

Utility of cyanoacetic acid hydrazide in heterocyclic synthesis

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Abstract

This review describes the synthesis and reactions of cyanoacetic acid hydrazide as building block for the synthesis of polyfunctionalized heterocyclic compounds with pharmacological interest.

Keywords: Cyanoacetic acid hydrazide, pyrazoles, thiadiazoles, pyridines, pyrans, pyridazines, pyrimidines, annelated heterocycles

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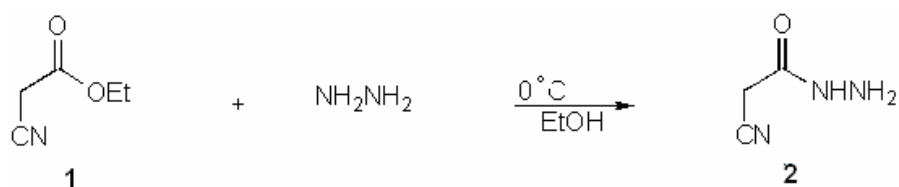
- 4.6.1. Thiadiazines
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1. Introduction

Cyanoacetic acid hydrazide is a versatile and convenient intermediate for the synthesis of wide variety of heterocyclic compounds. The β -functional nitrile¹⁻⁴ moiety of the molecule is a favorable unit for addition followed by cyclization or *via* cycloaddition with numerous reagents providing heterocyclic compounds of different ring sizes with one or several heteroatoms that are interesting as pharmaceuticals,^{5,6} as herbicides,⁷ as antibacterial agents,⁸ and as dyes.^{9,10} Their reactions with dinucleophiles usually result in the formation of polycyclic ring systems which may be the skeleton of important heterocyclic compounds. In previous publications, novel synthesis of azoles,^{11,12} azines,¹³ and azoloazines,¹⁴ had been reported utilizing β -functional nitriles as starting components. Among the β -functional nitriles, cyanoacetic acid hydrazide and their analogues are especially important starting materials or intermediates for the synthesis of various nitrogen-containing heterocyclic compounds. Our research deals with the effective use of cyanoacetic acid hydrazide in the synthesis of a variety of polyfunctional heterocyclic compounds with biological interest.

2. Synthesis of Cyanoacetic Acid Hydrazide

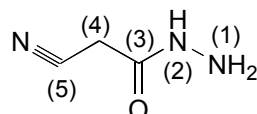
Cyanoacetic acid hydrazide was obtained by careful addition of hydrazine hydrate to ethyl cyanoacetate in ethanol with stirring at 0°C.¹⁵



Scheme 1

3. Chemical Reactivity

Cyanoacetic acid hydrazide can act as an ambident nucleophile, that is, as both an *N*- and a *C*-nucleophile. On treatment of cyanoacetic acid hydrazide with various reagents, the attack can take place at five possible sites: the nucleophile is able to attack the carbon of the carbonyl function (position 3) and the carbon atom of the nitrile function (position 5). While the active methylene group (position 4) and amino groups (positions 1 and 2) are able to attack electrophiles.



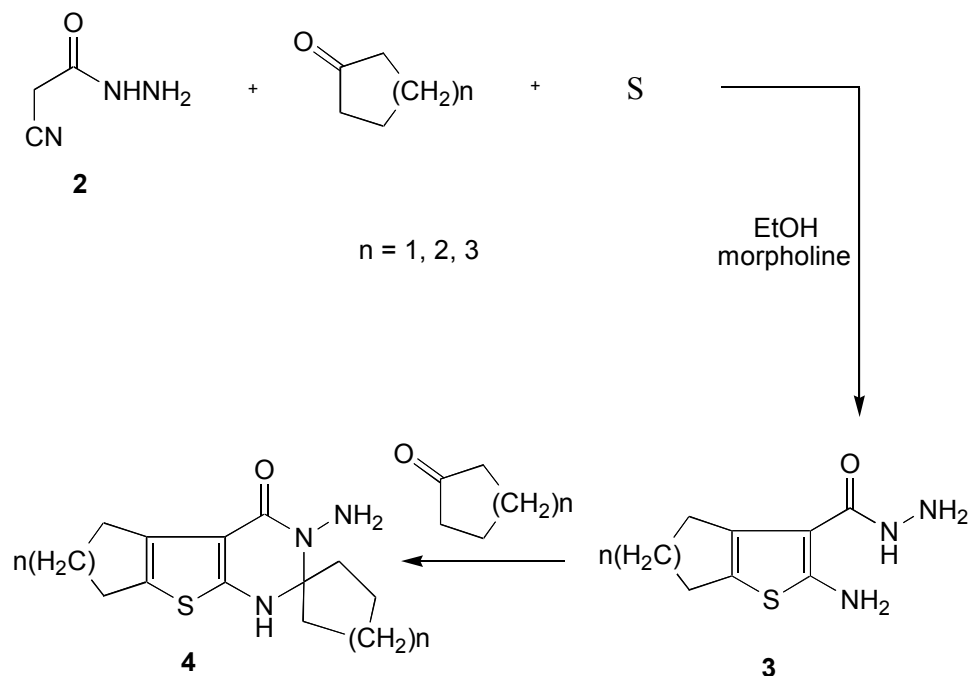
4. Reactions of Cyanoacetic Acid Hydrazide

The reactions of cyanoacetic acid hydrazide with numerous reagents are classified separately in one category due to the huge number of references. We have arranged this huge volume of data in terms of the type of the heterocycles formed, starting with five and six membered rings in order of increasing number of heteroatoms. Such systematic treatment provides a clear idea about the synthetic possibilities of the method and may be useful in selecting the direction of further research.

4.1. Synthesis of five-membered rings with one heteroatom

4.1.1. Thiophenes and their fused derivatives

Reaction of compound **2** with cyclic ketones and sulfur in the presence of morpholine under Gewald reaction conditions afforded thiophene derivatives **3** and **4**.¹⁶

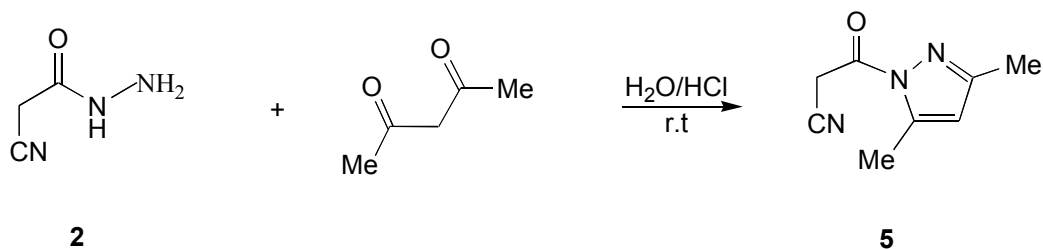


Scheme 2

4.2. Synthesis of five-membered rings with two heteroatoms

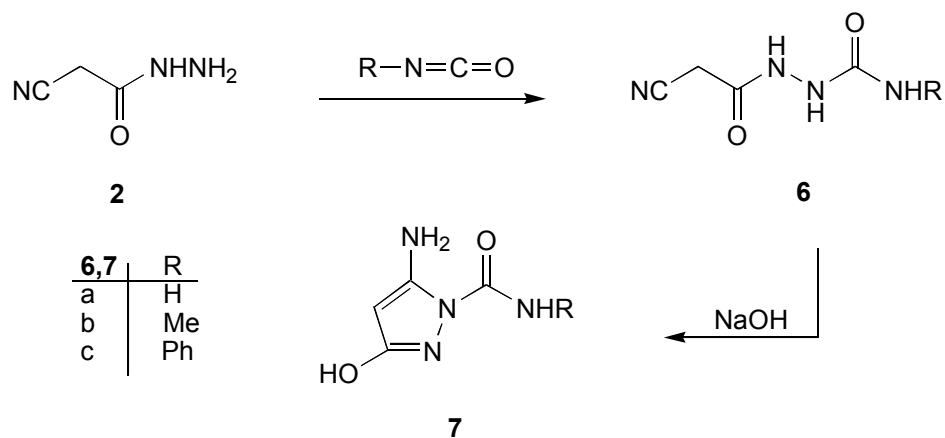
4.2.1. Pyrazoles and their fused derivatives

Treatment of **2** in water containing a catalytic amount of conc. HCl with acetyl acetone at room temperature afforded 1-cyanoacetyl-3, 5-dimethyl pyrazole **5**.¹⁵



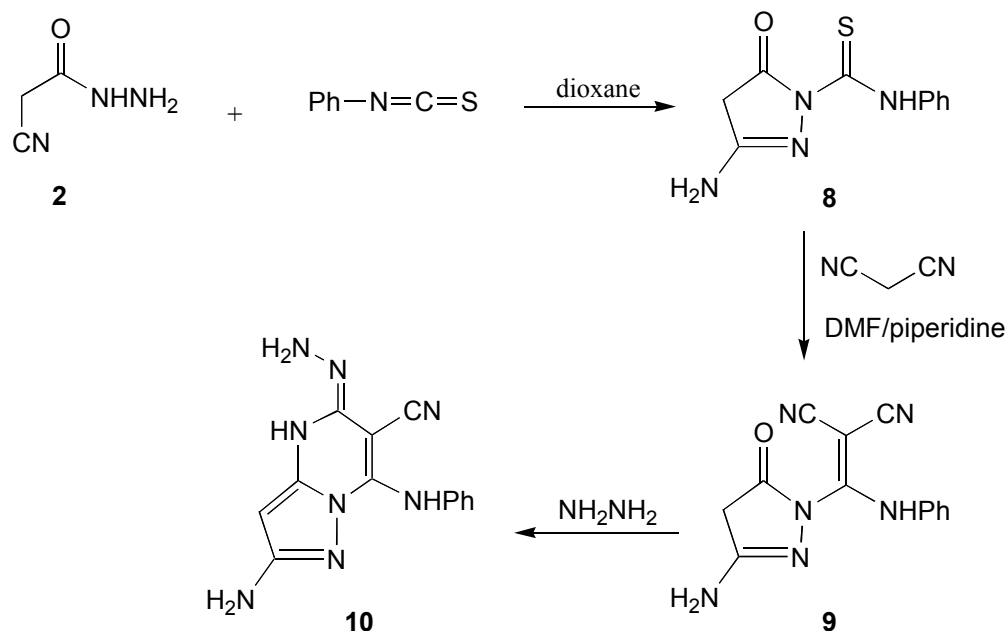
Scheme 3

The reaction of **2** with alkylisocyanate yields alkylcarbamoyl derivative **6** that cyclized into pyrazole derivative **7** up on treatment with 2N sodium hydroxide.¹⁷



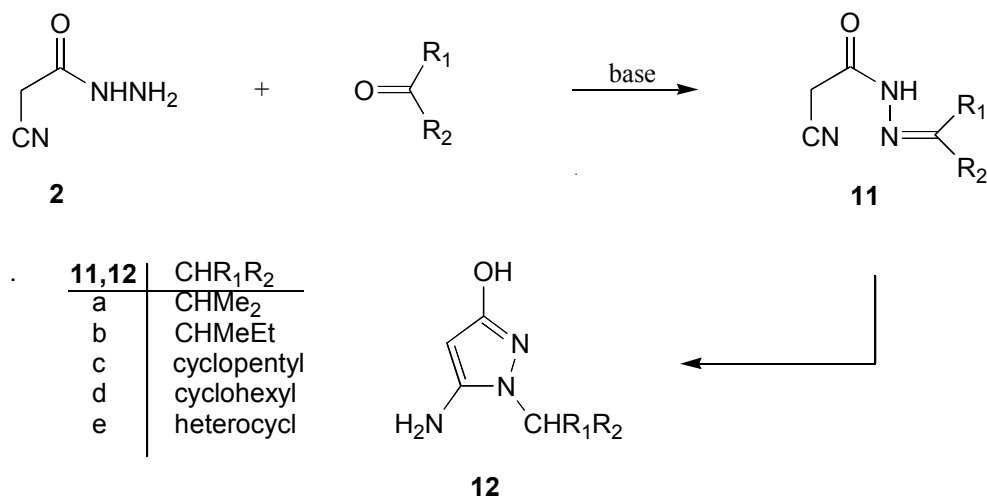
Scheme 4

Refluxing of **2** with phenyl isothiocyanate in basic dioxane solution afforded pyrazolinone derivative **8**. Treatment of **8** with malononitrile in DMF in the presence of piperidine gave [(3-amino-5-imino-4,5-dihydro-1*H*-pyrazol-1-yl)(anilino)methylene]malononitrile **9**, which underwent cyclocondensation with hydrazine hydrate to give pyrazolo[1,5-*a*]pyrimidine derivative **10**.¹⁸



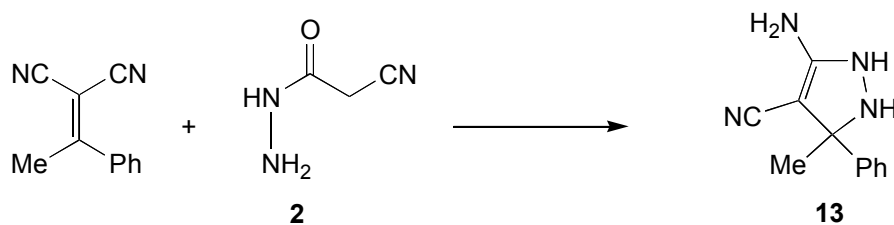
Scheme 5

5-Amino-3-hydroxypyrazole derivatives **12** were prepared from the reaction of **2** with ketones in the presence of a basic catalyst via the cyclization of hydrazone derivatives **11**.¹⁹



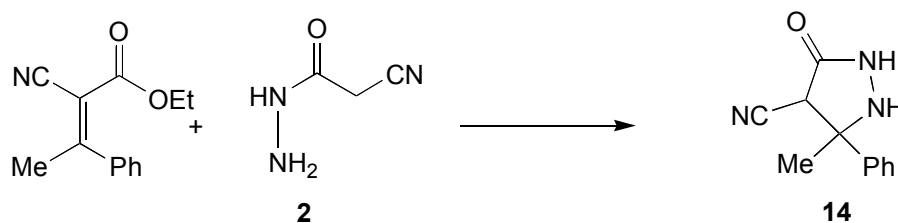
Scheme 6

Elnagdi and coworkers have reported the reaction of 2-(1-phenylethylidene)malononitrile with **2** furnished pyrazoline derivative **13**.²⁰



Scheme 7

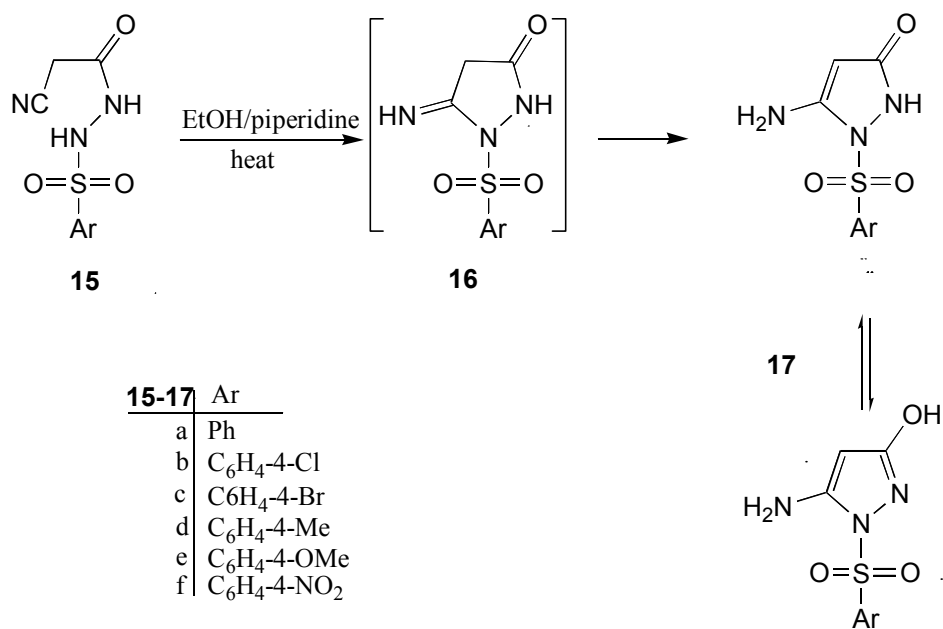
Pyrazolidinone derivative **14** was obtained by treatment of **2** with ethyl 2-cyano-3-phenylbut-2-enoate.²⁰



Scheme 8

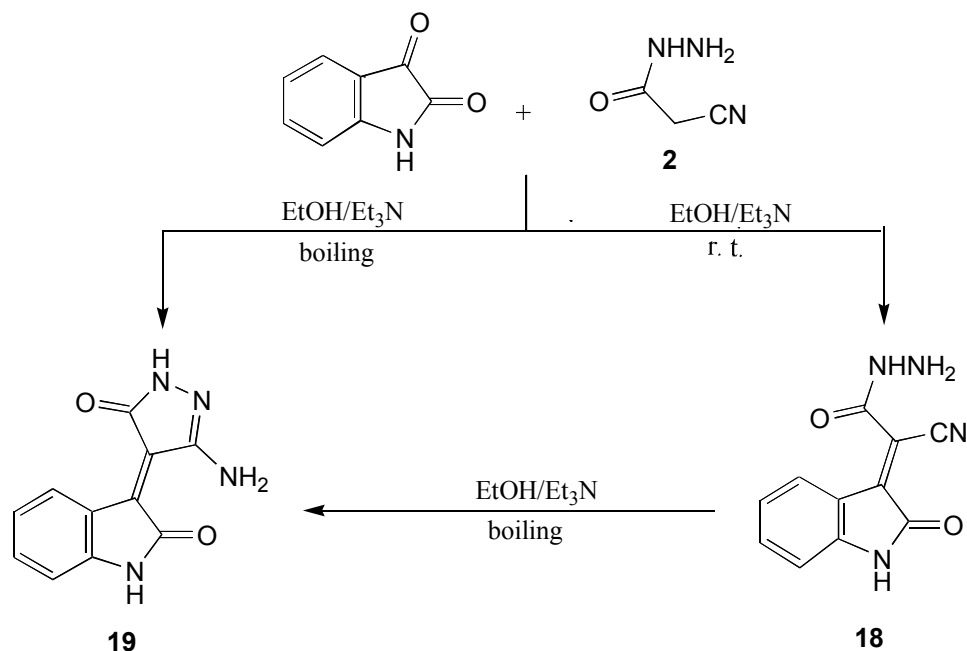
Cyanoaceto-*N*-arylsulfonylhydrazide **15** on refluxing in ethanol containing a catalytic amount of piperidine,²¹ or in presence of potassium hydroxide,²² undergo intramolecular

cyclization to give the 5-amino-1-arylsulfonyl-4-pyrazolin-3-one or the tautomeric 5-amino-1-arylsulfonyl-3-hydroxypyrazole structure **17**.



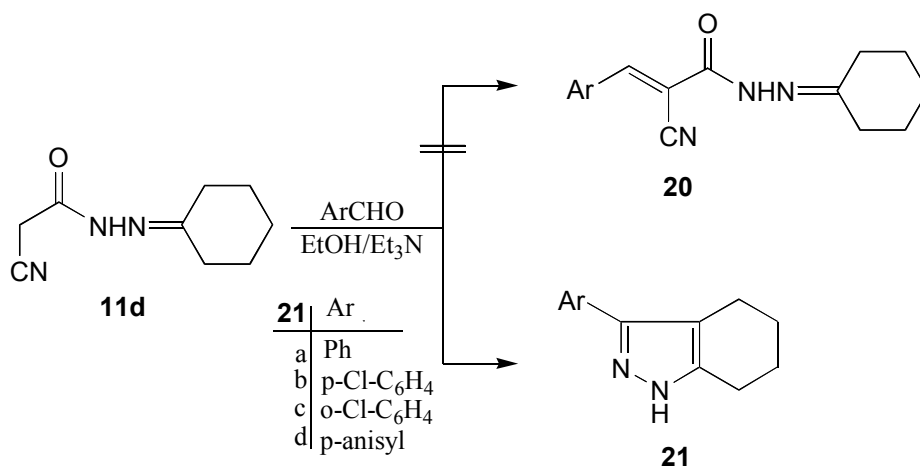
Scheme 9

The reaction of **2** with isatin in ethanol containing a catalytic amount of triethylamine at room temperature furnished the isolated intermediate (*2E*)-2-cyano-2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetohydrazide **18** which cyclized under heating to give (*2E*)-3-(3-amino-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-1,3-dihydro-2*H*-indol-2-one **19**.²³



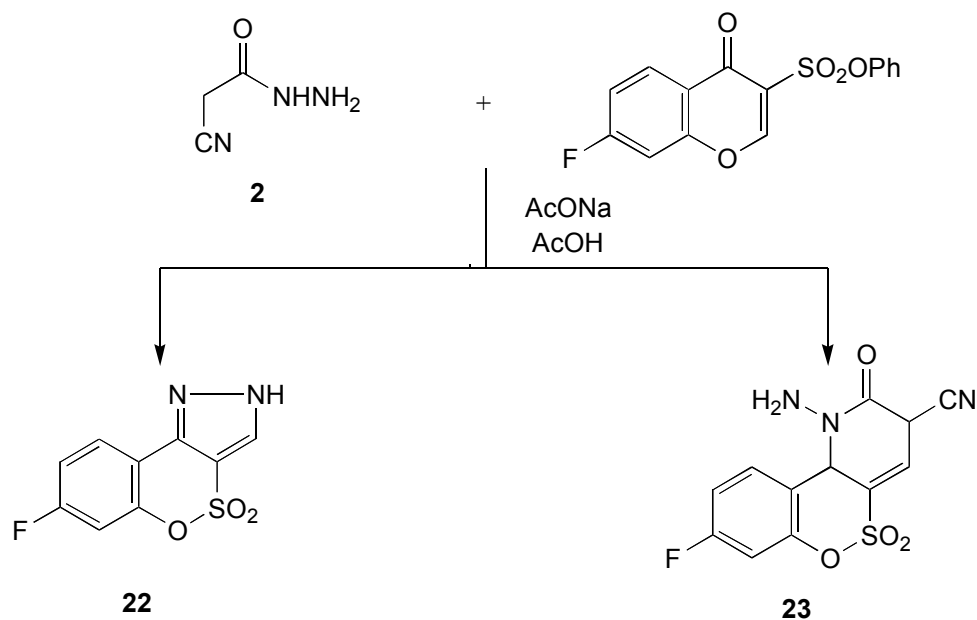
Scheme 10

Condensation of hydrazone derivative **11d** with aromatic aldehyde in ethanolic triethyl amine gave the unexpected 3-aryl-4,5,6,7-tetrahydro-1*H*-indazole **21**.²⁴



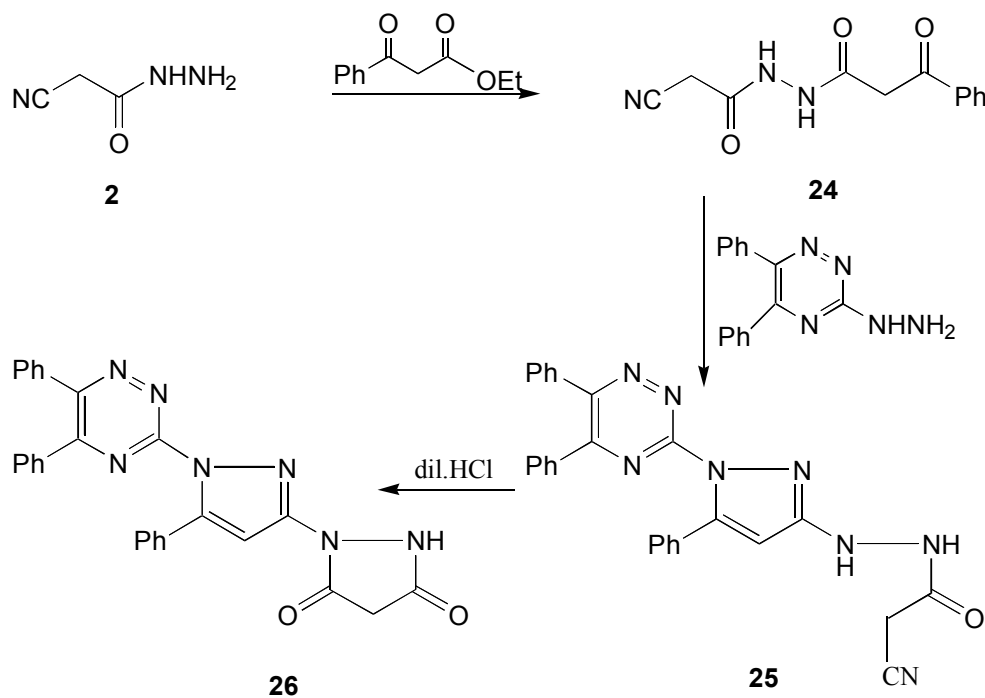
Scheme 11

Treatment of **2** with phenyl 7-fluoro-4-chromone-3-sulfonate in presence of sodium acetate and glacial acetic acid at 100°C afforded a mixture of 7-fluoro-2*H*-[1,2]benzoxathiino[4,3-*c*]pyrazole 4,4-dioxide **22** and 1-amino-8-fluoro-2-oxo-1,2,3,10*b*-tetrahydro[1,2]benzoxathiino[4,3-*b*]pyridine-3-carbonitrile 5,5-dioxide **23**.²⁵



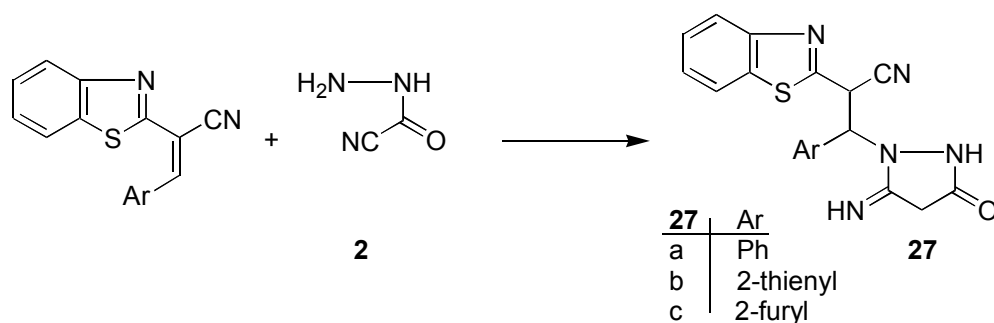
Scheme 12

Reaction of **2** with ethyl benzoylacetate at 140-150°C yield *1N*-cyanoacetyl-2*N*-benzoylacetylhydrazine **24** which underwent cyclocondensation with 3-hydrazino-5,6-diphenyl-1,2,4-triazine in absolute ethanol to yield compound **25** that when treated with dil. hydrochloric acid gives 1-[1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-phenyl-1*H*-pyrazol-3-yl]pyrazolidine-3,5-dione **26**.²⁶



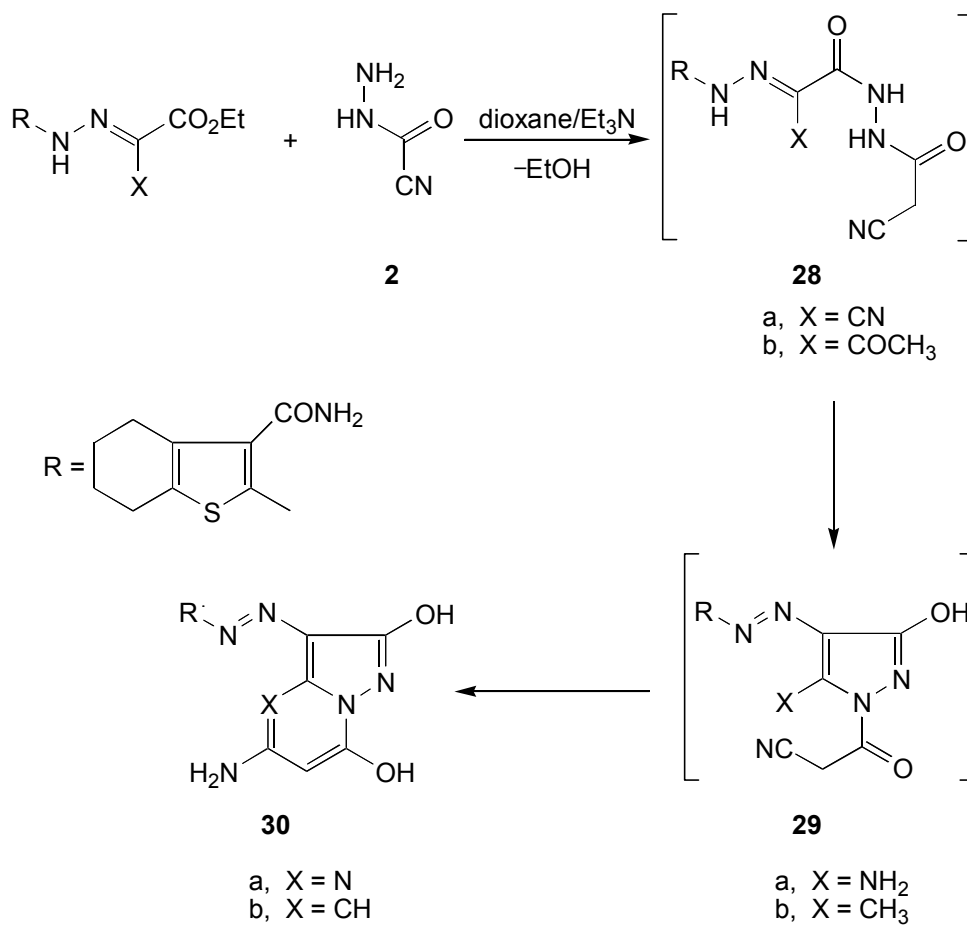
Scheme 13

Cycloaddition of **2** with arylidene of 2-cyanomethyl-1,3-benzothiazole yielded 3-aryl-2-(1,3-benzothiazol-2-yl)-3-(5-imino-3-oxopyrazolidin-1-yl)propanenitrile **27**.²⁷



Scheme 14

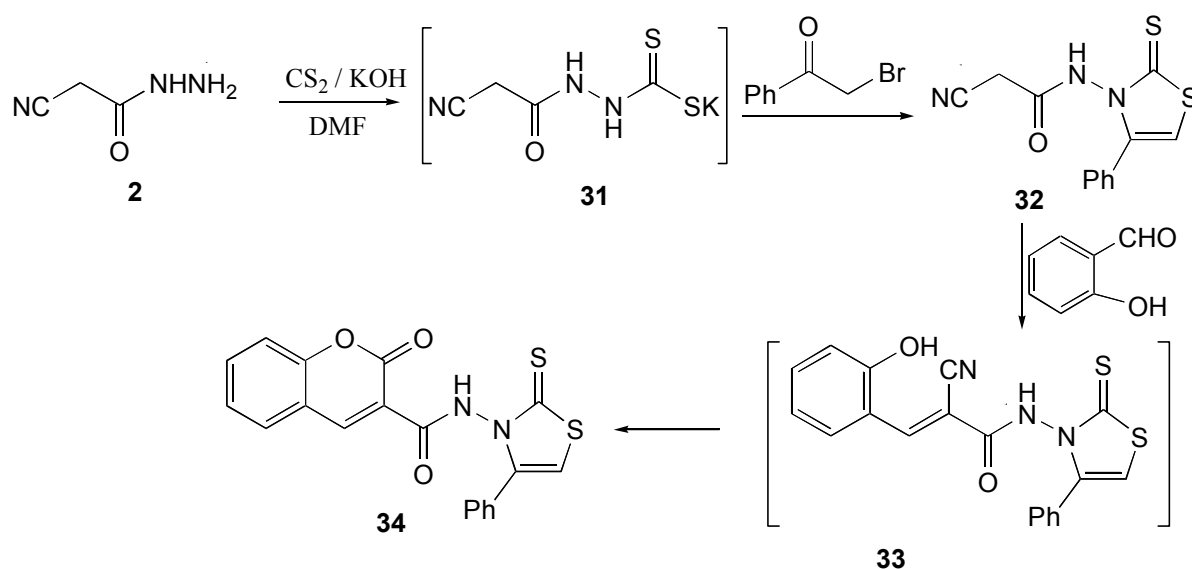
Compound **2** reacts with hydrazone derivatives in refluxing dioxane containing a catalytic amount of triethylamine to yield pyrazoloazine derivatives **30**.²⁸



Scheme 15

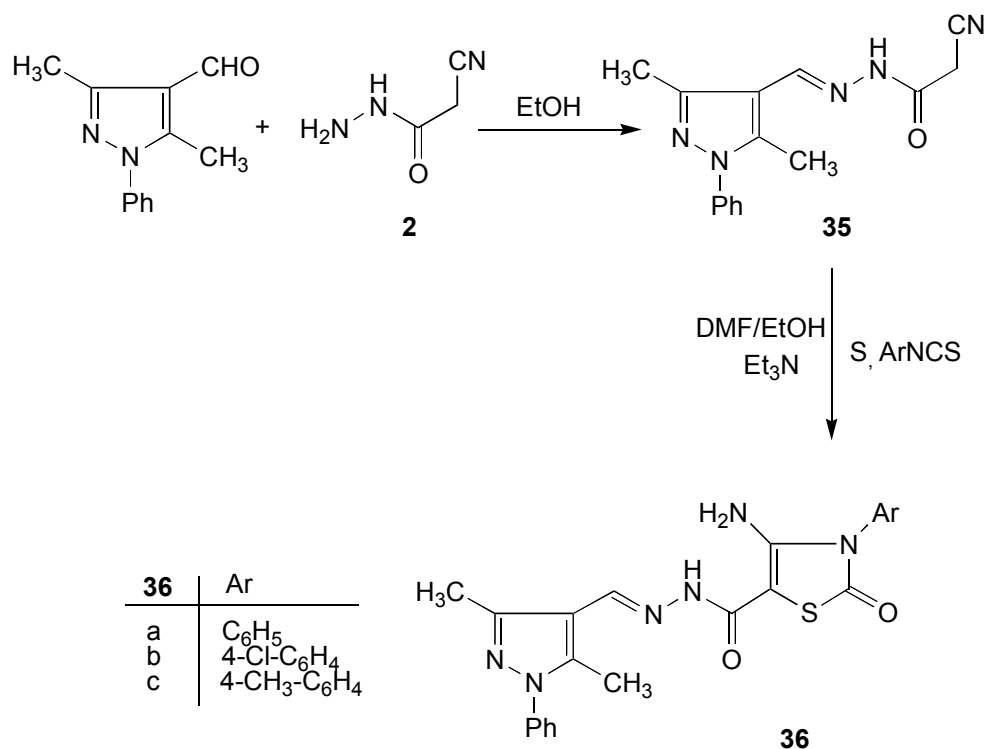
4.2.2. Thiazoles and their fused derivatives

Reaction of **2** with carbon disulfide in DMF and potassium hydroxide had been reported to afford nonisolable intermediate **31** that transformed into thiazole derivative **32** by the action of phenacyl bromide. On the other hand treatment of compound **32** with salicylaldehyde gave the 2*H*-chromen-2-one derivative **34** via the nonisolable arylidene **33** followed by intramolecular addition of hydroxy group to the nitrile function.²⁹



Scheme 16

Condensation of **2** with 3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde in ethanol under reflux afforded *N*-(3,5-dimethyl-1-phenyl-1*H*-pyrazole-4-methylidene) cyanoacetic acid hydrazide **35**. The conversion of **35** into thiazole derivatives **36** was achieved by Gewald reaction, by reacting **35** with sulfur and appropriate aryl isothiocyanate in the presence of mixture of dimethylformamide and ethanol containing triethylamine as a basic catalyst.³⁰

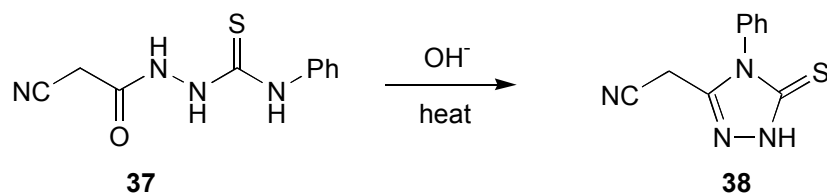


Scheme 17

4.3. Synthesis of five-membered rings with three heteroatoms

4.3.1. Triazoles and their fused derivatives

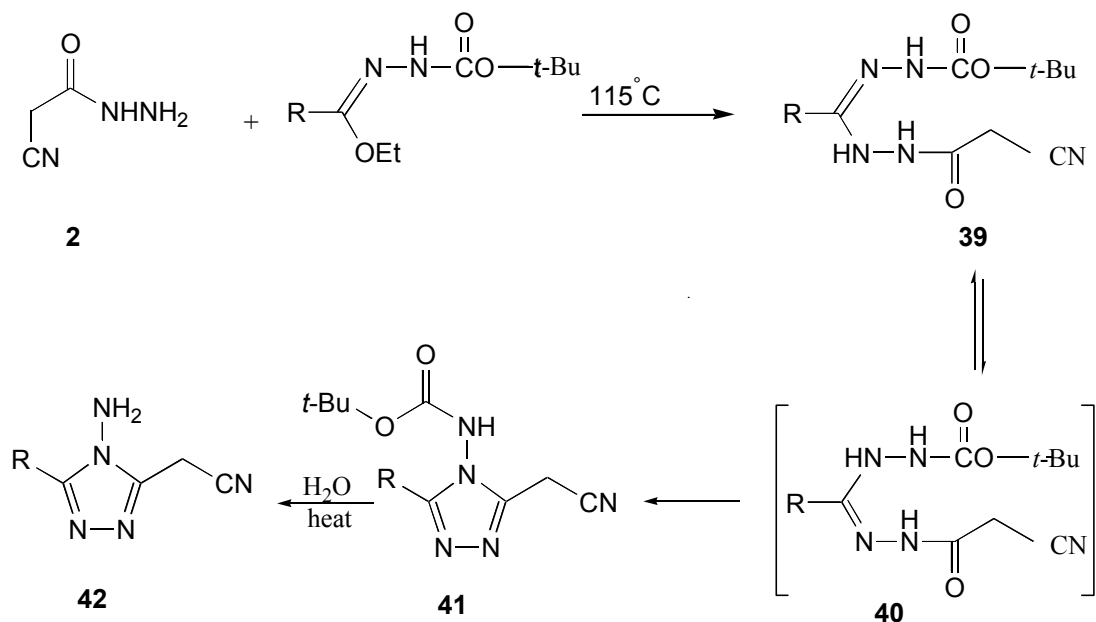
Cyclocondensation of 1-cyanoacetyl-4-phenylthiosemicarbazide **37** under basic conditions afforded 1,2,4-triazole derivative **38**.³¹



Scheme 18

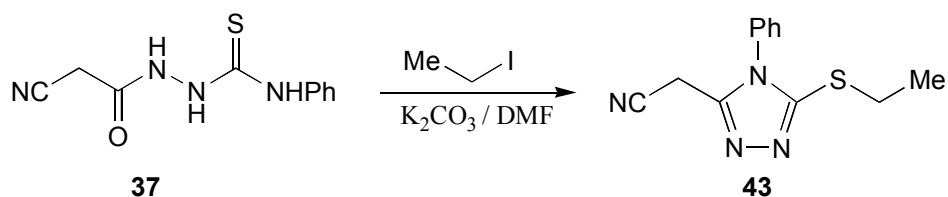
Scheme 18

By treating compound **2** with *tert*-butoxycarbonylhydrazone esters in an oil bath at 115°C, 1,2,4-triazole derivative **42** was obtained.³²



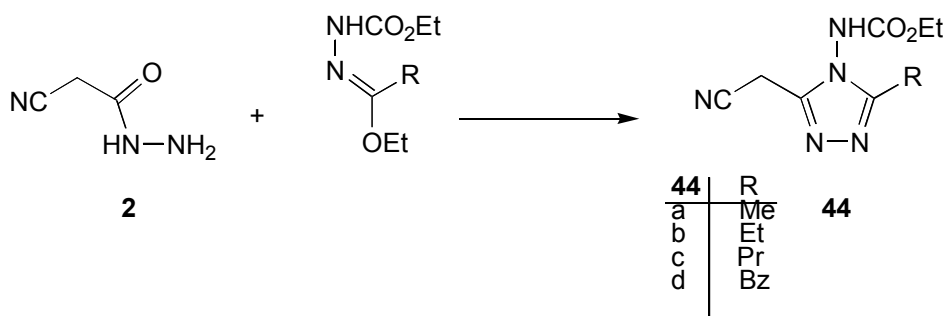
Scheme 19

The reaction of 1-cyanoacetyl-4-phenylthiosemicarbazide **37** with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate at room temperature gave 3-ethylsulfanyl-5-cyanomethyl-4-phenyl-1,2,4-triazole **43**.³³



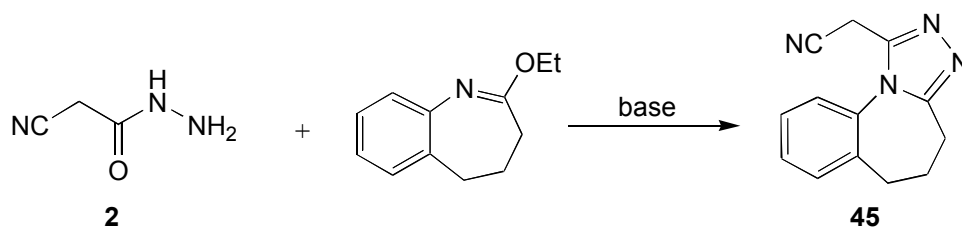
Scheme 20

The reaction of **2** with different hydrazones delivered 1,2,4-triazole derivatives **44**.³⁴



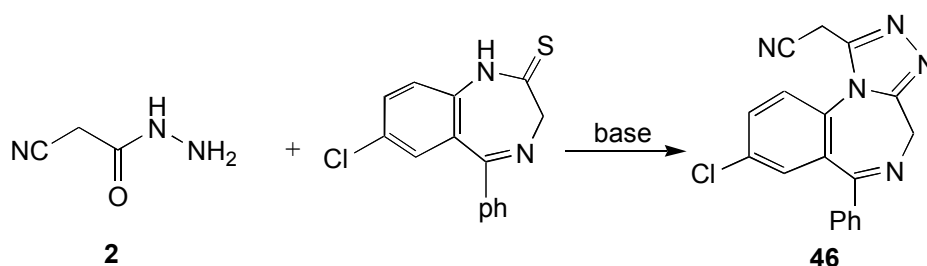
Scheme 21

Golovko and coworkers published the reaction of **2** with lactim ether furnished the 5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-ylacetonitrile **45**.³⁵



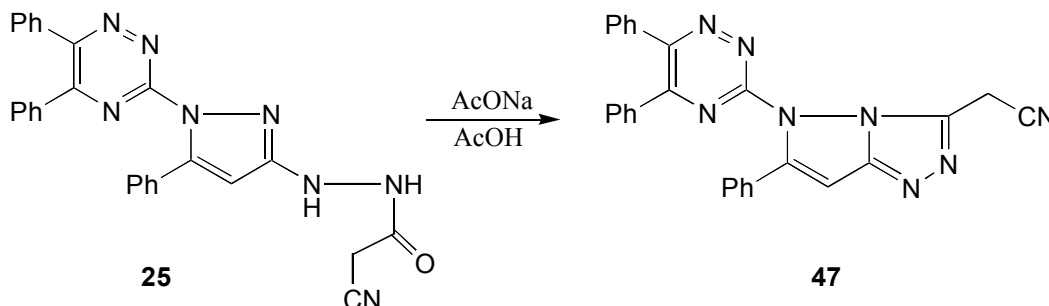
Scheme 22

Treatment of **2** with 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4 benzodiazepine-2-thione in the presence of a basic catalyst afforded 8-chloro-6-phenyl-4*H-s*- triazolo [4,3-*a*] [1,4] benzodiazepine-1-acetonitrile **46**.³⁶



Scheme 23

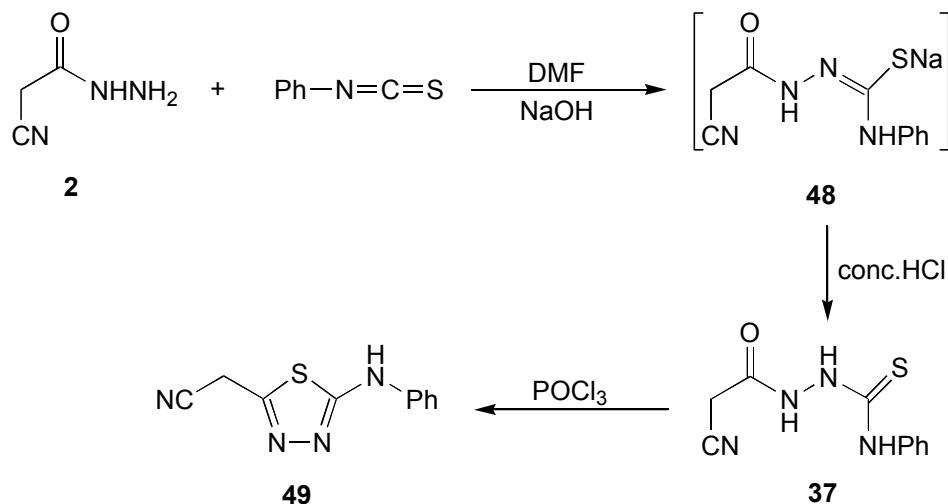
Refluxing of compound **25** in glacial acetic acid and anhydrous sodium acetate yielded [5-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-phenyl-5*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl]acetonitrile **47**.²⁶



Scheme 24

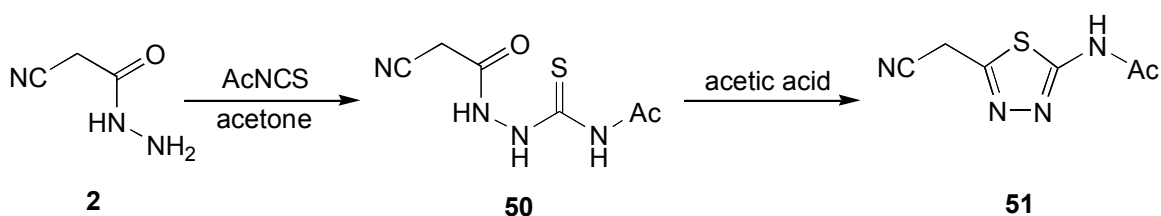
4.3.2. Thiadiazoles

The reaction of **2** with phenylisothiocyanate in DMF in presence of sodium hydride gave non-soluble intermediate **48** that was converted into 1-cyanoacetyl-4-phenylthiosemicarbazide **37** by treatment with conc. hydrochloric acid. Heating of **37** with phosphorous oxychloride yielded (5-anilino-1,3,4-thiadiazol-2-yl)acetonitrile **49**.^{31,33}



Scheme 25

Condensation of acylisothiocyanate with **2** in refluxing acetone gave 45% of thiocarbamoyl derivative **50** which underwent intramolecular cyclization in refluxing acetic acid to give 55% *N*-[5-(cyanomethyl)-1,3,4-thiadiazol-2-yl]acetamide **51**.³⁷

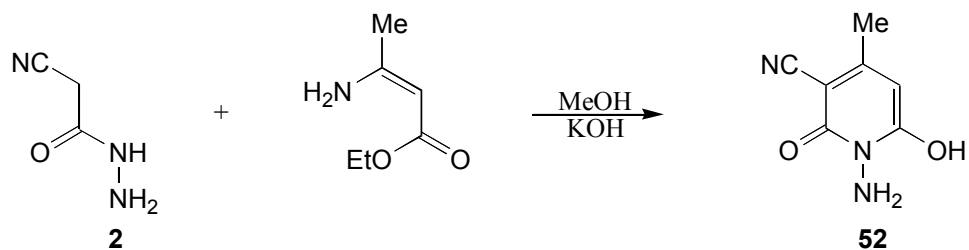


Scheme 26

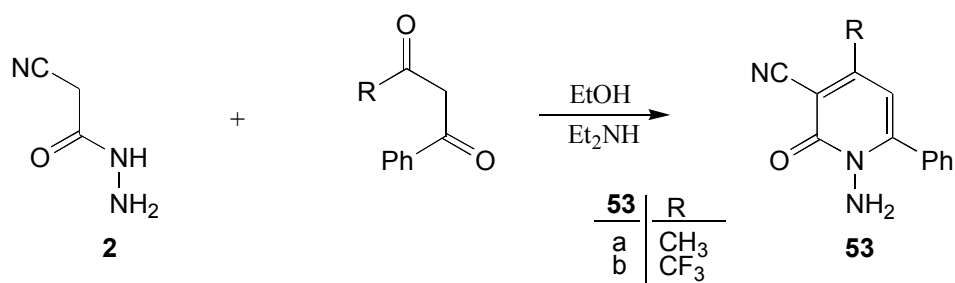
4.4. Synthesis of six-membered ring with one heteroatom

4.4.1. Pyridines and their fused derivatives

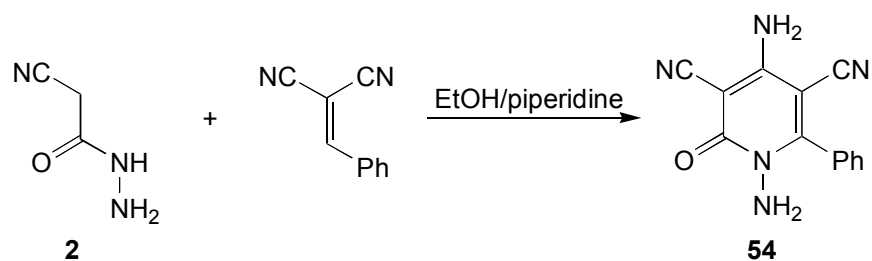
Cyclocondensation of **2** with ethyl 3-aminocrotonate in methanol in the presence of potassium hydroxide under reflux afforded 1-amino-3-cyano-6-hydroxy-4-methyl-pyridine-2-one **52**.³⁸

**Scheme 27**

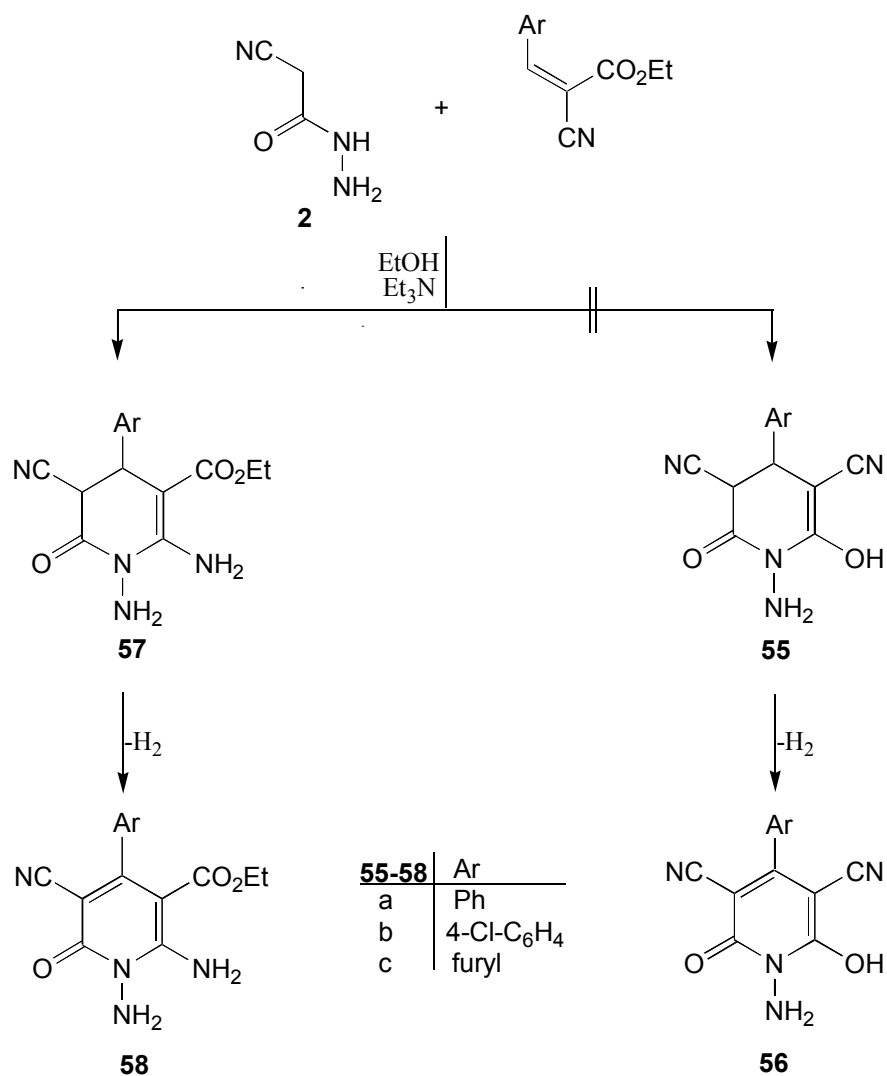
Cyclocondensation of **2** with benzoylacetone and/or benzoyl trifluoroacetone in refluxing ethanol containing a catalytic amount of diethyl amine yielded regioselectively 1-amino-4-alkyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile **53**.³⁹⁻⁴⁰

**Scheme 28**

Refluxing of **2** with benzylidenemalononitrile in ethanol in presence of piperidine gave pyridone derivative **54**.⁴¹

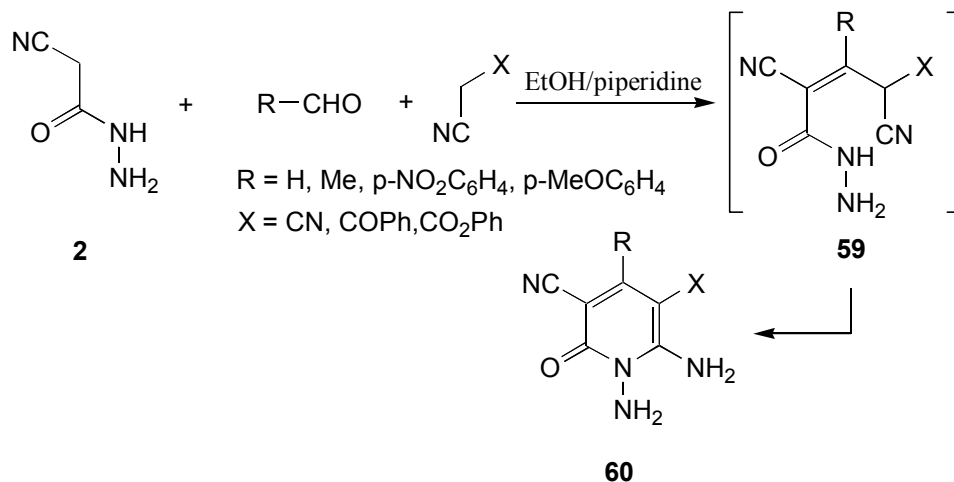
**Scheme 29**

On heating **2** and arylidene of ethyl cyanoacetate in ethanol containing triethyl amine under reflux afforded diaminopyridine derivative **58** rather than aminopyridine derivative **56**.^{42,43}



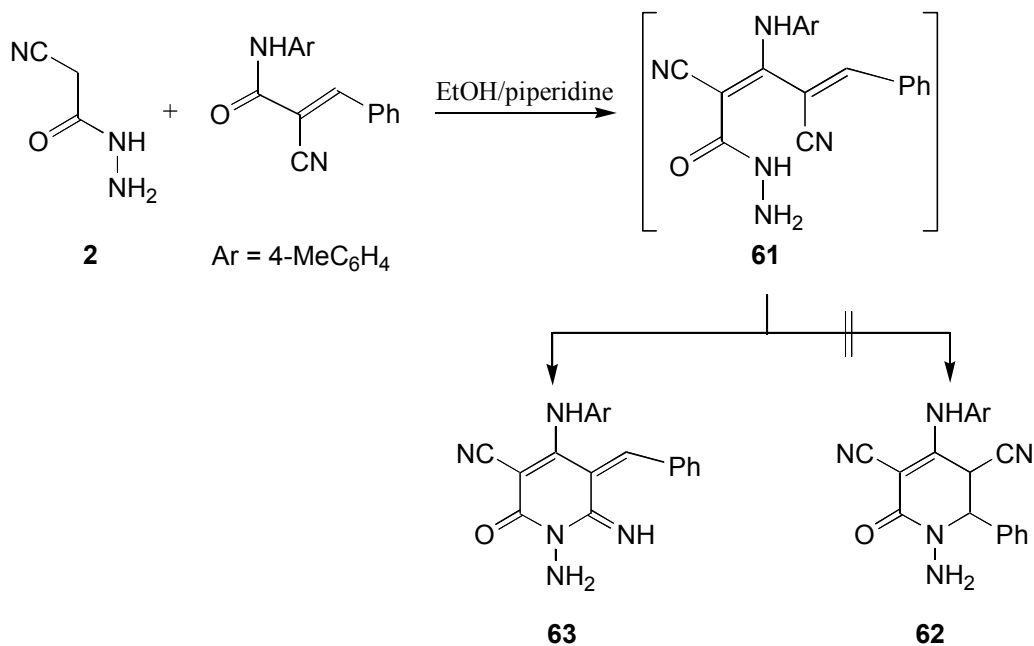
Scheme 30

The one-pot reaction of **2** with aldehyde and an activated nitrile in ethanol containing a catalytic amount of piperidine yielded pyridine-2-one derivative **60**.⁴⁴⁻⁴⁶



Scheme 31

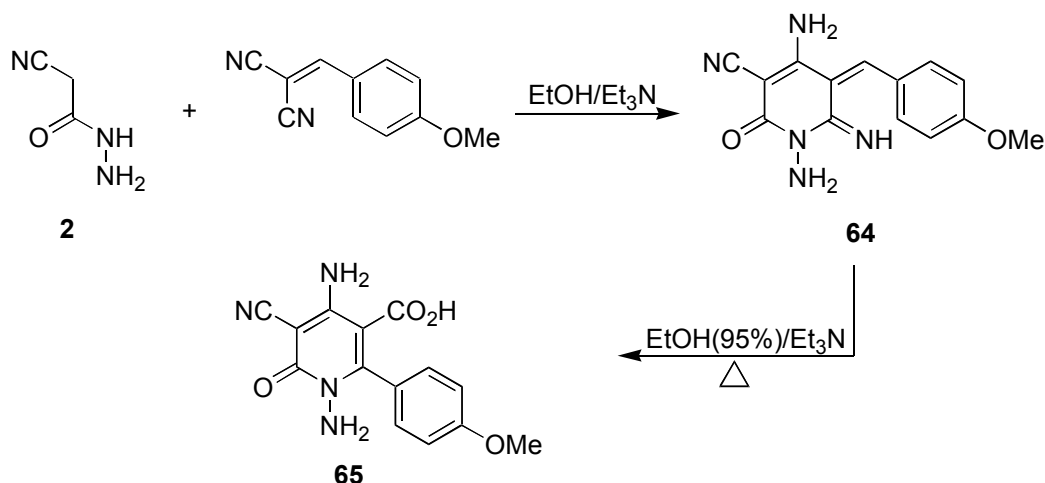
Compound **2** reacted with (2*E*)-2-cyano-*N*-(4-methylphenyl)-3-phenylacrylamide in dry ethanol containing catalytic amount of piperidine under reflux to afford pyridine derivative **63** instead of compound **62**.⁴⁷



Scheme 32

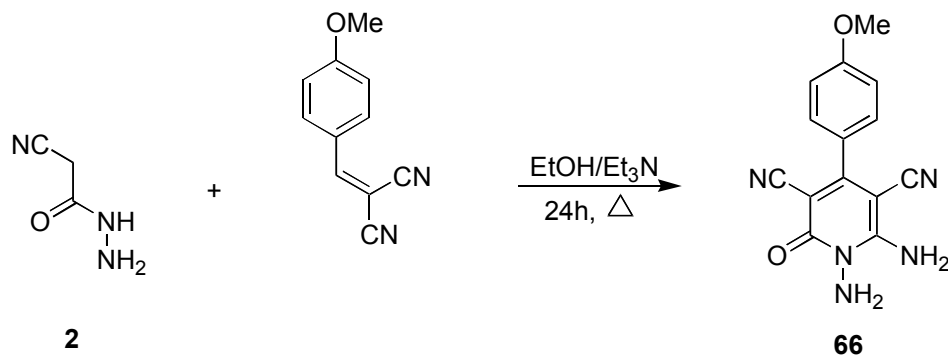
Cyclocondensation of **2** with (4-methoxybenzylidene)malononitrile in ethanol in the presence of triethylamine afforded 1-aminopyridine derivative **64**, which rearranged on heating

in 95% aqueous ethanol/triethylamine to give 1,4-diamino-5-cyano-2-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **65**.⁴⁸



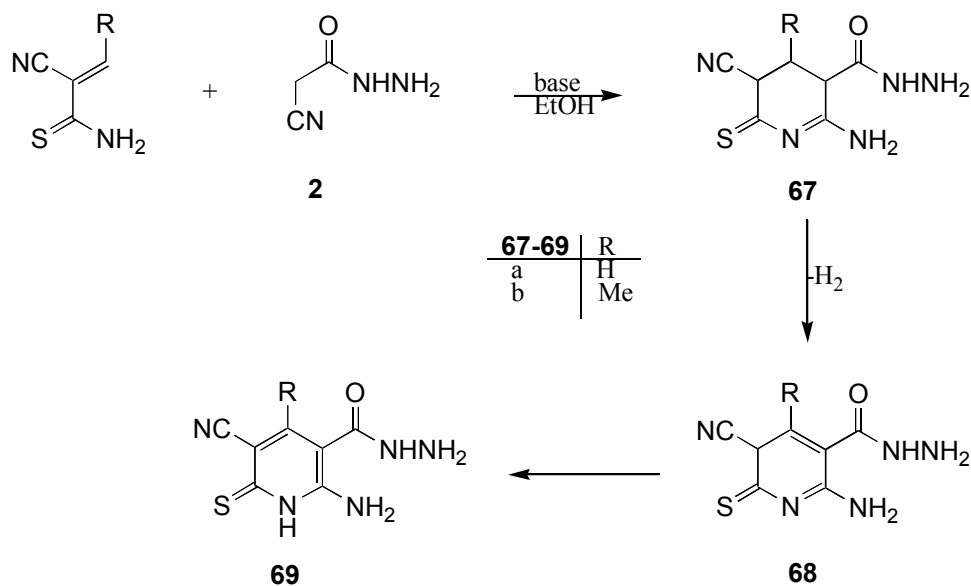
Scheme 33

Martin and coworkers reinvestigated the cyclocondensation of **2** with (4-methoxybenzylidene)malononitrile. They have found that prolonged heating lead only to the formation of 1,6-diamino-4-(4-methoxyphenyl)-3,5-dicyano-2-pyridone **66**. The structure of compound **66** had been confirmed on the basis of chemical and spectroscopic evidence.⁴⁹



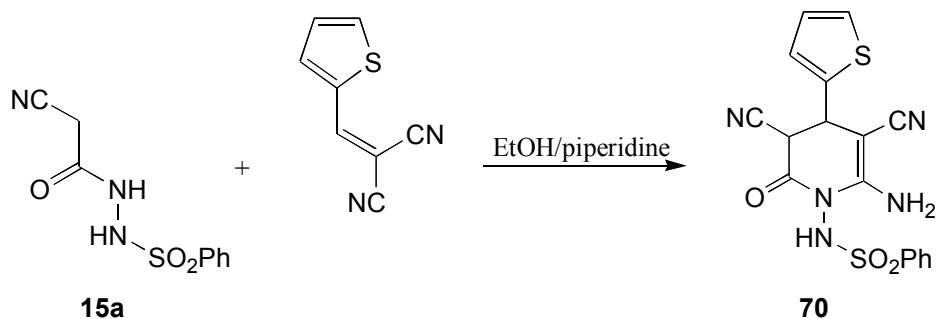
Scheme 34

Treatment of **2** with arylidene cyanothioacetamide in ethanol containing catalytic amount of piperidine yielded pyridine-thione derivatives **69**.⁴⁶



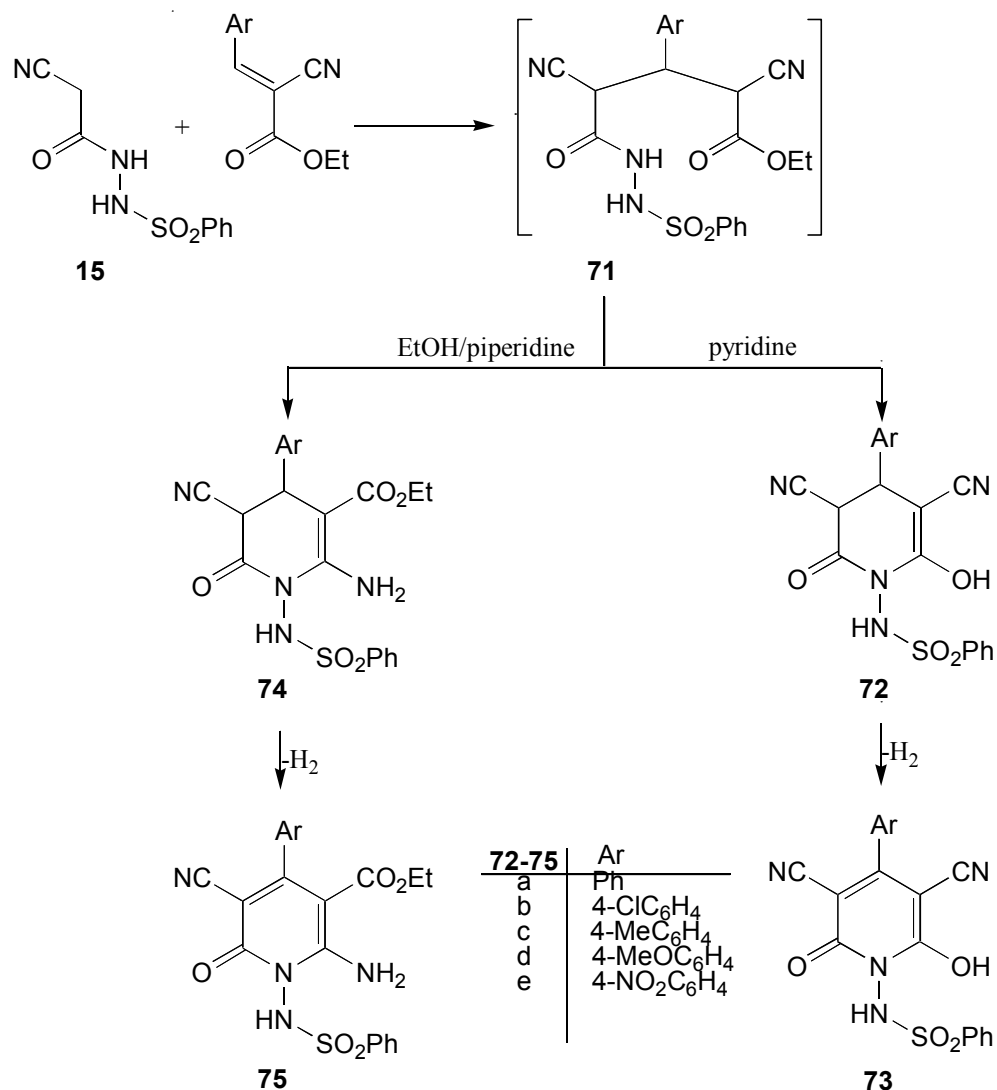
Scheme 35

Reaction of cyanoaceto-*N*-arylsulfonylhydrazide **15a** with 2-((thiophen-2-yl)methylene) malononitrile in ethanol containing a catalytic amount of piperidine furnished pyridin-2-one derivative **70**.⁵⁰



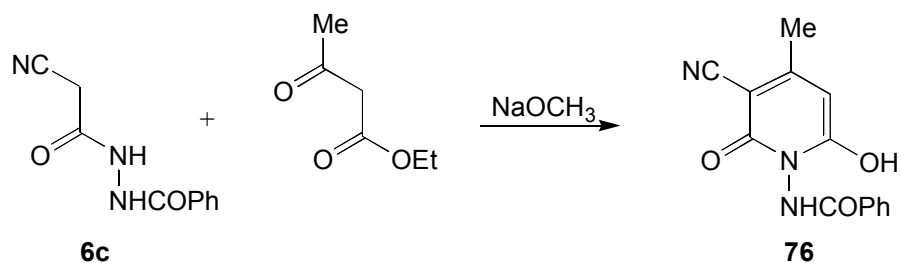
Scheme 36

Refluxing of cyanoaceto-*N*-arylsulfonylhydrazide **15** with arylidenecyanoacetate in presence of pyridine^{51,52} afforded pyridone derivative **73**, while in the presence of ethanol containing a catalytic amount of piperidine⁵¹ afforded pyridine-2-one derivative **75**.⁵²



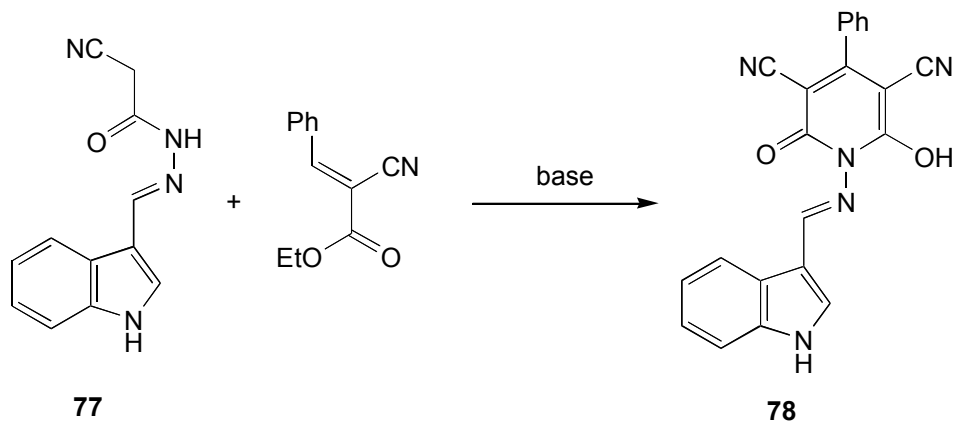
Scheme 37

Substituted *N*-benzoylaminopyridone **76** was prepared by cyclocondensation of *N*-benzoylcyanohydrin **6c** with ethyl acetoacetate in presence of sodium methoxide.⁵²



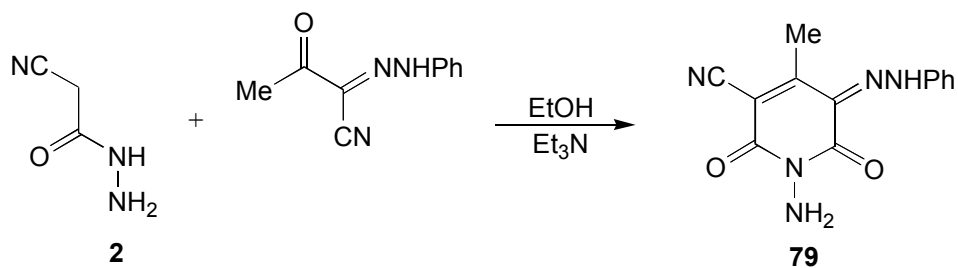
Scheme 38

Cyclocondensation of 3-indolylidenecyanoacetohydrazide **77** with ethyl benzylidenecyanoacetate in the presence of a base gave the corresponding 4-phenyl-3,5-dicyano-6-hydroxyl-1*N*-(3-indolylidene) pyridin-2-ones **78**.⁵³



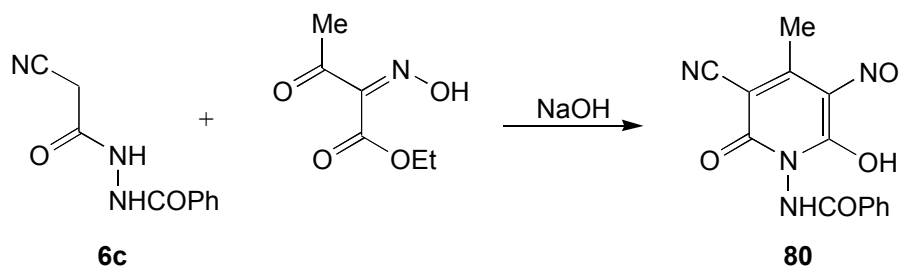
Scheme 39

On heating **2** with phenylhydrazono-3-oxobutyronitrile in refluxing ethanol containing a catalytic amount of triethyl amine yielded pyridine-2,6-dione derivative **79**.^{54,55}



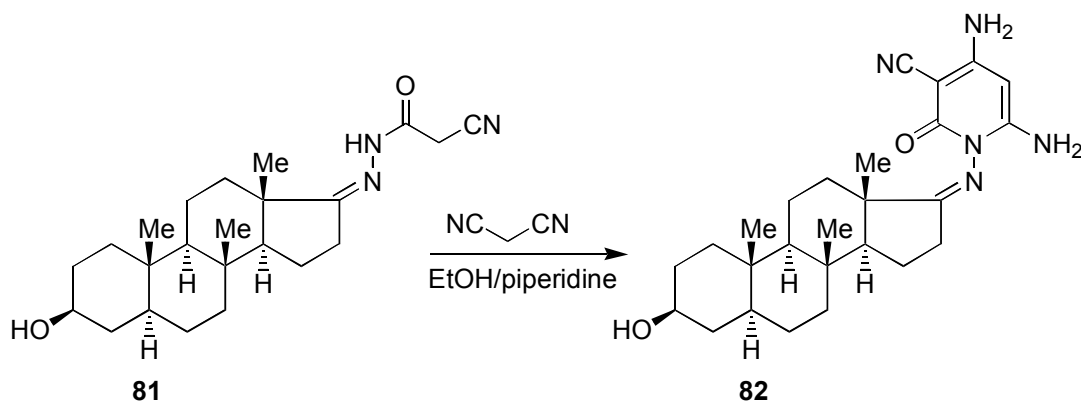
Scheme 40

Elzanate *et al.* have been reported a novel synthetic route to nitrosopyridinone derivative **80** via the reaction of oxime derivative of β -ketoester with *N*-benzoylcyaacetohydrazide.⁵⁶



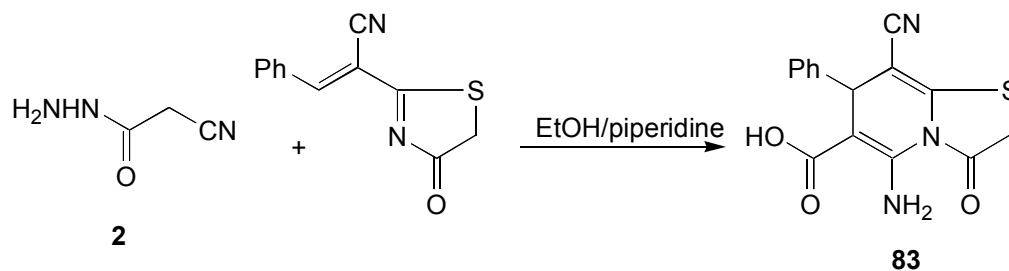
Scheme 41

The reaction of *N*-cyanoacetylhydrazone of epiandrosterone **81** with malononitrile in ethanol in the presence of a catalytic amount of piperidine afforded pyridine-2-one derivative **82**.⁵⁷



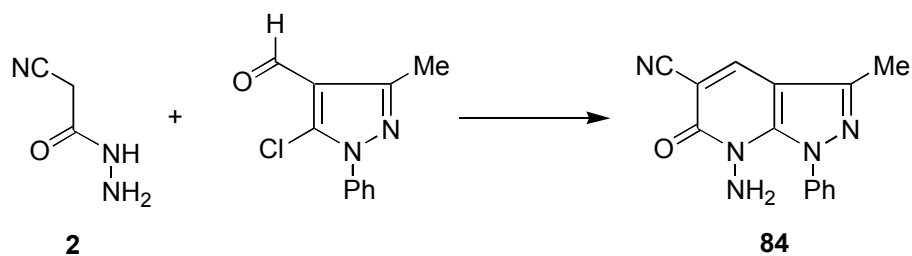
Scheme 42

Refluxing of **2** with 2-(4,5-dihydro-4-oxothiazol-2-yl)-3-phenylacrylonitrile in ethanol containing catalytic amount of piperidine gave 5-amino-8-cyano-3-oxo-7-phenyl-2,3-dihydro-7*H*-[1,3]thiazolo[3,2-*a*]pyridine-6-carboxylic acid **83**.⁴¹

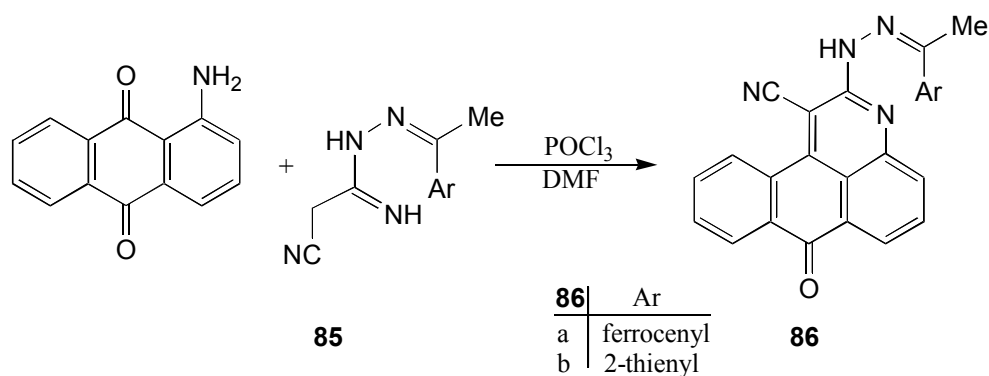


Scheme 43

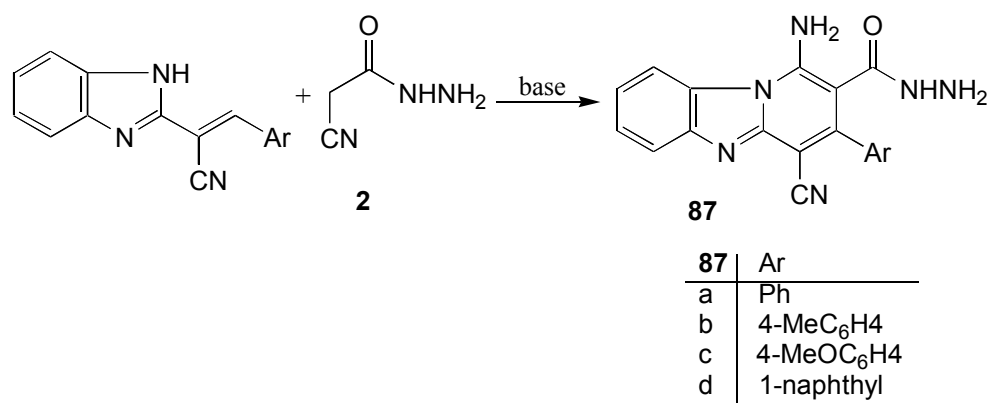
Cyclocondensation of **2** with 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde yielded 7-amino-3-methyl-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **84**.⁵⁸

**Scheme 44**

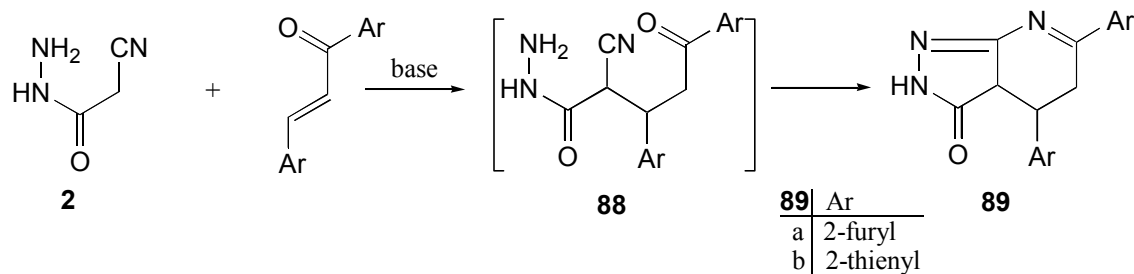
Condensation of cyanoacetic acid hydrazones **85** with 1-aminoanthraquinone under Vilsmeier reaction conditions afforded 3-azabenzanthrone derivatives **86**.⁵⁹

**Scheme 45**

Cyclocondensation of **2** with (*2E*)-2-(1*H*-benzimidazol-2-yl)-3-arylacrylonitrile under reflux in the presence of a base gave 1-amino-3-aryl-4-cyanopyrido[1,2-*a*]benzimidazole-2-carbohydrazide **87**.⁶⁰

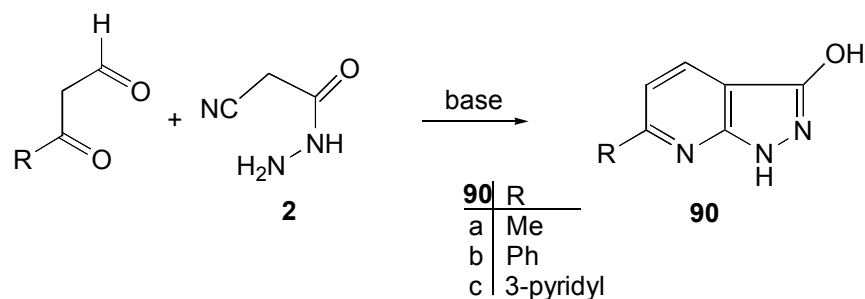
**Scheme 46**

The reaction of **2** with α,β -unsaturated ketones in the presence of a base gave pyrazolo[3,4-*b*]pyridine-3-one derivative **89**.⁶¹



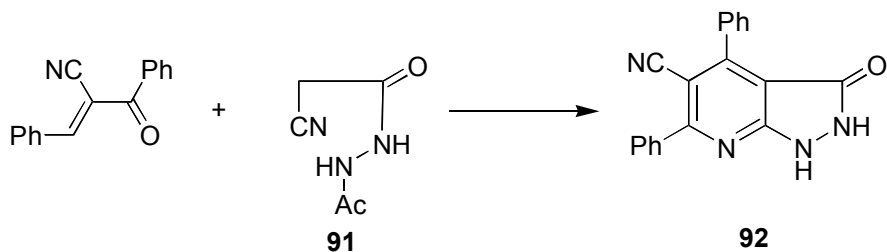
Scheme 47

Pyrazolopyridines **90** were obtained *via* cyclocondensation of β -ketoaldehyde with **2** in alkaline medium.⁶²



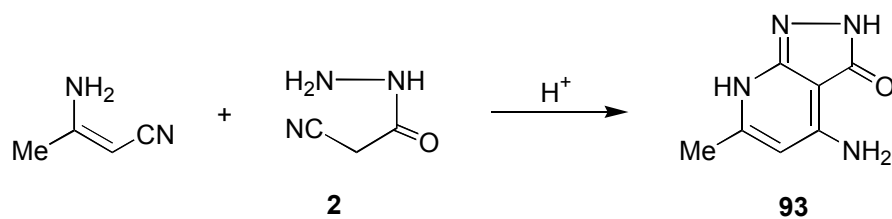
Scheme 48

Pyrazolo[3,4-*b*]pyridine derivative **92** was prepared *via* the reaction of α -benzoylcinnamionitrile with *N*-acetyl cyanoacetohydrazide **91**.⁶³



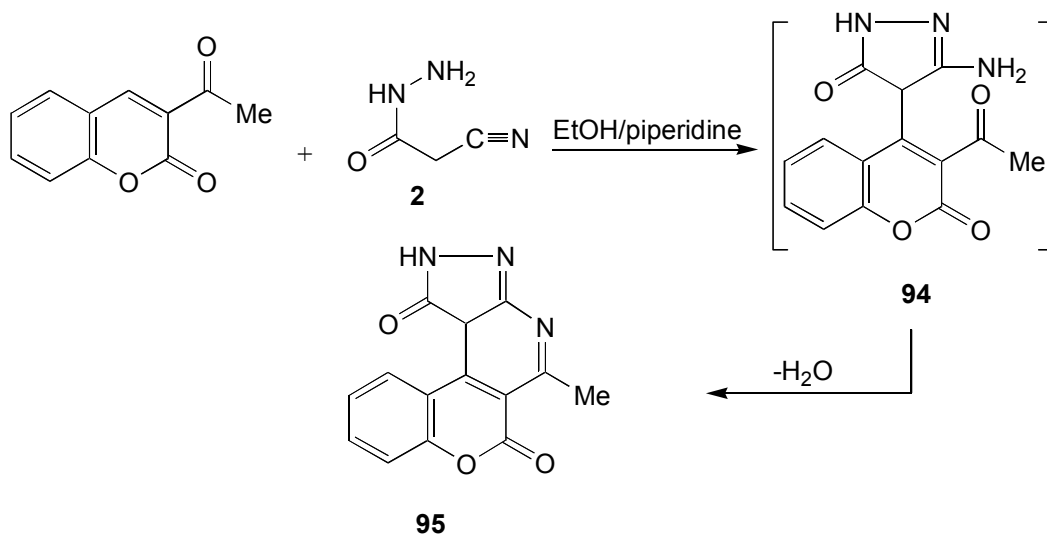
Scheme 49

Cyclocondensation of **2** with β -aminocrotononitrile in acidic medium yielded pyrazolo[3,4-*b*]pyridine derivative **93**.⁶⁴



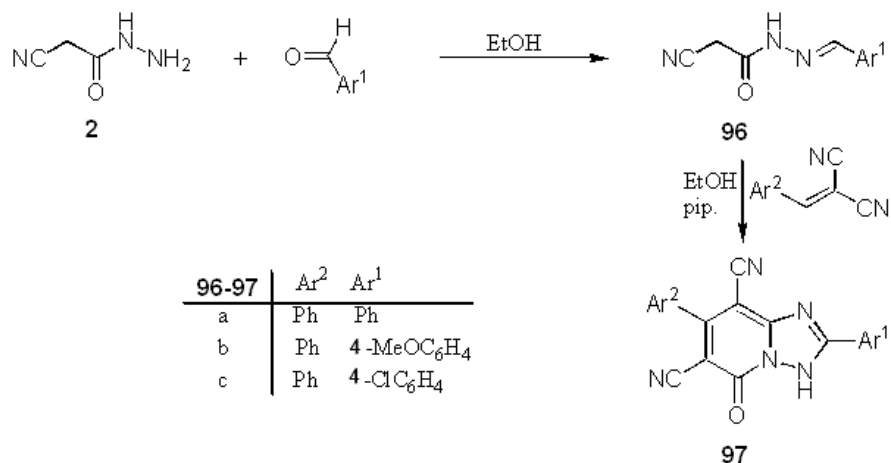
Scheme 50

The reaction of **2** with 3-acetylcoumarin in ethanol containing a catalytic amount of piperidine under reflux afforded 5-methyl-2,11c-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridine-1,6-dione **95**.⁶⁵



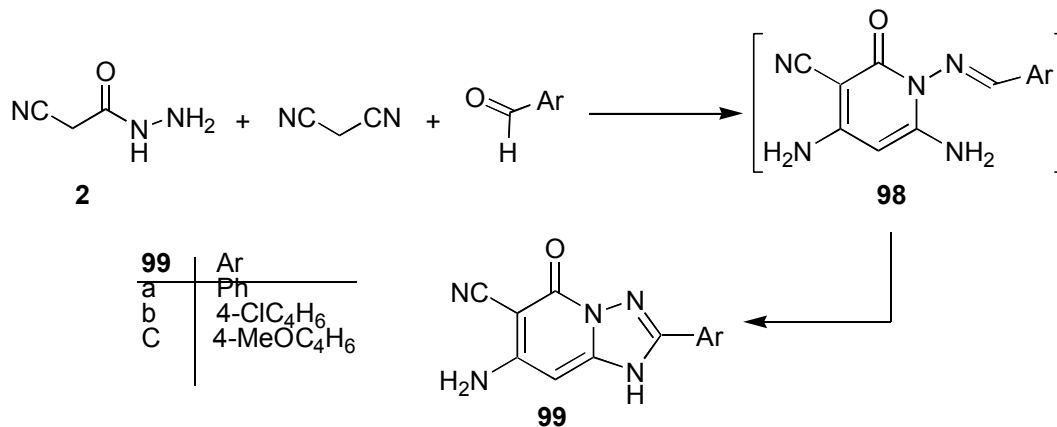
Scheme 51

Reaction of **2** with different aromatic aldehydes in ethanol under reflux afforded 1-*N*-arylmethylidene-2-cyanoacetohydrazides **96** that were treated with benzylidenemalononitrile to give [1,2,4]triazolo[1,5-*a*]pyridin-5(3*H*)-one derivatives **97**.⁶⁶



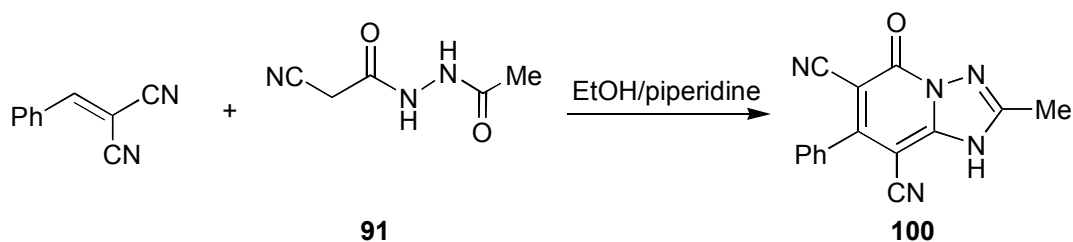
Scheme 52

[1,2,4]Triazolo[1,5-*a*]pyridin-5(1*H*)-one derivatives **99** were prepared in one pot reaction in excellent yields by the reaction of **2** with malononitrile and an aromatic aldehyde.⁶⁷



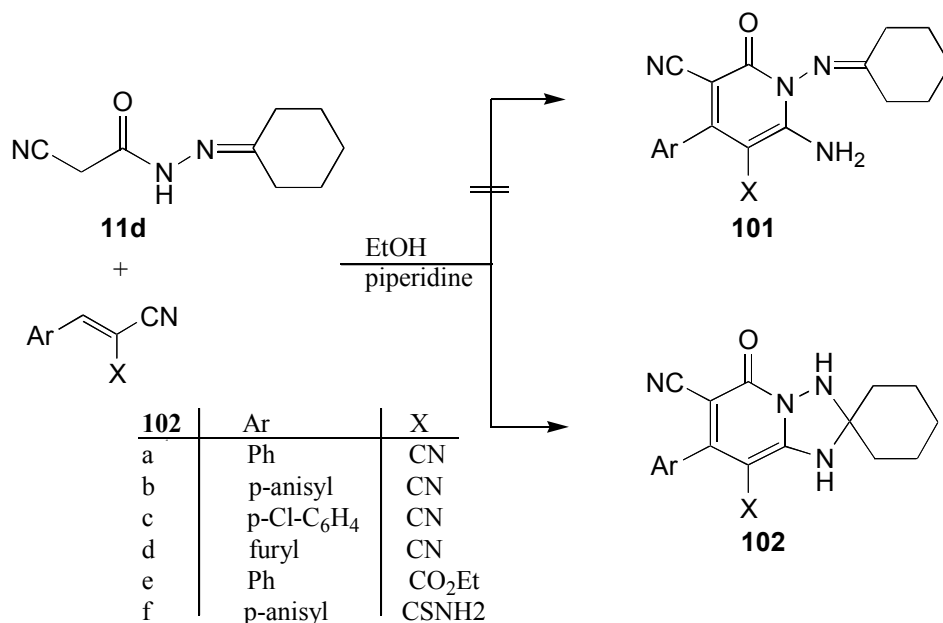
Scheme 53

Martin and coworkers have reported that an unexpected reaction between *N*-acetyl cyanoacetohydrazide **91** and α -cyanocinnamionitrile in ethanol containing catalytic amount of piperidine afforded a novel 2-methyl-5-oxo-7-phenyl-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **100**.⁶⁸



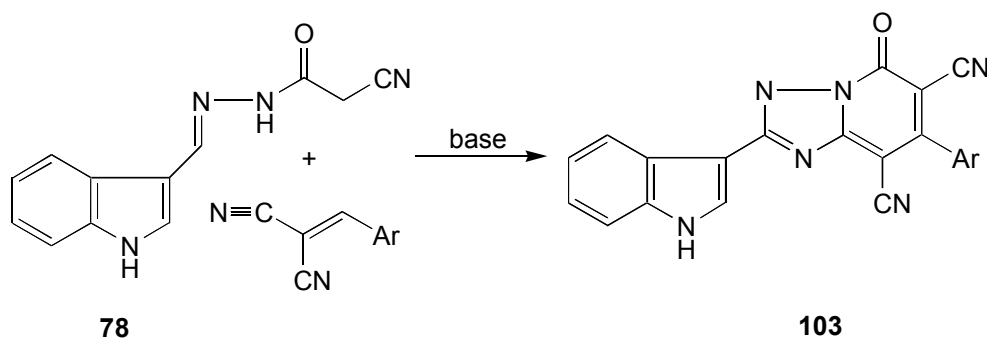
Scheme 54

Refluxing of hydrazone derivative **11d** and appropriate arylidene of activated nitriles in ethanolic piperidine yielded spiro[cyclohexane-1,2'-[1,2,4]triazolo[1,5-*a*]pyridine]-5'-(1'*H*)-one derivatives **102**.^{24,69}



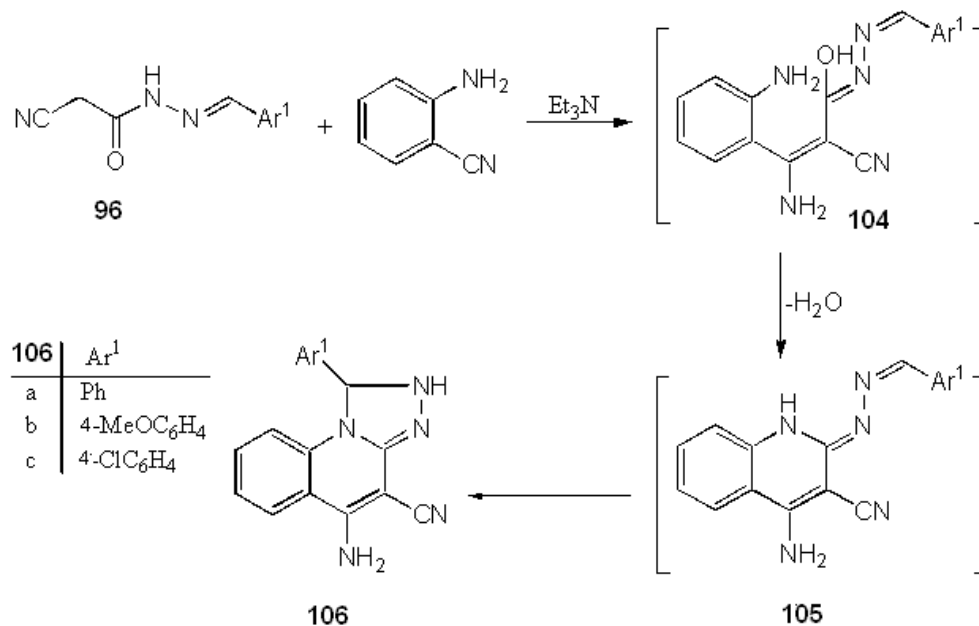
Scheme 55

On the other hand, 3-indolyldenecyanoacetohydrazide **77** condensed with different arylidenemalononitriles in presence of a base to give 7-aryl-6,8-dicyano-2-(3-indolyl)[1,2,4]triazolo[1,5-*a*]-pyridin-5-ones **103**.⁵³



Scheme 56

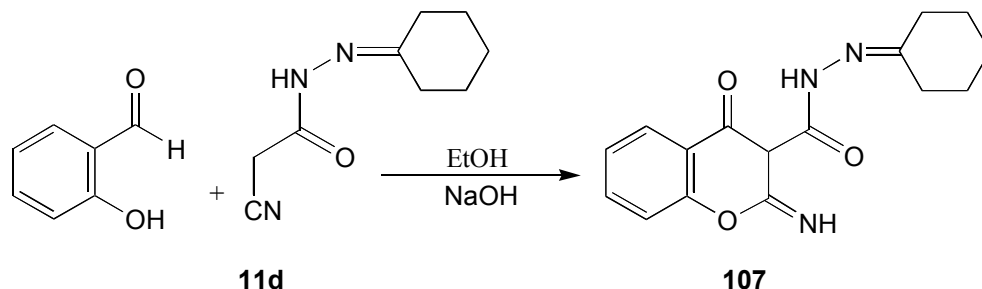
When anthranilonitrile was fused on an oil bath at 170 °C with different *N*-arylidenes of cyanoacetohydrazide **96** in presence of triethyl amine, it afforded triazolo[4,3-*a*]quinoline derivatives **106**. Compounds **106** are assumed to be formed by the initial Thorpe-Ziegler addition⁶⁵ of the methylene group **96** to the CN group of anthranilonitrile to afford the acyclic intermediates **104**, followed by loss of a water molecule to afford the acyclic intermediates **105**, which in turn undergo a further cyclization *via* addition of the NH to the activated C=N to give the final products **106**.⁷⁰



Scheme 57

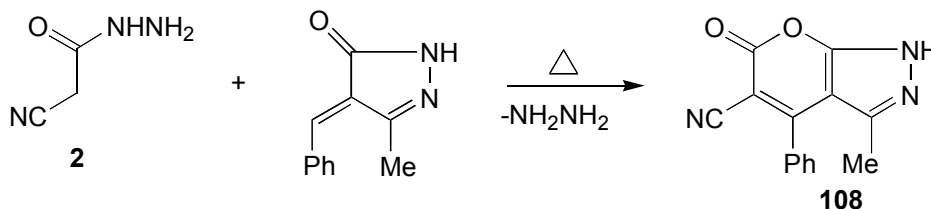
4.4.2. Pyrans and their fused derivatives

Refluxing of hydrazone derivative **11d** and salicylaldehyde in ethanol containing a catalytic amount of sodium hydroxide afforded *N*-cyclohexylidene-2-imino-4-oxochromane-3-carbohydrazone **107**.⁷¹



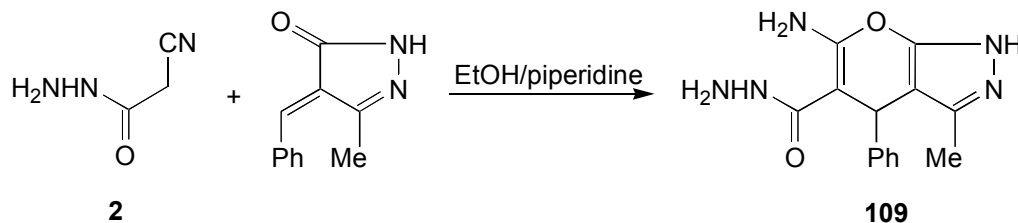
Scheme 58

3-Methyl-6-oxo-4-phenyl-1,6-dihydropyran[2,3-*c*]pyrazole-5-carbonitrile **108** was prepared *via* cyclocondensation of **2** with 4-benzylidene-3-methyl-2-pyrazolin-5-one.⁷²



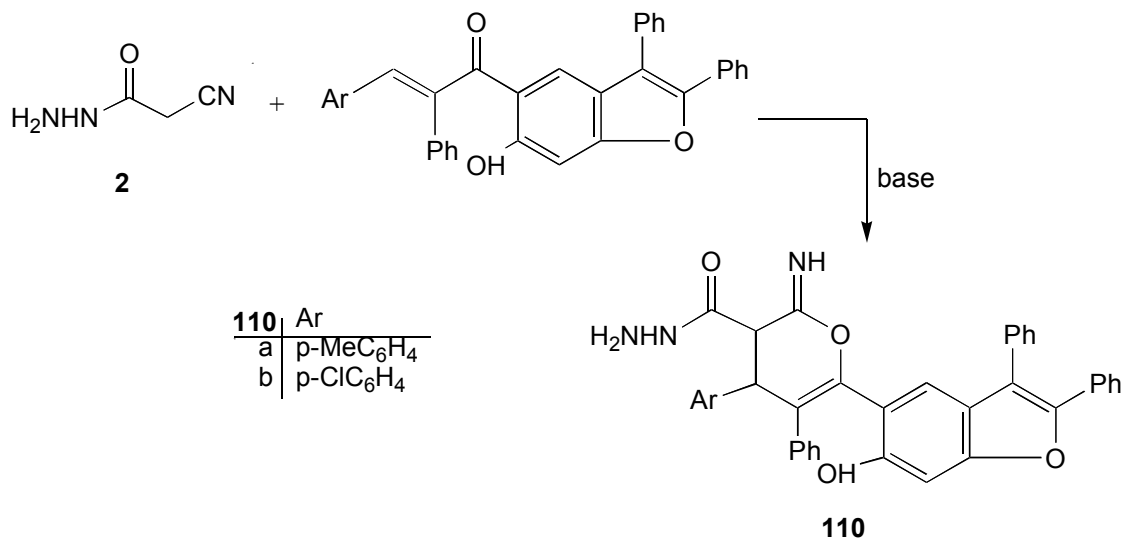
Scheme 59

Refluxing of **2** with pyrazolinone in ethanol in the presence of piperidine gave 6-amino-3-methyl-4-phenyl-1,4-dihydropyran[2,3-*c*]pyrazole-5-carbohydrazone **109**.⁴¹



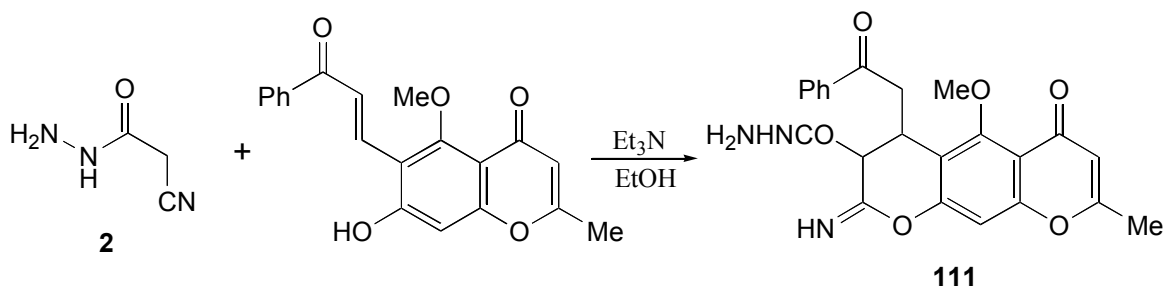
Scheme 60

Cyclocondensation of **2** with benzofuranyl derivatives under Claisen-Schmidt reaction yielded 4-aryl-6-(6-hydroxy-2,3-diphenyl-1-benzofuran-5-yl)-2-imino-3,4-dihydro-5-phenyl-2*H*-pyran-3-carbohydrazone **110**.⁷³



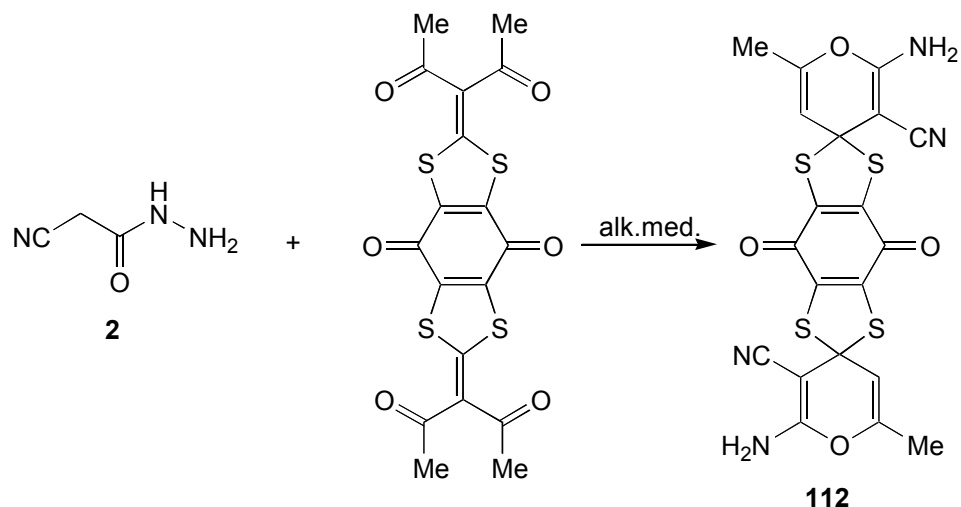
Scheme 61

Reaction of **2** with benzopyranone in ethanol containing a catalytic amount of triethyl amine under reflux afforded 2-imino-5-methoxy-8-methyl-6-oxo-4-(2-oxo-2-phenylethyl)-3,4-dihydro-2*H*,6*H*-pyrano[3,2-*g*]chromene-3-carbohydrazone **111**.⁷⁴



Scheme 62

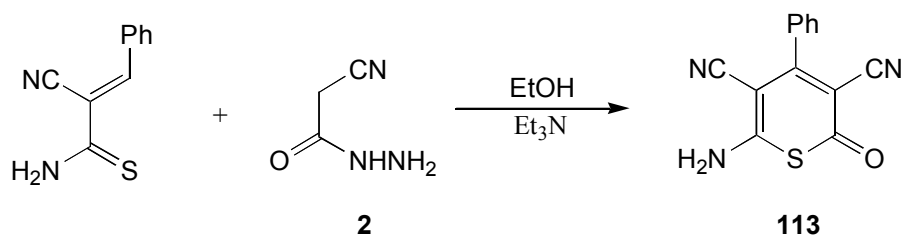
Reaction of bisdithiolobenzoquinone with **2** in a 1: 2 molar ratio in alkaline medium gave dispiro[4*H*-pyran-4,2'-[1,3]dithiolo[4,5-*f*][1,3]benzodithiole-6',4''-[4*H*]pyran]-3,3''-dicarbonitrile derivative **112**.⁷⁵



Scheme 63

4.4.3. Thiopyran

The reaction of **2** with benzalcyanothioacetamide in ethanol containing a catalytic amount of triethyl amine gave thiopyran derivative **113**.⁷⁶

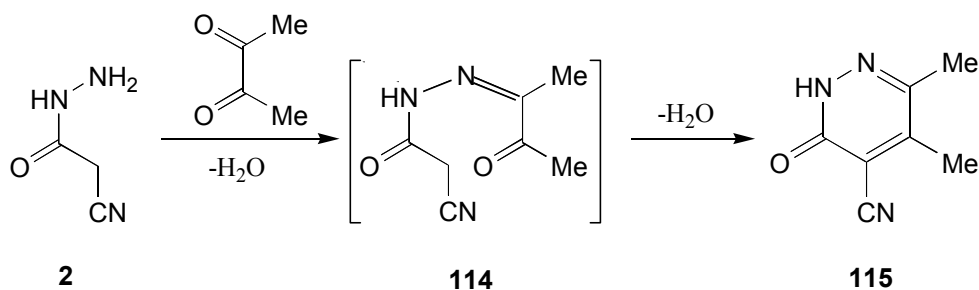


Scheme 64

4.5. Synthesis of Six-Membered Ring with Two Heteroatoms

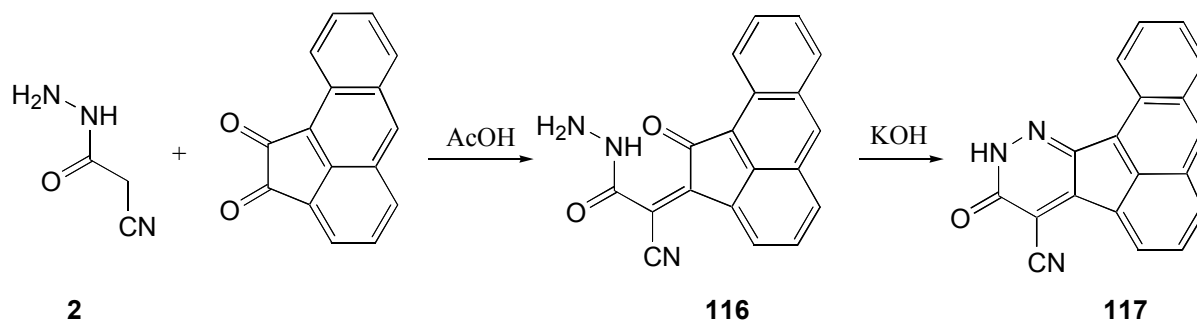
4.5.1. Pyridazines and their fused derivatives

Reaction of **2** with biacetyl in ethanol at room temperature yielded pyridazin-3-one derivative **115**.⁷⁷



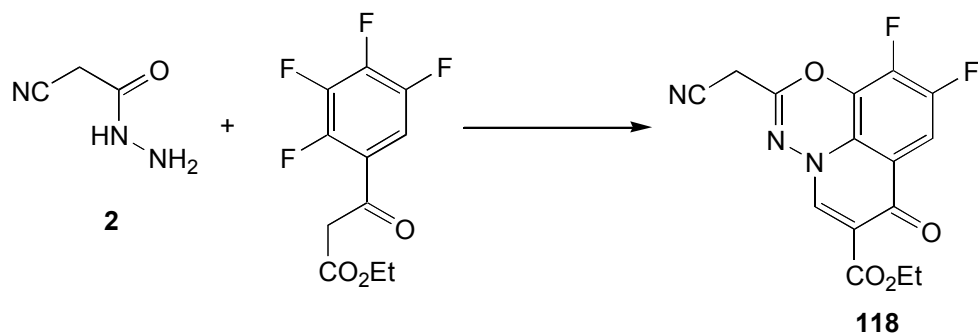
Scheme 65

Refluxing of **2** with aceanthraquinone in acetic acid gave **116** that transformed into aceanthryleno[1,2-*c*]pyridazine derivative **117** when treated with potassium hydroxide.⁷⁸



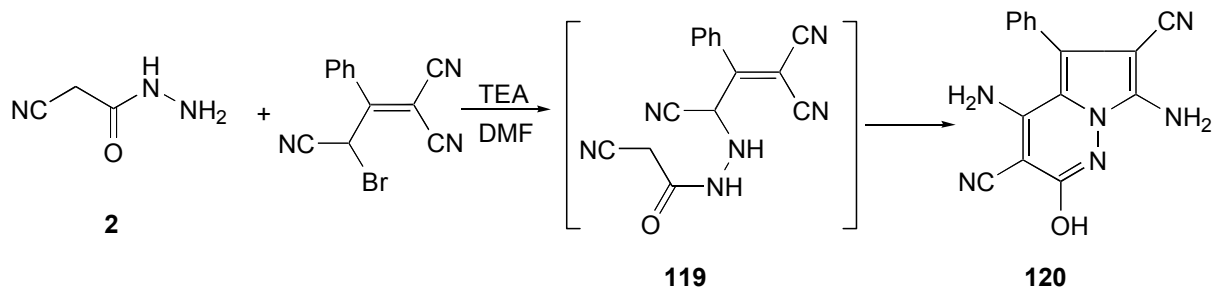
Scheme 66

Cyclocondensation of α -(ethoxymethylene)-2,3,4,5-tetrafluoro- β -oxobenzenepropanoic acid ethyl ester with **2** led to the formation of fluorinated 1,3,4-oxadiazino[6,5,4-*i,j*]quinolines **118**.⁷⁹



Scheme 67

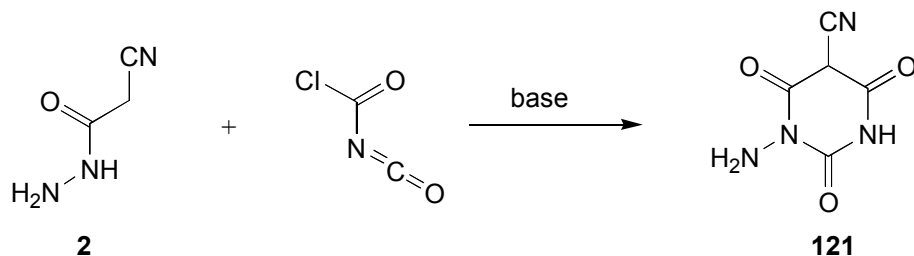
The reaction of **2** with 2-phenyl-1,1,3-tricyano-3-bromopropene in a basic medium gave the nonisolable acyclic intermediate **119**, which underwent cyclization *via* the addition of the active methylene to the CN group to afford the pyrrolo[1,2-*b*]pyridazine derivative **120**.⁸⁰



Scheme 68

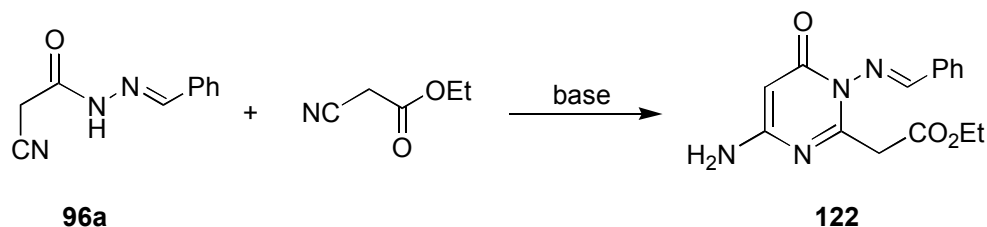
4.5.2. Pyrimidine and their fused derivatives

Barbituric acid derivative **121** could be obtained by the reaction of chlorocarbonylisocyanate with **2**.⁸¹



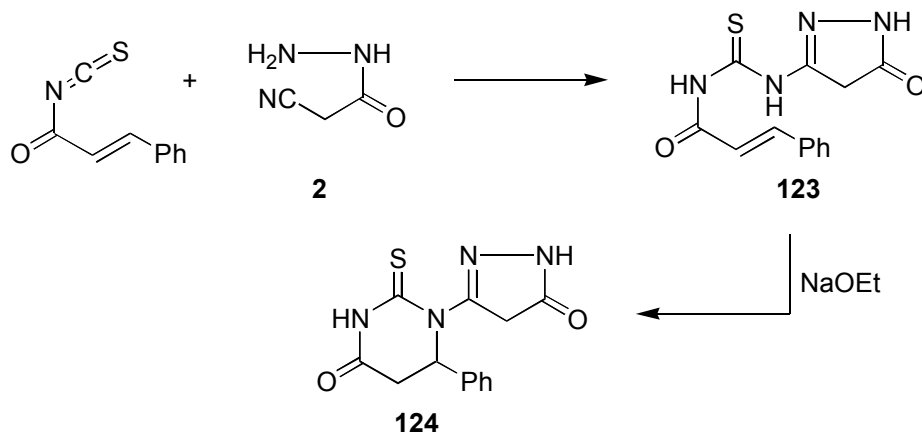
Scheme 69

Mohareb and coworkers reported that the reaction of *N*-benzylidene of cyanoacetohydrazide **97a** with ethyl cyanoacetate afforded pyrimidine derivative **122**.⁸²



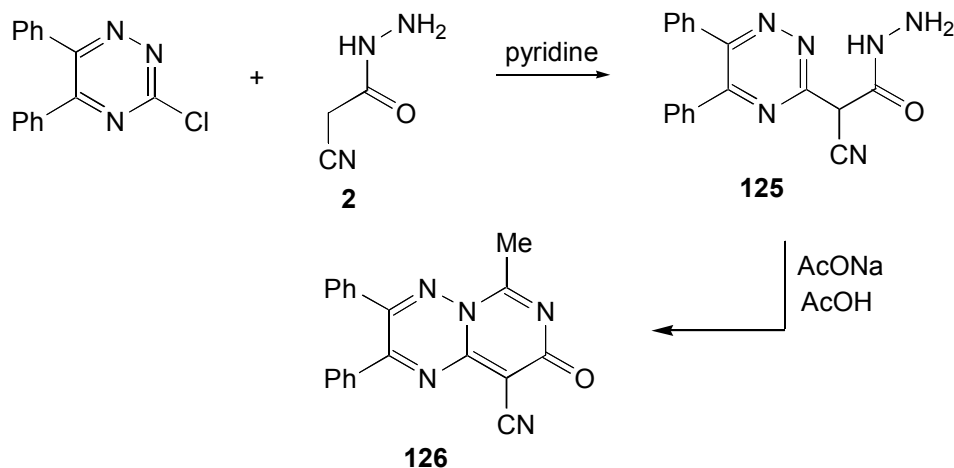
Scheme 70

Cinnamoyl isothiocyanate reacts with **2** to give the corresponding cinnamoyl thiourea **123** which undergo cyclization in refluxing sodium ethoxide solution to give the corresponding 1-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one **124**.⁸³



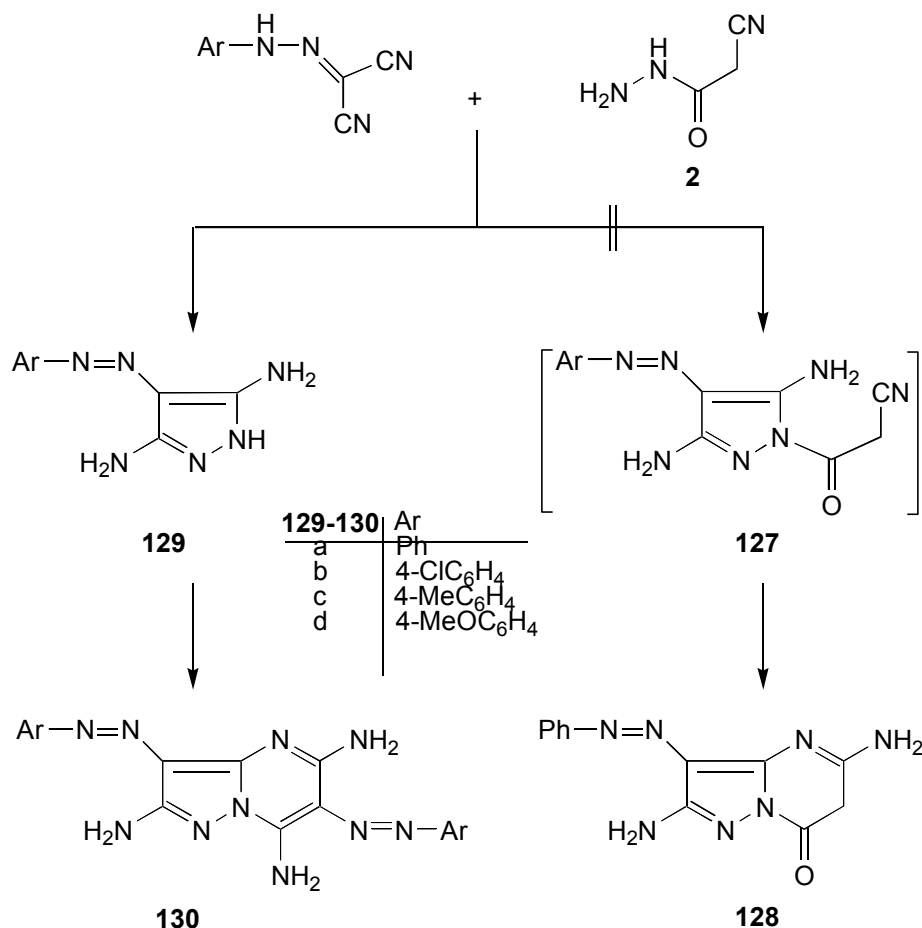
Scheme 71

Abdel Rahman *et al.* reported that treatment of 3-chloro-5,6-diphenyl-1,2,4-triazine with **2** in pyridine gave compound **125** which underwent dehydrocyclization by boiling in acetic acid containing catalytic amount of anhydrous sodium acetate to give 6-methyl-8-oxo-2,3-diphenyl-8*H*-pyrimido[1,6-*b*][1,2,4]triazine-9-carbonitrile **126**.⁸⁴



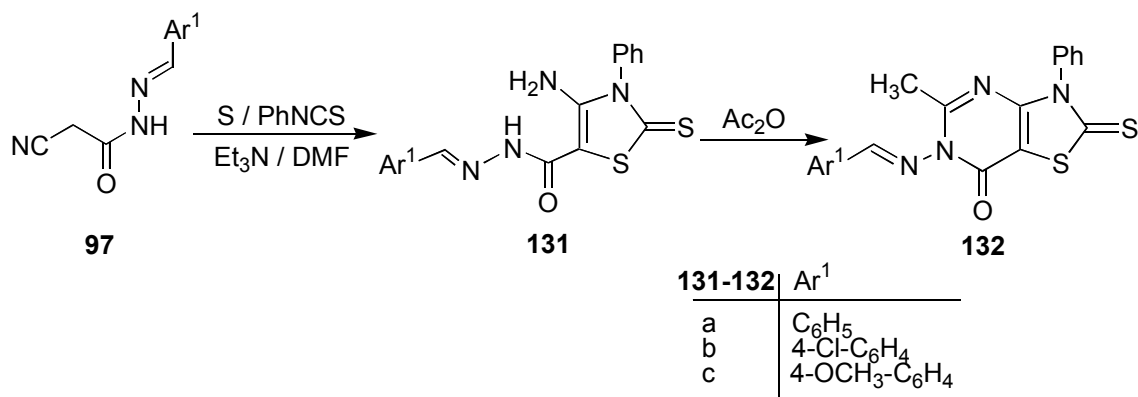
Scheme 72

The reaction of **2** with arylhydrazonomalononitrile in ethanol under reflux afforded pyrazolo[1,5-*a*]pyrimidine derivative **130**.⁸⁵



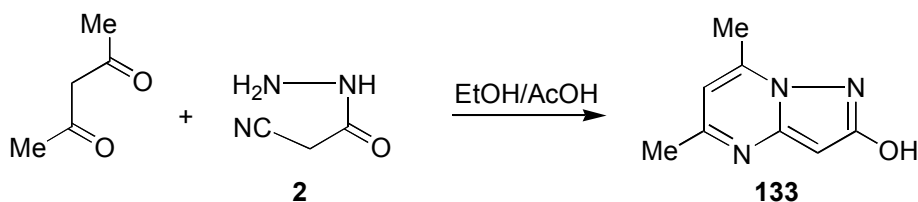
Scheme 73

4-Amino-5-arylidenehydrazinocarbonylthiazole-2(3*H*)-thiones **131** were prepared by the reaction of *N*-arylidene cyanoacetic acid hydrazides **96** with sulphur and phenyl isothiocyanate in the presence of triethyl amine. These compounds were cyclized by acetic anhydride to give the corresponding thiazolo[4,5-*d*]pyrimidines **132**.⁸⁶



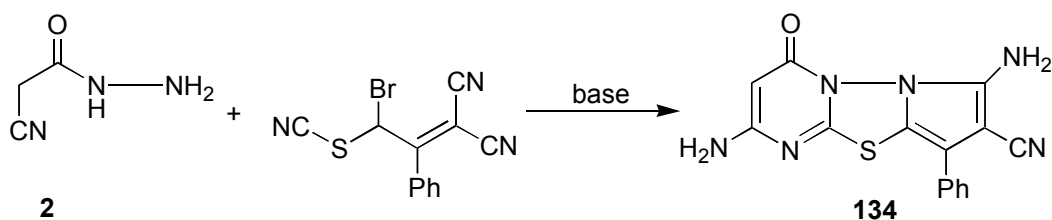
Scheme 74

Treatment of **2** with pentane-2,4-dione in ethanol in the presence of acetic acid led to the formation of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-2-ol **133**.⁸⁷



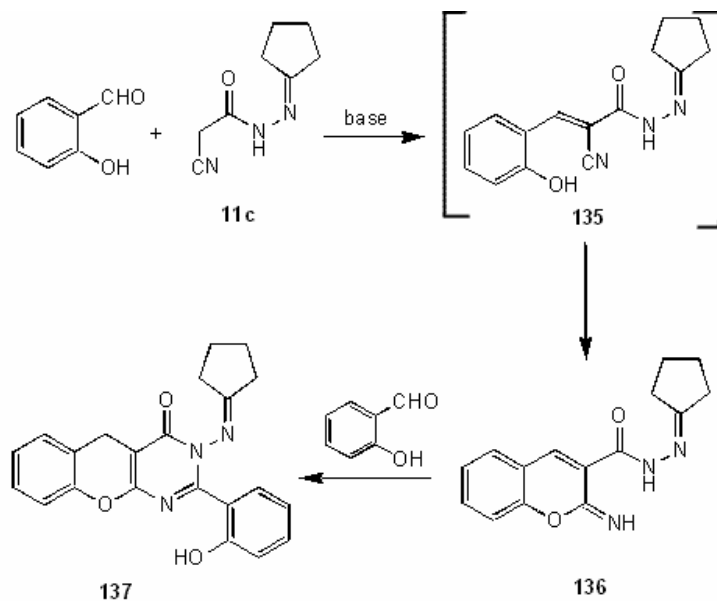
Scheme 75

2-(2-Bromo-1-phenyl-2-thiocyanatoethylidene)malononitrile reacts with **2** to afford 4*H*-pyrrolo[1',2':4,5][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-4-one derivative **134**.⁸⁸



Scheme 76

Heating of cyclopentylidene hydrazone of cyanoacetic acid **11c** with salicylaldehyde in presence of a base afforded 3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-one derivatives **137**.⁸⁹

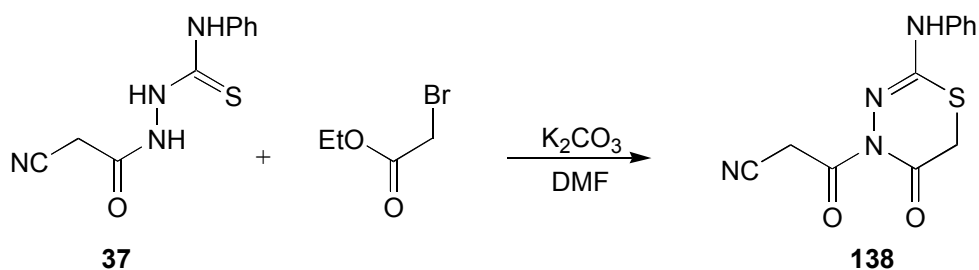


Scheme 77

4.6. Synthesis of Six-Membered Ring with Three Heteroatoms

4.6.1. Thiadiazine

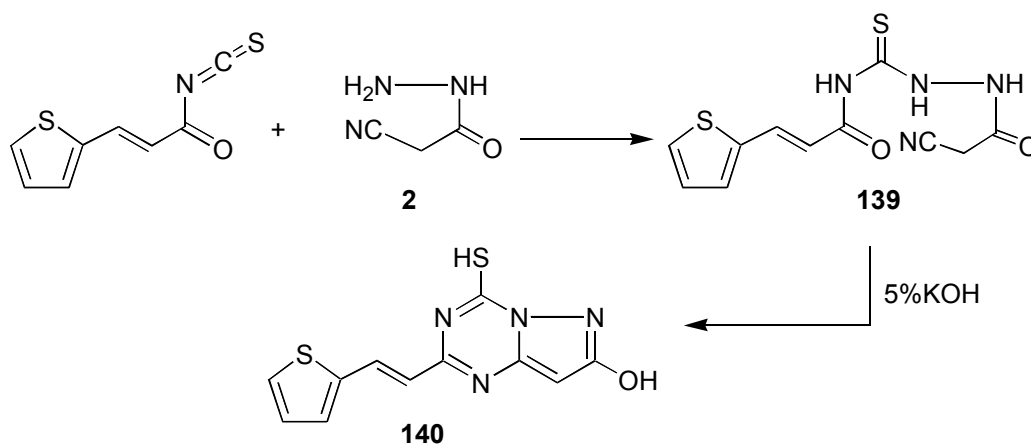
The reaction of 1-cyanoceto-4-phenylthiosemicarbazide **37** with ethyl bromoacetate in DMF and in the presence of anhydrous potassium carbonate at room temperature gave 1,3,4-thiadiazine derivative **138**.³³



Scheme 78

4.6.2. Triazine

Nucleophilic addition reaction of 3-thiophen-2-yl-acryloylisothiocyanate with **2** afforded thiocarbamoyl derivative **139** which gave pyrazolo[1,5-*a*][1,3,5]triazine derivative **140** on treatment with 5% potassium hydroxide.⁹⁰



Scheme 79

5. Conclusions

The data considered in this review clearly demonstrate the high synthetic potential of cyanoacetic acid hydrazide. Many biologically active heterocyclic compounds have been

obtained based on these reagents.¹⁻¹⁰ This suggests that cyanoacetic acid hydrazide can be particularly promising synthons in combinatorial synthesis of functionalized carbo- and heterocyclic compounds used in the design of novel highly effective pharmaceuticals with a broad spectrum of bioresponses. The great interest of chemists in such reagents is confirmed by the facts that more than 80 articles of 90 cited in this review are dated in the last two decades, along with a multitude of patents.

6. References

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