The Chemistry of β-Enaminonitriles as Versatile Reagents in Heterocyclic Synthesis

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Contents

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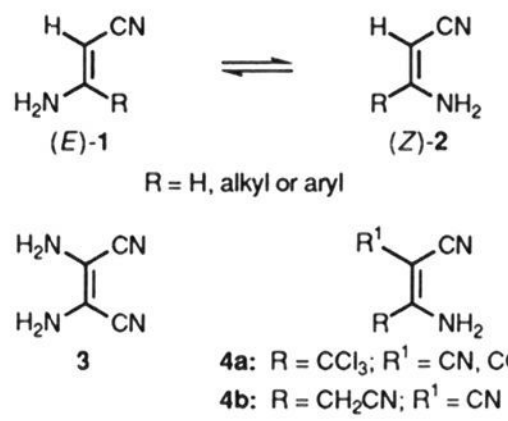
I. Introduction

Much synthetic heterocyclic organic chemistry involves specially designed reagents which are readily generated and then used to provide molecules with built-in functional moieties for further exploitation. Important examples of such reagents are β-enaminonitriles (β-aminoalkenonitrile) which have proven to be valuable tools in the synthesis of a wide variety of unique heterocyclic systems such as pharmaceuticals, fungicides, and solvatochromatic dyes. Numerous reports in the literature concerning their applications attest to their growing importance. Although reviews covering the chemistry of enamines,[1] heterocyclic enamines,[2] and heterocyclic β-enaminonitriles[3–6] have appeared, it is hoped that this review will remedy the lack of a more comprehensive review by providing an up-to-date coverage of the recent literature. This review covers the literature up to 1992 and considers the properties, reactions and applications of open-chain β-enaminonitriles (**1**–**4**). 3-Aminocrotononitrile (**1**,**2**, R = CH_3) and diaminomaleonitrile (DAMN) (**3**) are discussed in particular depth due to their frequent appearance in the literature as well as their potential biomedical and industrial importance.



II. Molecular Structures and Spectral Properties

β-Enaminonitriles exist in two stereoisomers. In *Z*-form (**2**), the amino and cyano groups are in adjacent positions on the double bond. An intramolecular hydrogen bond makes the *Z*-form more stable than the *E*-isomer (**1**).[7] In the case of β-aminocrotononitrile (**1**,**2**, R = CH_3), it has been established that isomerization in either solution or the solid state can occur.[8] A mixture of *E*- and *Z*-isomers, which are readily distinguishable by ^1H NMR, is formed. Only the *Z*-isomer (**2**) has a coupling constant of 0.8 Hz for the CH_3. In addition the *Z*-isomer absorbs in UV spectroscopy[9] at shorter wavelength and usually gives a more intense absorption band at (λ_{max} (MeCN) = 254 nm, $\epsilon = 11.77 \times 10^4$) than does the *E*-isomer at (λ_{max} (MeCN) = 255 nm, ϵ = 1.54

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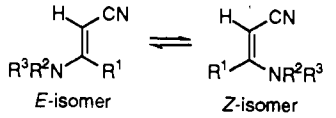
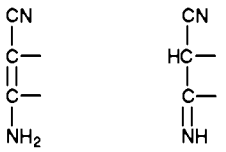
Table 1. ^{1}H NMR Spectra of Enaminonitriles



	nitrile				prevailing isomer	chemical shifts in isomers						
						HC=		H_3CC=		R^2		R^3=H
	R^1	R^2	R^3	solvent	(relative population, %)	*E*	*Z*	*E*	*Z*	*E*	*Z*	(NH)
A	CH_3	H	H	$(CD_3)_2SO$	*E*	3.94[a]		1.94[a]		6.48		6.48
				$CDCl_3$	*Z* (70)	4.10	3.89[b]	2.09	1.92[b]	4.68		4.68
				C_6H_6	*E* (60)	3.49[a]	3.22[b]	1.37	0.90[b]			
B	CH_3	CH_3	H	$CDCl_3$	*E* (85)	3.65	3.39	2.03	1.70	2.62 (d)[c]	2.96 (d)[c]	5.42
				C_6D_6	*E* (95)	3.51	3.44[b]	1.86	1.36[b]	2.21 (d)[c]	2.52 (d)[c]	
C	CH_3	C_6H_5	H	$CDCl_3$	*E* (90)	4.35	3.93	2.17	1.90	6.9–7.4 (m)		6.65
				C_6H_6	*E* (95)	4.06		1.50	1.09	6.4–6.9 (m)		4.70
D	C_6H_5	H	H	$CDCl_3$	*Z* (85)	4.35	4.14			5.12		5.12
				C_6D_6	*Z* (100)		3.90			4.52		4.52
E	CH_3	$C_6H_5CH_2$	H	$CDCl_3$	*E* (100)	3.80		2.07		4.10 (d)[c,d]		4.87
				C_6D_6	*E* (100)	3.44		2.43		3.26 (d)[a]		
F	CH_3	C_2H_5	C_2H_5	$CDCl_3$	*E* (100)	3.70		2.14		1.02 (t)[e]		
										3.22 (q)[e]		
				C_6D_6	*E* (100)	3.58		1.85		0.78 (t)[e]		
										2.70 (q)[e]		

[a] ^4J(HC=CCH$_3$) < 0.1 Hz. [b] ^4J(HC=CCH$_3$) = 0.75 ± 0.2 Hz. [c] C_6H_5 proton multiplet around δ = 7.3. [e] ^3J(HCCH) = 7 ± 1 Hz. For further examples and details, see ref 25.

× 10^4). The position of the photoequilibrium, as established by UV absorption data, is at (75%) *Z* form and (25%) *E* form.[10] Spectroscopic studies of enaminonitriles also showed that the enamine tautomeric structure **5** is preferred over the imino structure **6**.[7,11-17]

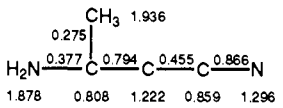


5 **6**

Two absorption bands found in the NH-stretching region of the IR are compatible with a primary amine groups (NH_2).[16] Furthermore, the lack of two IR absorption nitrile stretching bands led to the conclusion that enaminonitriles exist solely in form **5** rather than in an equilibrium mixture of **5** and **6**. ^{1}H NMR appears to support this conclusion, since the NH signal appears in a position typical for an amino group.[8,18,19]

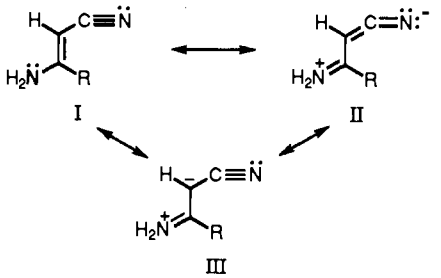
^{13}C NMR has also been used to study the structure of enaminonitriles in order to obtain information on the transmission of electronic effects of the amino group and their influence on the reactivity of the enaminonitrile system.[20] In cases where a considerable variation was observed in the contribution of the amino moiety to the chemical shift of the olefinic carbons this was attributed principally to a variation in the mesomeric contribution to the electron density.[21-24] Similarly ^{1}H NMR and nuclear Overhauser effects (NOE) studies of a series of 3-substituted 3-aminoacrylonitriles show that the olefinic proton is more shielded and that the proton–proton long-range coupling constants *J* (HC=CH_3) and *J* (HC=CNH_2) are larger in the *Z*-isomer (**2**) than in the isomer (**1**) (Table 1).[25]

Huckel's LCAO-MO method has been used to study the π-electronic structures of some enaminonitriles.[26] It was shown that conjugation of the electrons with the cyano group decreases the π-bond orders of the C—NH and C=C bonds at the same time as increasing the π-bond orders of the C—CN bonds. The π-electron distribution and densities of β-aminocrotononitrile are given in structure **7**.



7

It should also noted that the resonance hybrid enamine structure (cf. I, II, III) imparts certain nucleophilic character to some atoms while other atoms are electrophile,[7] since the Michael addition features so prominently.



I **II** **III**

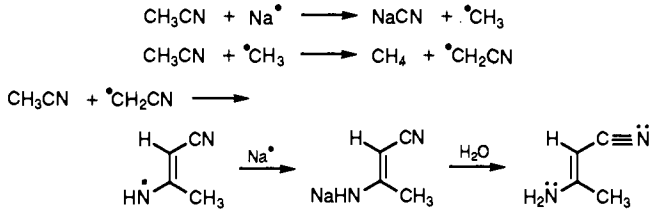
III. Methods of Preparation

Several methods have been reported for the synthesis of β-enaminonitriles, most of these involve the dimerization of substituted nitriles.

A. Preparation of β-Enaminonitriles

The dimerization of acetonitrile using sodium in organic solvents is the most common approach for the synthesis of β-aminocrotononitriles.[7,27-36] Treatment of acetonitrile with sodium gave β-aminocrotononitrile (**1,2**, R = CH_3) in quantitative yield. The reaction is processing via a free-radical mechanism (Scheme 1).[7]

Scheme 1

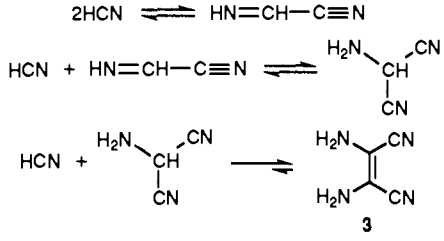


This is only reported mechanism for such a reaction and looks least likely in view of lack of evidence as isolation of other products that should be formed in such radical reactions. A mechanism including formation of carbanion $Na^+ {}^-CH_2CN$ looks more logical. Cross condensation between acetonitrile and aromatic nitriles[37-39] or higher aliphatic nitriles leads to substitute β-enaminonitriles (**1,2**, R = alkyl or aryl).[40]

B. Preparation of Diaminomaleonitrile

Diaminomaleonitrile (**3**) is readily formed in dilute aqueous solutions of HCN at room temperature (Scheme 2).[34,41] The initial step is the dimerization of

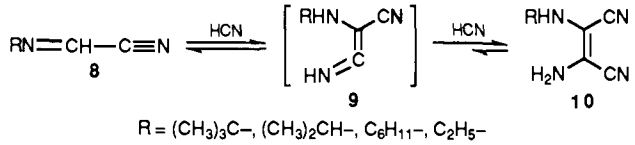
Scheme 2



HCN to iminoacetonitrile which combines with another molecule of HCN to give the aminomalononitrile. The latter reacts with another HCN molecule to give the isolable product diaminomaleonitrile (DAMN) (**3**). DAMN is the lowest oligomer isolable from an aqueous solution of HCN, and its formation can be readily assayed by using its characteristic UV absorption band (λ_{max} = 296 nm, π = 13 500).[34]

The postulated stepwise condensation of hydrogen cyanide to form DAMN is supported by the formation of the maleonitrile derivatives **10** via the intermediate **9** (Scheme 3).[42] Addition of formaldehyde, acetalde-

Scheme 3

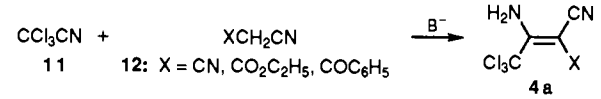


R = $(CH_3)_3C$–, $(CH_3)_2CH$–, C_6H_{11}–, C_2H_5–

hyde, or acetone was reported as accelerating the formation of diaminomaleonitrile, although the mechanism of this process is unclear.[43] In addition, halogens or Cu^{2+} ions can catalyze the tetramerization of hydrogen cyanide.[44,45]

C. Preparation of 3-Amino-2-Substituted-4,4,4-Trichlorocrotononitriles

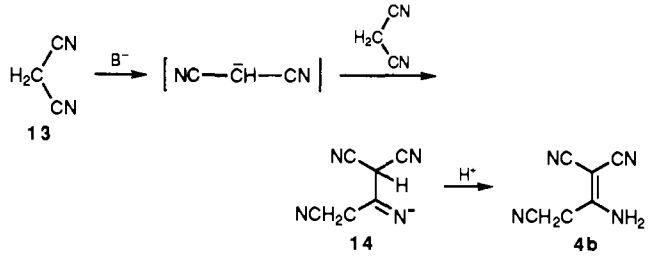
The condensation of active methylenecarbonitriles XCH_2CN (X = CN, CO_2R, COPh) with trichloroacetonitrile (**11**) using a base catalyst gives the title compound in good yields after only short reaction times.[46,47]



D. Preparation of 2-Amino-1,1,3-Tricyanopropene

Although the self-condensation of malononitrile can produce dimers, trimers, or, in certain cases, polymer[48] the reaction may be controlled to give the dimer as the main product. The reaction can be catalyzed by a base, acid, or a Lewis acid. The α-methylene group in malononitrile is sufficiently acidic to afford a carbanion in the presence of a base catalyst; the carbanion can then react further to produce the dimer (Scheme 4).[48]

Scheme 4



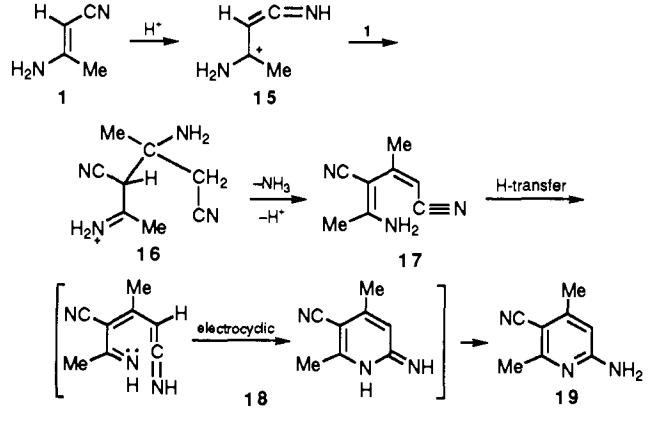
A Thorpe condensation of two malononitrile molecules yields the dimer **4b** which exists mainly in the enamine form.[13,49-53]

IV. Utility in Heterocyclic Synthesis and Synthesis of Monocyclic Azines

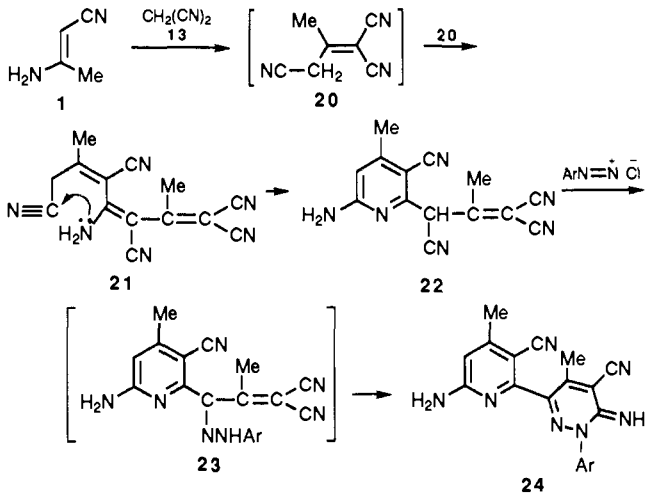
A. Synthesis of Pyridines

It has been reported that the dimerization of β-aminocrotononitrile (**1**) under various reaction conditions produces 2,4-lutidine (**19**).[54-59] Sato[59] has reported a convenient method for the preparation of **19** by means of the polyphosphoric acid (PPA) catalyzed self-condensation of **1**. In contrast, under milder conditions **1** gave dienaminonitrile **17** (13% yield), in addition to the 2,4-lutidine (**19**). Intramolecular cyclization of the dienaminonitrile **17** when heated in PPA or an alkaline solution gave its isomer **19** (Scheme 5).

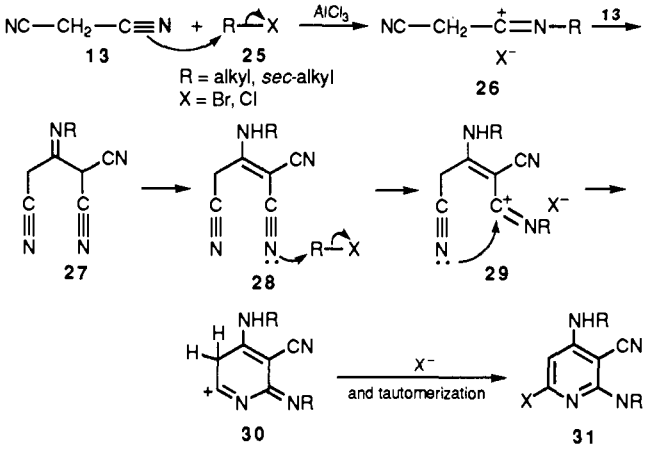
Scheme 5



Scheme 6



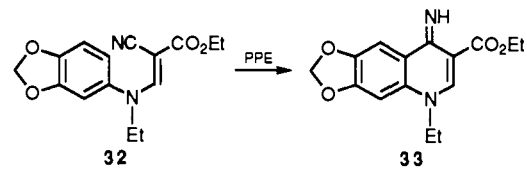
Scheme 7



The antischistosomal agents pyridylpyridazines **24** were synthesized via the reaction of β-aminocrotononitrile (**1**) with malononitrile (**13**) to yield the pyridine derivative **22**. **22** couples easily with suitable aryldiazonium salts to form **23** which after a Japp–Klingeman reaction yields the desired product **24** (Scheme 6).[60]

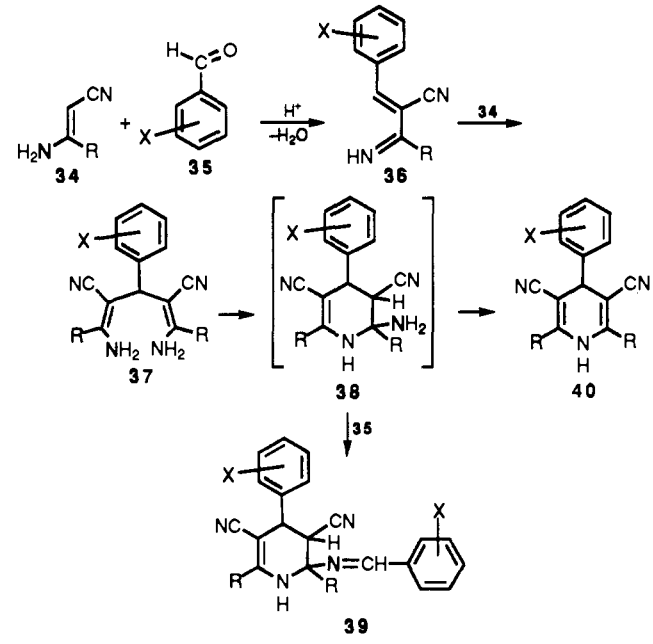
2,4-Bis(*sec*-alkylamino)pyridines **31** were obtained from the reaction of malononitrile (**13**) with *sec*-alkyl halides **25** under Friedel–Crafts condition. The reaction is assumed to proceed via intermediate of enaminonitrile **28** (Scheme 7).[61]

One example of a large number of β-enaminonitriles of the general formula ArNHC(R′)=C(X)CN which have been cyclized using ethyl phosphate (PPE), is **33** which was prepared from **32**.[62,63]



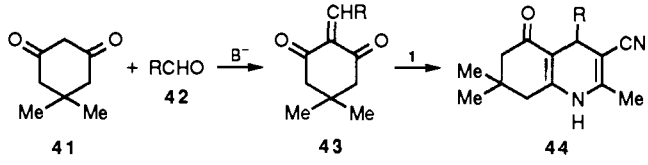
The first reported synthesis of dihydropyridines **40** involved the condensation of β-enaminonitrile **34** and aromatic aldehydes **35**.[64] 1,4-Dihydropyridines **40** have had widespread use in recent years in medicinal chemistry.[65–75] The synthesis of 1,4-dihydropyridines **40** (Table 2) takes place according to (Scheme 8);[76,77]

Scheme 8



the reaction of aldehydes with β-enaminonitrile **34** yields the benzylidene derivatives **36** which in turn reacts with **34**, in acetic acid, to form the intermediate diamines **37**. The latter was isolated from the reaction of **34** with the aldehyde **35** in ethanol at room temperature.[78] The diamines **37** are readily converted into the 1,4-dihydropyridines **40** in acetic acid solution. Evidence for Scheme 8 was found by O'Callaghan et al.[77,78] who isolated the dihydropyridine **39** by trapping the intermediate **38** using excess aldehyde **35** in the reaction mixture. The effect of the basic reagents in nonhydroxylic solvents on the Hantzsch-type 1,4-dihydropyridine **40** has been discussed briefly by Tinker.[79]

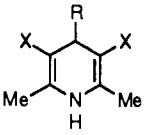
Treatment of the dimedone **41** with aldehydes **42** and β-aminocrotononitrile (**1**) gave **44**. The reaction was initiated by the condensation of dimedone with the aldehyde to give the intermediate **43**, followed by the addition of **1** and cyclization.[80]

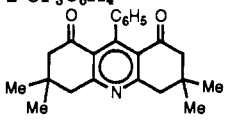
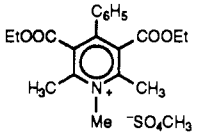
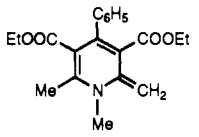


Nucleophilic attack by **1** at the C-2 of the acylchromones **45** produces the benzopyranopyridines **47**. The reaction is believed to involve the intermediate **46** (Scheme 9).[81] In a similar reaction, **1** with the aldehyde **48** gave good yields of the product **49**.[82,83]

The reaction of carbethoxymalonaldehyde (**52**) with tosyl chloride followed by treatment with β-aminocrotononitrile (**1**) produce the biologically and medicinally important nicotinic acid derivatives **55**. Scheme 10 shows the mechanism proposed by Torii et al.[84,85] The first step of which involves the sulfonylation of **52** to form the β-tosyloxyacrylate **53**. In the subsequent step, the intermediate **53** undergoes a nucleophilic attack by the enamine **1** to give the intermediate **54**. The latter

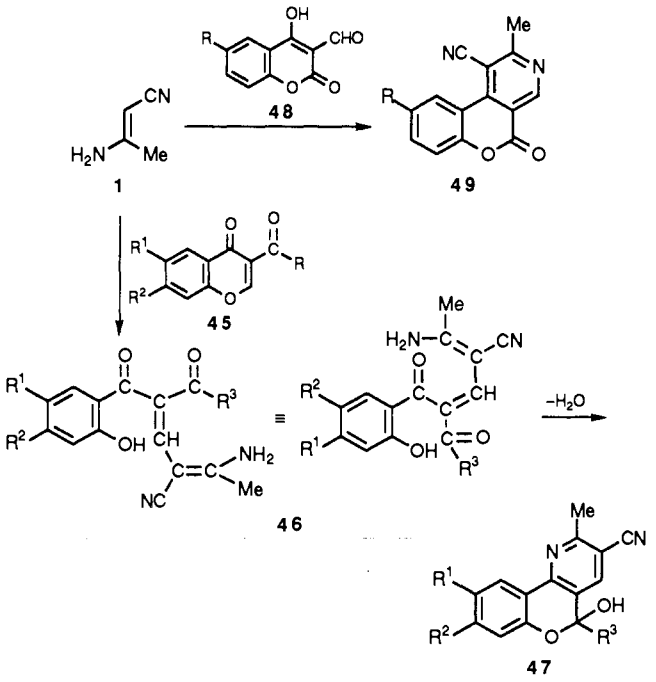
Table 2[a]



R	X	yield, %	mp or bp (mm), °C	formula
i-Pr	CN	50	148–149	$C_{12}H_{15}N_3$
t-Bu	CN	38	208–210	$C_{12}H_{17}N_2$
3-cyclohexenyl	CN	40	220–273	$C_{15}H_{17}N_3$
3-cyclohexenyl	COMe	33	159–169	$C_{17}H_{23}NO_2$
3-cyclohexenyl	cyclohexanamido	7	129–131	$C_{27}H_{41}N_3O_2$
3-cyclohexenyl	2-pyridinamido	50	218–222	$C_{22}H_{27}N_5O_2$
3-cyclohexenyl	2-pyrimidinamido	5	182 dec	$C_{23}H_{25}N_7O_2$
benzyl	CN	20	167–170	$C_{16}H_{15}N_3$
C_6H_5	COMe	41	180–182	
C_6H_5	$CONHC_6H_5$	50	237–239	$C_{27}H_{25}N_3O_2$
$2\text{-}CF_3C_6H_4$	COMe	7	187.5–190.5	$C_{16}H_{18}F_3NO_2$
cyclopentyl	CN	30	132–133.5	$C_{14}H_{17}N_3$
H	COOEt	44	72–73	$C_{13}H_{17}NO_4$
i-Pr	CN	68	82–83	$C_{12}H_{13}N_3$
styryl	COOEt	60	162–165	$C_{21}H_{23}NO_4 \cdot HCl \cdot 2H_2O$
C_6H_5	COOEt	73	63–64.5	
$2\text{-}CF_3C_6H_4$	COOEt	77	71–73	$C_{20}H_{20}F_3NO_4$
		20	258–261	$C_{22}H_{25}NO_2$
		63	143–146	$C_{21}H_{27}NO_8S$
		41	103–104	$C_{20}H_{23}NO_1$

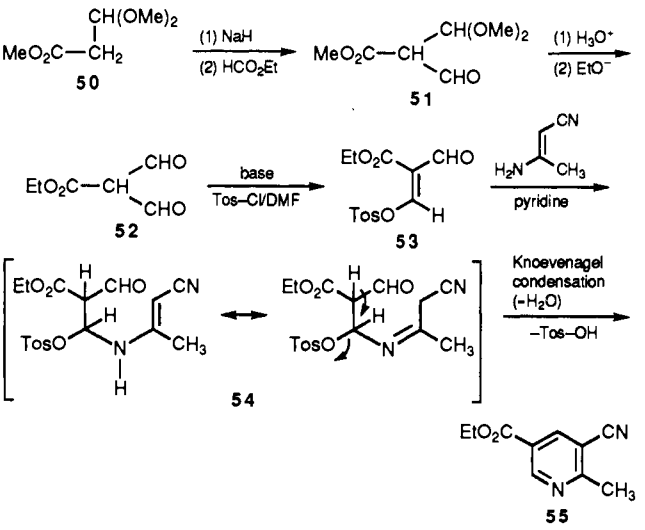
[a] Taken from ref 76.

Scheme 9



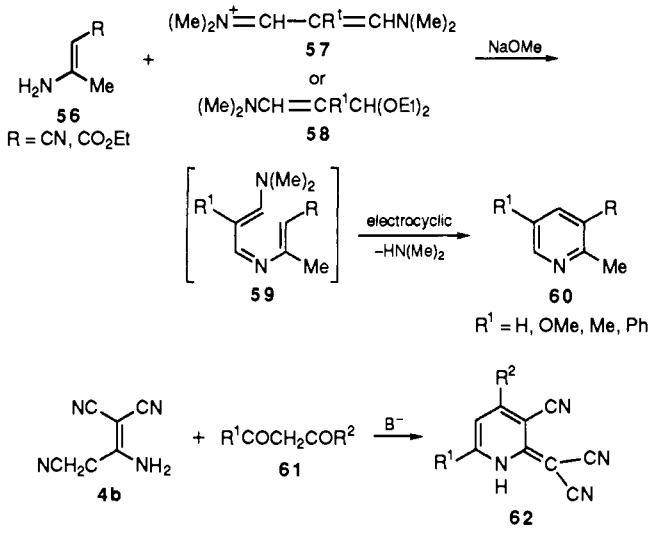
undergoes base-catalyzed elimination of sulfonic acid produces the nicotinic acid derivatives **55** (Scheme 10).

Scheme 10



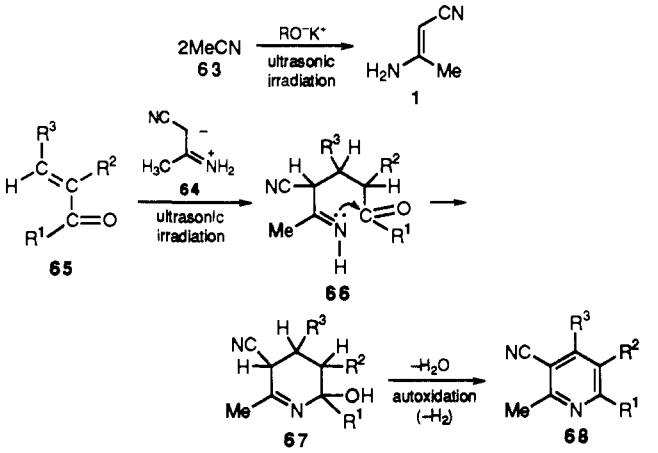
Masked 1,3-dialdehydes, such as the iminium salts **57** or the enaminoacetals **58**, are condensed with either β-amino nitriles or the carboxylate **56** to give trisubstituted pyridines **60** in 52–95% yield.[86,87]

The amino tricarbonitrile **4b** behaved as an aminoacrylonitrile and reacted with **61** to give (dicyanomethylene)pyridines **62** in good to excellent yields.[88]



Ultrasonic irradiation of α,β-unsaturated carbonyl compounds **65** with acetonitrile in the presence of potassium alkoxide gave nicotinonitriles **68**. A possible mechanism for this process is shown in Scheme 11.[89,90]

Scheme 11



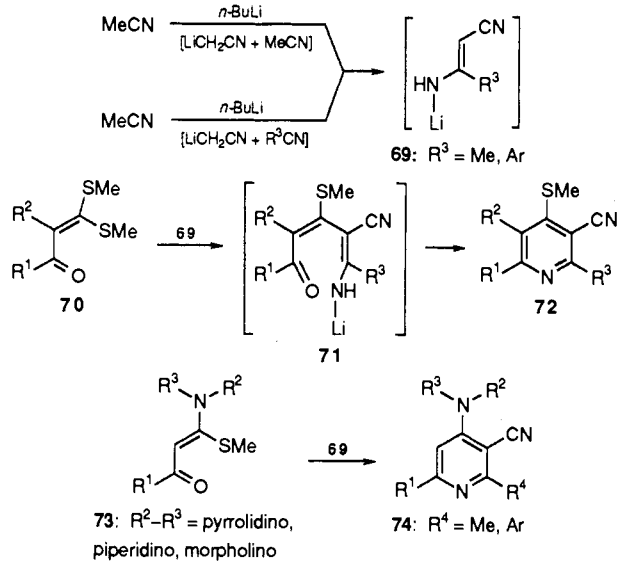
Ultrasonic irradiation of acetonitrile **63** gives 3-aminocrotononitrile (**1**) which then undergoes Michael addition reaction, via **64**, to the unsaturated carbon in **65** to give the adduct **66**. The adduct **66** easily undergoes ring closure to give the intermediate **67** which on dehydration and dehydrogenation under reaction condition gives nicotinonitrile **68**.[90]

Lithiated β-substituted β-amino-acrylonitriles **69** are generated, in situ, from the reaction of acetonitrile and butyl lithium which then undergoes a 1,4-cycloaddition reaction with α-oxo ketene dithioacetals **70** to give 2,6-substituted 4-(methylthio)-3-cyanopyridines **72** probably via an intermediate **71**. 2,6-Substituted 3-cyano-4-(dialkylamino)pyridines **74** have been similarly prepared by the reaction of 2-oxo ketene *N,S*-acetals **73** with **69** (Scheme 12).[91,92]

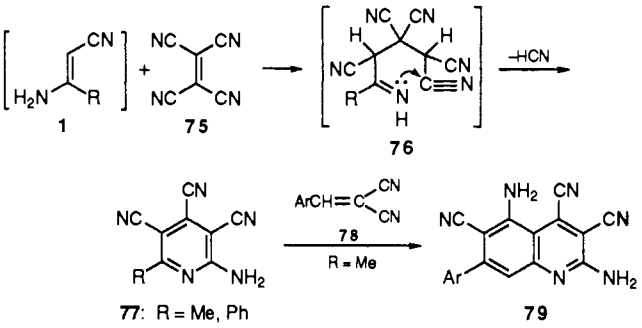
A Michael condensation of β-enaminonitrile **1** with tetracyanoethylene **75** produces 2-amino-3,4,5-tricyanopyridines **77** which readily undergo a further Michael addition with cinnamonitriles **78** to yield substituted quinolines **79** (Scheme 13).[93,94]

Aminopentadienones **82** were obtained from the

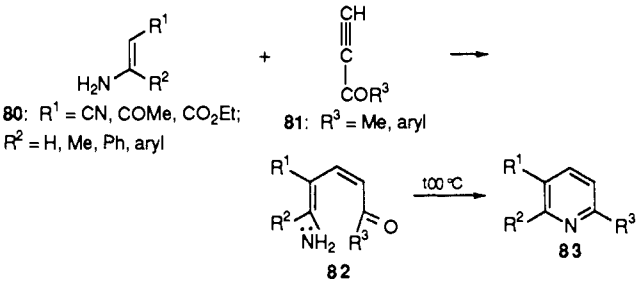
Scheme 12



Scheme 13

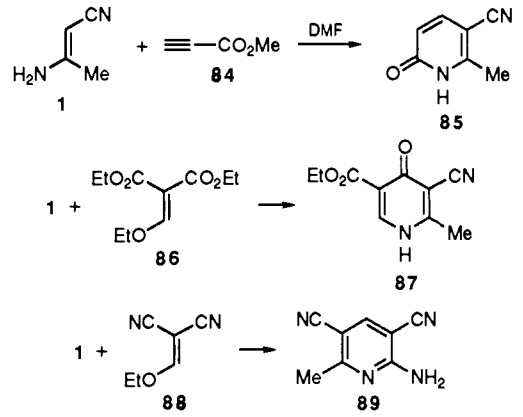


reaction of β-aminocrotonates **80** and ethynyl ketones **81**. Cyclization of **82** produces trisubstituted pyridines **83**.[95]

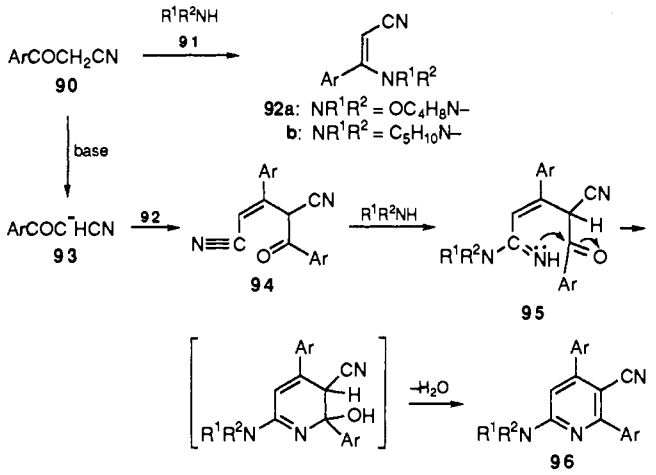


The pyridinone derivative **85** was prepared in good yields via a Michael addition of β-aminocrotononitrile **1** to the more reactive methyl 2-propynolate (**84**) followed by cyclization to give **85**.[96] In a similar reaction **1** with diethyl (ethoxymethylene)malonate (**86**) gave the pyridinone **87**.[97] On the other hand, treatment of **1** with (ethoxymethylene)malononitrile (**88**) afforded the nicotinonitrile derivatives **89**.[98]

Treatment of aroylacetonitriles **90** with morpholine or piperidine affords 6-amino-3-cyano-2,4-diarylpyridines (**96**) in good yield. The reaction of **90** with **91** gives initially the β-enaminonitrile **92**, which is consequently attacked by the nucleophile **93** to yield **94**. The product **94** reacts further with another molecule of **91** to give the intermediate **95**. Dehydration affords the final product, the substituted pyridine **96** (Scheme 14).[99]

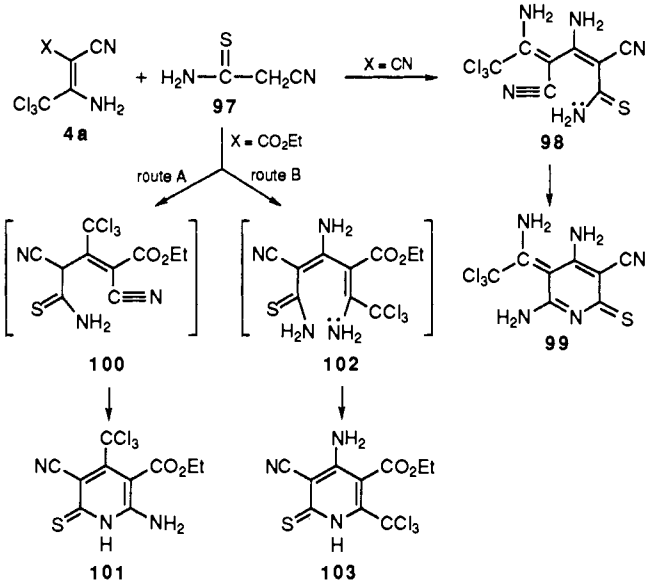


Scheme 14

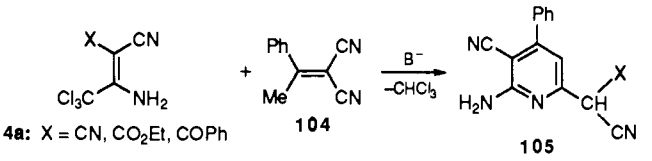


β-Enaminonitriles **4a** (X = CN) react with **97** to yield the intermediate adduct **98** that cyclizes to **99**. Compound **4a** (X = $CO_2C_2H_5$) reacts with **97** to yield a mixture of **101** and **103**. Compound **100** and **102** are assumed to be intermediates for the formation of these products (Scheme 15).[100]

Scheme 15



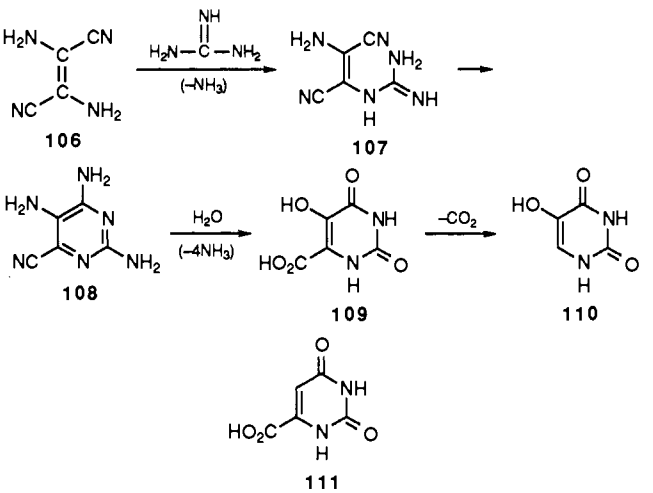
Elnagdi et al.[101] have reported the synthesis of **105** via the reaction of **104** with enaminonitriles **4a**.



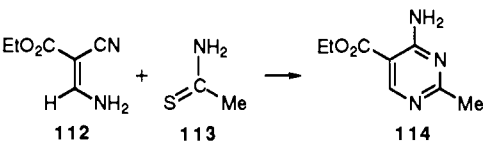
B. Synthesis of Pyrimidines

Two of the pyrimidines obtainable from diaminomaleonitrile are found in contemporary biological systems. 5-Hydroxyuracil (**110**) is a minor component of yeast RNA.[102,103] Orotic acid (**111**) is a crucial intermediate in the biosynthesis of pyrimidine nucleotides.[104] Ferris et al.[105,106] have proposed a reaction pathway for the synthesis of 5-hydroxyuracil via the reaction of diaminofumaronitrile (**106**) with guanidine similar to that for orotic acid (**111**) (Scheme 16).[105,106]

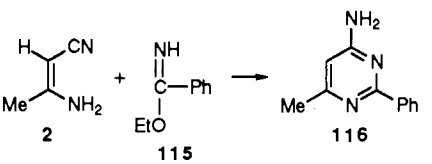
Scheme 16



The base-catalyzed condensation of ethyl 3-amino-2-cyanoacrylate (**112**) and thioacetamide (**113**) yields ethyl 4-amino-2-methylpyrimidine-5-carboxylate (**114**).[107]

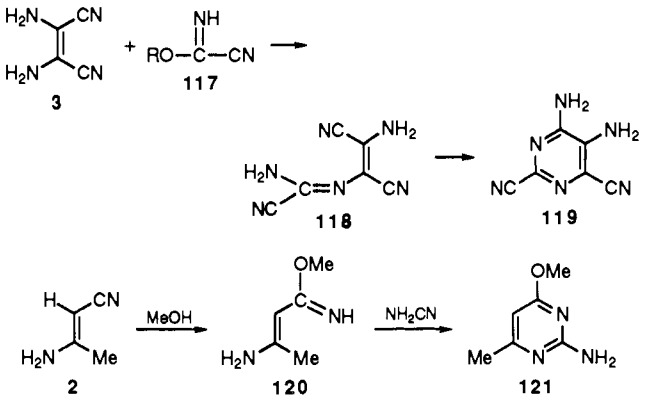


Although the reaction of imino ethers or imidoyl chlorides with aminomethylene derivaives is known to easily afford 4-aminopyrimidines, it is less widely used. **2** reacts with ethyl benzimidate **115** to give 4-amino-6-methyl-2-phenylpyrimidine (**116**).[108]



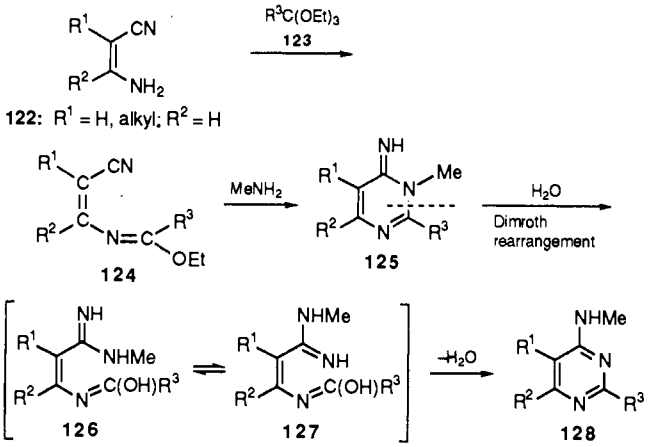
Pyrimidines, such as **119**, are formed by the reaction of diaminomaleonitrile (**3**) and cyanoformimidates **117**.[109]

An important herbicide intermediate was obtained by treating **2** with methanol at room temperature to give the imino ether **120**. The latter was treated with cyanamide at 40 °C to give 2-amino-4-methoxy-6-methylpyrimidine (**121**).[110]

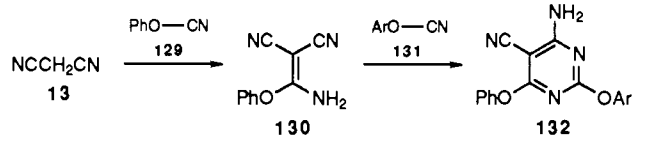


The reaction of enaminonitriles **122** with triethyl orthoformate (**123**) yields the corresponding ethoxyalkylidene derivative **124**. Subsequent reaction with methylamine leads to spontaneous cyclization, which gives the imine **125**. **125** undergoes a Dimroth rearrangement on treatment with base to yield (methylamino)pyrimidines **127** probably through an intermediate of type **126** (Scheme 17).[111]

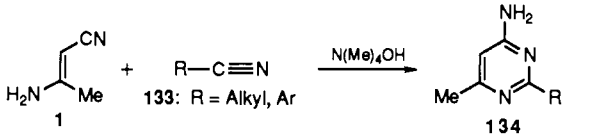
Scheme 17



Malononitrile reacts with phenyl cyanate to give the intermediate **130**, which in turn reacts with aryl cyanate **131** to yield 4-aminopyrimidine **132**.[112]

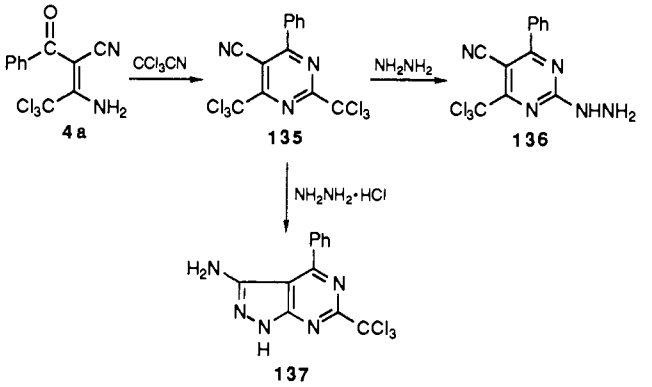


A general method for the synthesis of a wide variety of 2-substituted 4-amino-6-methylpyrimidines **134** from nitriles **133** by using tetramethylammonium hydroxide as a catalyst was reported by Smithwick et al.[113] The reaction involves addition of enamino amino function to cyano group in the nitrile **133** and subsequent cyclization.

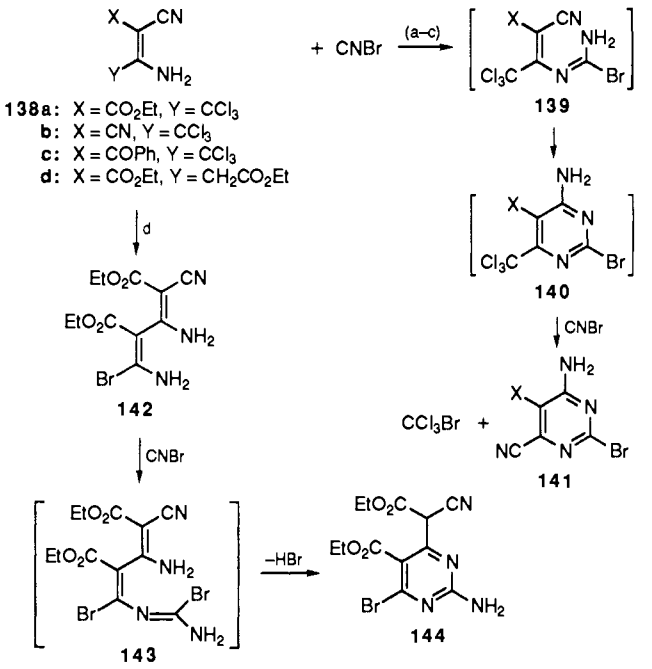


Elnagdi et al.[114] reported the preparation of pyrimidines **135** by condensing trichloroacetonitrile with

Scheme 18



Scheme 19

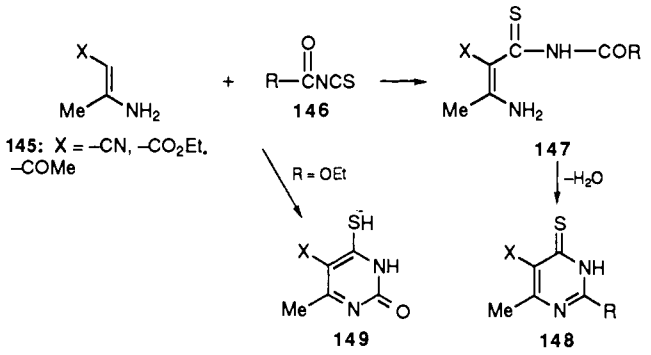


enaminonitrile **4a**. Either the hydrazine derivatives **136** or pyrazolopyrimidine **137** was produced depending on the reaction conditions (Scheme 18).

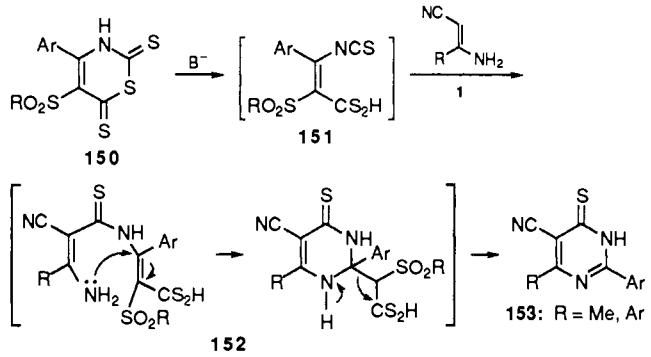
Enaminonitriles such as **138a–c** yield 2-bromopyrimidine **141** when treated with cyanogen bromide. Compound **141** is assumed to be formed via the addition of the amino function in **138** to the cyano group in BrCN to yield an adduct **139** which would readily cyclize into **140**; the latter then undergoes nucleophilic displacement of the trichloromethyl moiety by the CN group to give **141**. Compound **138d** reacted with BrCN, under the same reaction conditions, to give pyrimidine derivatives such as **144** (Scheme 19).[115]

Isothiocyanates **146** react with 3-aminocrotonates **145** in acetonitrile with the formation of 1:1 cyclocondensation products **148** via addition intermediates such as **147**. In the case of ethoxycarbonyl isothiocyanate only the addition product **149** was isolated.[116–118]

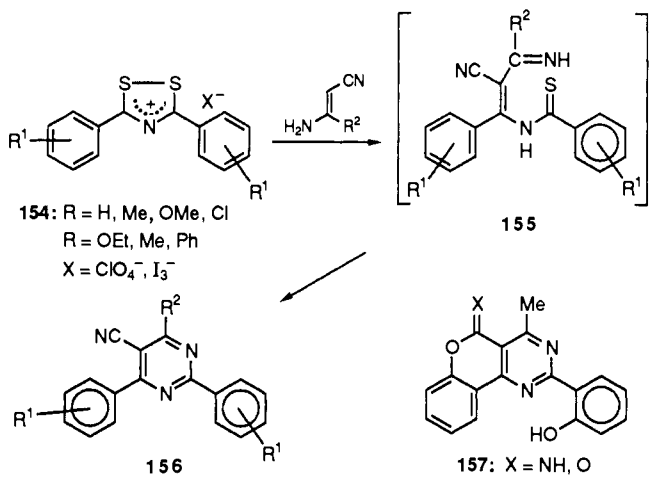
A general synthetic route for pyrimidine thiones such as **153** starting from thiazine-2,6-dithiones **150** is reported by Muraoka et al.[119,120] It is assumed that, in presence of base **150** affords the isothiocyanates **151** that on reaction with enaminonitrile **1** gives **152**. The latter cyclizes into **153** (Scheme 20).



Scheme 20

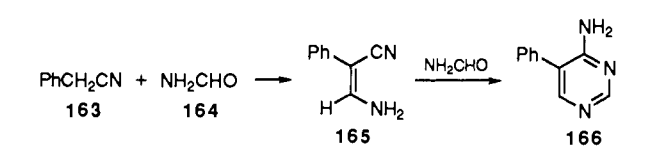


1,2,4-Dithiazolium salts **154** were effectively converted to pyrimidines **156** when treated with **1** via the intermediate **155**.[121,122] Benzopyranopyrimidinone **157** was prepared by using dithiazolinylidenebis(cyclohexadienone) as the starting material.[123]

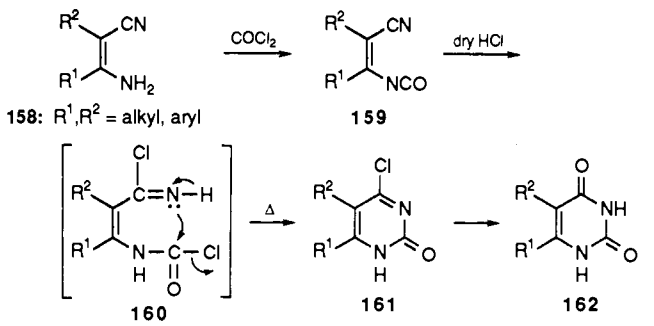


The reaction of β-enaminonitriles **158** with phosgene in ethyl acetate under reflux gave the corresponding β-cyano-α,β-unsaturated isocyanates **159**. The latter reacted with dry hydrogen chloride in dioxane to give the intermediate **161** which led to the final product 5,6-disubstituted uracil **162**, at 60 °C **161** was stable enough to be isolated, whereas at 100 °C only **162** was isolable (Scheme 21).[124]

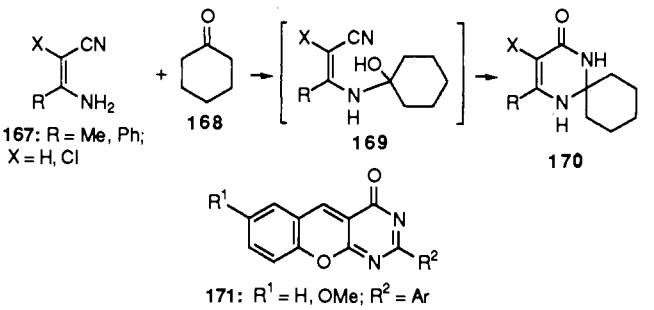
The reaction of phenylacetonitrile with formamide in the presence of ammonia at 180 °C gives 5-phenylpyrimidine-4-amine (**166**) via the intermediate **165**.[125]



Scheme 21



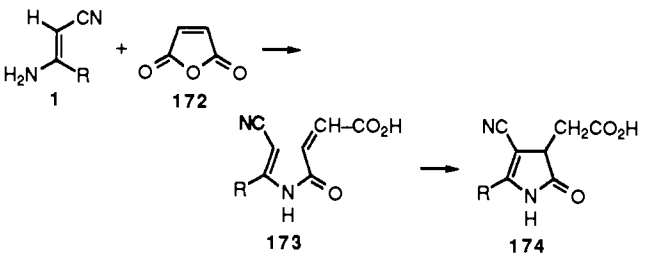
The pyrimidones **170** are prepared in one step by the cyclocondensation of cyclohexanone with **167**.[126] The analogous pyrimidinones **171** were obtained by treating β-enaminonitriles with salicylaldehydes.[127,128]



V. Synthesis of Five-Membered Rings with One Heteroatom

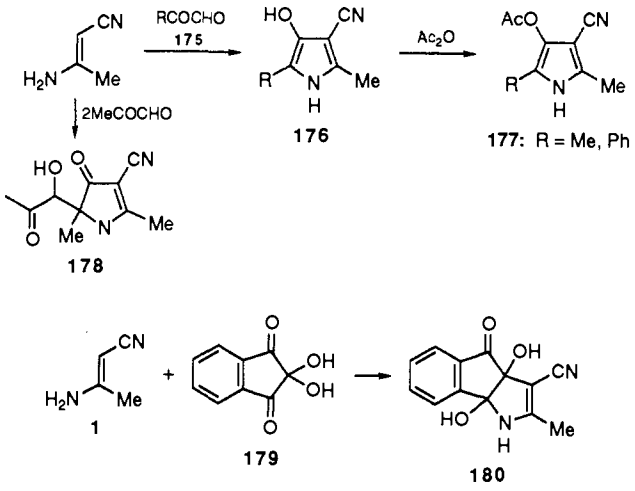
A. Pyrroles and Their Benzo Derivatives

The pyrrolinones **174** were prepared from the reaction of maleic anhydride **172** and enamines **1** according to procedures described by Hantzsch and Feist.[129,130]

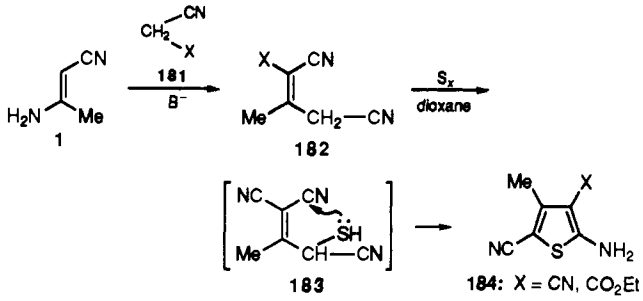


The reaction of the glyoxal derivatives **175** with **1** afforded the corresponding hydroxypyrroles **176** and **178**, depending on the molar ratio between the enamine and the keto aldehyde.[131,132]

The indenopyrrole system **180** can be prepared by the cycloaddition of **1** to ninhydrin (**179**).[133]



The condensation of 1 with active methylene compounds 181 in basic medium affords the reactive intermediate 182 which readily reacts with elemental sulfur to give the thiophenes 184 via 183.[134]



VI. Synthesis of Five-Membered Rings with Two or More Heteroatoms

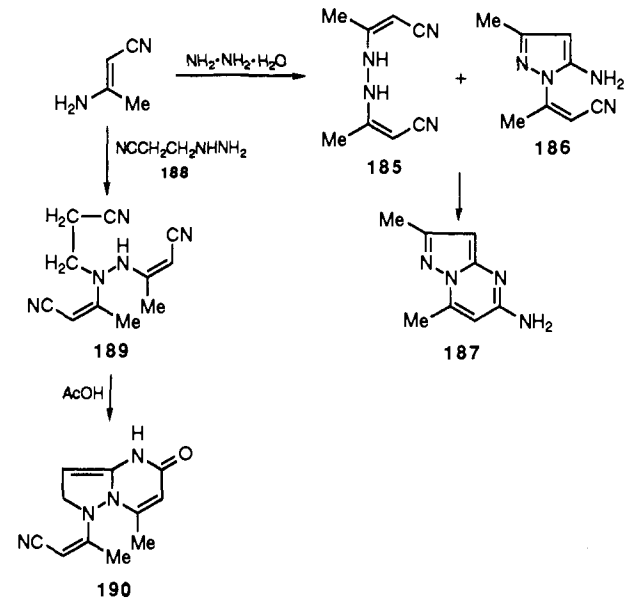
A. Pyrazoles and Their Fused Six- or Five-Membered Heterocyclic Rings

The synthesis of aminopyrazoles is generally achieved using classical methods. The most important method is the reaction between hydrazines and the β-enaminonitriles.[135-138] Reaction of 1 with hydrazine hydrate gives a mixture of 185, 186, and 187. Both 185 and 186 cyclize to pyrazolopyrimidine 187 when treated with hydrogen chloride.[139-141] Similarly, 190 is obtained from the reaction of β-cyanoethylhydrazine 188 and 1 followed by treatment of the resulting 189 with acetic acid (Scheme 22).[142,143]

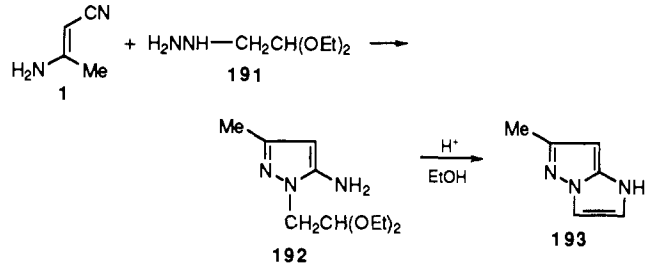
The azapentalene 193 can be prepared by the cycloaddition of hydrazinoacetaldehyde diethyl acetal (191) with 1 to give the pyrazole derivative 192 which gives 193 in H_2SO_4/EtOH.[144]

Reaction of 1 with phenylhydrazine or 1-adamantylhydrazine gives 5-aminopyrazoles 194 as the main product.[145,146] The formation of 195, 196, and 197 from the condensation of hydrazines with 1 has been reported.[147-149] 1,4-Bis(5-amino-1-pyrazino)phthalazines (198), which are useful compounds of azo dye intermediates, have been prepared by Bloch et al.[150]

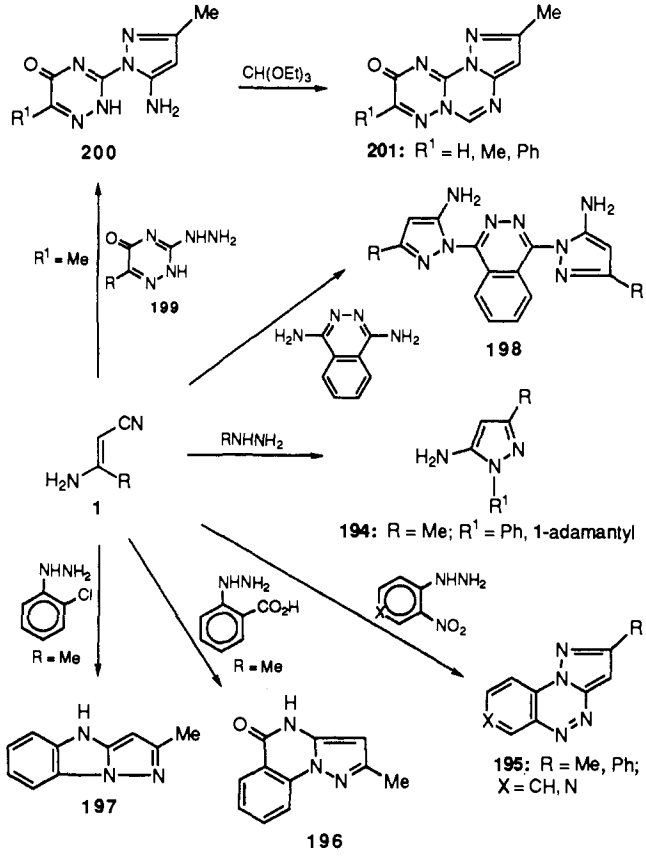
Scheme 22



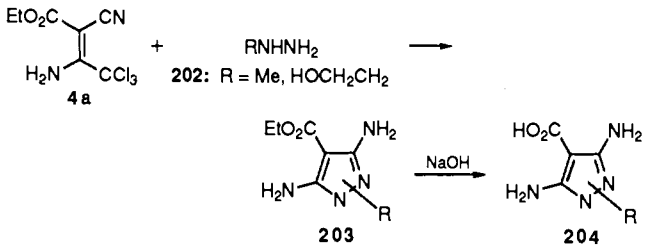
201 is obtained by treating 1 with triazines 199 via pyrazole derivatives 200[151,152] (Scheme 23).



Scheme 23

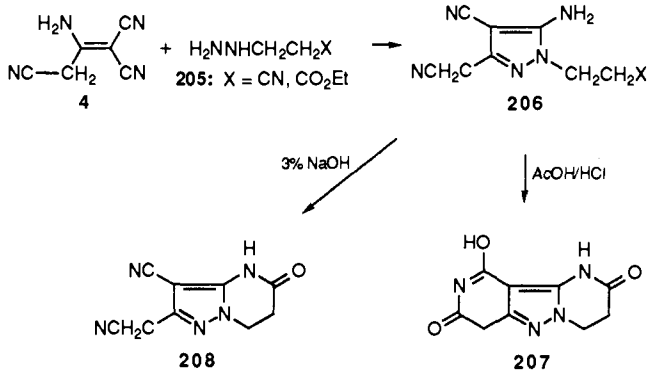


The important antibacterial pyrazolecarboxylic acid derivatives **204** were prepared by the cyclization of **202** with the enaminonitrile **4a** to give **203**. This was hydrolyzed by aqueous sodium hydroxide at room temperature to give **204**.[153]

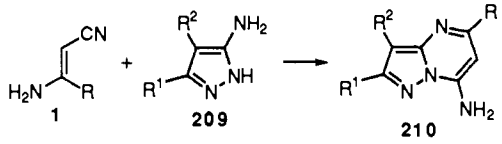


Depending on the reaction medium, **205** reacts with malononitrile dimer to yield pyrazole **206**, which cyclizes into either of the tetrahydropyrazolo[1,5-*a*]pyrimidines **207** and **208** (Scheme 24).[154]

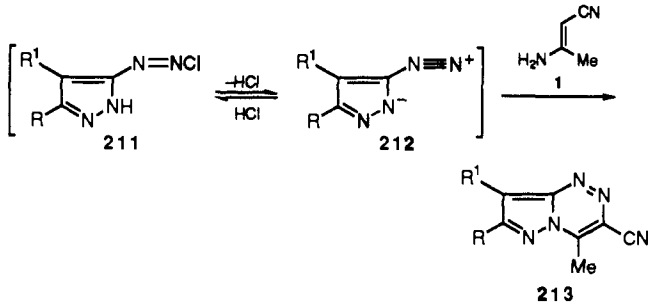
Scheme 24



Condensation of β-enaminonitriles with 3(5)-aminopyrazoles **209** have been used extensively to synthesize pyrazolo[1,5-*a*]pyrimidines **210**.[155-161]

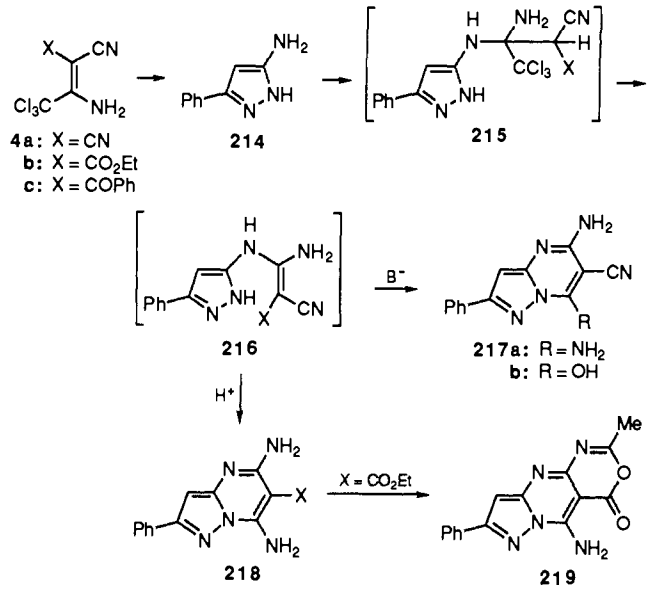


Elnagdi et al.[162] assumed that an equilibrium between **211** and diazobetaine **212** exists and the addition of the betaine to 3-aminocrotononitrile **1** was reported to yield **213**.[163,164]



The enaminonitriles **4a** and **4c** reacted with 3-aminopyrazole **214** in pyridine under reflux to give **217a** and **217b**. In contrast, **214** and **4b** reacted in acetic acid to give the oxazino[4,5:5,6]pyrazolo[1,5-*a*]pyrimidines **219**. It was assumed that the amino group in **214** added to the activated double bond in **4** to yield the

Scheme 25

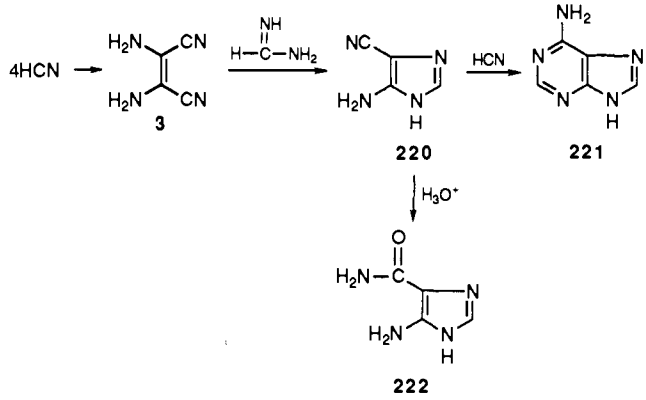


intermediate adduct **215**, which loses chloroform to give **216** which in turn cyclizes under conditions to yield **217a** and **217b**. In acetic acid **218b** is converted to the oxazino[4,5:5,6]pyrazolo[1,5-*a*]pyrimidine derivative **219** (Scheme 25).[165]

B. Imidazoles and Their Fused Six-Membered Heterocyclic Rings

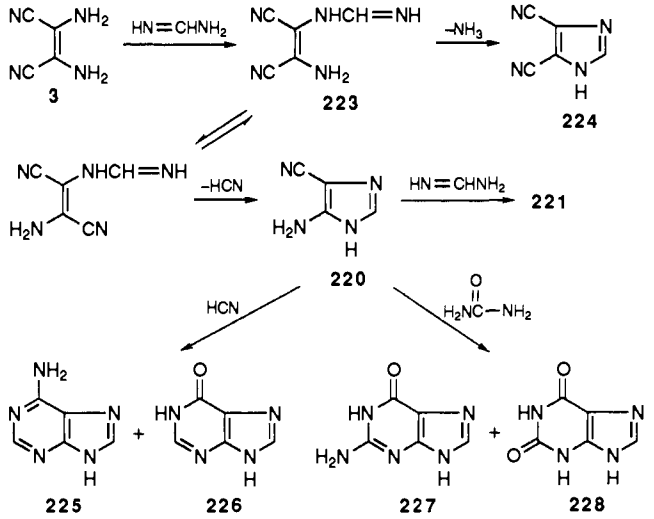
An early synthesis of adenine (**221**) from ammonium cyanide and concentrated hydrochloric acid was reported by Oro and Lowe et al.[166-169] who were pioneers in synthesizing imidazoles and purines. These results were confirmed by Ferris et al.[105] who observed the formation of adenine after the hydrolysis of HCN oligomers under mild alkaline conditions (Scheme 26).

Scheme 26

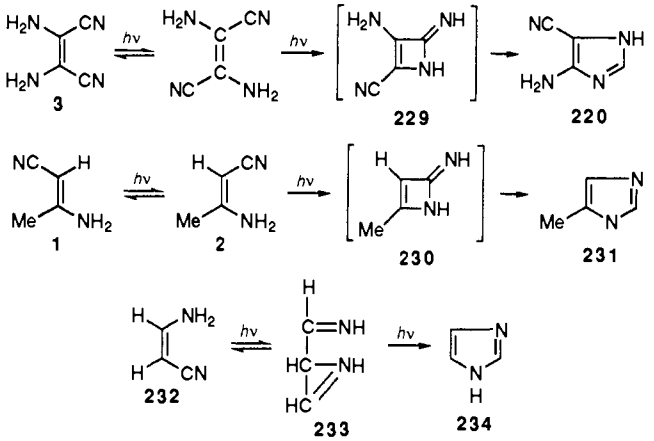


There are two ways that imidazoles can form when diaminomaleonitrile reacts with formamidine to give the initial formed product **223**. Direct loss of ammonia gives 4,5-dicyanoimidazole **224**, or isomerization followed by cyclization in which HCN is eliminated gives 4-amino-5-cyanoimidazole (**220**). In the presence of excess formamidine the latter product is converted into adenine **221**. Compound **220** is a useful precursor in the chemical synthesis of a variety of purines. Sanchez et al.[170] have shown that **220** reacts with HCN to give

Scheme 27



Scheme 28



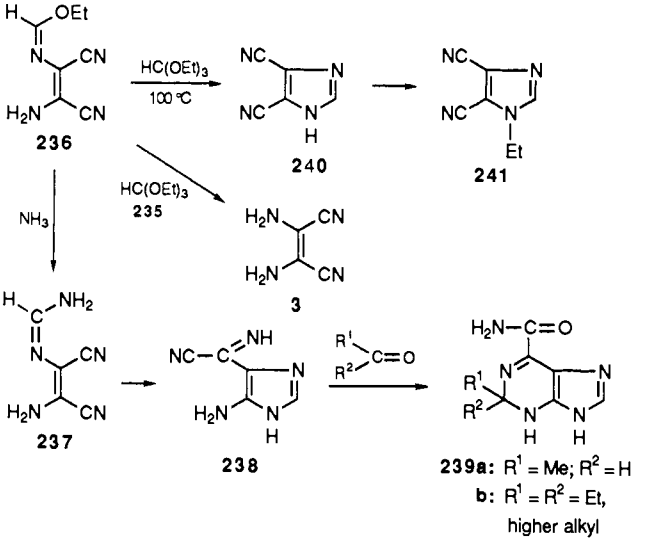
adenine (**225**) and hypoxanthine (**226**). Guanine (**227**) and **228** are obtained from **220** and urea (Scheme 27).[171,172]

In addition to the diaminomaleonitrile reactions shown in Scheme 27, there are also some examples of photochemical transformations which lead to imidazole products presented in Scheme 28.[10,105,173,174] The first reaction involves the isomerization of *cis*- and *trans*-dinitrile which then forms a 5-aminoimidazole-4-carbonitrile **220** via the iminoazetine **229**.

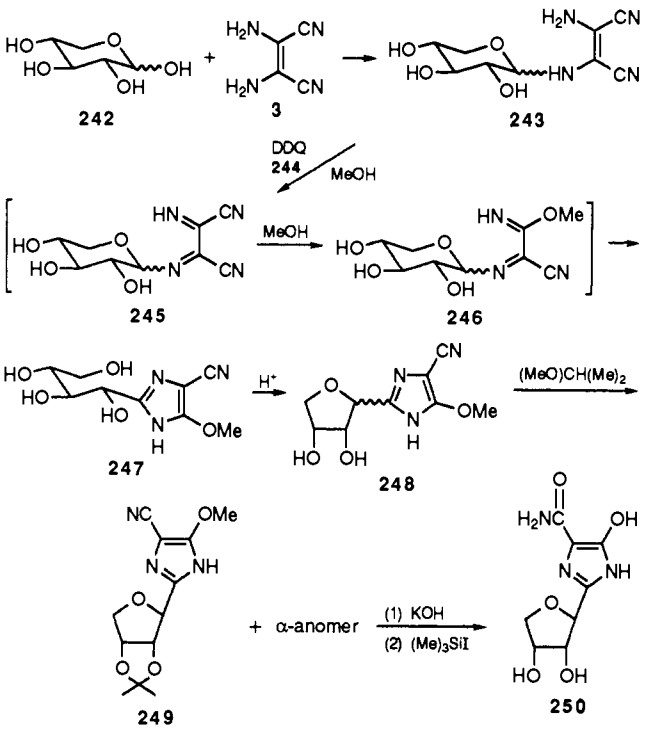
Booth et al.[175,176] have also observed that diaminomaleonitrile (**3**) reacts with triethyl orthoformate (**235**) in dry dioxane under reflux to give the imidate **236**. The latter reacts with ammonia gas to form the imidazole **238**, which reacts with ketones at room temperature to give 6-carbamoyl-1,2-dihydropurines (**239**). It has been reported that 4,5-dicyano-1-ethylimidazole (**241**) is formed as the main product from the reaction of **3** with ethyl orthoformate followed by vacuum distillation (Scheme 29).[177]

Diaminomaleonitrile has been used in the synthesis of several nucleosides.[178,179] The outline in Scheme 30 illustrates an efficient route to C-nucleosides **250**; the corresponding arabinofuranosyl imidazoles can be obtained by starting with D-glucose or D-mannose in place of D-ribose (**242**).

Scheme 29

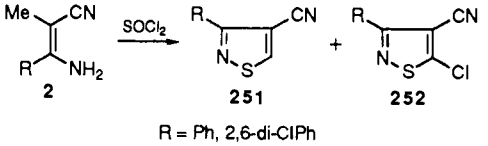


Scheme 30



VII. Miscellaneous

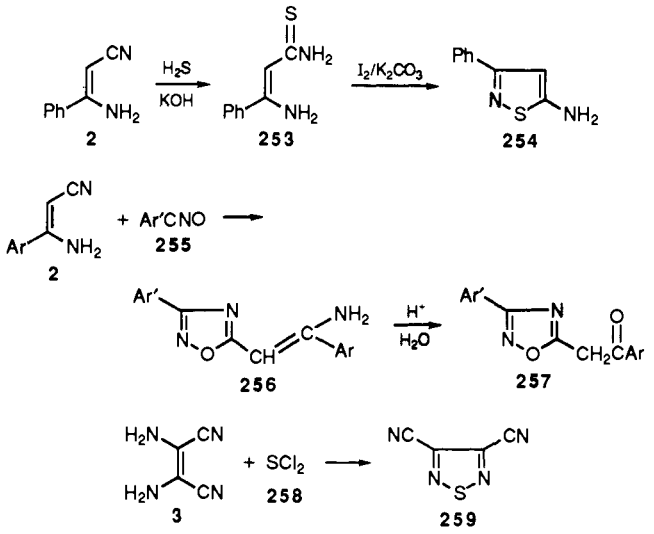
4-Cyanoisothiazoles **251** and **252** have been prepared directly from the reaction of **2** with thionyl chloride or sulfur monochloride.[180]



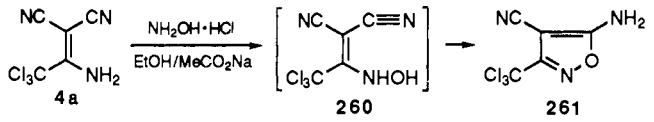
The isothiazole **254** is formed by the treatment of **2** with H_2S in the presence of KOH via the intermediate **253**.[181,182]

The cycloaddition of **2** and arylonitrile oxides **255** gives the cycloadduct **256**.[23,183]

The reaction of **3** with sulfur dichloride gives 3,4-dicyano-1,2,5-thiadiazole **259** in 93% yield.[184]

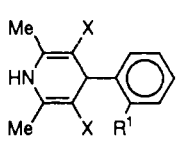


3-Amino-4-trichloro-2-cyanocrotonitrile (**4a**) reacts with hydroxylamine to yield the isoxazole derivative **261**. This compound is formed by the addition of the hydroxylamine to the α,β-unsaturated linkage followed by cyclization.[185,186]



VIII. Conclusion and Outlook

The aim of this review has been to demonstrate the wide synthetic and preparative applications of a particularly versatile class of compounds i.e. the β-enaminonitriles. It is hoped that a greater understanding of their potential in the synthesis of novel heterocycles, natural products, and biologically active compounds and drugs will result. The importance of purine nucleosides, nucleotides, and pyrazolopyrimidines has been obvious for more than a decade.[76,187-192] Recently the flood of papers and patents concerning the biologically active compound dihydropyridine **262** testifies to its terrific potential. Finally, it is hoped that this review will fill what was an obvious gap by providing an overview of the subject.



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