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Chemistry of Crotononitrile

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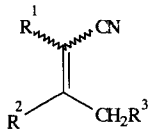
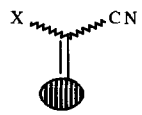
I Introduction

Substituted crotononitriles **1a–q** are versatile reagents and has been extensively utilized in synthesis. These molecules are reactive both toward electrophilic and nucleophilic reagents. Thus, whereas the double bond and cyano group are both electrophilic centers, the alkyl function is capable of producing carbanion under mild conditions and is nucleophilic. Despite their extensive utility in organic synthesis no survey of reported literature of these compounds has ever been made although review articles on some derivatives exist [1–3]. The chemistry of aminocrotonitrile **1a** [1] as well as malononitrile dimer **1b** [2, 3] has been reviewed earlier. Thus, in this review only literature reports on **1a,b** of significance that has not been surveyed in these reviews will be reported.

Malononitrile, ethyl cyanoacetate and cyanothioacetamide condense with cyclic ketones yielding cor-



1a-q



2	X
a	CN
b	COOEt
c	$CSNH_2$

	R^1	R^2	R^3
1a	H	NH_2	H
1b	CN	NH_2	CN
1c	CN	Ph	H
1d	CO_2Et	Ph	H
1e	CO_2Me	Ph	H
1f	CO_2Et	H	Et
1g	CO_2Me	NH_2	CN
1h	CO_2Et	CH_3	H
1i	CO_2Et	NH_2	CO_2Et
1j	CO_2NH_2	NH_2	$CONH_2$
1k	H	H	Et
1l	CO_2Et	NH_2	CN
1m	CN	NH_2	CO_2Et
1n	CO_2Et	Et	H
1o	CO_2Me	NH_2	CO_2Me
1p	CN	CN	H
1q	CN	CH_3	CO_2Et

responding ylidenes (cf. **2a–c**), and these compounds have the active moieties present in **1** and their chemistry will thus be included in this review.

II Methods of Preparation

1 Condensation of Active Methylene Nitriles with Ketones

Crotononitriles are readily obtainable either *via* condensing active methylene nitriles with aldehydes or ketones or *via* addition of methylene the moiety in these nitriles to methylene or methyl nitriles [4]. The first synthetic approach is usually conducted in a mixture of benzene, acetic acid and ammonium acetate. The reaction mixture is then heated under reflux with continual elimination of water. In this way, derivatives of **1** are prepared [5–9]. Silica gel functionalized with amino groups is a useful insoluble catalyst for this Knoevenagel condensation [10, 11].The reaction is carried out under continuous flow conditions and good yield were obtained when acetophenone reacts with ethyl cyanoacetate or malononitrile to give **1c,d** [10, 11].

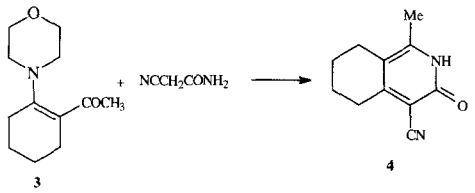
Another experimental procedure includes heating the active methylenenitrile with the ketone in presence of β-alanine and subsequent distillation of resulting oily product [12]. Condensation of this type with malononitrile produces only one isomer whereas condensation with other active methylene should produce a mixture of isomers, and little effort has ever been made to establish with certainly the structure of these isomeric crotononitrile derivatives [12].

Knoevenagel condensation of aldehydes with ethyl, or methyl cyanoacetate or malononitrile to yield **1c–e** is effected by treating the mixture with alumina, and NaOCl or ($AlPO_4$–Al_2O_3) [13, 14]. Aluminium oxide has also been used as catalyst for Knoevenagel condensation of aldehydes and ketones with active methylene nitrile [15].

Malononitrile and ethyl cyanoacetate both condense readily with aliphatic aldehydes such as acetaldehyde, propionaldehyde and phenylacetaldehyde to yield the corresponding substituted crotononitriles. However, reported procedures for these syntheses are rather tedious and produces the desired products in only very low yield. Elnagdi *et al.* [16] have however, *in situ* generated these derivatives and utilized them in heterocyclic synthesis and yields of product so formed are usually high. Also, propylidenemalononitrile could be generated *in situ* [17].

Aldol condensation of ethyl cyanoacetate and butyraldehyde in THF in the presence of $RuH_2(PPh_3)_4$, at 20 °C for 24 h gave 83% **1f** [10, 18].

Synthesis of **4** *via* condensing **3** with cyanoacetamide has been reported [19].



3 4

2 Addition of Active Methylene Nitriles to Nitriles

The addition of active methylene nitriles to methyl and methylene nitriles affords 3-aminocrotononitriles. The oldest example of such reaction is the reported addition of the methyl moiety in acetonitrile to the cyano group in another molecules affording 3-aminocrotononitrile [20]. The addition of carbanions produced from acetonitrile to several other nitriles has been reported, and reactions of this type are usually conducted in presence of sodium metal or sodium ethoxide [20–30]. Taylor and Hartke [31] could dimerize malononitrile in presence of sodium ethoxide to yield malononitrile dimer **1b**. Similarly, malononitrile added to methyl or ethyl cyanoacetate in toluene in presence of sodium methoxide to give after treatment with aq. HCl 61% of **1g** and 41% of **1h** [32]. Dimerization of malononitrile by reaction with NaOH at pH 9 has been reported [33]. Also, dimerization with NaOH or KOH in methanol or 96% ethanol, has been claimed to afford the dimer **1b** [34].

Platinum and palladium complexes catalyze dimerization of malononitrile to **1b**. The reaction is conducted in benzene for 1 h under argon and the yield depends on the catalyst. Table 1 lists catalyst and reaction yields of this dimerization procedure [35, 36].

Table 1 Catalysts Used in Dimerization of Malononitrile and Yields

Catalyst	Yield (%)
Cl_2Pt-$(Ph_3P)_2$–PhONa	80.3
$Pd(Ph_3P)_4$	39.5
$Pd(Ph_3P)_4$–maleic anhydride	13.6
$Cl_2Pd(Ph_3P)_2$–PhONa	33.4

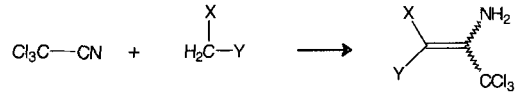
Similarly, **1b** could be obtained by reaction of malononitrile in presence of Ni-trivalent organic phosphorus complexes; *e.g.* $Ni[P(OEt)_3]$ and $P(OEt)_3$ in benzene for 4 hours under nitrogen to give 13.3% **1b** [37]. 1,1,5,5-Tetracyano-2,4-diamino-1,4-pentadienes were also prepared under the same condition in 45.5% yield [37].

Phosphorous and arsenic complexes of palladium or platinum compounds were also reported as catalyst in the synthesis of **1b,i,j** [38].

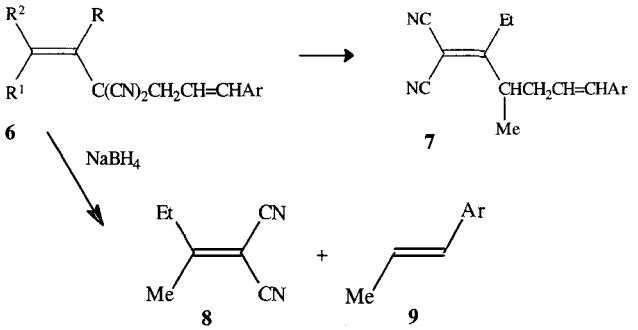
Treatment of alkyl β-oxo esters with palladium acetate or palladium dibenzylideneacetone complex and triphenylphophine in acetonitrile or propionitrile leads to decarboxylation and dehydration to give 65% **1k** [39].

Dimerization of ethyl cyanoacetate has been report-

ed by Junek *et al.* [32] who could also add ethyl cyanoacetate to malononitrile affording 41% **1l**, and malononitrile to cyano function in ethyl cyanoacetate affording 61% **1m** [32, 35]. Dimerization of ethyl cyanoacetate with platinum catalysts has also affected and with these catalyze cyanoacetamide could be dimerized **1j** [35]. Active methylene reagents add very readily to the cyano function in trichloroacetonitrile under mild conditions [40]. This addition has been extensively utilized [40, 41] for synthesis of derivative of **5**.



Pyrolysis of **6** gave **7** by an ionic [1,3]-shift. Addition of $NaBH_4$ to the reaction enabled the ionic intermediates to be trapped, giving **8** and **9** and supporting the proposed ionic Cope rearrangement mechanisms [42].



Treatment of 1,3-dithietane derivatives with (arylalkylidene)malononitriles in the presence of base affords *N*-[bis(alkylthio)methylene]-5-aryl-2,6,6-tricyano-3-mercapto-2,5-hexadienoic acid hydrazide in 67% [43].

III Chemical Reactivity

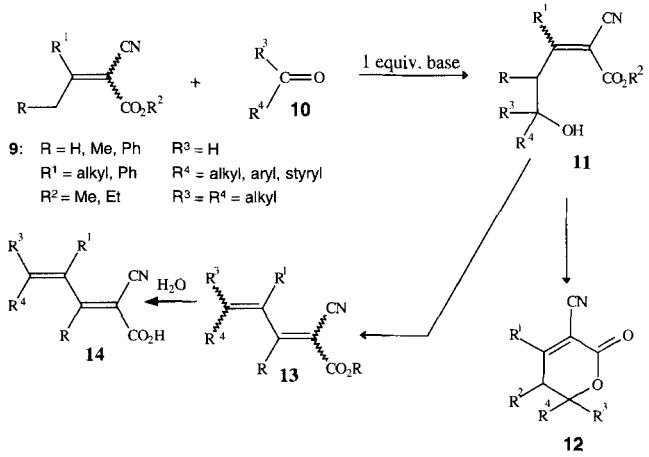
General Considerations

Crotononitriles are polydentate reagents. The methyl group is acidic, and carbanions are produced under mild conditions and for this reasons these compounds react with a variety of nucleophiles under mild conditions. Both the double bond and cyano group are active towards electrophiles. In fact, this activity has been also extensively utilized, and reaction with polydentate reagents at both active methyl and the cyano group constitute the base of plenty of heterocyclic synthesis.

IV Reaction with Electrophilic Reagents

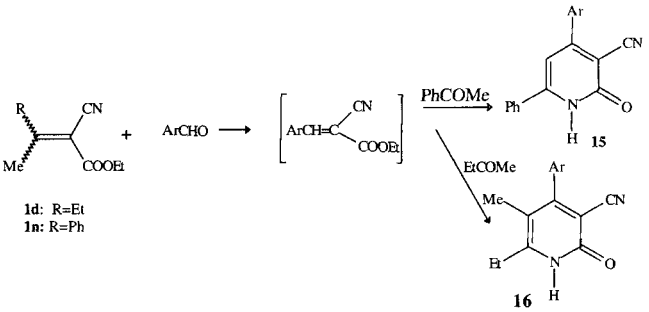
1 Carbon Electrophiles

Aromatic aldehydes condense readily with functionally substituted methylcrotononitriles yielding products of condensation *via* water elimination [44].



Condensation of the crotononitrile derivatives **9** with aliphatic or aromatic aldehydes or ketones using one equivalent of base gave the gem-deactivated alkenes or the lactones [44]. Thus, initial addition to carbonyl group affords **11**. This then either cyclizes into the lactone **12** or eliminate water to yield **13**. Water eliminated hydrolyzes the ester function to yield **14** [44].

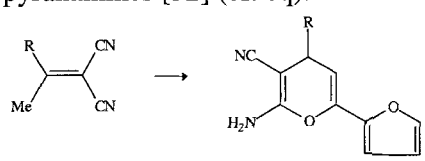
Pyridones **15** and **16** were prepared in 9–26% yield by reaction of **1d,n** with aromatic aldehydes and ketones in presence of ammonium acetate [45].

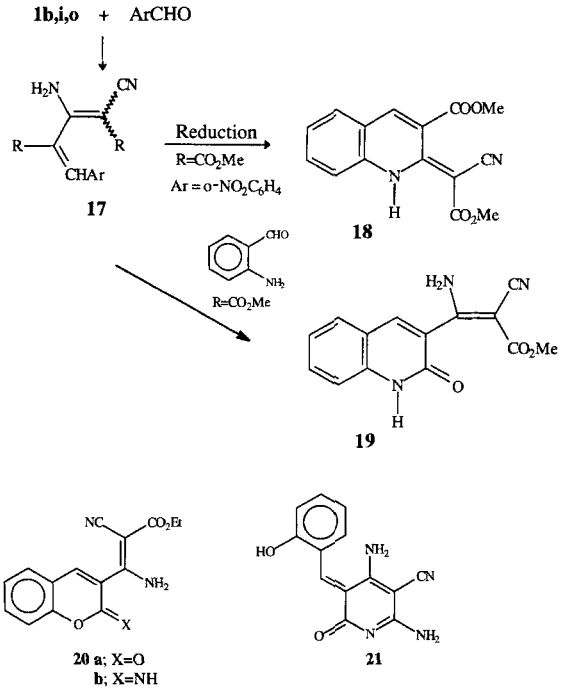


Aromatic aldehydes undergo condensation with **1b,i,o** to give **17**. Reduction of **17** (Ar: *p*-NO_2–C_6H_4) gave **18**. Attempted synthesis of the latter *via* condensing **1b,i,o** with *o*-aminobenzaldehyde gave **19** [46, 47].

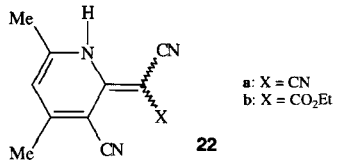
Condensation of **1j** with salicylaldehyde gave **20a**. Similarly, **1i** reacted with salicylaldehyde to give **20b** [48] while similar reaction of salicylaldehyde with **1b** gave **21** [49–51].

While the methyl function in crotononitrile itself does not condense with carbonyl compounds, the methyl function in α-cyanocrotononitrile undergoes condensation with great ease. Thus, 2-furaldehyde affords 4*H*-pyranamines [52] (cf. eq).

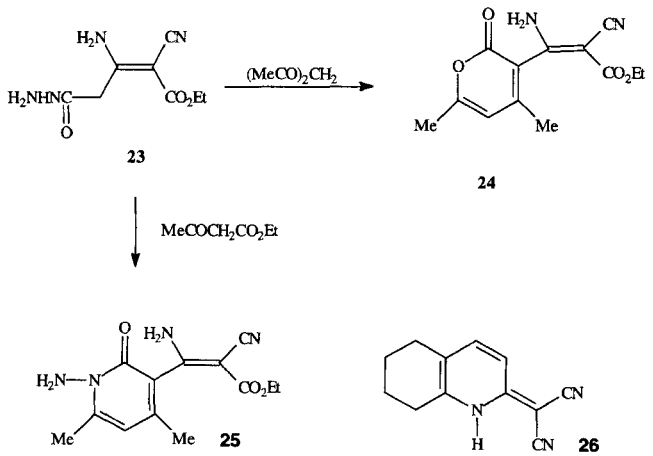




The reaction of **1b,j** with acetylacetone gave the pyridine derivatives **22a,b** respectively [49, 50, 53].

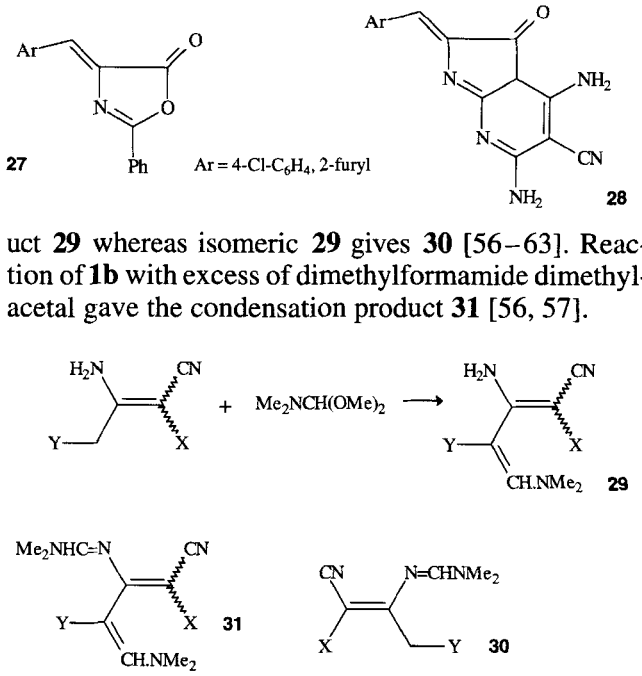


The condensation of **23** with acetylacetone affords **24**, with ethyl acetoacetate **25** is formed [54]. Condensation of **1b** with **2** gives **26** [19].

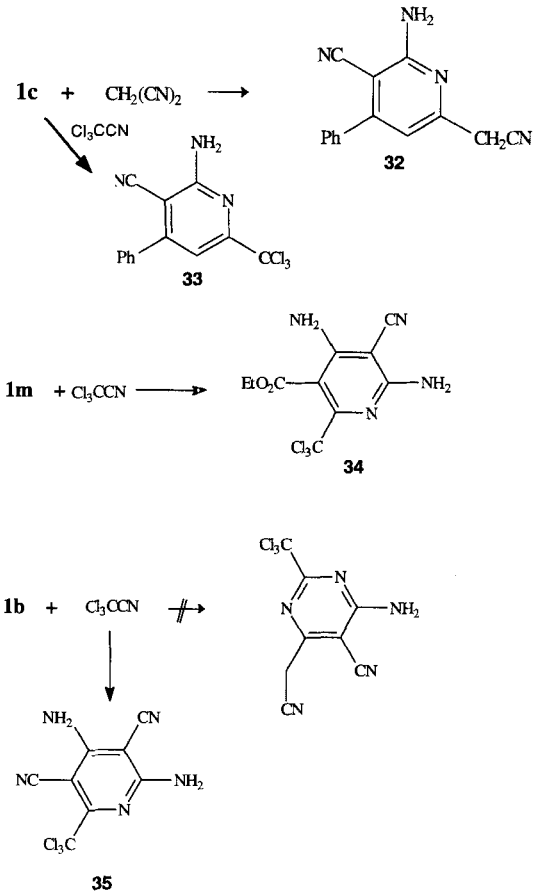


Compound **1b** reacted with **27** to yield **28**. The same product is obtained from reaction of **27** with malononitrile. Initial dimerization of the latter into **1b** under reaction conditions was suggested [55].

Reaction of crotononitrile derivatives with dimethyl formamide dimethylacetal gave the condensation product **29** whereas isomeric **29** gives **30** [56–63]. Reaction of **1b** with excess of dimethylformamide dimethylacetal gave the condensation product **31** [56, 57].

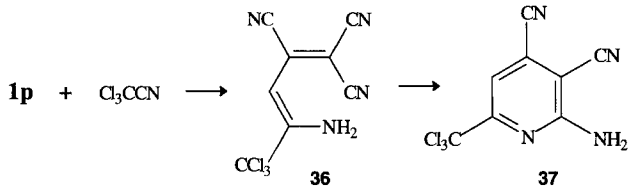


Activated nitriles also add carbanions generated from functionally substituted crotononitrile under very mild conditions. The formed adducts were never been isolated as they cyclized under the reaction condition yielding pyridine. To our knowledge reaction of this type

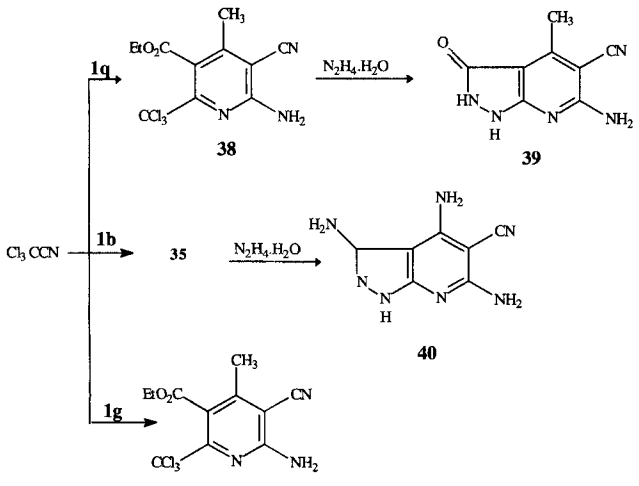


has firstly reported by Elnagdi *et al.* [64, 65] who added malononitrile to **1c** affording corresponding pyridine **32**, and trichloroacetonitrile to both **1c** and **1m** yielding also pyridine **33** and **34** [66, 67]. This reaction has been reported later by Mittelbach [68]. Elnagdi *et al.* [64] has reported the addition of trichloroacetonitrile to malononitrile dimer **1b** and suggested formation of the pyrimidine. Later the reaction product was shown to be the pyridine **35** [41].

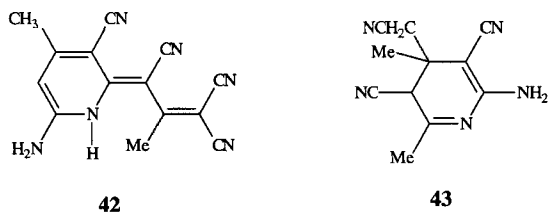
The α,β-dicyanocrotononitrile **1p** was treated with trichloroacetonitrile in presence of triethylamine to give the nicotinonitrile derivatives **37** in 75% yield [69]. Compound **37** is formed most probably *via* intermediate **36**.



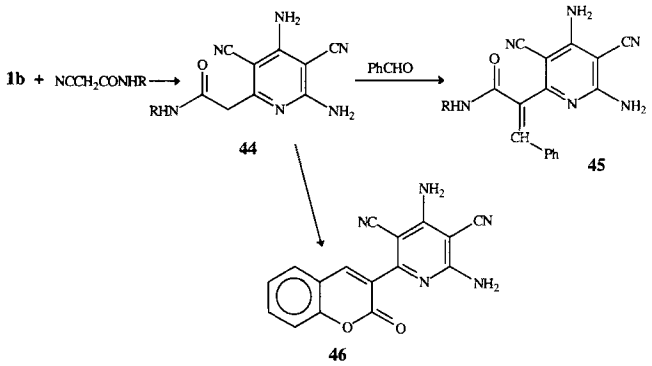
Base-catalyzed addition of **1q** to trichloroacetonitrile gave pyridine carboxylate **38** which was treated with hydrazine hydrate to give **39**. Similarly, **1b** reacted with trichloroacetonitrile affording pyridine dicarbonitrile **35**, which cyclized with hydrazine hydrate to give **40**. Compound **1g** reacted with trichloroacetonitrile to yield **41** [41]. In the light of this reported reaction course [70] of **1g** with trichloroacetonitrile needs further inspection.



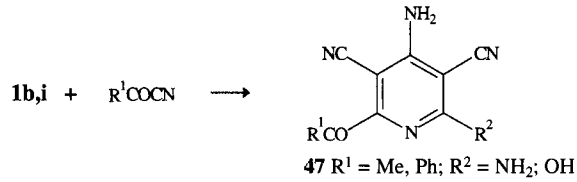
Condensing β-aminocrotononitrile **1a** with malononitrile affords the pyridine derivatives **42** and **43** [71].



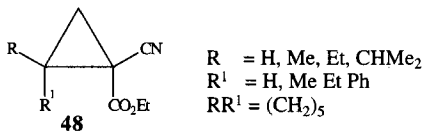
Malononitrile dimer **1b** reacts with active methylene nitriles under acidic or basic conditions to afford substituted pyridines **44** which were condensed with aromatic aldehyde to give **45**. Reaction of **44** with salicylaldehyde gave **46** [72].



Reaction of **1b** or **1i** with benzoylcyanide or pyrovonitrile gives the pyridine derivative **47** [73].

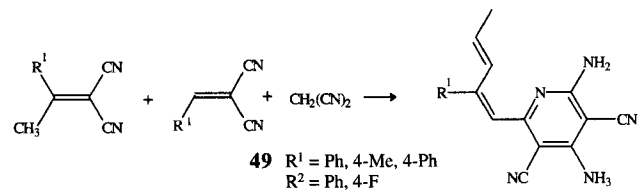


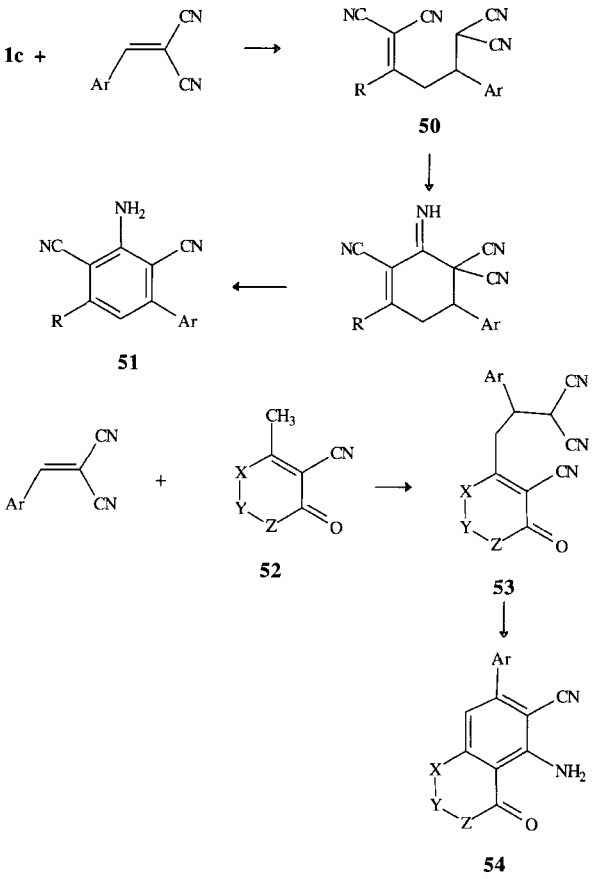
Crotononitrile derivatives were treated with MeS^+ OCH_2^- to give the cyclopropane carboxylate **48** [74].



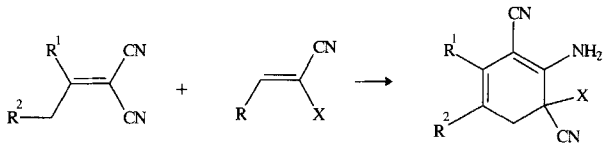
It has been claimed that reaction of ylidene malononitrile, β-substituted ethylidenemalononitrile and malononitrile in alcoholic KOH give **49** [75]. However, Elnagdi *et al.* [52, 76] have shown that reaction of **1c** with cinnamonitrile gives **51** *via* intermediate compound **50**. The latter reaction [77] has been extensively utilized for synthesis of polyfunctionally aminonitriles. Reaction of alkylheteroaromatic carbonitriles **52** with cinnamonitriles proceeds in a similar way producing **54** *via* intermediate **53** [76]. In the light of this, it seems that the structure of **49** should be reinvestigated.

The reaction of arylidenemalononitrile with substituted crotononitrile has been extensively utilized for synthesis of substituted anilines. To our knowledge first





reported reactions of this type have appeared in old literature where cyclohexylidenemalononitrile reacted with arylidenemalononitrile yielding **55** [78].



$R^1R^2 = (CH_2)_4$
R^1 = Ph, Et
R^2 = CH_3

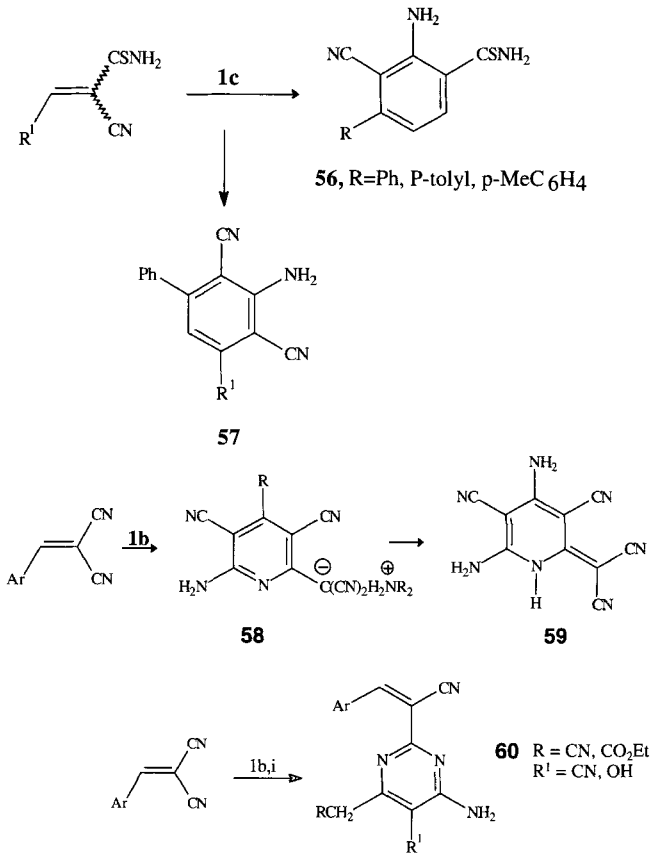
X = CN, CO_2Et

55

Elgemeie *et al.* [79] has reported the isolation of the thioamide **56** from the reaction at low temperature. They suggested that under kinetic control thioamides **56** are the reaction product, whereas thermodynamically controlled reaction conducted under reflux would afford the dicarbonitriles **57** [52, 79].

Addition of **1b** to ylidenemalononitrile gave 60–68% of **58** which, in acid medium, liberated **59** [80]. However, this structure **59** seems least likely as reaction of active methylene with α,β-unsaturated nitriles is established to occur at the β-carbon. Crotononitriles **1b,i** were treated with arylidenemalononitrile derivatives to give the pyrimidineacetonitrile derivatives **60** [75].

The reaction of crotononitrile derivatives with ylidenemalononitrile or ethyl cyanoacetate gave dihydropyridine derivative **61** [81–86].



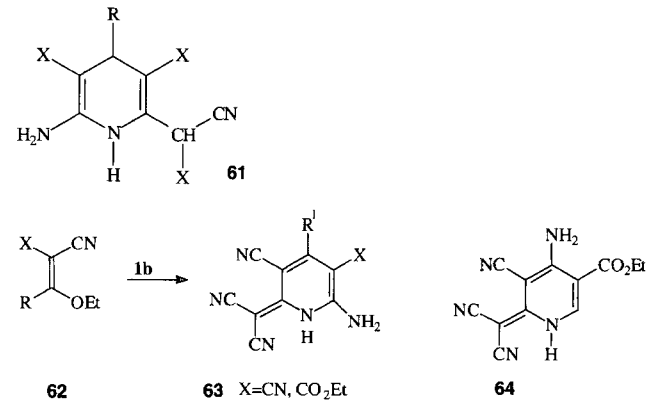
56, R=Ph, P-tolyl, p-MeC$_6$H$_4$

57

58 **59**

60 R = CN, CO_2Et
R^1 = CN, OH

The reaction of **1b** with **62** has been reported to yield **63** [87]. Later Fahmy *et al.* [88] reported isolation of **64** from reaction of **1b** with **62** (R=H). However, X-ray diffraction has revealed that **64** is really **63**; $R^1 = NH_2$ [89].



61

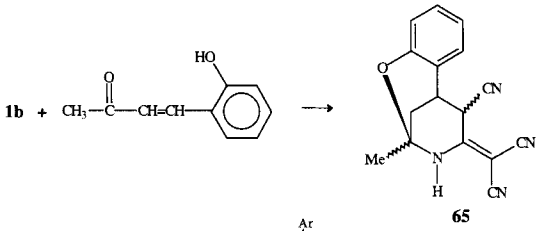
62 **63** X=CN, CO_2Et **64**

Cyclocondensation of 4-(2-hydroxyphenyl)-but-3-en-2-one with **1b** gave the tricyclic compound **65** [90].

Cyclocondensation of **1d** with ethyl cinnamate derivatives gave 33–52% of **66** [91].

The reaction of **1b,g,i** with *S*-methylisothiourea gives **67** which is cyclized readily into **68** [92].

The reaction of **1b** with **69** gives the pyridine **70** which is converted into pyridopyridazine **71** on coupling with benzene diazonium chloride [76].



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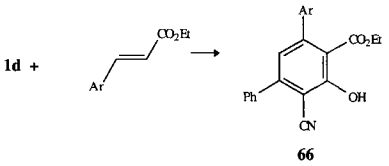

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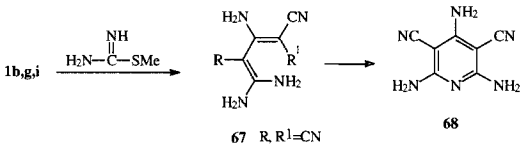
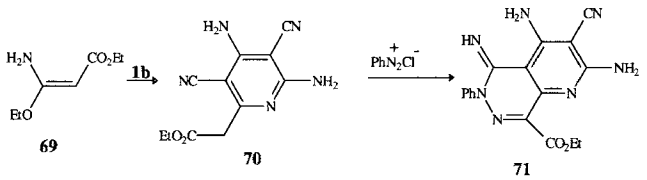


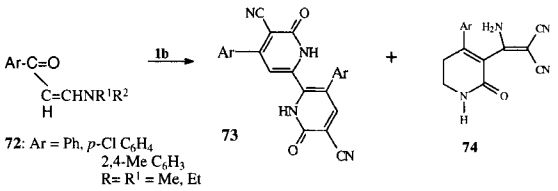
67 R, R¹=CN

68



69 70 71

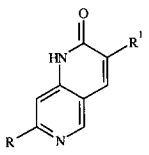
The enaminones **72** react with **1b** to yield a mixture of **73** and **74** [93].



72: Ar = Ph, *p*-Cl C_6H_4, 2,4-Me C_6H_3; R= R¹ = Me, Et

73 74

The analogues of medorinone **75a,b** were prepared in 5 steps from (*Z*)-β-aminocrotononitrile (**1a**) and methyl methacrylate or methyl propiolate, respectively [94].

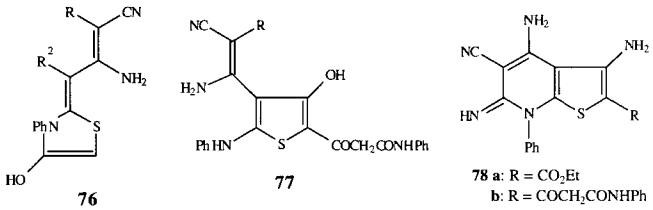


75 a: R = R¹ = H

b: R = H; R¹ = Me

Carbon electrophiles in both substituted isocyanates and isothiocyanates add readily the carbanions resulting from **1b** yielding adducts that cyclize under the reaction condition into pyridines. It has been reported that the enaminonitriles **1b,i** react with phenylisothiocyanate followed by cyclization with α-haloketones, to yield either thiazole **76**, thiophene **77** or the thieno[2,3-*b*]pyridine derivatives **78a,b** depending on the nature of reacting reagents [95–98].

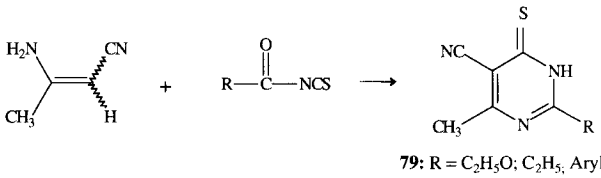
3-Aminocrotononitrile readily reacted with aryl isothiocyanate to afford acyclic adducts that were cyclized into the pyrimidine derivatives **79** on treatment with ethanolic potassium hydroxide [99].



76 77

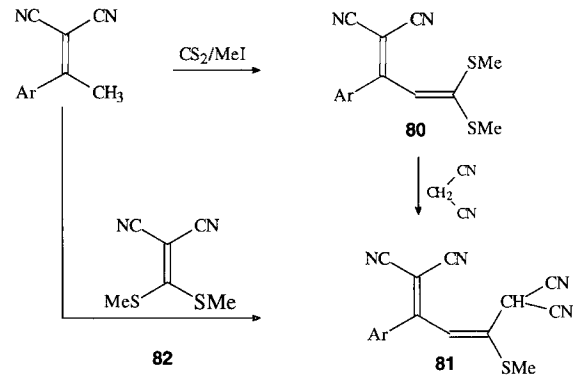
78 a: R = CO_2Et

b: R = $COCH_2CONHPh$



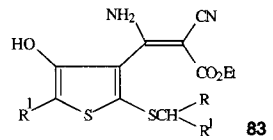
79: R = C_2H_5O; C_2H_5; Aryl

The reaction of **1c** with carbon disulphide and methyl iodide gives the dithioacetal **80** which when treated with malononitrile gives **81**. The latter was also obtained from reaction of **1c** with **82** [100].



80 81 82

Compound **1l** also reacts with CS_2 to give the dithiocarboxylic acid derivative. This was trapped by treatment with α-haloketones, α-haloesters and bromomalononitrile and ethyl bromocyanoacetate yielding the substituted thiophenes **83** [101]. Similar results were reported for reaction of **1b** with carbondisulphide and α-haloketones [101].

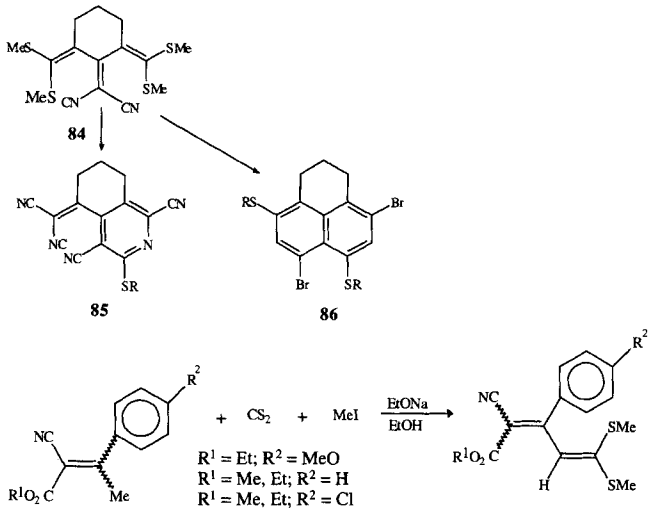


83

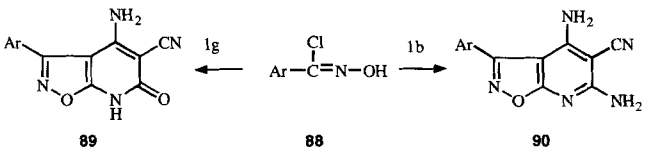
Treatment of **2a** with carbon disulphide and methylhalide gives **84** [102] which is cyclized into **85** by action of alkyl mercaptanes and into **86** by action of bromine.

Successively treating sodium methoxide/methanol (or sodium ethoxide/ethanol) with (*E*) – (*Z*) mixtures of crotononitrile derivative, CS_2 and MeI, for 4h at 20 °C gave 6–18% (*E*)-**87** with small amounts of the (*Z*)-isomers [103].

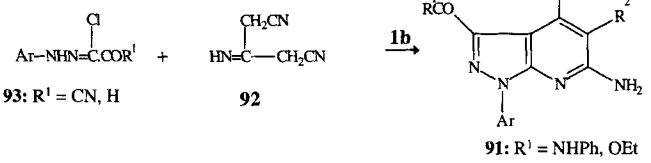
Push-pull butadienes were prepared in 36–50% yield by adding **1c** to NaOEt then adding a mixture of CS_2 and MeI [104].



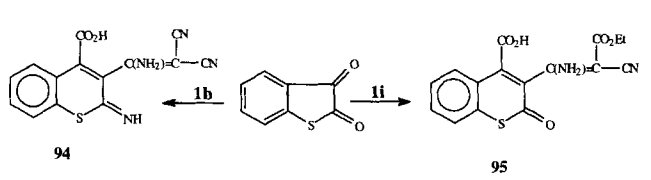
Crotononitriles reacted with α-chloroaldoximes to form condensed isoxazoles [105, 106]. For example, reaction of **1b** with **88** gave **90** in 32–75% yield. Similar reaction of **1g** with **88** gave the isoxazolopyridines **89** in 58–62% yield [105].



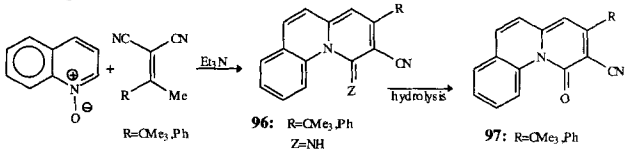
Reaction of **1b** with hydrazonyl halides has also been reported [107]. Condensed pyrazoles are the products of such reactions. For example, **1b** reacted with both **91** and **92** to yield **93** [107].



Condensation of benzo[*b*]thiophene-2,3-dione with **1b** or **1i** in presence of Et_3N gave benzothiopyrans **94** and **95** respectively [108].

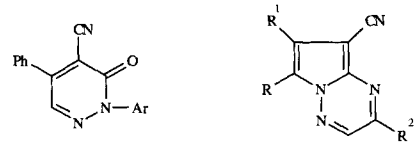


Quinoline-1-oxide and Ac_2O in glycine was treated with crotononitrile derivatives and Et_3N in glycine at room temperature to give benzoquinolizines **96** which were hydrolyzed with aqueous AcOH/HBr-solution to give 60.4% of **97** ($R=CMe_3$) and 68.2% of **97** (R=Ph) [109].



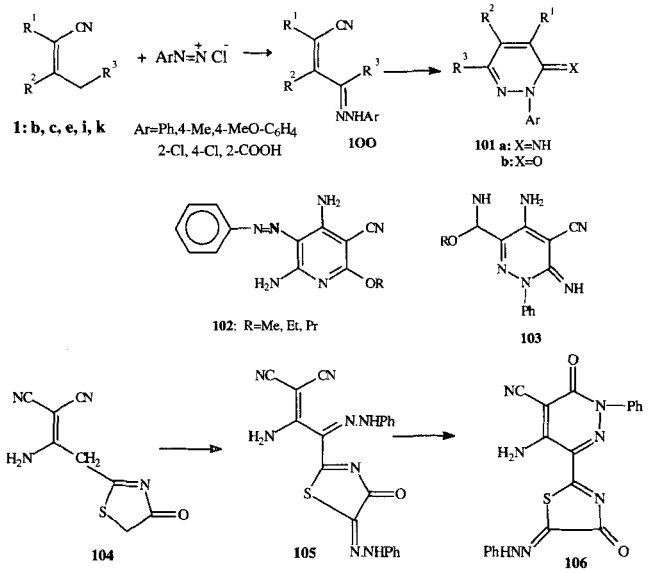
2 Nitrogen Electrophiles

Crotononitrile **1c** reacts with diazoketones to yield the pyridazinones **98**. Similar reaction with diazoesters affords **99** [110].

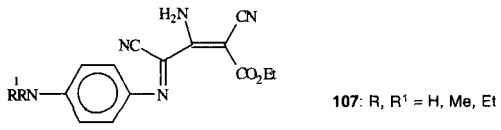


Aromatic diazonium salt couples readily with functionally substituted crotononitriles affording arylhydrazones that cyclize readily into pyridazinimine and pyridazinone. Synthesis of this type has firstly been reported by Elnagdi *et al.* [53, 111–117] who coupled **1b** with aromatic diazonium salts and cyclized the resulting hydrazones **100** into a pyridazinimine **101a**. Also, aromatic diazonium salts coupled with **1i** and the product was cyclized into pyridazinone **101b**. Junek has reported that the product of coupling **1b** with aromatic diazonium salts cyclizes into the pyridine **102** on treatment with sodium alkoxides [118]. Recently Elnagdi *et al.* [119] suggested that **102** is really **103**. Later Gewald *et al.* [120] have reported a similar reaction sequence on coupling **1q** with benzene diazonium chloride. While the product of coupling **1l** has been thought by Elnagdi et al. [53] to be the acylic hydrazone **100**. 1-Amino-2-(4-oxo-2-thiazolin-2-yl)ethylidene malononitrile **104** has also been coupled with benzene diazonium chloride to yield corresponding diphenylhydrazones **105** that were cyclized into the thiazolylpyridazine **106** [121]. Mittelbach *et al.* [122] has reported later that this product in his opinion is the cyclic pyridazinimine **101a**. Elnagdi *et al.* [115, 116] has later reported ^{13}C NMR data, pK_a value as well as electrochemical behaviour of this product that support their believe that the product is really, the hydrazone **100**. It has been reported that attempted coupling of **1c** with aromatic diazonium salts in aqueous NaOH affords arylhydrazonomesoxalonitriles. In contrast to this Elnagdi *et al.* [113] could show that in AcOH in presence of AcONa or in ethanolic sodium acetate coupling reaction occur at the alkyl function. Thus **1c** couples with benzene diazonium chloride

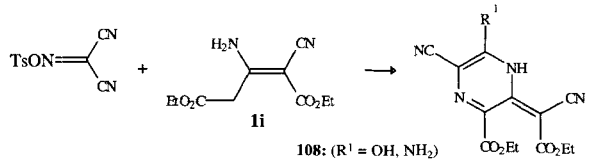
in AcOH in presence of AcONa to yield a hydrazone that cyclized readily into the pyridazinimine **101a**. Coupling of this same compound in ethanolic sodium acetate affords the amidrazones which cyclized yielding arylazo pyridazinimines [113]. The reported isolation of arylhydrazonomesoxalonitriles on coupling in ethanolic NaOH is thus assumed to be preceded by hydrolysis of **1c** into acetophenone and malononitrile in the strong alkaline medium used in this work. Elnagdi *et al.* [123] could show also that replacement of the phenyl moiety of **1c** by π-excessive thiophene or furan deactivates the methyl function toward aromatic diazonium salt, whereas replacement with chlorophenyl, coumarinyl and pyridyl increases the activity in the coupling reaction. Benzenediazonium chloride condensed with **1b,c,e,i,k,l** to give the hydrazone derivative **100** which cyclized in HOAc to give pyridazinone derivative **101.**



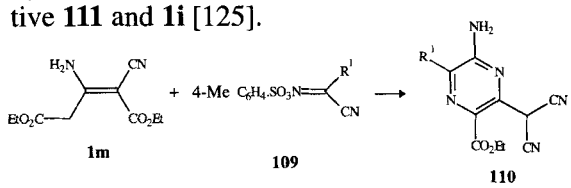
The reaction of **1l** with *p*-nitrosodialkylanilines gives **107** [48].

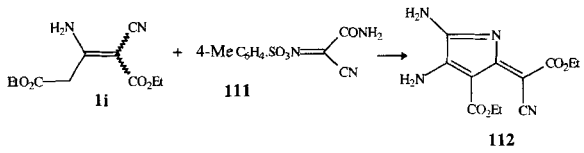


Reaction of crotononitrile derivative **1i** with α-tosyloximinonitrile, gives pyrazine derivative **108** [124]. Similar reaction of α-tosyloximinonitrile with **1b** affords also pyrazines [123, 124].



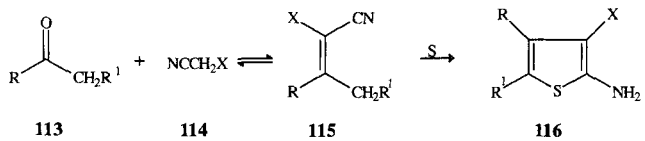
Crotononitrile derivative **1m** was treated with tosyl derivative **109** to give the pyrazinylmalononitrile **110**. Pyrrole derivative **112** was obtained from tosyl derivative **111** and **1i** [125].



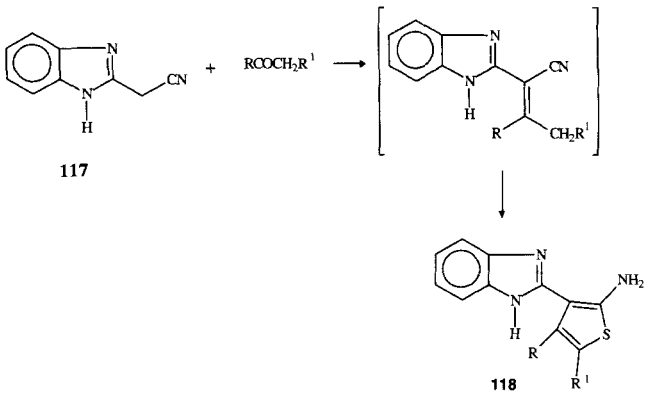


3 *Sulfur Electrophiles*

Reactions of this type constitutes the base of the Gewald thiophen synthesis [48, 126–129] and in a typical synthesis of this type methyl or methylene ketones **113** are mixed with active methylene nitriles **114** in basic solution in presence of sulfur where substituted crotononitrile intermediate derivatives **115** will be formed in equilibrium with starting materials. The equilibrium lies heavily in direction of starts. Sulfur then reacts with the formed crotononitrile derivative affording a thiophen **116** thus continually disturbing the equilibrium and in this way this synthesis proceeds generally in high yields, and these thiophens has found extensive utility in dye industry [130, 131].

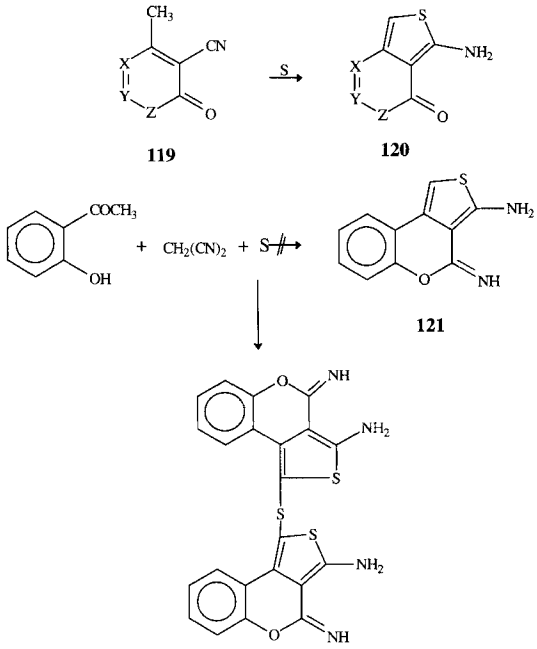


The crotononitrile derivative (**115**: R=Ph; R^1=H) has been firstly prepared then treated with sulfur yielding also thiophens **116,** and in recent literature there is still report on utility of this synthetic approach for synthesis of amino thiophens [132]. Of interest of these application is a recent report [133] on the formation of thienyl-



azoles **118** from the reaction of azolylacetonitrile **117** with methyl ketones and sulfur.

The Gewald thiophene synthesis has recently been extended to enable synthesis of thienoazines as well as thienocoumarines [134–139]. Thus treating alkyl azinyl carbonitrile **119** with sulfur has produced amino thienoazines in excellent yields **120**. Also, reaction of *o*-hydroxyacetophenone with malononitrile and sulfur has been reported by Reid *et al.* [140] to yield thienobenzopyranimines **121**. Elnagdi *et al.* [141] has recently found that the sulfide **122** is the really formed product under reported reaction conditions.

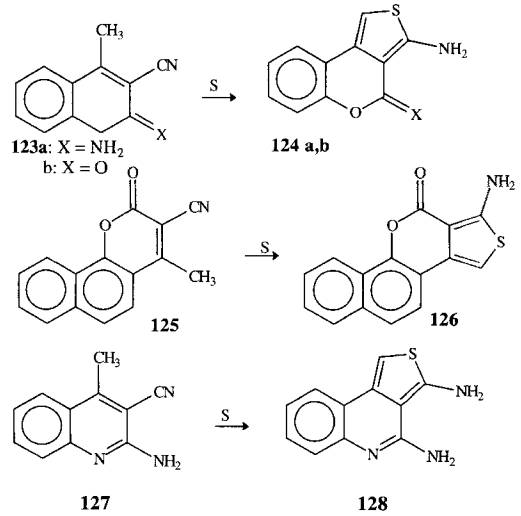


119 **120**

121

122

Aminothienobenzopyranimine **124a** and aminothienobenzopyranone **124b** as well as aminothienonaphthopyranone **126** and aminothienoquinoleine **128** could be recently obtained by Elnagdi *et al.* [134] *via* reacting the carbonitriles **123, 125, 127** with sulfur.



123a: X = NH_2
b: X = O

124 a,b

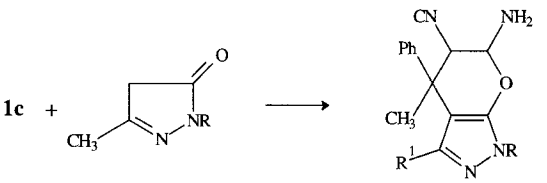
125 **126**

127 **128**

V Reaction with Nucleophilic Reagent

1 Carbon Nucleophiles

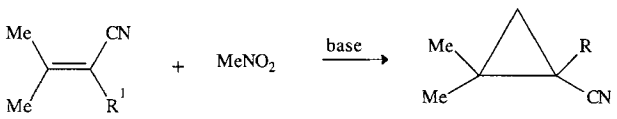
Carbanions also readily add across the activated double bond in **1c**. It is due to this activity that several attempts to prepare crotononitrile derivatives afforded the dimeric materials. Elnagdi *et al.* [142] have reported the addition of active methylene pyrazoles to **1c** and to **1q** yields the pyranopyrazoles **129a–e.**



a: R = H; R^1 = CH_3; **b**: R = Ph, R^1 = CH_3;
c: R = H; R^1 = NH_2; **d**: R = Ph; R^1 = OH;
e: R = Ph; R^1 = NH_2

129 a-e

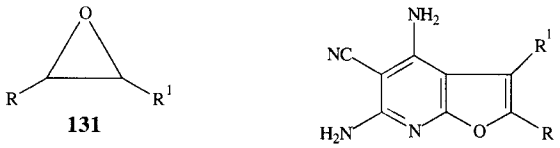
Crotononitrile derivatives are converted to cyclopropyl derivative **130** by $MeNO_2$ in presence of base [143].



R^1 = CN; CO_2Me

130

Furopyridines **132** were prepared in 8–82% yield by treating sodium salt of **1b** with the oxiranes **131** in presence of base [144].

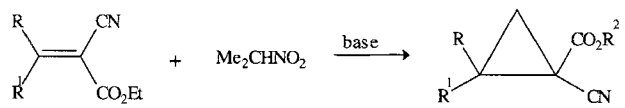


131

R = H, Me, Et, CH_2Cl, CH_2OH, CCl_3: R^1 = H
R = H, Ph: R^1 = Ph; RR^1 = $(CH_2)_4$

132

Cyclopropanoid cyanoesters **134** were prepared by cycloaddition of crotononitrile derivatives **133** with Me_2CHNO_2 in alcoholic solvents in presence of a base [145].



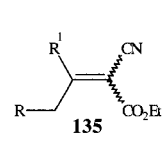
133

R = H; R^1 = (halo)alkyl....etc

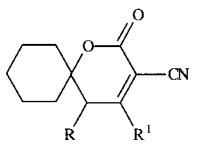
134

Reaction of **135** with cyclohexanone in ethanolic sodium ethoxide gave 15–75% spiro pyranones **136** [146].

The reaction of **1h, 2a** with substituted cyanoacetamides gives **137** [147].

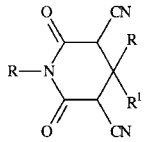


135



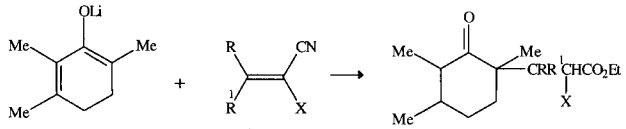
136

R = H, R^1 = Et, Pr; R = Me; R^1 = Et; $RR^1 = (CH_2)_n$; n = 3, 4



137

Ketone and ester enolates readily underwent Michael addition to crotononitrile derivatives at –78 °C in aprotic solvents. Thus, treating the cyclohexanone lithium enolate with crotononitrile derivatives gave 83% of the Michael addition product **138** [148].

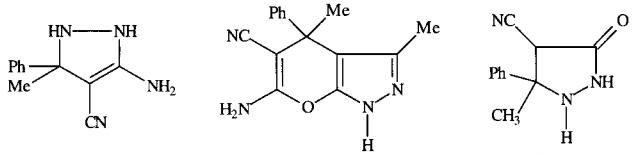


R = H; R^1 = Me; X = CN
$RR^1 = (CH_2)_5$; X = CN
$RR^1 = (CH_2)_5$; X = CO_2Et

138

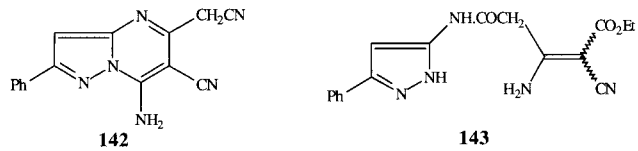
2 Nitrogen Nucleophiles

Compound **1c** reacts with cyanoethanoic hydrazide to give the pyrazoline derivative **139**, and with pyrazolinone to give **140** [149]. Similarly, **1d** gives **141** [149].



139 140 141

5-Amino-3-phenylpyrazole reacts with enaminonitriles, **1b,i** to afford the pyrazolopyrimidines **142** and the 5-substituted aminopyrazole **143** [150].

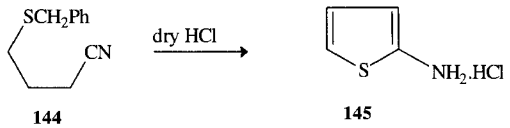


142 143

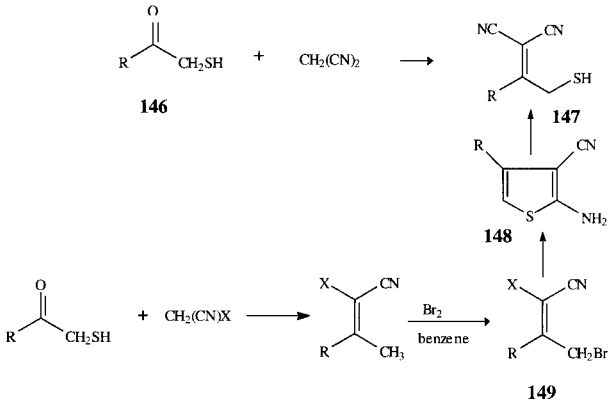
3 Sulfur Nucleophiles

Treatment of **144** in anhydrous ether with a current of dry HCl gas affords the amine hydrochloride **145** in reasonable yield [151].

The reaction of α-oxomercaptans **146** and active methylene nitriles give **147** which was cyclized into thiophenes **148**. Latter compound is also obtained from the reaction of sodium hydrosulfide with **149** [152].



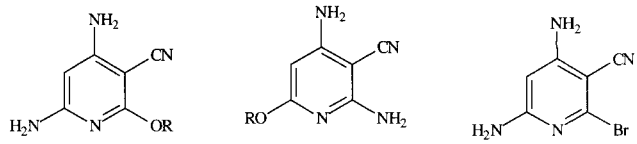
144 145



146 147 148 149

VI Oxygen Nucleophiles

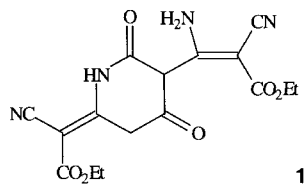
Compound **1b** is cyclized by alkoxide into a mixture of **150** and **151**. Reaction of **1b** with hydrobromic acid affords **152** which when treated with sodium alkoxides gives **150** [118].



150 151 152

VII Reaction with Bidentate Reagents

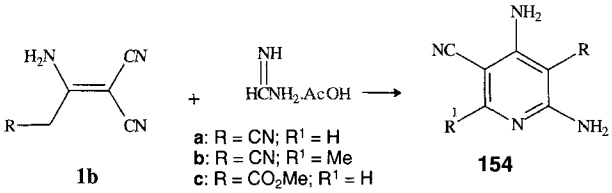
The reaction of **1b** with hydrazines has been extensively utilized for synthesis of 1*H*-pyrazole-5-amines [153] as well as 1*H*-pyrazole-3-amines [154]. Functionally substituted hydrazines affords condensed pyrazoles [155]. Reaction with hydroxylamine gives isoxazoles [156]. Refluxing **1l** in pyridine gives **153** [54].



153

The condensation of formamidine acetate with **1b** gave 94% of the pyridine **154a**. Similarly, acetamidine hydrochloride condensed with **1b** to give 23% **154b**.

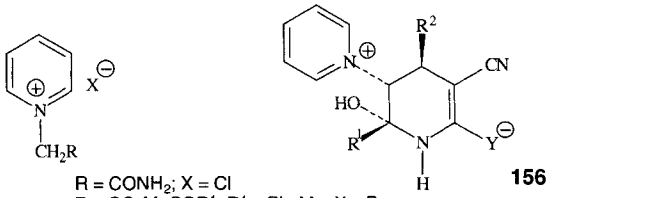
The reaction of crotononitrile **1g** with formamidine gave 75% of the pyridine derivative **154c** [157].



1b **154**

a: R = CN; R^1 = H
b: R = CN; R^1 = Me
c: R = CO_2Me; R^1 = H

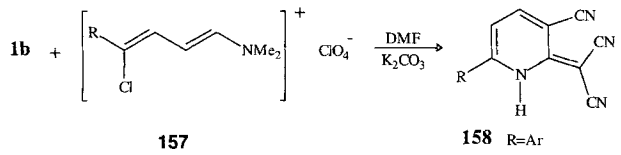
Treating the alkylpyridinium halides **155** with R_2CHO and **1b** yields **156** [158].



155 R = $CONH_2$; X = Cl
R = CO_2MeCOR^1; R^1 = Ph, Me; X = Br
R = CS_2Me; X = 1

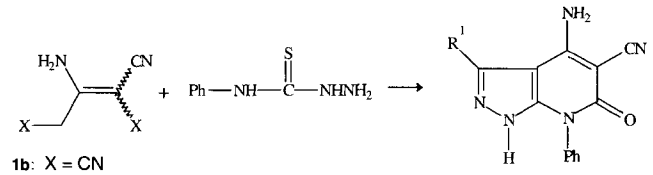
156 R = Ph, 4-FC_6H_4, 3-Pyridyl

The malononitrile derivative **1b** was treated with **157** in the presence of bases to give the dihydropyridines **158** [159].



157 **158** R=Ar

Cyclocondensation of phenylthiosemicarbazide with **1b** or **1i** gave pyrazolopyridine derivative **159** [160].



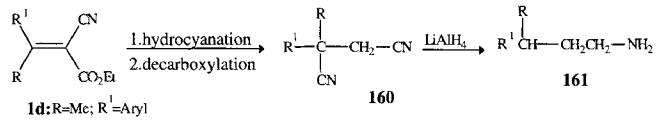
1b: X = CN
i: X = CO_2Et

159: R^1 = NH_2, OH

VIII Reduction

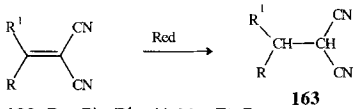
Reduction of alkylidenemalononitriles by Cervinka's reagent ($LiAlH_4$ complexes of chiral amino alcohols yields the same asymmetric induction as the reduction of ketones, but the reduction by these same reagents of the *Z* and *E* isomers of alkylidenecyanoacetic esters gives opposite induction. This last results suggest the formation of an intermediate complex between the electrophilic reagent, the hydride, and the chiral amino alcohol [161]. Hydrocyanation and decarboxylation of **1d** gave 54–99% of **160** which was reduced with $LiAlH_4$ to give 32–62% of **161** [162].

2-Phenylbenzimidazoline selectively reduces the ethylenic double bonds in dinitriles **162** to give 63–96% **163** [163].



1d: R=Me; R^1=Aryl

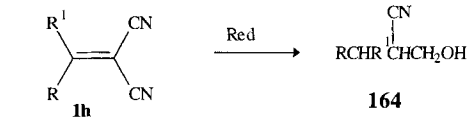
160 **161**



162: R = Ph; R^1 = H, Me, Et, Pr
R = Me OR Et

163

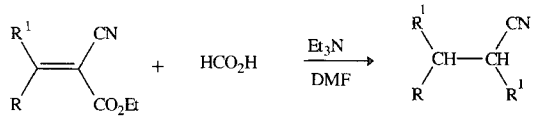
The electrochemical reduction of **1d** in aprotic solvents was studied by cyclic voltammetry and ESR Spectroscopy. Reversible one-electron reduction to a radical anion occurred, followed by irreversible reduction to a dianion at higher cathodic potentials. In the presence of proton donors, 2-electron cathodic hydrogenation of the ethylenic double bond occurred at the first reduction peak potential, and the effect of these donors on the reversibility of this peak is discussed. For **1d** irreversible one-electron reduction with dimerization was observed even with added proton donor; rapid dimerization of the radical anions was proposed [164]. Borohydride reduction of the crotononitrile derivative **1h** gave 2-cyanoalkanols **164** [165].



1h **164**

R = Me; R^1 = $EtCH_2CHMe_2$; R^1 = CMe_3

The reduction of alkylidencyanoacetic ester (*Z*- and *E*-ethyl 2-cyano-3-phenyl-butenoates) and acetophenone by chiral organomagnesium halides give the opposite stereoselectivities. These results are rationalized by a cyclic mechanism for the ketone reduction and by a noncyclic mechanism with polar orientation of the reagents in the reduction of the ethylenic compounds. Also, reduction of **1c** with the same reagent was reported [166, 167]. Also, crotononitrile derivatives were reduced by formic acid in triethylamine-DMF mixtures to yield **165** [168].



R = Ph, Et; R^1 = H. Me, Et, $PhCH_2$
RR^1 = $(CH_2)_5$; R^2 = CN, CO_2Et, SO_2Ph

165

IX Miscellaneous

Crystals of **1b** are monoclinic, space group $P2_1/c$ with cell dimensions a 2.66_3, b 7.54_1, c 7.02_9 A, and β 99.99°. Apart from the cyano group and H atoms of the CH_2CN group, the molecule is roughly planar, the dihedral angle (H_2N)–C–CH_2–(CN) is 27°. The sp–sp^2 C–C and

sp^2–sp^2 C–C bond lengths are 1.422 Å and 1.382 Å respectively. Intermolecular H-bonds between the amino group and N atoms of cyano groups from infinite double chains in the [010] direction [169–171].

The oxidation of **1b** in the presence of H_2O_2 and Cu is favored by imidazole, 4-methylimidazole, or any other compound possessing the imidazole ring. This fluorescent reaction was used for the individual determination of imidazole and 4-methylimidazole at 10^{-5} M level by application of several kinetic methods with relative standard deviation of about ± 1% [172, 173].

Also, fluorescence characteristics of **1b** as an analytical reagent and kinetic-fluorometric method for determination of histidinol were reported [174].

Kinetic fluorometric determination of copper was based on Cu-catalyzed oxidation of the reagent, **1b**, rather than on complex formation [175, 176].

Crotononitriles, have two isomeric forms, (*Z*)- and (*E*)-form, the *Z*-form more is stable than the (*E*)-form and this due to intermolecular H-bond [177]. It was reported [178] that crotononitrile **1a** isomerized in either solution or solid state, and its mixture from *E*- and *Z*-forms are readily distinguishable by ^{1}H NMR. Spectral data of **1a** and its derivatives were also reported [1]. The reactivities of (*Z*)- and (*E*)-form of the crotononitrile **1g**, toward Grignard reagent were reported [179].

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