Turkish Journal of Chemistry

Volume 32 | Number 3 Article 1

1-1-2008

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Recommended Citation

FADDA, AHMED ALI; BONDOCK, SAMIR; RABIE, RAMY; and ETMAN, HASSAN ALI (2008) "Cyanoacetamide Derivatives as Synthons in Heterocyclic Synthesis," *Turkish Journal of Chemistry*: Vol. 32: No. 3, Article 1. Available at: https://journals.tubitak.gov.tr/chem/vol32/iss3/1

Turk J Chem
32 (2008) , 259 – 286.

Review

Cyanoacetamide Derivatives as Synthons in Heterocyclic Synthesis

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Received 09.10.2007

This review presents a systematic and comprehensive survey of the methods of preparation and the chemical reactivity of cyanoacetamide derivatives. These compounds are important intermediates for the synthesis of a variety of otherwise difficult to obtain synthetically useful and novel heterocyclic systems.

Key Words: Cyanoacetanilide, thiophene, pyrazole, thiazole, pyridine, pyridazine, pyrimidine, heterocycles

Introduction

Cyanoacetamides are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates since the carbonyl and the cyano functions of these compounds are suitably situated to enable reactions with common bidentate reagents to form a variety of heterocyclic compounds. Moreover, the active hydrogen on C-2 of these compounds can take part in a variety of condensation and substitution reactions. In addition, the diverse biological activities reported for many derivatives of cyanoacetamide have also drawn the attention of biochemists in the last decade. The literature covering the chemistry of cyanoacetamide derivatives has been limited. However, a review of the chemistry and reactions of cyanothioacetamide (in Russian) was published in 1999.[1] The main objective of the present survey is to provide a comprehensive account of the synthetic utility of *N*-aryl and/or heteryl cyanoacetamides in building various organic heterocycles and to highlight their potential in evolving better chemotherapeutic agents.

Synthesis

The synthesis of cyanoacetamides may be carried out in several ways. The most versatile and economical method involves the treatment of various substituted aryl or heteryl amines with alkyl cyanoacetates using

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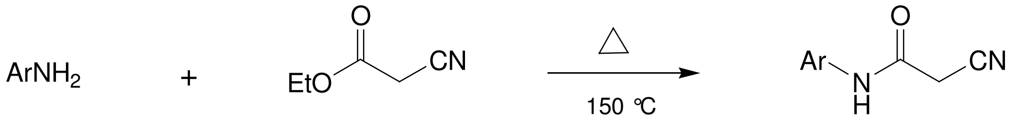
different reaction conditions to yield cyanoacetamide derivatives. The following are some of the methods that have been used to prepare *N*-aryl or *N*-heteryl cyanoacetamides.

Fusion Method

The solvent-free reaction of arylamines with ethyl cyanoacetate constitutes one of the most widely used methods for the preparation of cyanoacetanilides. Thus, fusion of aromatic amines with an excess amount of ethyl cyanoacetate at 150 °C afforded cyanoacetanilide derivatives **1**.[2]



1

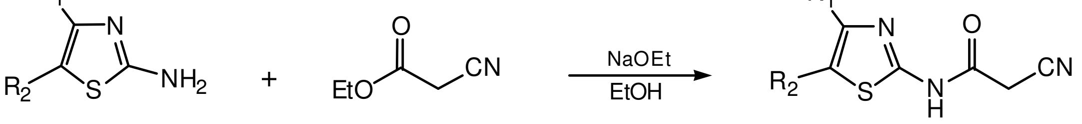
1	Ar	1	Ar
a	C_6H_5	h	4-CF_3-C_6H_4
b	2-NO_2-C_6H_4	i	4-Br-C_6H_4
c	4-MeO-C_6H_4	j	2,4,6-Cl_3-C_6H_2
d	4-Cl-C_6H_4	k	2-F-C_6H_4
e	antipyryl	l	4-F-C_6H_4
f	4-Me-C_6H_4	m	Pyridyl
g	3-Cl-4-F-C_6H_3	n	2-OCF_3-C_6H_4

Scheme 1

Using Different Basic Medium Conditions

Sodium ethoxide solution

Metwally and coworkers have recently reported that the base catalyzed condensation of 2-aminothiazole derivatives **2** with ethyl cyanoacetate afforded *N*-(thiazol-2-yl) cyanoacetamide derivatives **3**.[3]



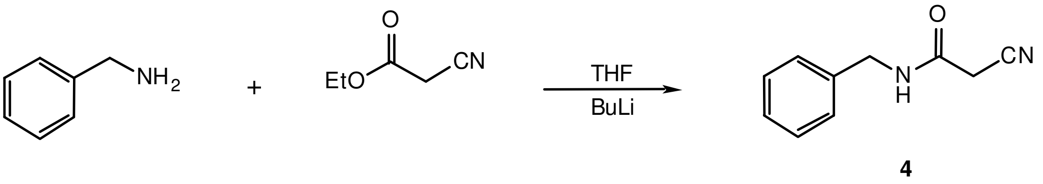
2 **3**

3	R$_1$	R$_2$
a	Ph	H
b	C_4H_4	

Scheme 2

Butyl lithium/THF

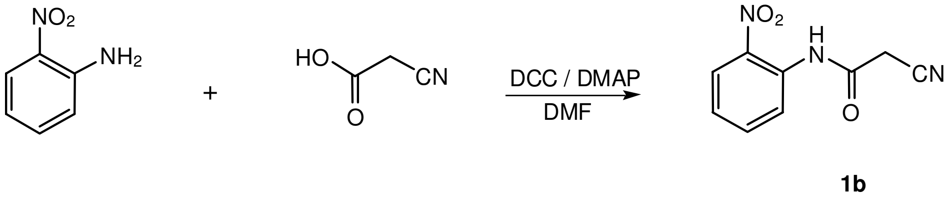
Bhawal et al. reported that the reaction of benzylamine with ethyl cyanoacetate in THF containing butyl lithium as a basic catalyst afforded *N*-benzylcyanoacetamide **4** in 91% yield.[4]



Scheme 3

Dicyclohexyl carbodiimide (DCC) & 4-N,N-dimethylaminopyridine (DMAP)

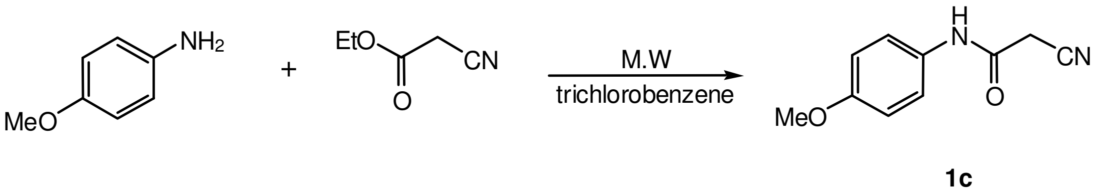
2-Cyano—*N*-(4-nitrophenyl)acetamide **1b** was obtained by condensation of 2-nitroaniline with cyanoacetic acid in dimethylforamide containing dicyclohexyl carbodiimide and 4-*N*,*N*-dimethylaminopyridine.[5]



Scheme 4

Microwave method

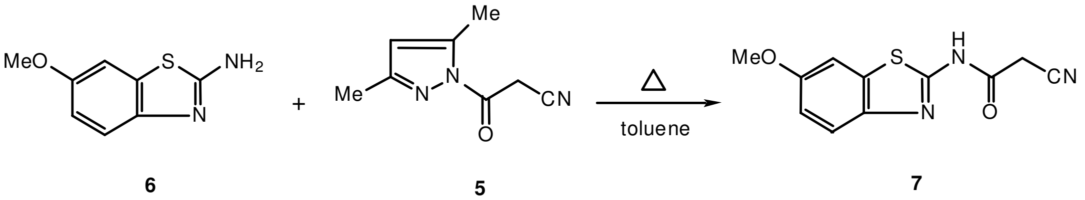
Microwave irradiation has become an important method in organic synthesis that can be applied to a wide range of reactions within short reaction times and with high yields. The microwave irradiation of *p*-anisidine with ethyl cyanoacetate in trichlorobenzene afforded 2-cyano-*N*-(4-methoxyphenyl) acetamide **1c** in 90% yield.[6]



Scheme 5

Utilization of 1-Cyanoacetyl-3,5-Dimethylpyrazole as Cyanoacetylation Reagent

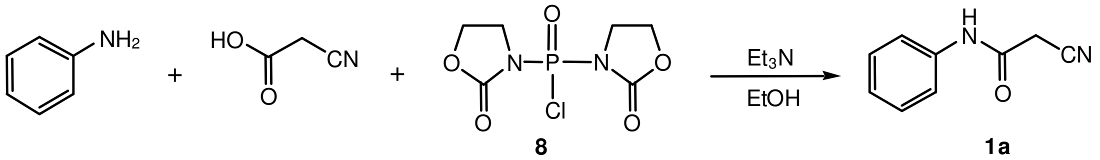
Cyanoacetylpyrazole **5** is a very handy and cheap cyanoacetylation reagent, which was first synthesized and introduced in common practice in the late 1950s by Ried and Scheimer.[7] It was successfully applied for the synthesis of various *N*-alkyl and *N*-aryl cyanoacetamides. Thus, treatment of 2-amino-6-methoxybenzothiazole **6** with **5** in boiling dry toluene resulted in the formation of the corresponding *N*-(6-methoxybenzothiazol-2-yl) cyanoacetamide **7** in 85% yields. [8,9,48]



Scheme 6

N,N-Bis[2-oxo-3-oxazolidenyl]phosphorodiamidic Chloride Reagent

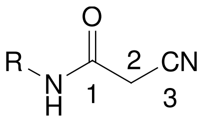
The reaction of cyanoacetic acid with aniline in boiling ethanol containing $N, N-$ bis[2-oxo-3-oxazolidenyl] phosphorodiamidic chloride **8** and triethylamine furnished cyanoacetamide derivative **1a.**[10]



Scheme 7

Typical Reactivity of Cyanoacetamide Derivatives

Cyanoacetamides are polyfunctional compounds possessing both electrophilic and nucleophilic properties. Typical nucleophilic positions are NH and$C-2$ with reactivity order C-2 > NH. These chemical properties have been used to design different heterocyclic moiety with different ring sizes such as azirine, pyrrole, thiophene, pyrazole, imidazole, thiazole, thiadiazole, pyridine, pyrane, pyridazine, pyrimidine, and triazine. On the other hand, cyanoacetamide possesses electrophilic positions, especially at $C-3, C-1$ with reactivity order $C_3 > C_1$.

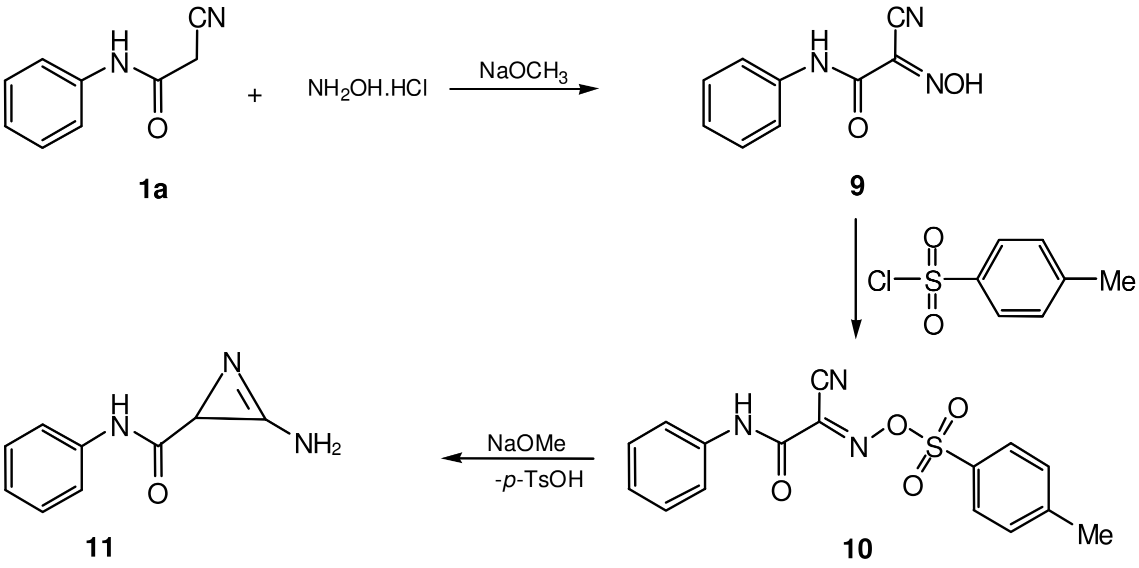


Reactions of Cyanoacetamide Derivatives

Synthesis of 3 Membered Ring with 1 Hetero Atom

Azirine derivatives

Treatment of cyanoacetanilide **1a** with hydroxylamine in the presence of sodium methoxide as a basic catalyst afforded the oxime **9**, which upon treating with *p*-toluene sulfonyl chloride, gave compound **10**. Intramolecular nucleophilic substitution of **10** in sodium methoxide furnished 3-amino-*N*-phenyl$-1H-$azirine-2-carboxamide **11.**[11]

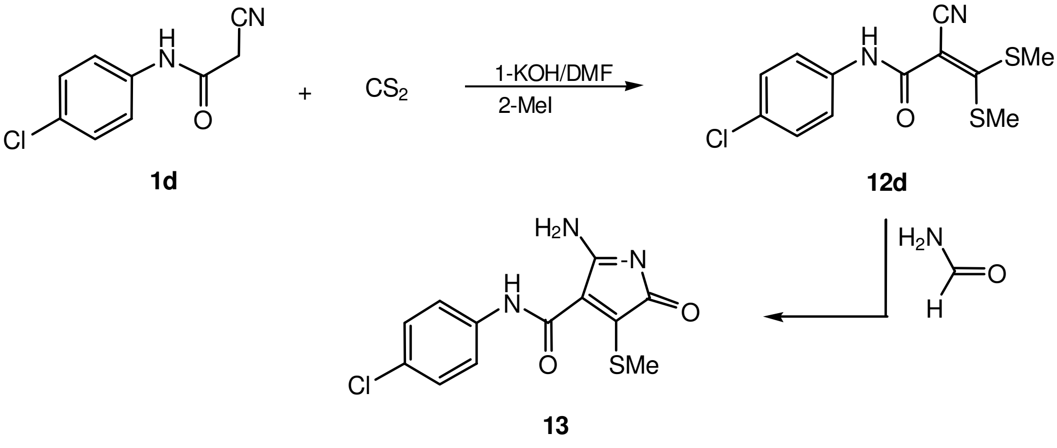


Scheme 8

Synthesis of 5 Membered Ring with 1 Heteroatom

Pyrrole derivatives

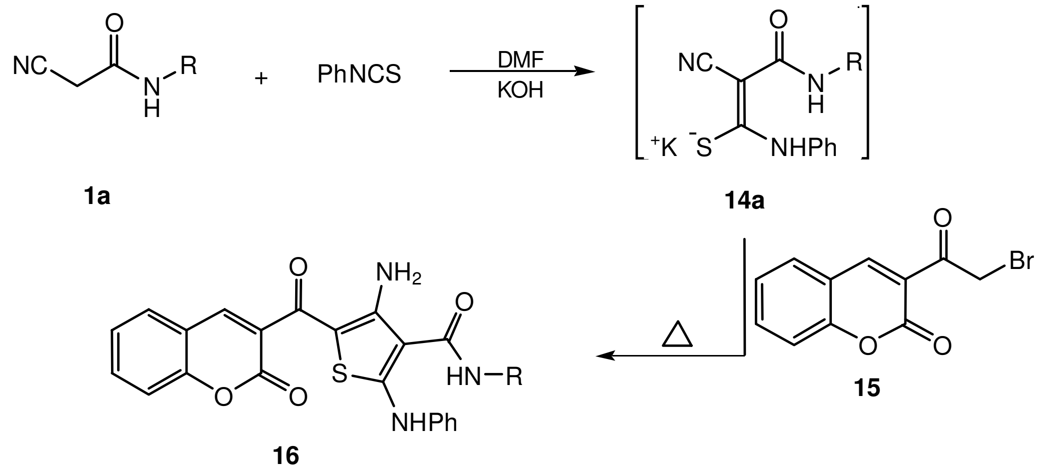
Reaction of *p*-chlorocyanoacetanilide **1d** with carbon disulfide in DMF and potassium hydroxide, followed by addition of methyl iodide, has been reported to afford the ketene dithioacetals **12**, which were transformed by the action of formamide into 4-amino-2-(methylsulfanyl)-5-oxo-*N*-phenyl-5*H*-pyrrole-3-carboxamide **13**.[12]



Scheme 9

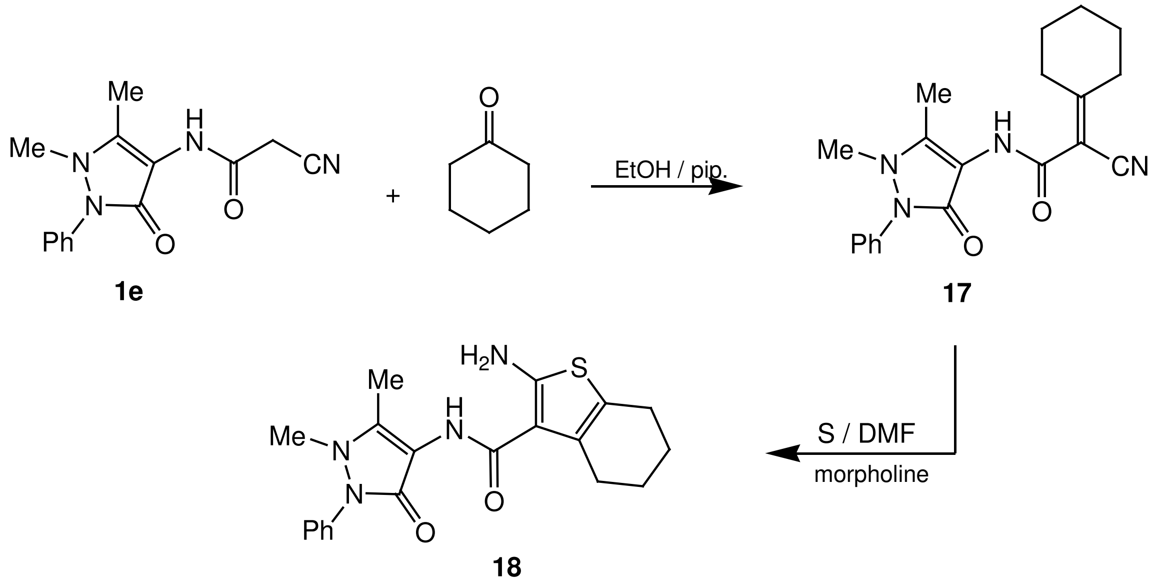
Thiophene and its fused derivatives

The reaction of cyanoacetanilide **1a** with phenyl isothiocyanate in DMF containing potassium hydroxide gave the non-isolable intermediate **14a**, which underwent heterocyclization with 3-(2-bromoacetyl)-2*H*-chromen-2-one **15** to give thiophene derivative **16**.[13]



Scheme 10

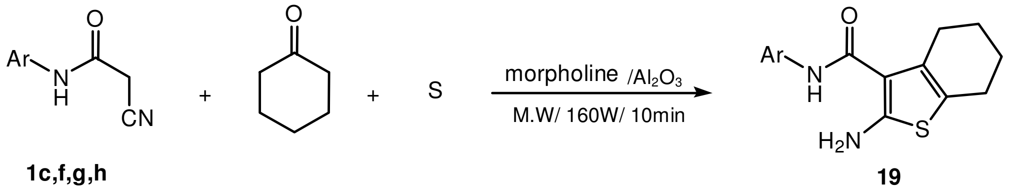
Condensation of 4-antipyrinylcyanoacetamide **1e** with cyclohexanone in boiling ethanol containing a catalytic amount of piperidine afforded arylidene derivative **17.** Heterocyclization of **17** with elemental sulfur in warming ethanol containing a few drops of morpholine as a basic catalyst under Gewald reaction conditions afforded the corresponding thiophene derivative **18**.[14]



Scheme 11

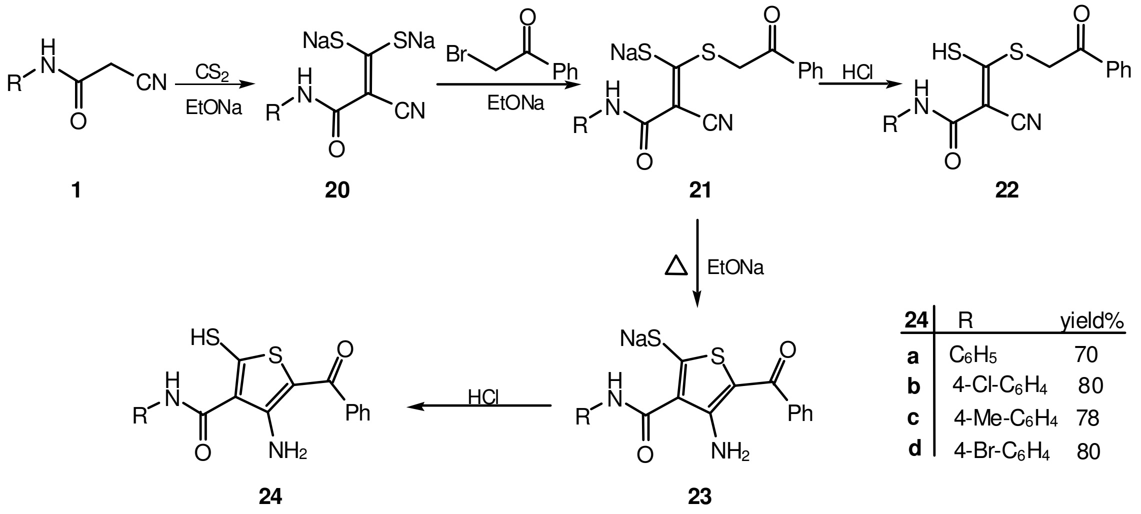
Huang and coworkers have reported a simple and convenient synthesis of thiophene derivatives via *a* solvent-free microwave assisted reaction. The microwave irradiation of cyanoacetamides $\mathbf{1}_{c,f,g,h}$ with cyclohexanone, sulfur, and aluminum oxide as a solid support in the presence of morpholine as a basic catalyst under solvent-free conditions for several minutes gave thiophene derivatives **19** in high yields.[15]

Reaction of substituted cyanoacetanilide derivatives **1** with carbon disulfide in boiling sodium ethoxide gave the sodium dithiolate salts **20**. Compounds **20** are readily alkylated with phenacyl bromide to give the stable sodium salts of monoalkylthio derivatives **21**. Acidification of **21** with hydrochloric acid gave the mercapto products **22**. The sodium α-cyanoketene dithiolates **21** were cyclized on refluxing in sodium ethoxide to give the corresponding sodium thiophene thiolates **23**, which were acidified with hydrochloric acid to give 2-mercaptothiophenes **24**.[16]



19	Ar	M.W yield%
a	4-MeO-C_6H_4	93
b	4-Me-C_6H_4	95
c	3-Cl-4-F-C_6H_3	86
d	4-CF_3-C_6H_4	84

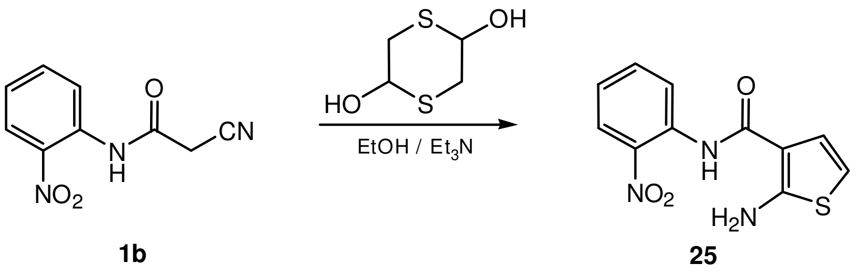
Scheme 12



24	R	yield%
a	C_6H_5	70
b	4-Cl-C_6H_4	80
c	4-Me-C_6H_4	78
d	4-Br-C_6H_4	80

Scheme 13

Walser and coworkers have reported that treatment of 2-cyano−*N*−(2-nitrophenyl) acetamide **1b** with 1,4-dithiane-2,5-diol in boiling ethanol containing a catalytic amount of triethylamine furnished 2-amino-*N*-(2-nitrophenyl)thiophene-3-carboxamide **25**.[5]

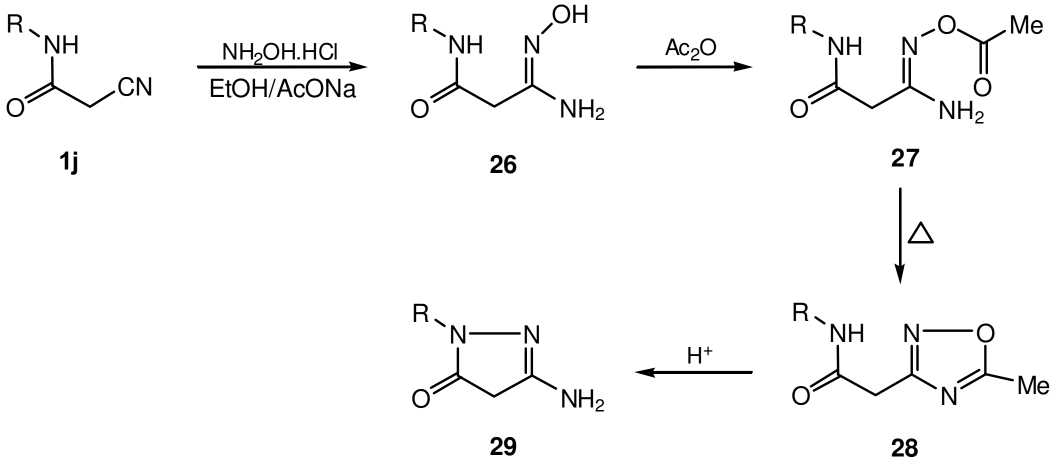


Scheme 14

Synthesis of 5 Membered Ring with 2 Hetero Atoms

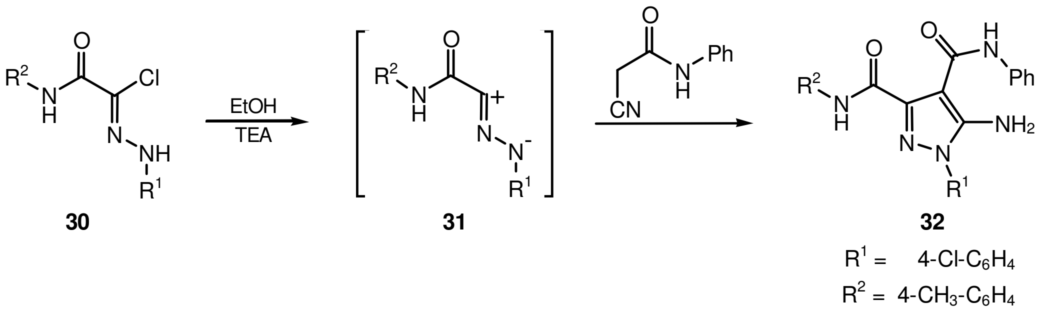
Pyrazole derivatives

Treatment of *N*-(2,4,6-trichlorophenyl) cyanoacetamide **1j** with hydroxylamine in boiling ethanol containing a catalytic amount of sodium acetate furnished amidoxime **26**. Acetylation of **26** with acetic anhydride afforded *o*-acetyltion product **27**. Thermal cyclization of **27** delivered 1,2,4-oxadiazole derivatives **28**. Acid catalyzed rearrangement of 1,2,4-oxadiazole **28** led to the formation of pyrazolin-5-one derivative **29**.[17]



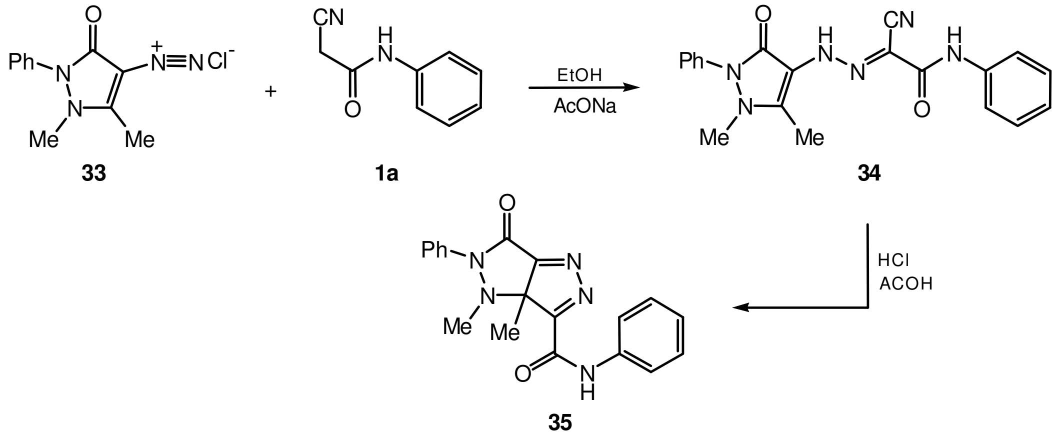
Scheme 15

The 1,3-dipolar cycloaddition of nitrile imine **31** (generated in situ from the treatment of hydrozonyl halide **30** with triethylamine) with cyanoacetanilide **1a** furnished pyrazole derivative **32**.[18]



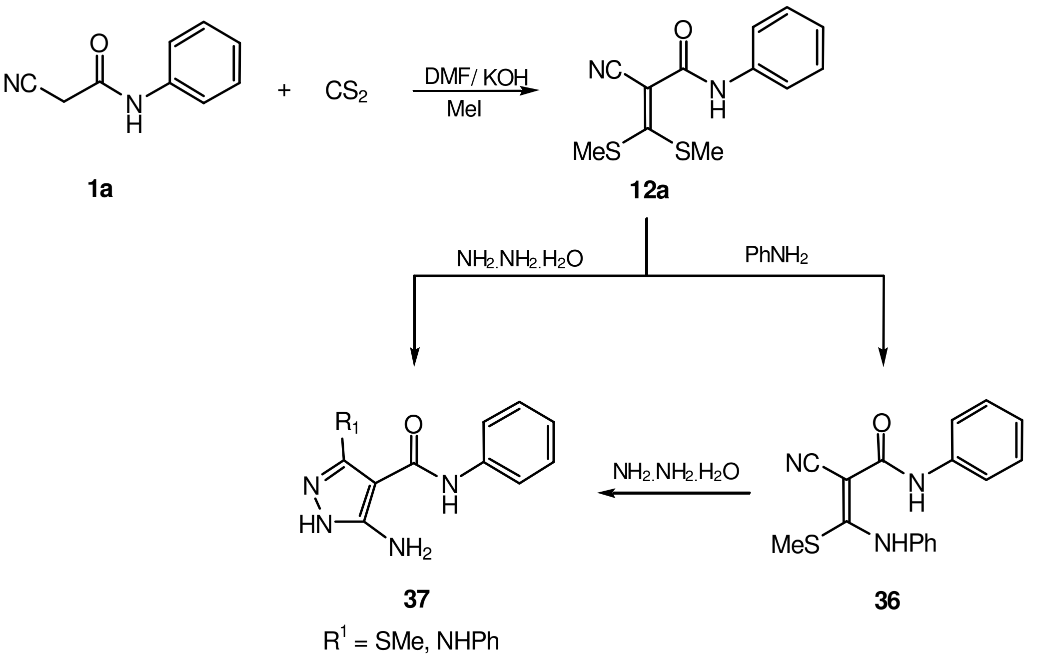
Scheme 16

The coupling reaction of 4-antipyrinyl diazonium chloride **33** with cyanoacetanilide **1a** in ethanol buffered with sodium acetate gave the corresponding antipyrinyl hydrazone derivative **34**, which upon treatment with a mixture of acetic acid and hydrochloric acid gave 3*a*,4,5,6-tetrahydro-3*a*,4-dimethyl-6-oxo–*N*,5-diphenylpyrazolo[4,3-*c*]pyrazole-3-carboxamide **35**. The reaction mechanism for the formation of **35** involved the intramolecular addition of enamine to the azomethine group of **34**, followed by elimination of HCN.[19]



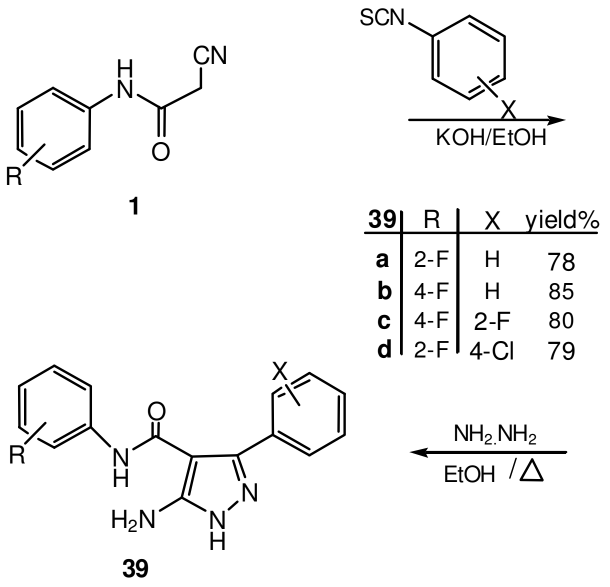
Scheme 17

Reaction of cyanoacetamide **1a** with carbon disulfide in DMF and potassium hydroxide, followed by alkylation with methyl iodide, gave dimethylsulfanyl acrylamide **12a**. The reactivity of **12a** towards nitrogen nucleophilies was reported. Treatment of **12a** with aniline gave acrylamide **36** through Michael addition of the amino group to the ethylenic bond in **12a** followed by elimination of methanethiol. The acrylamide **12a** was converted to pyrazole derivative **37** (R^1 = SMe) by treatment with hydrazine hydrate. Compound **37** (R^1 = NHPh) could be also obtained via heating of **36** with hydrazine hydrate in ethanol.[20]



Scheme 18

Heating of fluorosubstituted cyanoacetanilide derivatives **1k, 1** with aryl isothiocyanate in ethanolic potassium hydroxide gave the corresponding potassium 2-cyanoethylene-1-thiolate salts **14**. The latter, on alkylation with methyl iodide, afforded ketene*N*, *S*—acetals **38**. Reaction of compounds **38** with hydrazine hydrates in refluxing ethanol containing a catalytic amount of piperidine gave the corresponding pyrazole derivatives **39**.[21]

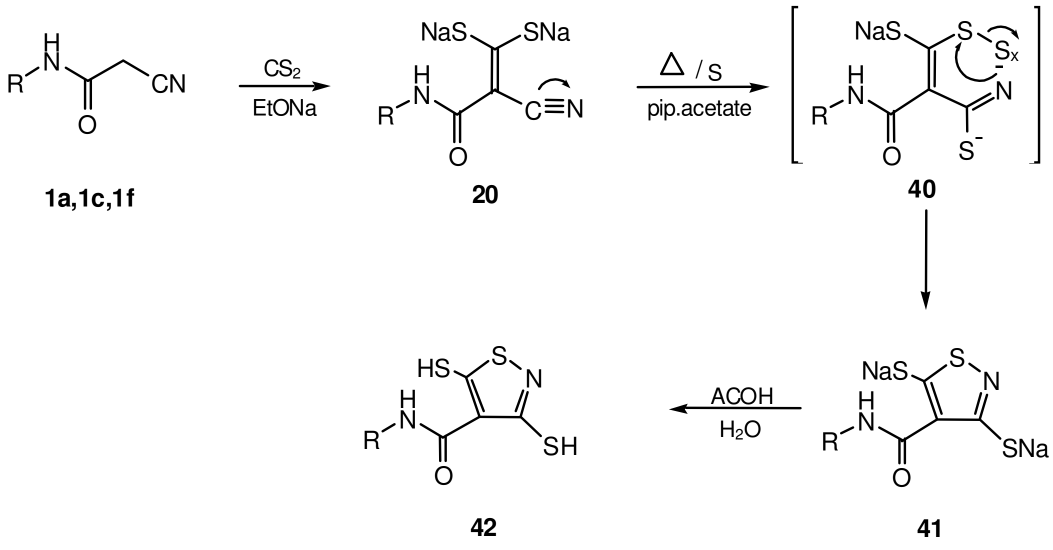


39	R	X	yield%
a	2-F	H	78
b	4-F	H	85
c	4-F	2-F	80
d	2-F	4-Cl	79

Scheme 19

Isothiazole derivatives

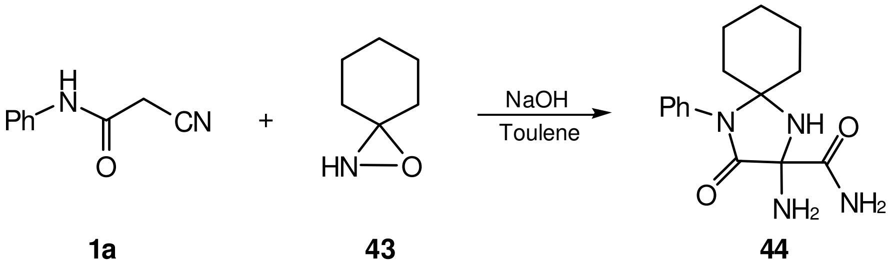
Elgemeie and coworkers have recently reported that the reaction of cyanoacetamide derivatives **1a, 1c, 1f** with carbon disulfide containing sodium ethoxide gave the ketene dithioacetal derivatives **20**. Heating of **20** in ethanol with sulfur and piperidine acetate gave the corresponding disodium isothiazole-3,5-dithiolates **41**, which were acidified with acetic acid to give the 3,5-disulfanylisothiazoles **42**.[22]



Scheme 20

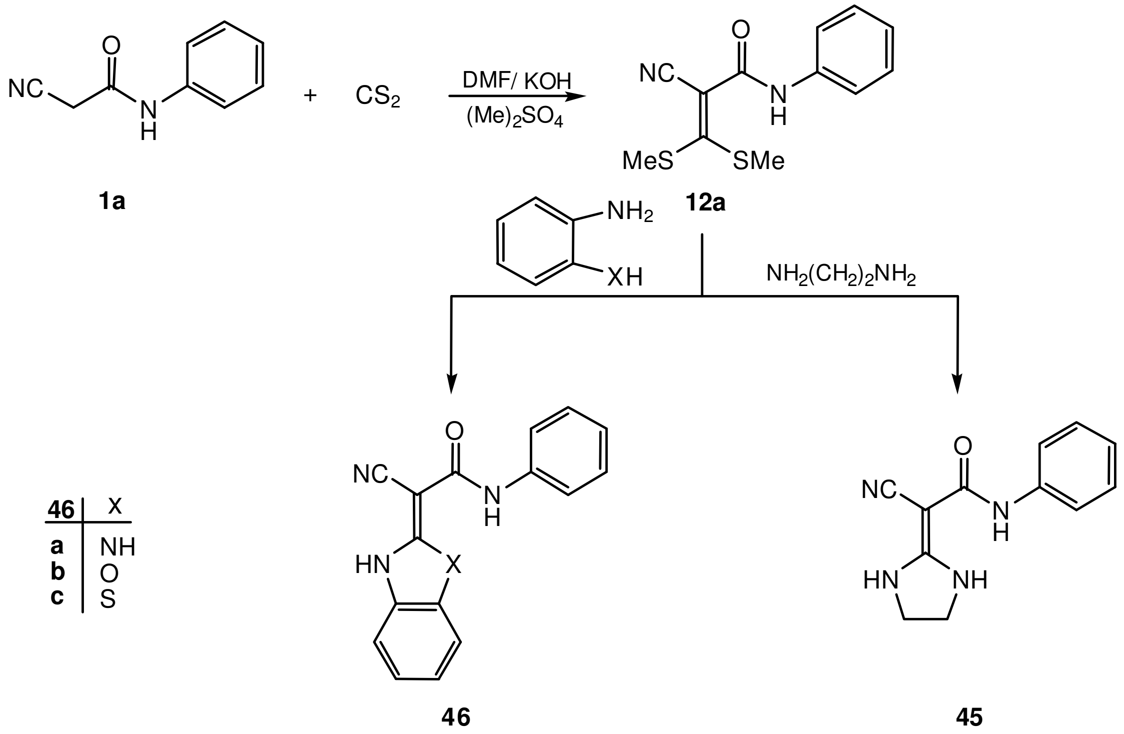
Imidazole and its derivatives

Schmitz and coworkers have reported that the reaction of cyanoacetanilide **1a** with 1-oxo-2-aza-spiro[2,5]octane **43** in boiling dry toluene containing sodium hydroxide as a basic catalyst gave the spiro imidazole derivative **44**.[23]



Scheme 21

The reaction of cyanoacetamide derivatives **1a, 12c** with carbon disulfide and dimethyl sulfate in DMF containing potassium hydroxide gave the ketene $S,S-$dithioacetals **12a, c**, which, on treatment with bifunctional nucleophilic reagents such as ethylene diamine, *o*-phenylenediamine, 2-aminophenol, and 2-aminothiophenol gave the imidazole **45**, benzimidazole **46a**, benzoxazole **46b,** and benzothiazole **46c** derivatives.[20,24,25.]

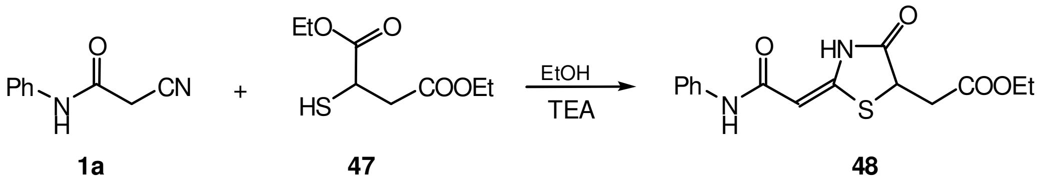


Scheme 22

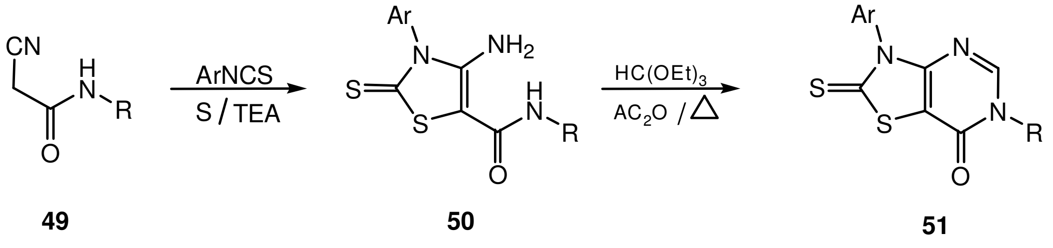
Thiazole and its derivatives

Rad and coworkers have prepared the thiazolidin-4-one**48** with high regioselectivity via the base catalyzed cyclocondensation of cyanoacetanilide **1a** with diethyl 2-sulfanyl-1,4-butandioate **47** in boiling ethanol.[26]

In view of the growing biological importance of fused thiazoles, and particularly of thiazolo[4,5-*d*]pyrimidines, it was considered of interest to synthesize **51**. Thus, the reaction of **49** with sulfur and an appropriate aryl isothiocyanate in ethanol containing a catalytic amount of triethyl amine furnished thiazole derivatives **50**. Heterocyclization of **50** with a mixture of triethylorthoformate and acetic anhydride delivered thiazolo[5,4-*d*]pyrimidine derivatives **51**.[27]



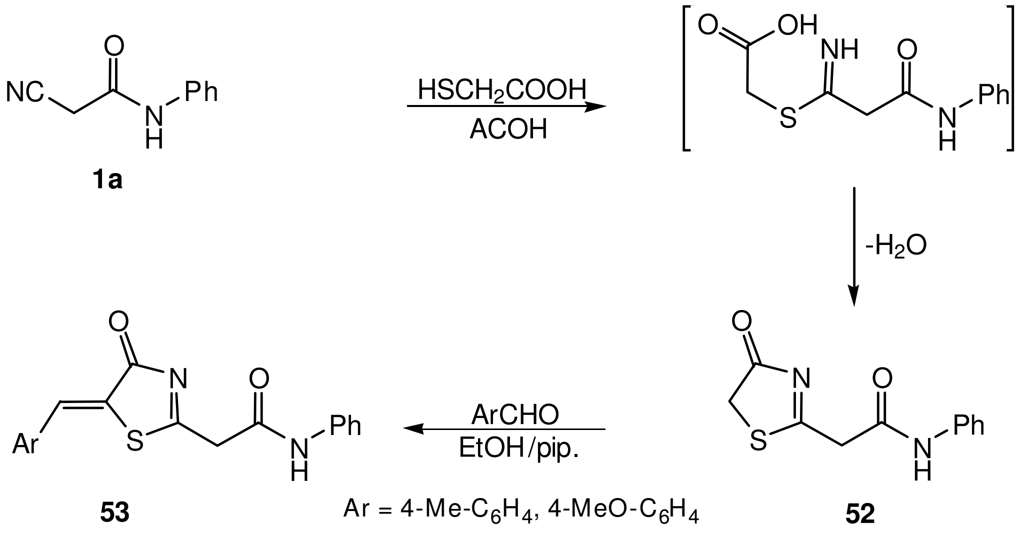
Scheme 23



51	R	Ar
a	piperidino	Ph
b	piperidino	$PhCH_2$
c	piperidino	Tolyl

Scheme 24

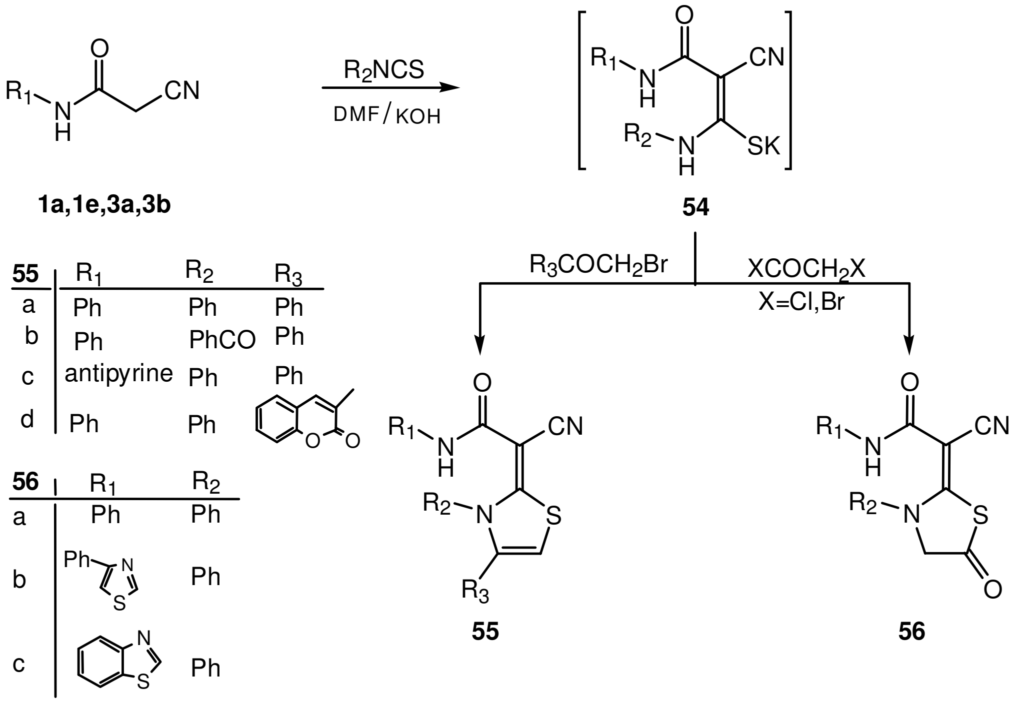
Cyclocondensation of cyanoacetanilide **1a** with thioglycolic acid in boiling glacial acetic acid furnished the thiazolinone derivatives **52** in 95% yields. Formation of **52** is assumed to proceed via the initial nucleophilic addition of the mercapto function to the nitrile group, followed by intramolecular cyclization by the elimination of the water molecule to afford **52**. The thiazolinone **52** was condensed with aromatic aldehydes in boiling ethanol containing a catalytic amount of piperidine to give compounds **53**.[28,29]



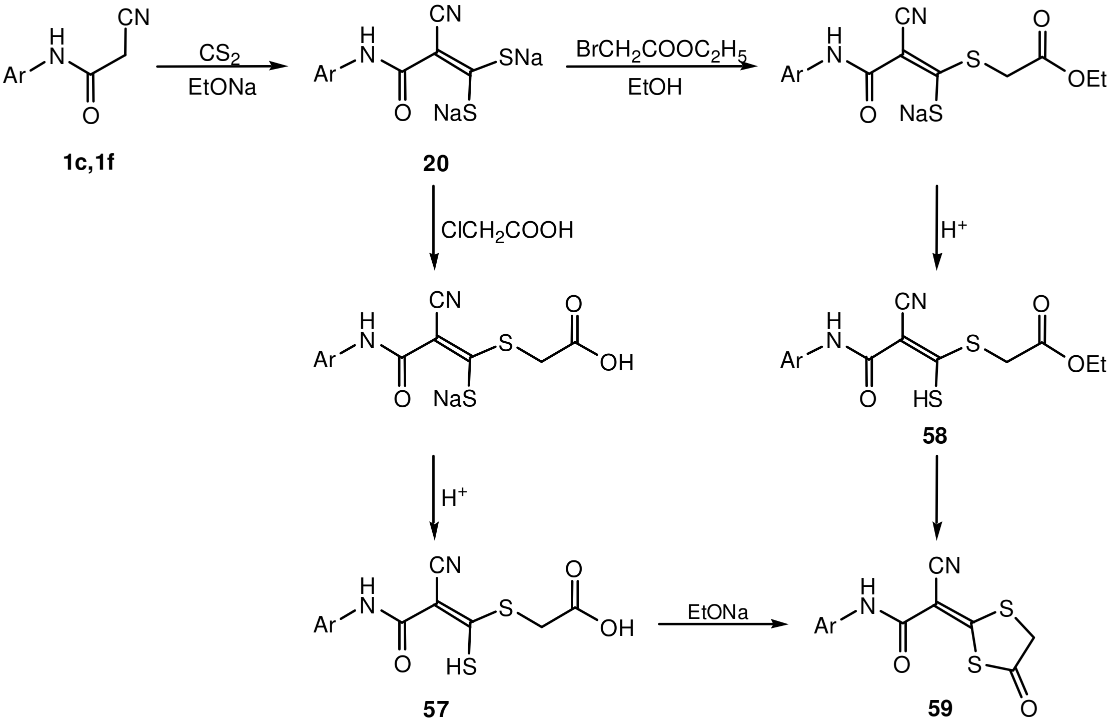
Ar = 4-Me-C_6H_4, 4-MeO-C_6H_4

Scheme 25

The active methylene group in the cyanoacetamides **1a, 1e, 3a, 3b** readily adds to isothiocyanate derivatives in DMF containing potassium hydroxide to give the non-isolable enaminonitrile **54**, which underwent heterocyclization upon treatment with α-halocarbonyl compounds to give the corresponding thiazole derivatives **55** and **56**.[3,13,30–32]



Scheme 26



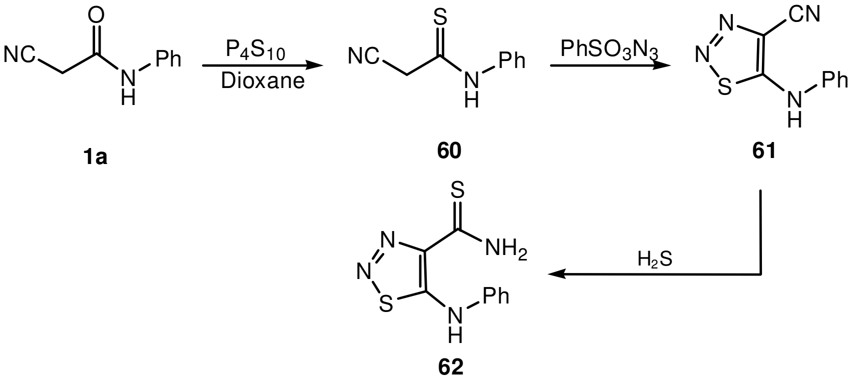
Scheme 27

A novel and efficient method for the synthesis of 1,3-dithiolan-2-ones **59** was recently reported by Elgemeie and coworkers. Thus, treatment of cyanoacetamides **1c, f** with carbon disulfied and sodium ethoxide gave the corresponding ketene diothioacetals **20**. Alkylation of **20** with chloroacetic acid furnished the monoalkylated product **57**. When **57** was refluxed in ethanolic sodium ethoxide, it underwent heterocyclization to give the corresponding 1,3-dithiolane derivatives **59**. Compound **59** can also be obtained by alkylation of the dithiolate **20** with ethyl bromoacetate, followed by heterocyclization of the resulting acyclic product **58**.[33]

Synthesis of 5 Membered Ring with 3 Hetero Atoms

Thiadiazole derivatives

Dankova and coworkers have reported that cyanothioacetanilide **60** could be obtained by boiling **1a** with P_4S_{10} in dioxane. Treatment of **60** with azidobenzenesulfite gave 5-anilino-1,2,3-thiadiazole-4-carbonitrile **61**. Thiation of **61** with hydrogen sulfide furnished 5-anilino-1,2,3-thiadiazole-4-carbothioamide **62**.[34,35]

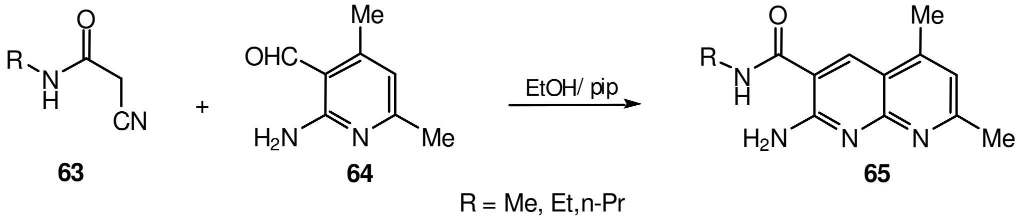


Scheme 28

Synthesis of 6 Membered Ring with 1 Hetero Atom

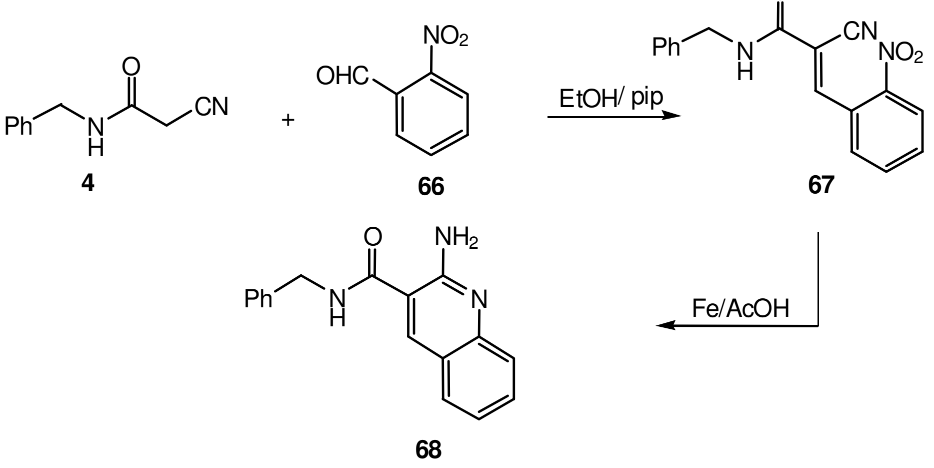
Pyridine derivatives

The Friedlander cyclocondensation of 2-amino-4,6-dimethyl nicotinaldehyde **64** with cyanoacetamide derivatives **63** in boiling ethanol containing a catalytic amount of piperidine gave 1,8-naphthyridine derivatives **65**.[36]



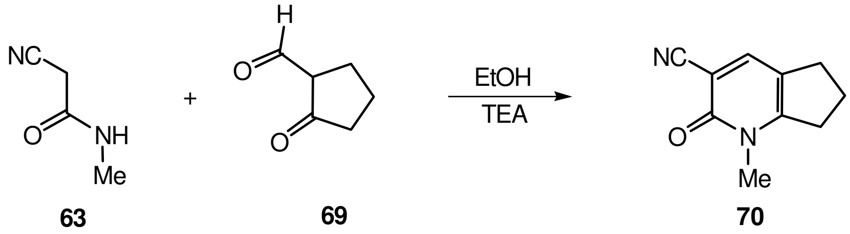
Scheme 29

The Knoevengel condensation of *N*-benzyl-2-cyanoacetamide **4** with *o*-nitrobenzaldehyde **66** afforded cyanocinnamides **67**. Reductive cyclization of **67** with iron in boiling acetic acid gave 2-amino-*N*-benzylquinoline-3-carboxamide **68**.[37]



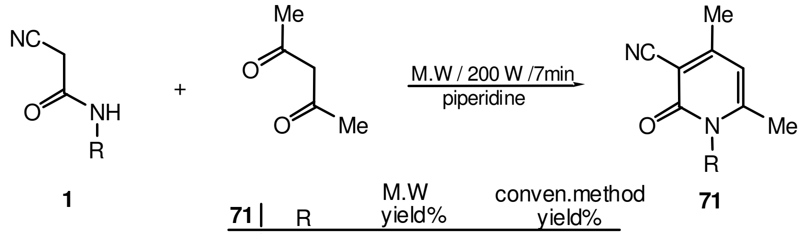
Scheme 30

Treatment of cyanoacetamide derivative **63** with 2-formylcyclopentanone **69** in boiling ethanol afforded 2,5,6,7-tetrahydro-1-methyl-2-oxo-1*H*-cyclopenta[*b*] pyridine-3-carbonitrile **70**.[38]



Scheme 31

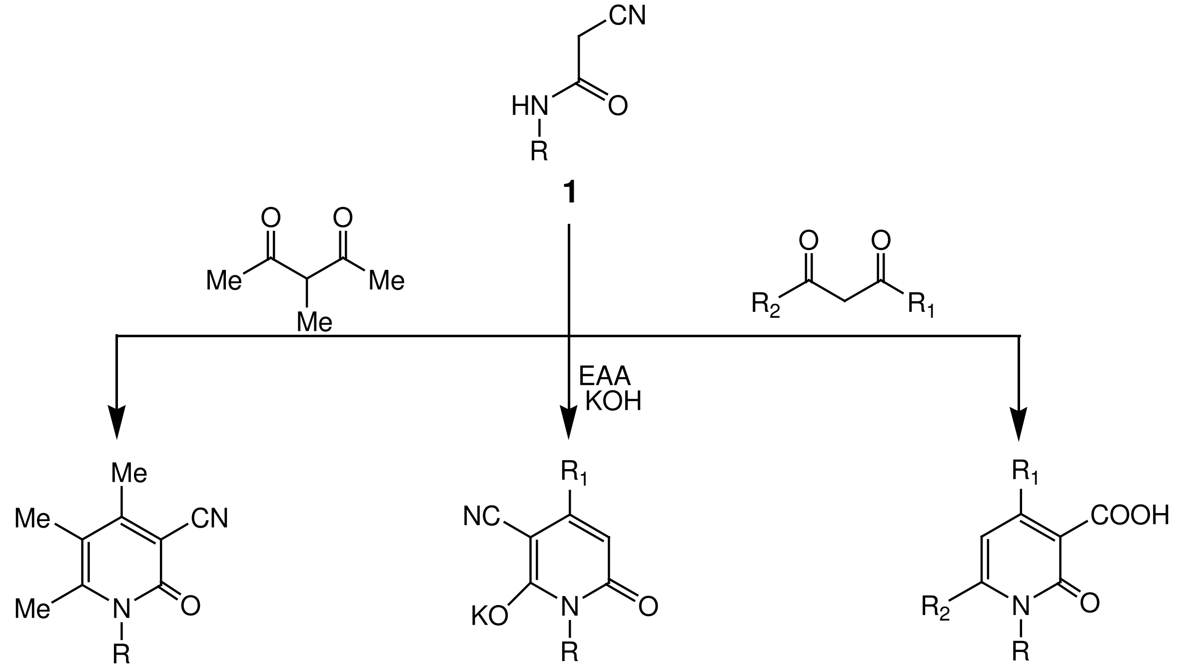
Taking the advantages of microwave irradiation such as short reaction times, the absence of solvent reduces the risk of explosion, simplifies the workup and the products are high in yield and purity, which encouraged Mijin and coworkers to investigate the yields % of the reaction of **1** with acetylacetone. Thus, refluxing of cyanoacetanilides **1** with acetylacetone furnished 4-substituted phenyl-4,6-dimethyl-3-cyano–2-pyridones **71**.[39]



71	R	M.W yield%	conven.method yield%
a	ph	96	75
b	4-MeO-C_6H_4	95	72
c	4-Me-C_6H_4	97	75
d	4-NO_2-C_6H_4	84	64

Scheme 32

The cyclocondensation of cyanoacetamide derivatives **1** with β-diketones in boiling ethanol containing a catalytic amount of a base yielded pyridine-2-ones **72**, **73**, and **74**.[40−42]



74

R = Ph, 4-Me-Ph, 4-MeO-Ph

73

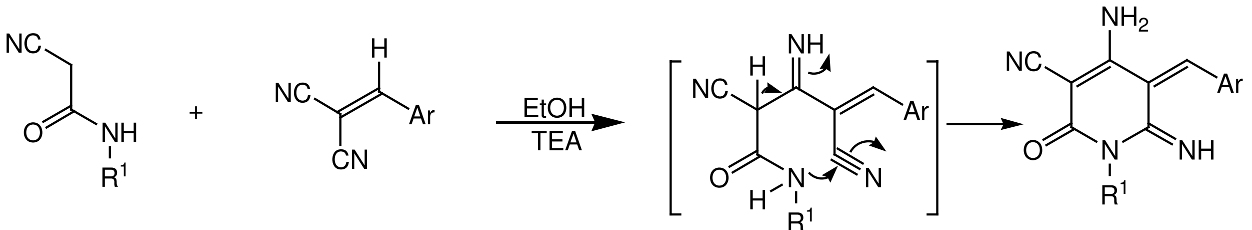
R = Ph, R^1 = Me

72

R = Ph, R^1 = R^2 = Me

Scheme 33

The Michael addition of cyanoacetamides **1a, 1m** to arylidene malononitrile in refluxing ethanol containing a catalytic amount of triethylamine furnished the pyridinone derivatives **76**.[43,44]



1a,1m

73

75

76

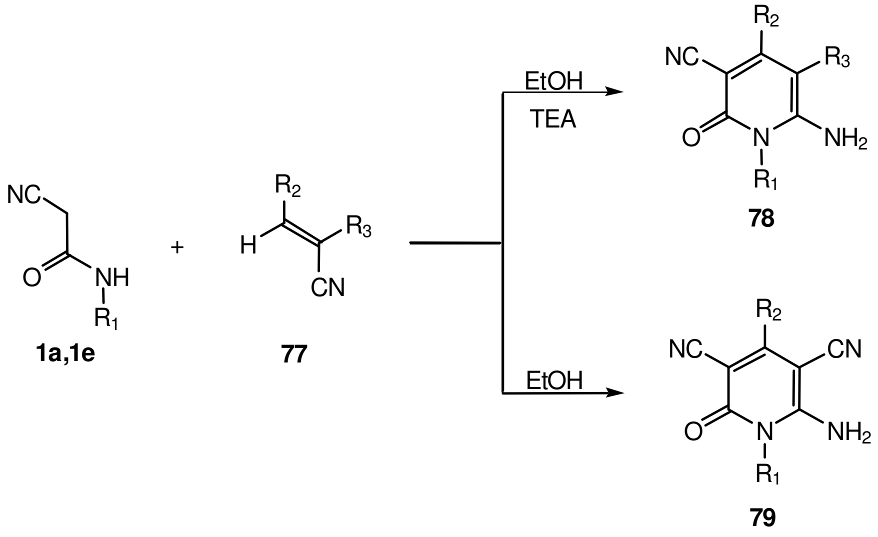
76	R^1	Ar
a	Ph	3-Pyridyl
b	Ph	2-furyl
c	2-Pyridyl	3-Pyridyl
d	Ph	Ph

Scheme 34

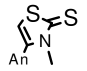
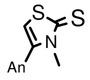
In addition, it has been reported that the pyridine-2-ones **78** and **79** were obtained via the treatment of cyanoacetamide derivatives **1a, 1e** with acrylonitrile derivatives **77** in a basic medium. The reaction mechanism for the formation of **78** and **79** was assumed to proceed via the initial Michael addition of the activated methylene group to the double bond of the arylidene **77** to afford the non-isolable Michael adduct, which cyclized to give pyridine-2-ones **78** and **79**.[30,45,46]

The Knoevenagel condensation of (*N*-pyridyl)-2-cyanoacetamide **1m** with benzaldehyde in refluxing ethanol containing a catalytic amount of piperidine resulted in the formation of (*E*) – *N*-pyridyl-2-cyanoacrylamide **80**. The reaction of **80** as a Michael acceptor with malononitrile in boiling ethanol containing a few drops of piperidine afforded *N*-pyridylpyridinone derivative **81.**[47,48]

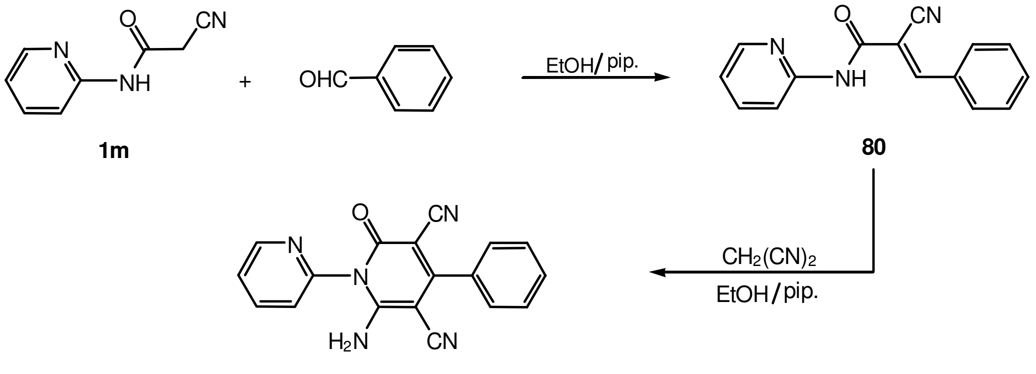
Condensation of cyanoacetamide derivatives **82** with ketene dithioacetals **83** in DMF catalyzed by anhydrous potassium carbonate afforded pyridine-2–one derivatives **84.**[49,50]



78	R_1	R_2	R_3
a	Ph	Ph	CONHPh
b	Ph	p-MeOPh	CONHPh

79	R_1	R_2	R_3
a	antipyrine	Ph	CN
b	antipyrine	p-Me Ph	CN
c	antipyrine	p-MeOPh	CN
d		p-BrPh	CN
e		2-thienyl	CN

Scheme 35

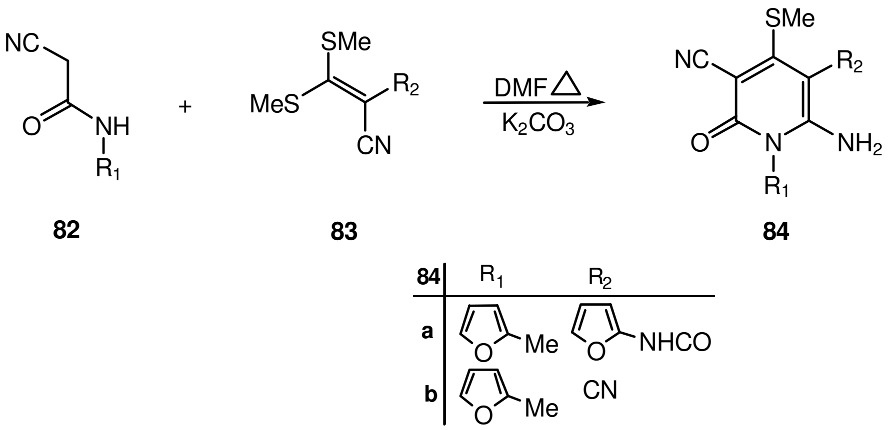


Scheme 36

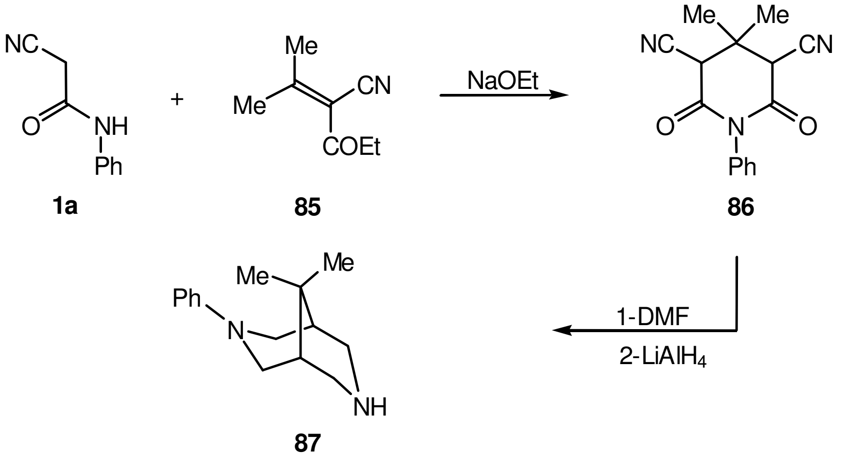
Cyclocondensation of cyanoacetanilide **1a** with ethyl 3-cyano-2-methyl-but-2-enate **85** in a basic medium gave pyridine-2,6-dione derivative **86**. Reductive cyclization **86** with lithium aluminum hydride afforded bispidine derivative **87**.[51]

Treatment of cyanoacetanilide **1a** with 2-(2-bromo-2-thiocyanate-1-phenyldiene)malononitrile **88** in a basic medium furnished pyridinone **89**.[52]

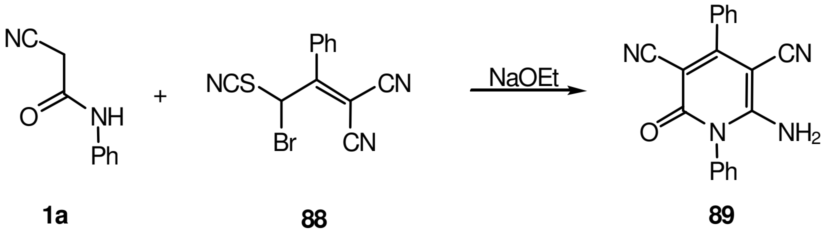
The base catalyzed cyclocondensation of cyanoacetanilide **1a** with 3,5-diphenyl-1,2-dithiolium perchlorate **90** delivered the pyridinone derivative **91** in good yield.[53]



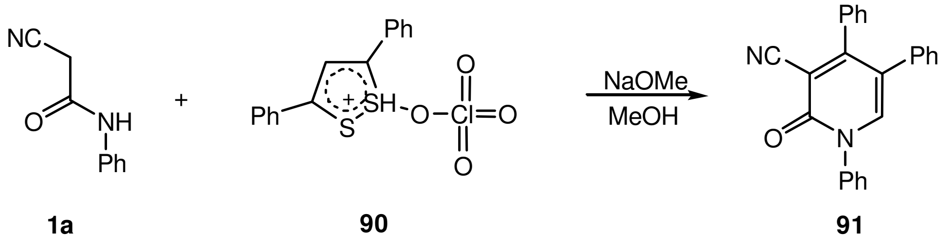
Scheme 37



Scheme 38

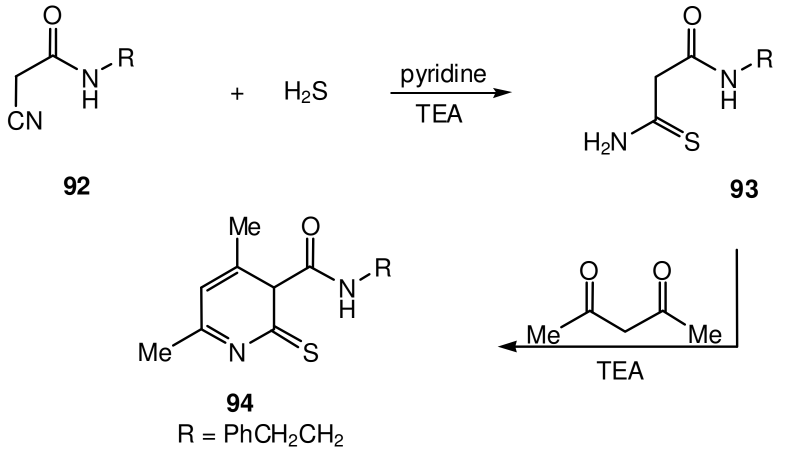


Scheme 39



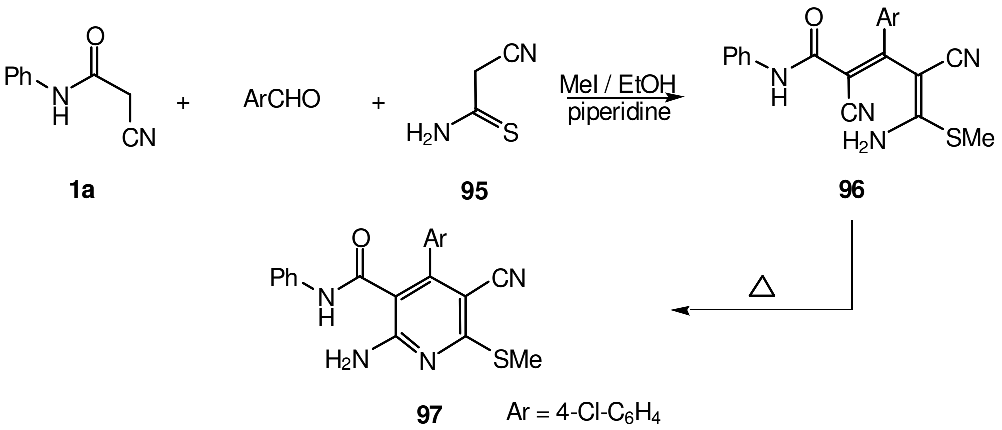
Scheme 40

The monothiomalonamide **93** was prepared from the reaction of 2-cyano-*N*‘-phenylacetohydrazide **92** with hydrogen sulfide. Treatment of **93** with acetylacetone in refluxing ethanol containing a catalytic amount of triethylamine gave pyridine-2-thione derivative **94**.[54]



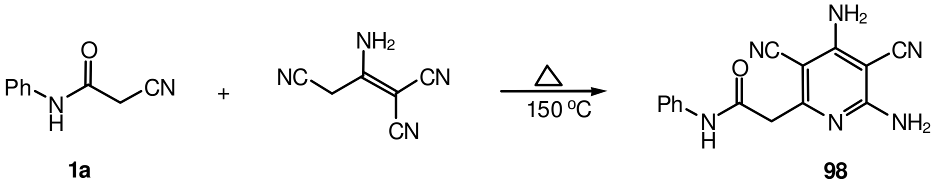
Scheme 41

The one-pot reaction of cyanoacetanilide **1a**, 4-chlorobenzaldehyde, cyanothioacetamide **95**, and methyl iodide in boiling ethanol in the presence of piperidine gave the isolable intermediate ketene *N*, *S*-acetal **96**, which underwent heterocyclization upon prolonged heating to give the pyridine derivative **97**.[55]



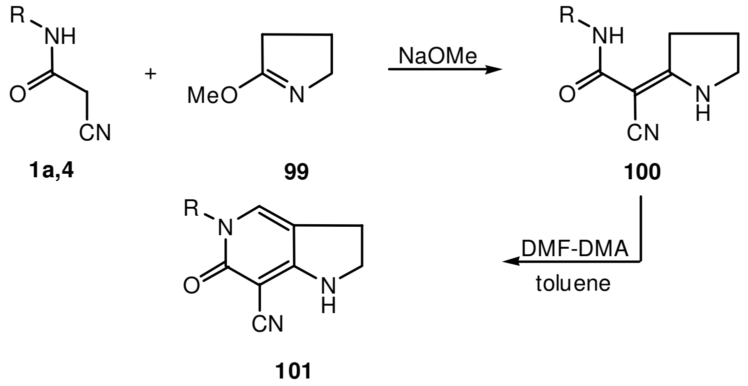
Scheme 42

Heating of **1a** with malononitrile dimer under solvent-free conditions gave the pyridine derivative **98**, which could also be obtained when **1a** was heated with 2 moles of malononitrile in boiling ethanol containing a few drops of triethyl amine.[56]



Scheme 43

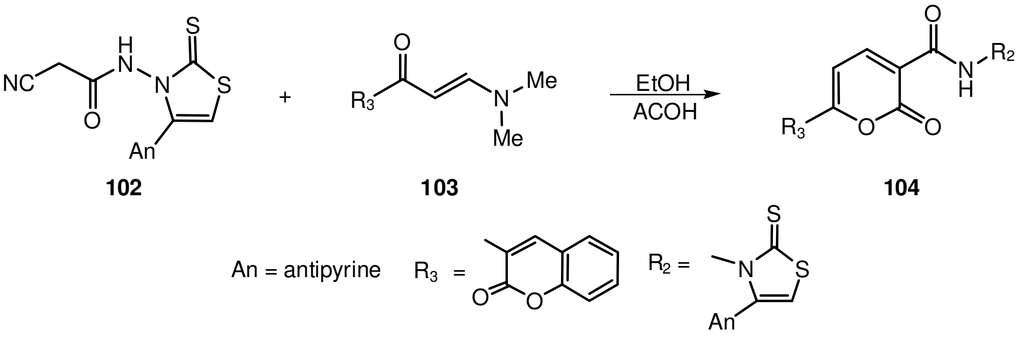
Enaminonitriles **100** were prepared in 75% yields from the reaction of cyanoacetamide derivatives **1a, 4**, and 3,4-dihydro-5-methoxy-2H-pyrrole **99** in a basic medium. Treatment of **100** with dimethylformamide dimethylacetal (DMF-DMA) in boiling dry toluene furnished pyrrolo[2,3−*c*]pyridinone derivatives **101**.[57]



Scheme 44

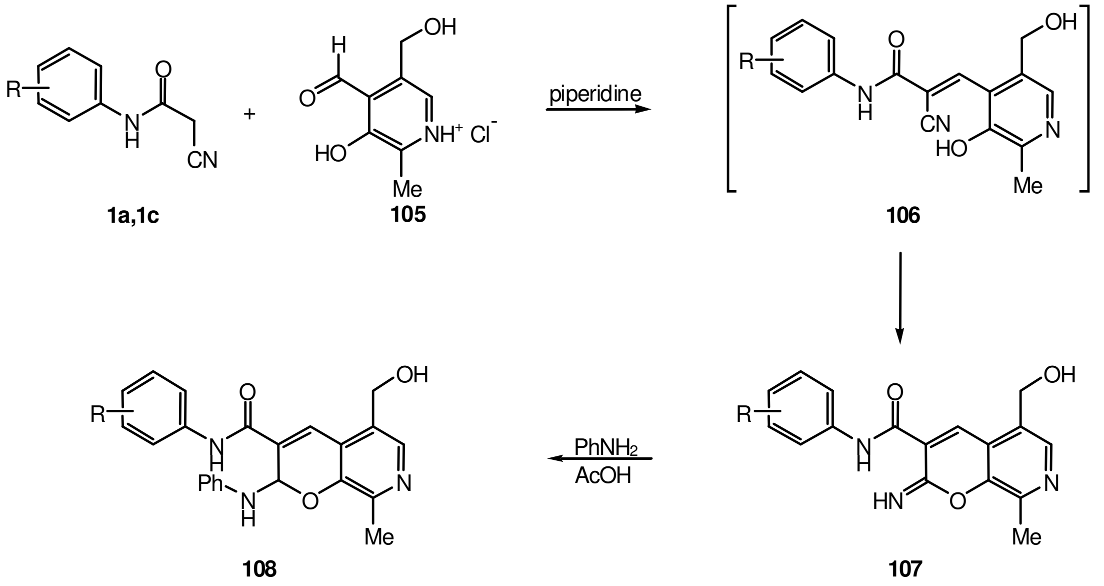
Pyrane derivatives

El-Taweel et al. have reported that heating of cyanoacetamide derivative **102** with enaminone **103** in boiling ethanol containing a few drops of acetic acid delivered α-pyrone derivatives **104**.[46]



Scheme 45

The interaction of an equimolar amounts of pyridoxal hydrochloride **105** with cyanoacetanilides **1a, 1c** in refluxing absolute methanol containing a catalytic amount of piperidine afforded the 2-H-pyrano[2,3-*c*] pyridine **107**. The reaction mechanism proceeds smoothly via the formation of the non-isolable intermediate **106**. 5-Hydroxymethyl-2-imino-8-methyl-2H-pyrano[2,3−*c*]pyridine-3-carboxamide **107** can readily react with nucleophilic reagents such as aromatic amines in boiling acetic acid to give the N-arylimino-pyrano[2,3−*c*]pyridine derivatives **108**.[58]

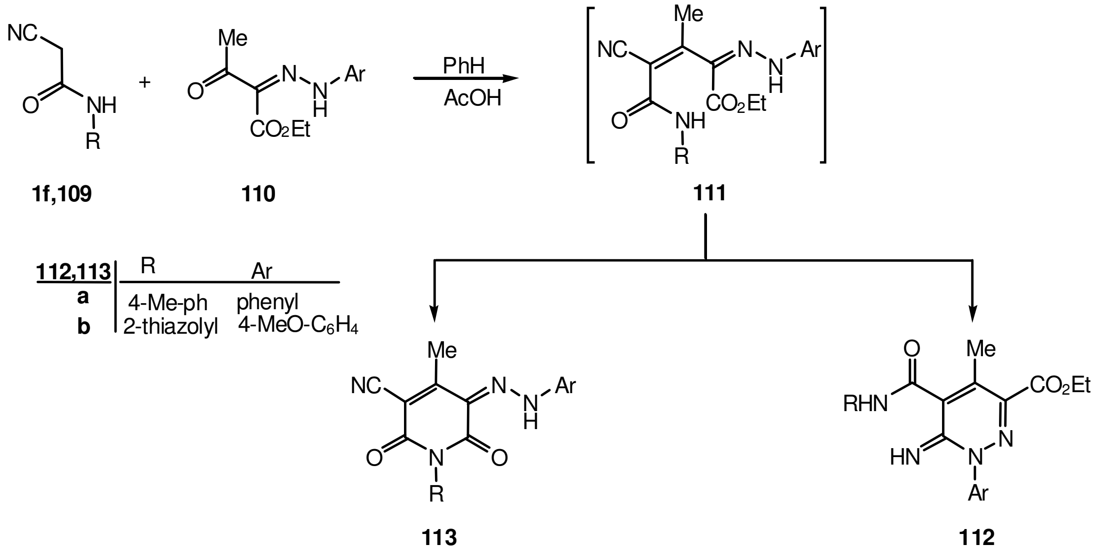


Scheme 46

Six Membered Ring with 2 Hetero Atoms

Pyridazine derivatives

Elrady and coworkers have recently reported a convenient and facile synthesis of pyridazine **112** and pyridindione **113** derivatives via the reaction of cyanoactamide derivatives **1f, 109** with ethyl 2-arylhydrazono-3-butyrates **110** in a boiling mixture of benzene/acetic acid. The key precursor for the products is the expected Knoevnagel condensation intermediate **111**. Elimination of the ethanol molecule yielded the isolable intermediate pyridindione **113**, while an intramolecular cycloaddition of hydrazohydrogen to the cyano group afforded the pyridazine derivative **112**.[59]

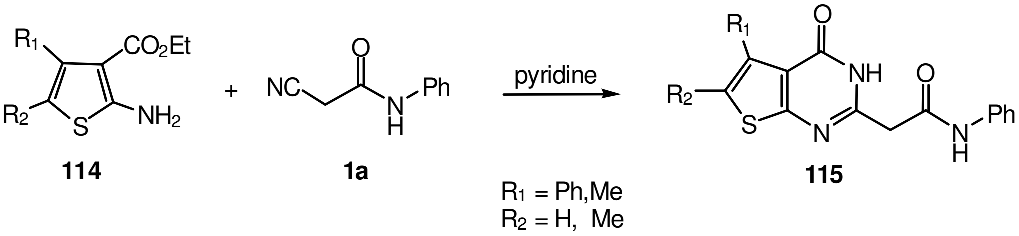


112,113	R	Ar
a	4-Me-ph	phenyl
b	2-thiazolyl	4-MeO-C_6H_4

Scheme 47

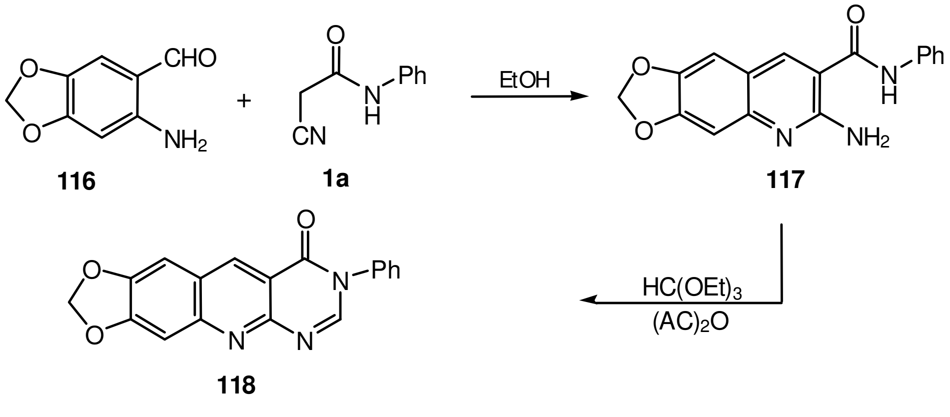
Pyrimidine derivatives

The interaction of cyanoacetanilide **1a** with ethyl 2-amino-3-ethoxycarbonylthiophenes carboxylate **114** in boiling pyridine gave the dihydrothieno [2,3-*d*]pyrimidinones **115.**[60,61]



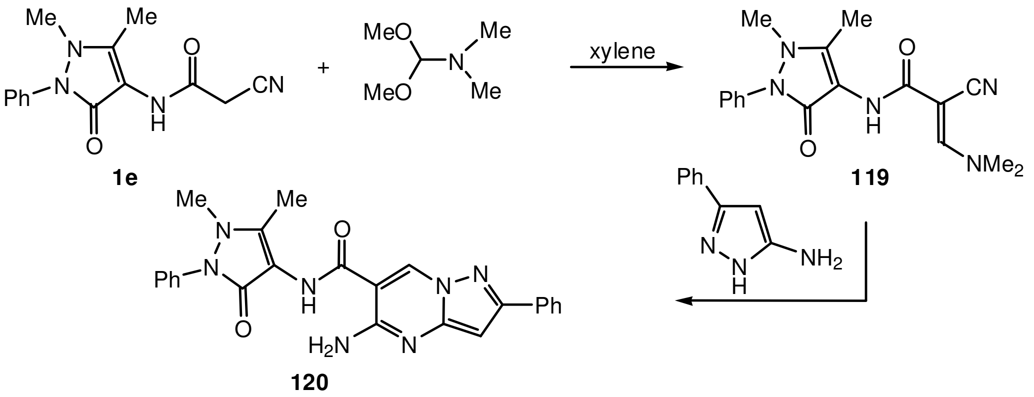
Scheme 48

Cyclocondensation of cyanoacetanilide **1a** and 2-aminopiperonal **116** in refluxing ethanol gave the corresponding quinoline derivative **117**. The reaction mechanism for the formation of **117** involves the formation of a non-isolable arylidene intermediate, followed by an intramolecular addition of the amino group to the nitrile function. Compound **117** was transformed to **118** by heating with a mixture of triethylorthoformate and acetic acid.[62]



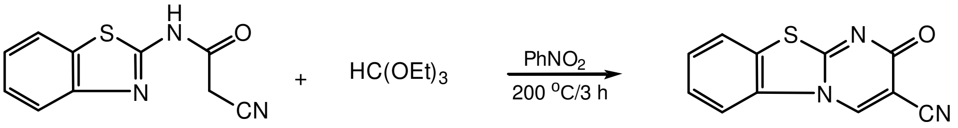
Scheme 49

Reaction of 4-antipyrinylcyanoacetamide **1e** with DMF-DMA in boiling dry xylene afforded the corresponding enaminonitrile derivative **119** in good yield. Treatment of the enaminonitrile **119** with 5-phenyl-3-aminopyrazole in boiling DMF containing a catalytic amount of piperidine resulted in the formation of pyrazolo[1,5-*a*]pyrimidine derivative **120**.[30]



Scheme 50

Heterocyclization of *N*-(benzothiazol-2-yl)cyanoacetamide **3b** with triethylorthoformate in boiling nitrobenzene furnished 2-oxo-2*H*-pyrimido[3,1-*b*]benzothiazole-3-carbonitrile **121** in 79% good yield.[8]

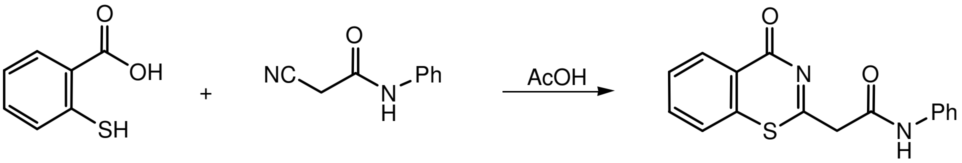


3b **121**

Scheme 51

Thiazine derivatives

Kandeel and coworkers have reported that treatment of cyanoacetanilide **1a** with 2-sulfanyl benzoic acid **122** in boiling acetic acid delivered 2-(4-oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl)-*N*-phenylacetamide **123**.[63]



122 **1a** **123**

Scheme 52

Liepa et al. have synthesized 2-(5,6-dihydro-4,4-dimethyl-4*H*-1,3-thian-2-yl)-*N*−(2- trifluoromethoxy) phenylacetamide **125** via the treatment of 2-trifluoromethoxy cyanoacetanilide **1n** with 4-sulfanyl-2-methyl-butan-2-ol **124** in methane sulfonic acid.[64]

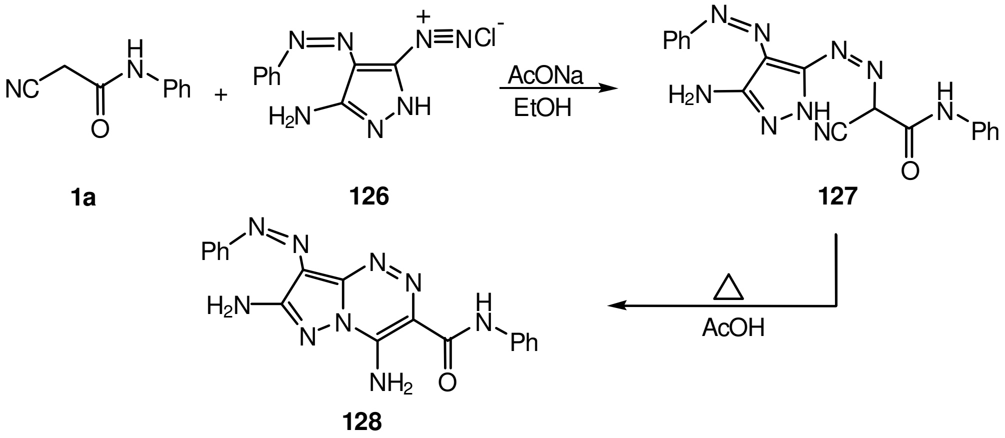
1n **124** **125**

Scheme 53

Six Membered Ring with 3 Hetero Atoms

Triazine derivatives

The diazo coupling reaction of the active methylene of cyanoacetanilide **1a** with pyrazolyl diazonium chloride **126** in ethanol buffered with sodium acetate, at 0-5 °C, gave the corresponding hydrazone derivative **127**. Cyclization of **127** into pyrazolo[5,1-*c*]triazine **128** was achieved upon refluxing in acetic acid. The reaction mechanism for the formation of **128** involves the nucleophilic attack of the ring nitrogen atom on the cyano group in **127**.[30,65,66]



Scheme 54

Biological Activities

Cyanoacetamide derivatives and related heterocycles moieties have generated recent interest due to their interesting biological[67–69] and pharmaceutical[51,60,70] activities. These derivatives have anti-microbial[58] activities and have been found useful as herbicidals[71] and plant growth regulators;[40] in addition, they have been reported to be active against neoplastic disorder.[72]

Furthermore, these derivatives have been used as kynurenine-3-hydroxykase inhibitors.[73,74]

They have also been used for their anti-inflammatory,[72] anti-viral,[14] anti-bacterial,[76,77] anti-tumor,[78] neoplasm inhibitory,[79] tyrosine kinase inhibitory,[80] and analgesic properties,[81] and for the treatment of disorders related to vasculogenesis.[82]

Conclusion

The present survey has clearly demonstrated that cyanoacetamide may be successfully used to synthesize a wide variety of heterocycles of academic and pharmaceutical interest. Moreover, in general, the desired compounds may be obtained in a single step with high yield.

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