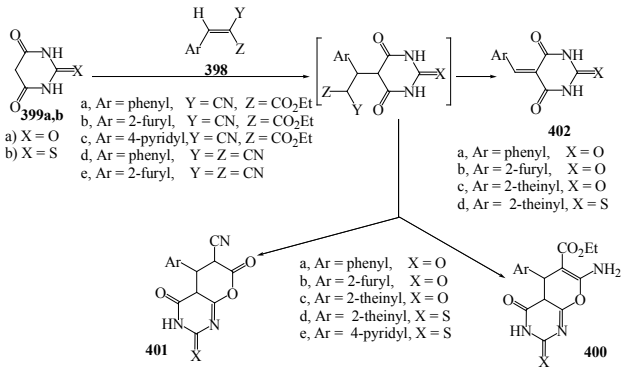
as depicted in Scheme 140

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 benzoylisothio-cyanate in refluxing dioxane to yield the pyrimidine derivative **397** is depicted in Scheme 141 [240].



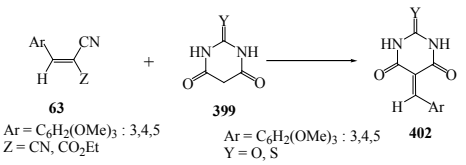
Scheme 141

The reaction of barbituric acid, thiobarbituric acid and 4-bromo-3-methyl pyrazolin-5-one with acrylonitriles **398** was reported by Abdel-Latif [303], thus, the compound **399a** reacted with **398a-c** to give the pyrano[3,2-d]pyrimidines **400a-c**. The alternative structure **401** was excluded on the basis of spectral data. Similarly, the acid **399b** reacted with **398a,d** to give the corresponding pyrano[3,2-d] pyrimidines **400de**. On the contrary, attempts to bring about addition of **399b** to **398b,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 introduction of a π-excessive heterocycle decrease its reactivity. In contrast to the behaviour of **398a-d** towards **399a,b** attempts to bring about addition of **373f-h** to **399a,**b resulted in the formation of ylidene derivatives **402a-d**, which assumed to be formed *via* elimination of a malononitrile molecule from the Michael adduct intermediate. Similar ylidene formation by the addition of α,β-unsaturated nitriles to active methylene reagents has been observed earlier in several reactions [101,250], as shown in Scheme 142**.**



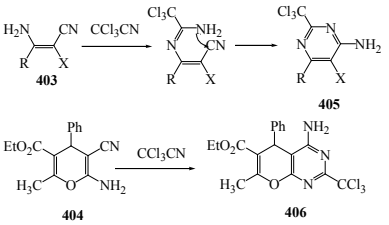
Scheme 142

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



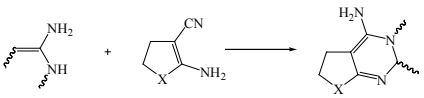
Scheme 143

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**.**



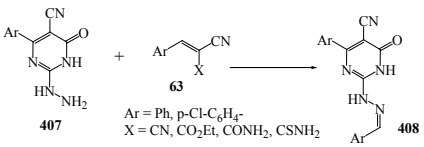
Scheme 144

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



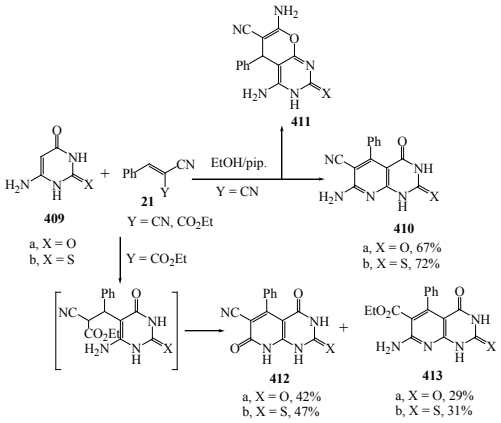
Scheme 145

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



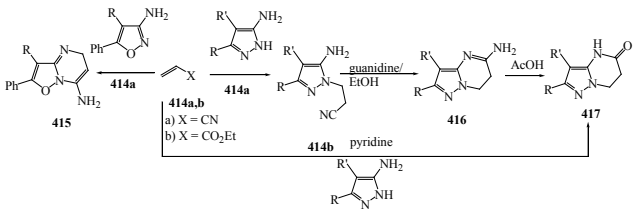
Scheme 146

Geies [311] has been reported that 6-aminouracil and 6-aminothiouracil **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**.**



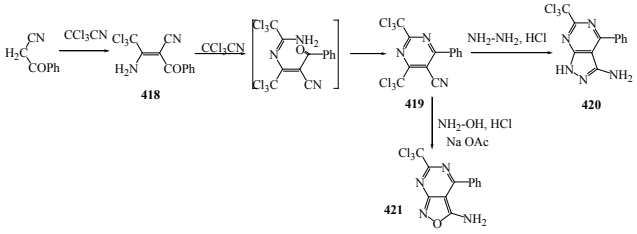
Scheme 147

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 benzylideneethylcyanoacetate 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.



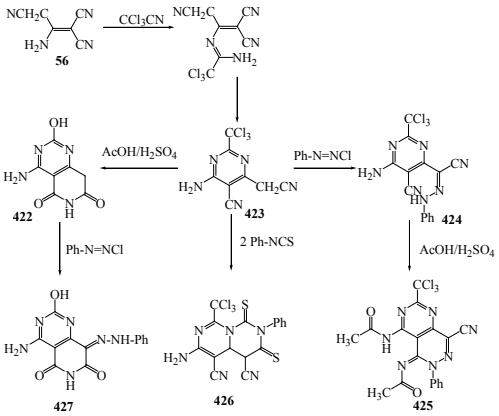
Scheme 148

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].



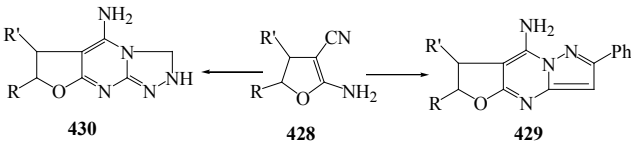
Scheme 149

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



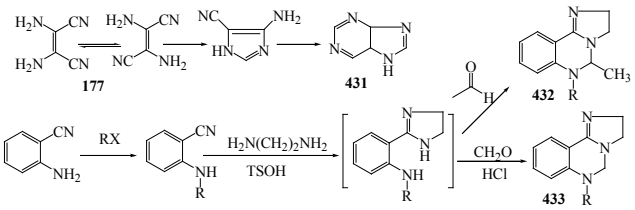
Scheme 150

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 deicted in Scheme 151 [320].



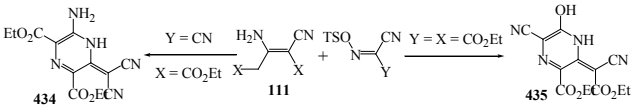
Scheme 151

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



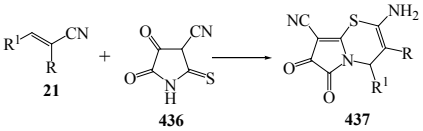
Scheme 152

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.



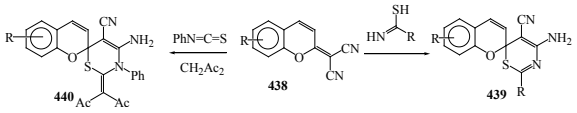
Scheme 153

Synthesis of thiazine derivatives: Several new pyrolidino[1,2-a]-3,1-thiazine-5,6-dione derivative **436** was synthesized via the reaction of 4-cyano-2,3-dioxo-5-thienopyrolidine **437** with a variety of activated nitriles, as depicted in Scheme 154 [327].



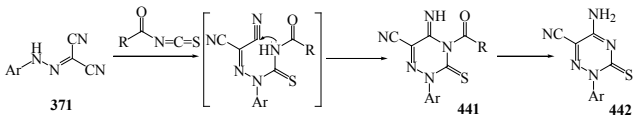
Scheme 154

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

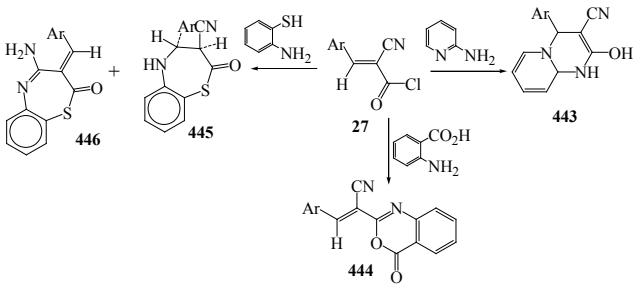
Six-membered rings with three heteroatoms: Several triazine syntheses starting from α,β-unsaturated nitriles have appeared in some literature [41,287,288]. An interesting example of these syntheses is shown in Scheme 156 [328,329].



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 industriasl 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) and 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.

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