Synthesis of Some Heterocyclic Compounds Using Cyanoacetohydrazide as Versatile Precursor

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Abstract

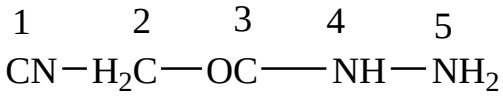
This study reviewed the use of cyanoacetohydrazide as versatile precursor for synthesis of some heterocyclic compounds, as it contains five different functional groups (cyano group, No. 1, active methylene group, No. 2, carbonyl group, No. 3, amido group, No. 4 and hydrazine group, No.5) The reviewed reactions were classified according to the active centers of cyanoacetohydrazide involved. Accordingly, they are divided into 12 classes in which heterocycles was obtained via the utility of the following functional groups: a - groups No. 1, 2, b - groups No. 1,5, c - groups No. 2, 3 , d - groups No. 2,4 , e - groups No. 2,5 , f- groups No. 3,5 , g- groups No. 4,5 , h- groups No. 1,2,5, i- groups No. 1,4,5, j- groups No. 2,4,5, k- groups No. 1,2,4,5, l-groups No. 2,3,4,5 .This review covers literature up to 2021.

Keywords Cyanoacetohydrazides ,Cyanoacetic acid hydrazide, Heterocycles, Cyclization.

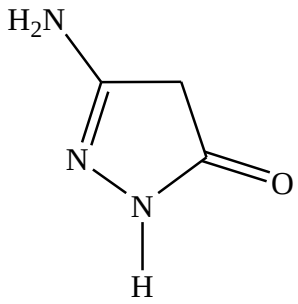
Introduction

Cyanoacetohydrazide is a versatile reagent as it contains five different functional groups (cyano, active methylene, carbonyl, amido and hydrazino groups) . Some of them could act as a nucleophile or as an electrophile. Also they could act in pairs as a bidentate reagent affording several probabilities . the predominance of which depends on the reaction conditions and the other reactants.

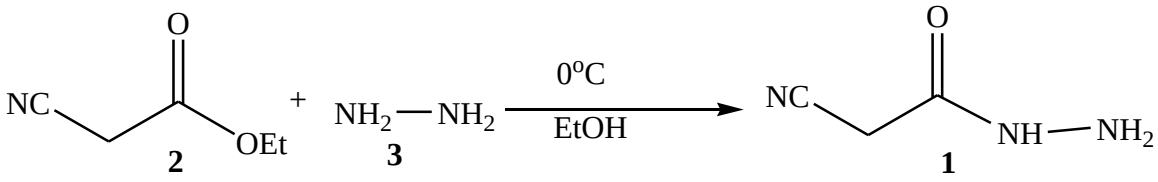
Moreover, the versatility of this reagent could be extended to form condensed heterocycles via the involvement of more than two centers in the reaction course .



In addition, cyanoacetohydrazide could be easily self - cyclized to afford a new versatile reagent namely 3-amino-5-pyrazolone, which has extensive use in the synthesis of condensed pyrazoles[1].



This beside the simplicity of its preparation from cheap chemicals and in good yield renders it a good precursor in heterocyclic synthesis from both the theoretical practical point of view and it can be prepared[2] as shown in Scheme1.



Scheme1

These facts made us interested to review this subject here, however, the behavior of cyanoacetohydrazide which doesn't lead to heterocycles will be dropped.

The reviewed reactions were classified according to the active centers of cyanoacetohydrazide involved. Accordingly, they are divided into the following classes:

a - Heterocycles obtained via the utility of functional groups No. 1, 2 (The cyano and methylene groups .)

b - Heterocycles obtained via the utility of functional groups No. 1,5 (The cyano and hydrazino groups .)

c - Heterocycles obtained via the utility of functional groups No. 2, 3 (The methylene and carbonyl groups .)

d - Heterocycles obtained via the utility of functional groups No. 2,4 (The methylene and amido groups .)

e - Heterocycles obtained via the utility of functional groups No. 2,5 (The methylene and hydrazino groups .)

f- Heterocycles obtained via the utility of functional groups No. 3,5 (The carbonyl and hydrazino groups .)

g- Heterocycles obtained via the utility of functional groups No. 4,5 (The amido and hydrazino groups .)

h- Heterocycles obtained via the utility of functional groups No. 1,2,5 (The cyano, methylene and hydrazino groups .)

i- Heterocycles obtained via the utility of functional groups No. 1,4,5 (The cyano, amido and hydrazino groups .)

j- Heterocycles obtained via the utility of functional groups No. 2,4,5 (The methylene, amido and hydrazino groups .)

k- Heterocycles obtained via the utility of functional groups No. 1,2,4,5 (The cyano, methylene, amido and hydrazino groups .)

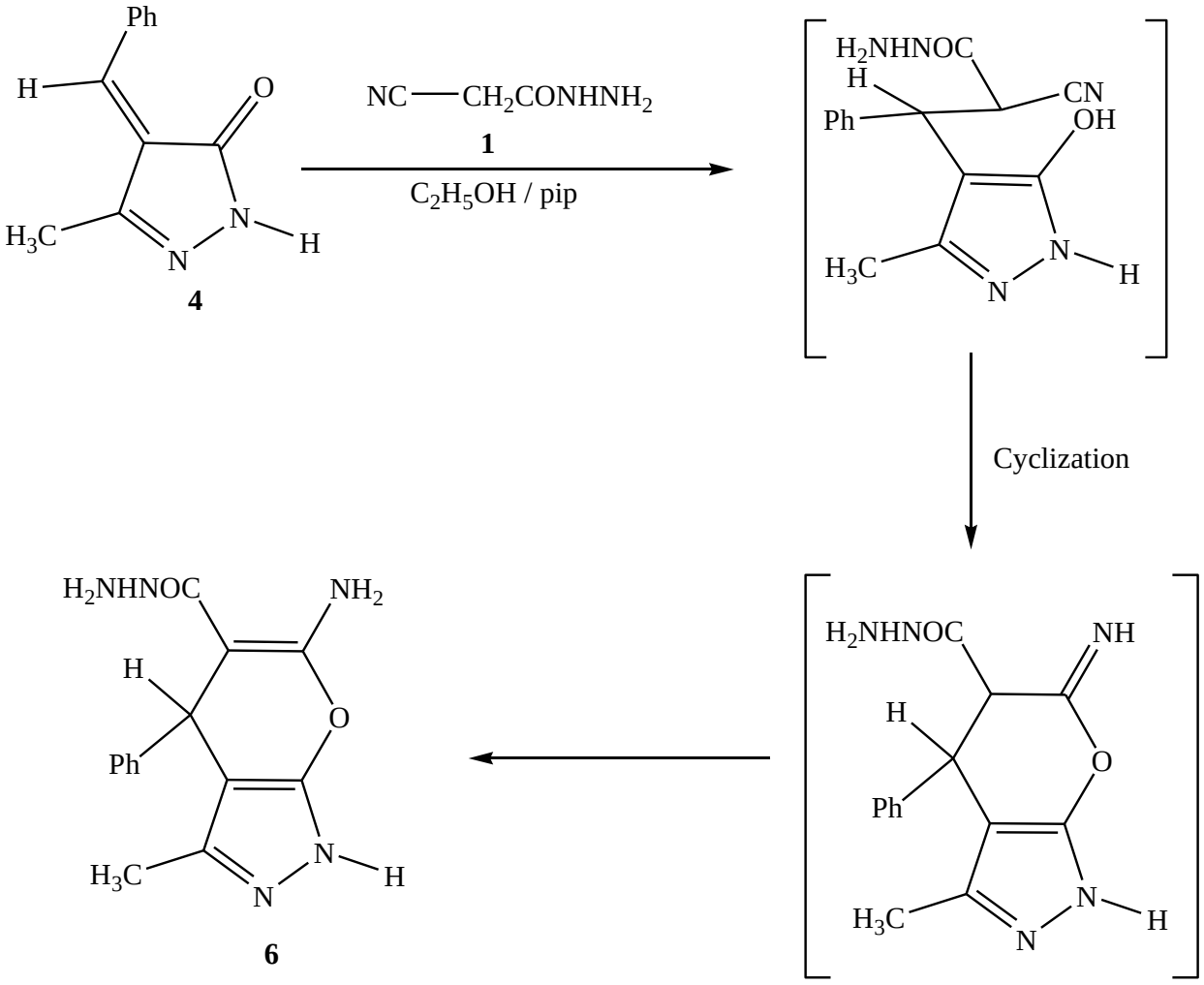
l- Heterocycles obtained via the utility of functional groups No. 2,3,45 (The methylene, carbonyl, amido and hydrazino groups.)

a - Heterocycles obtained via the utility of functional groups No. 1, 2 (The cyano and methylene groups .)

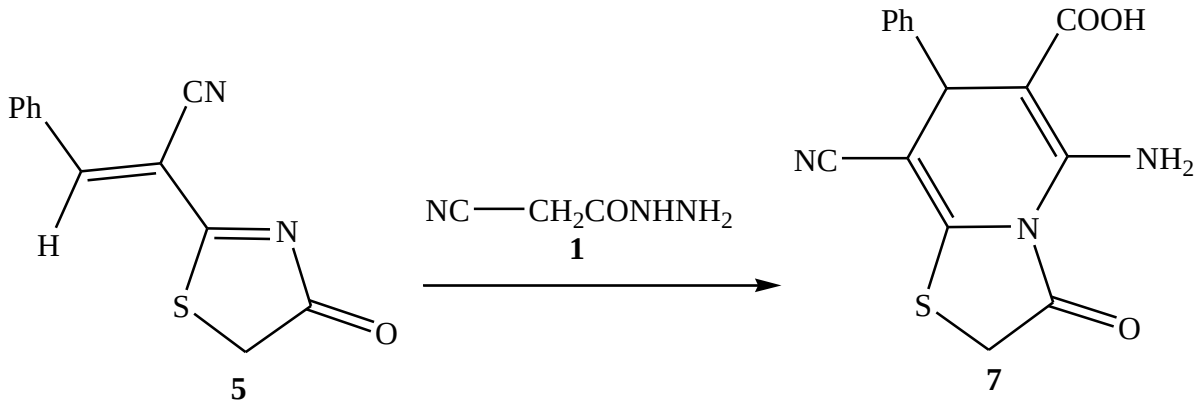
Cyanoacetohydrazide **1** behaves as a nucleophile in a Michael type reaction via its active methylene group to afford the 1:1 adduct intermediate which may cyclize

involving the cyano group of **1** together with the oxygen or nitrogen nucleophile from the other reagent to form heterocyclic compounds.

Thus, El-Moghayer et al[3] reported that, the reaction of **1** with benzylidenes **4** or **5** in boiling ethyl alcohol in the presence of piperidine, as a basic catalyst, gave the corresponding pyranopyrazole **6** and thiazolopyridine **7**, respectively (Scheme 2a,b).

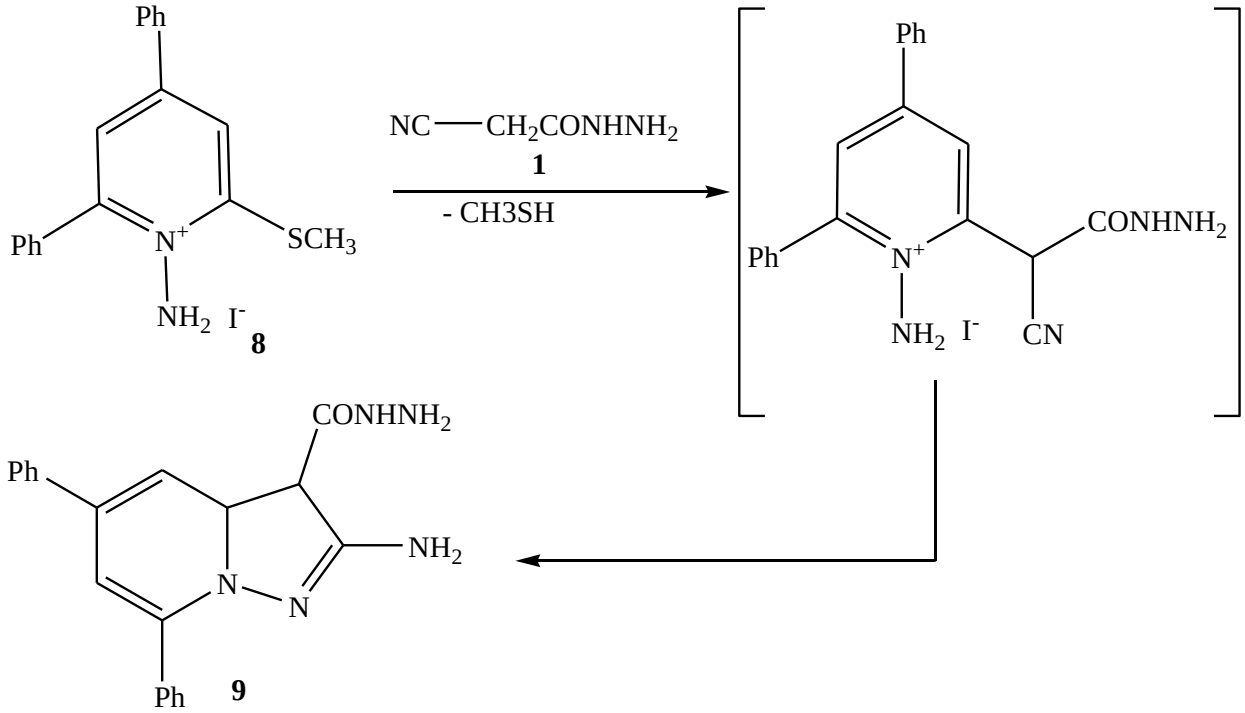


Scheme 2a



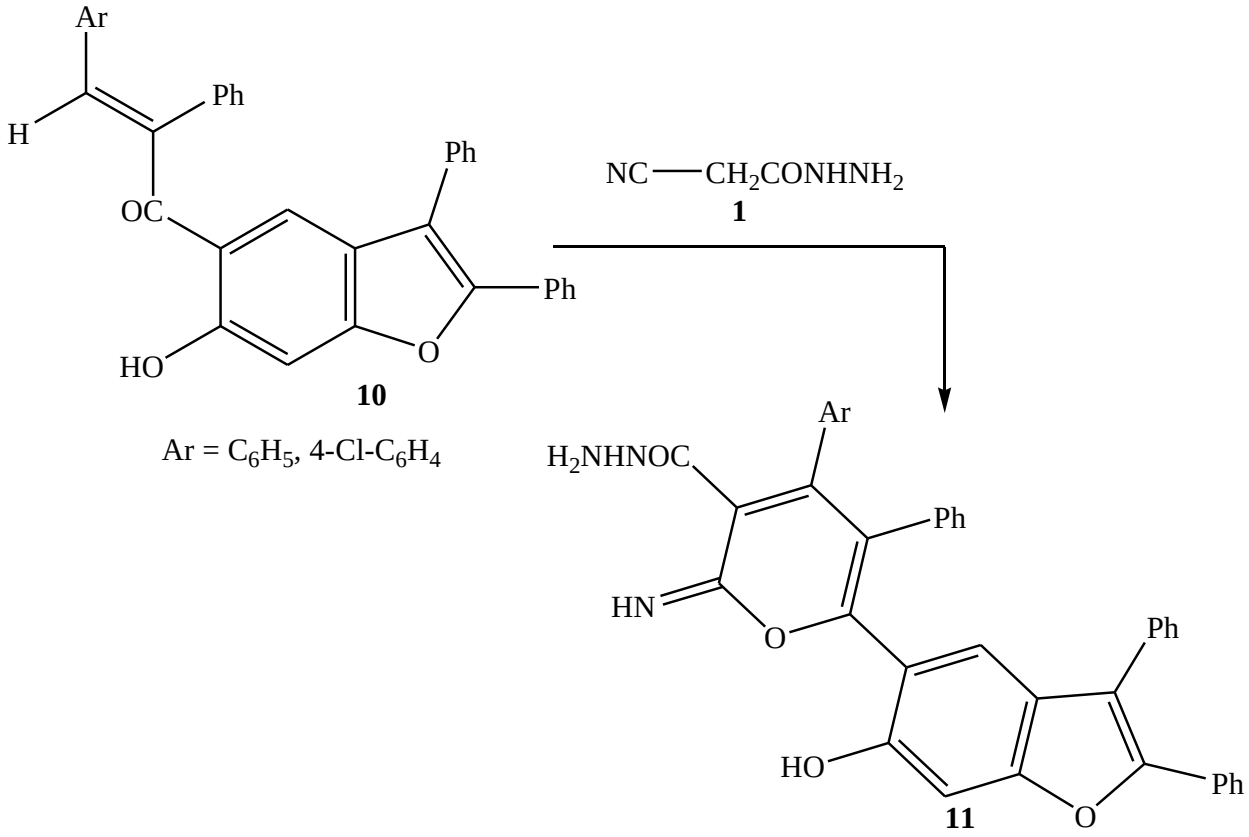
Scheme 2b

Another condensed pyrazole could be obtained when **1** was refluxed with 1-amino-4,6-diphenyl-2-methylthiopyridinium iodide **8**, where cyclization took place giving a product which was identified as 2 -amino-3- hydrazinocarbox– 5,7 -diphenylpyrazoio[2, 3- a]pyridine **9**[4] (Scheme 3).



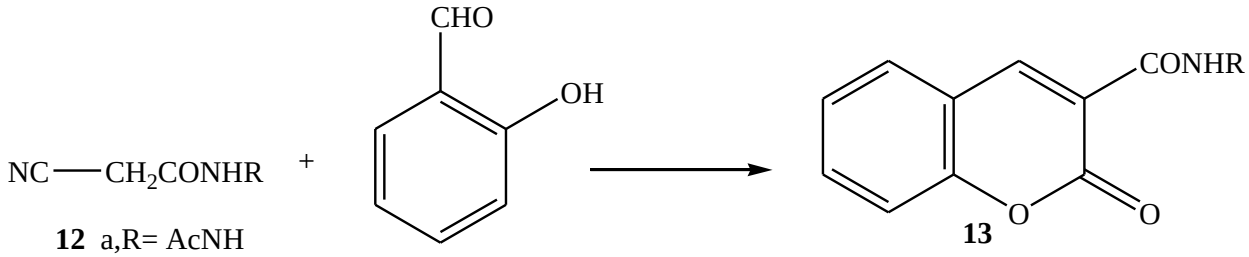
Scheme 3

Moreover, it was found that the reaction of compound **10** with cyanoaceto-hydrazide **1**, yield a product which was interpreted as the α-iminopyran derivative **11**[5] (Scheme 4).



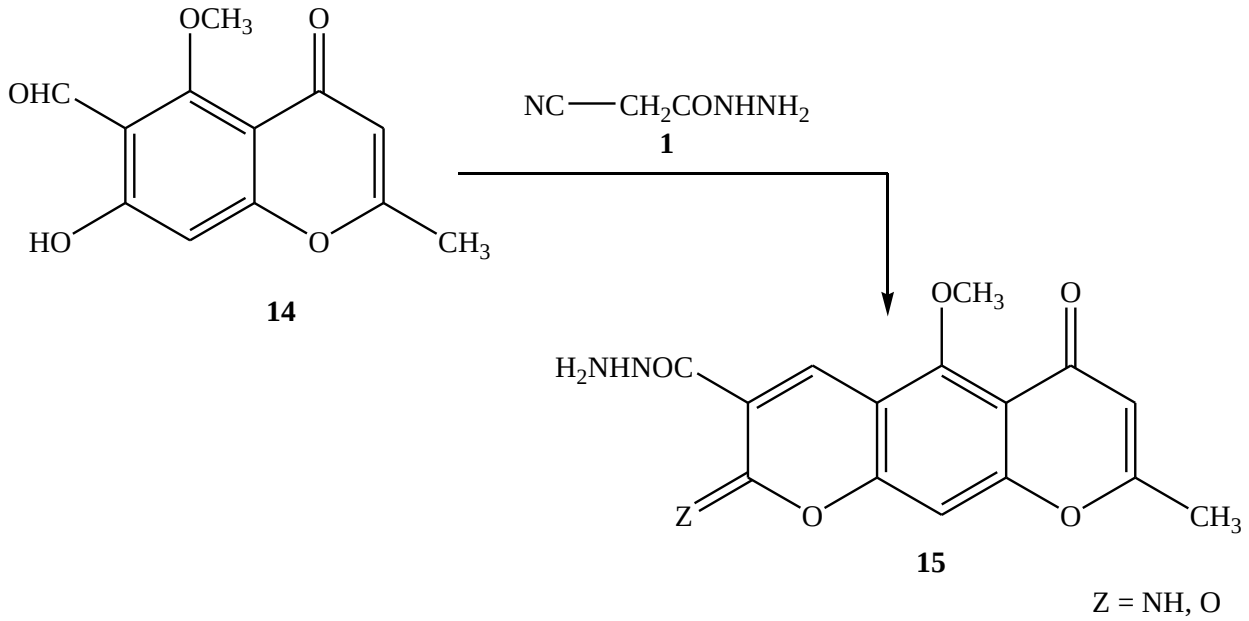
Scheme 4

Similarly, it has been reported that, the reaction of N – substituted cyanoaceto-hydrazide **12** with salicylaldehyde gave α-coumarin derivatives **13**[6] as shown in Scheme 5.



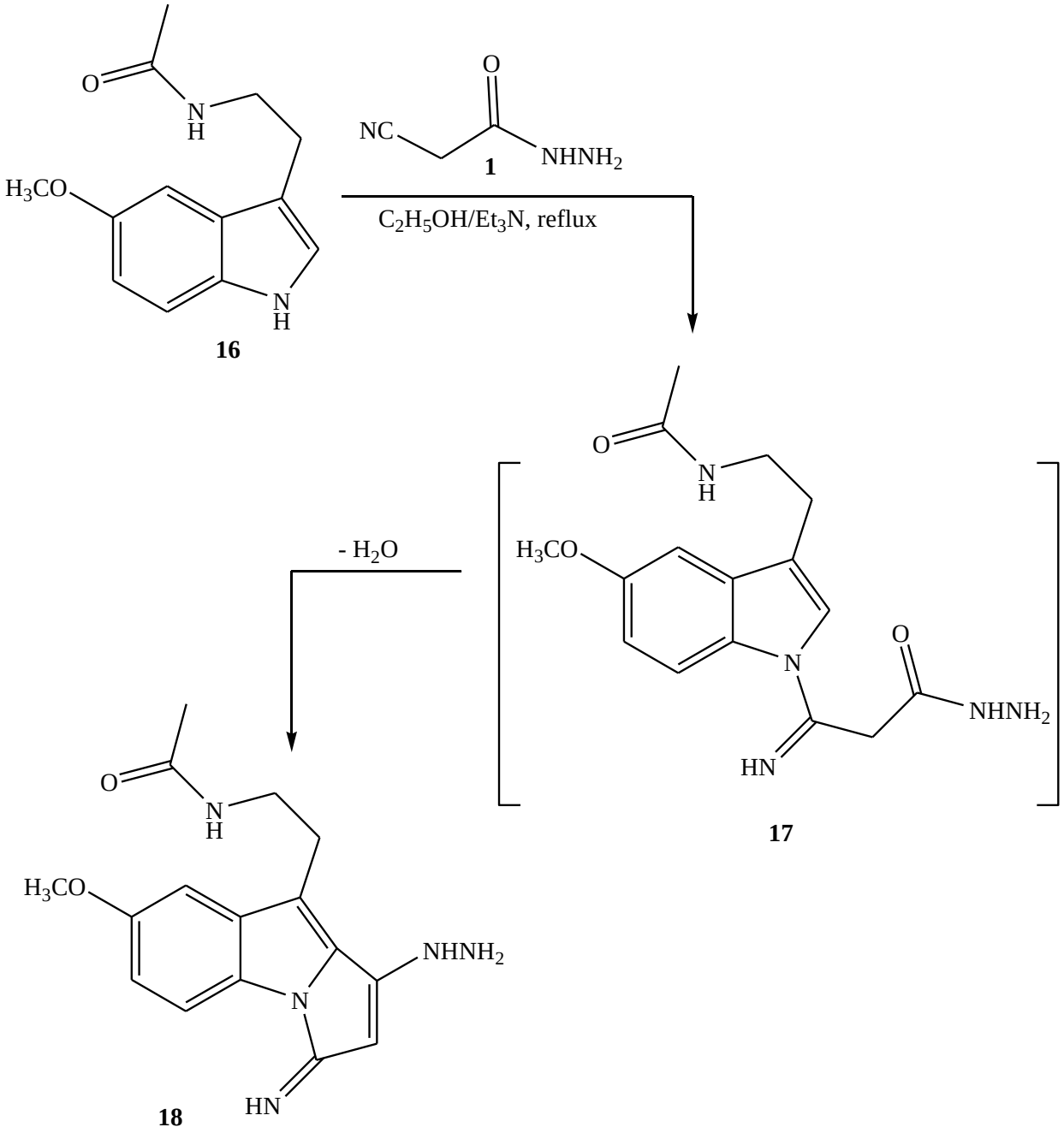
Scheme 5

Goher et al[7] reported the isolation of both the α-coumarin derivative and its imino analogue **15** from the reaction of **1** with the condensed salicylaldehyde **14** in ethyl alcohol containing catalytic amount of piperidine (Scheme 6) .



Scheme 6

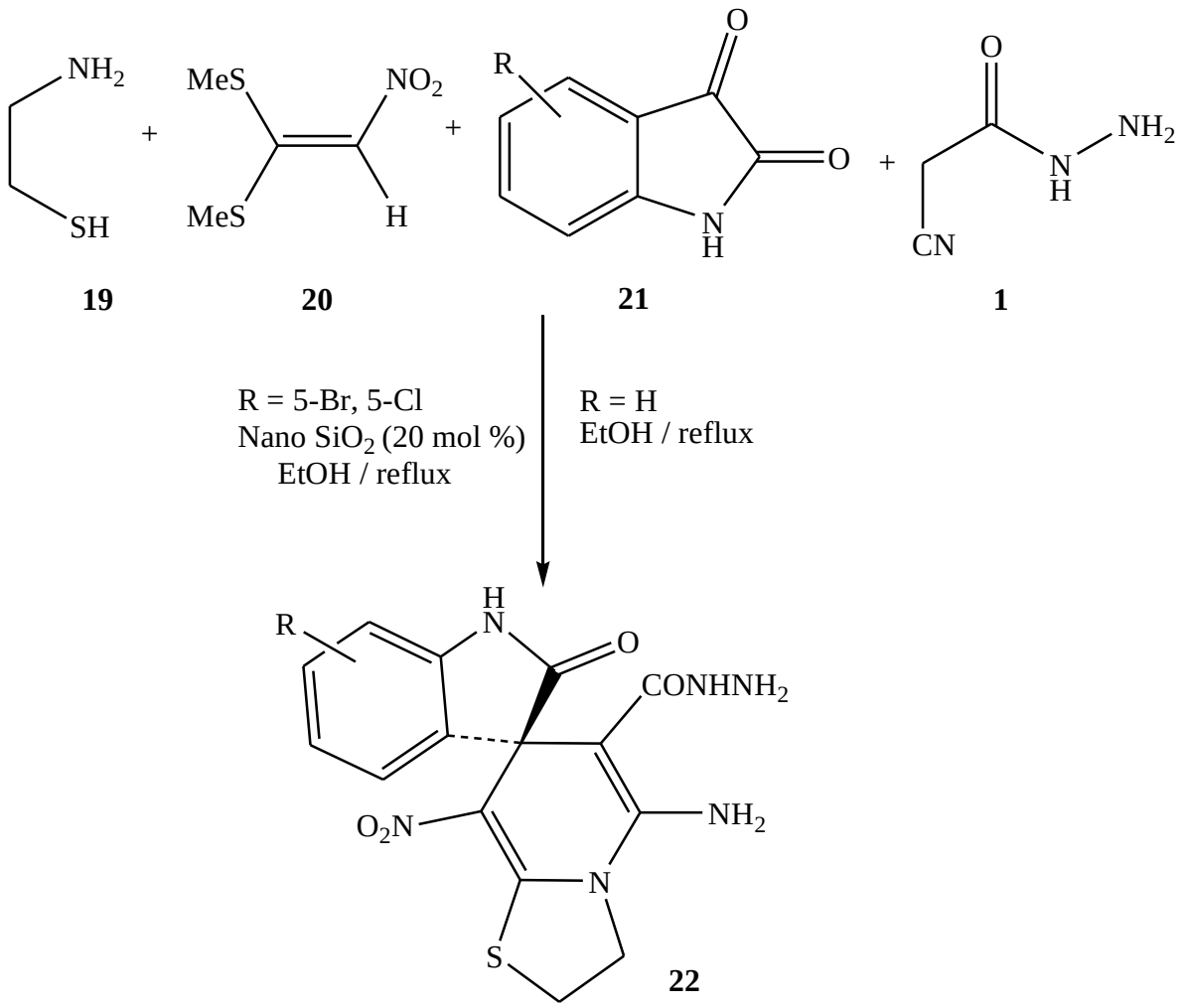
Moreover, the addition reaction of cyanoacetohydrazide **1** to melatonin **16** pass through an intermediate **17** which cyclize to afford the benzopyrrolizine **18**[8], Scheme 7.



Scheme 7

Additionally, novel structures containing thiazolo pyridine-fused spirooxindole **22** were synthesized[9] by a four-component domino reaction of cysteamine hydrochloride **19**, nitroketene dithioacetals **20**, isatin or its derivatives **21** and cyanoacetohydrazide **1** (active methylene compound) in ethanol under reflux conditions (Scheme 8). As for isatin derivatives (5-bromoisatin and 5-chloroisatin), due to the relatively less activity of these derivatives than isatin, the reaction was

conducted via using nanoSiO_2 (20 mol%) as an effective heterogeneous Lewis acid promoter.

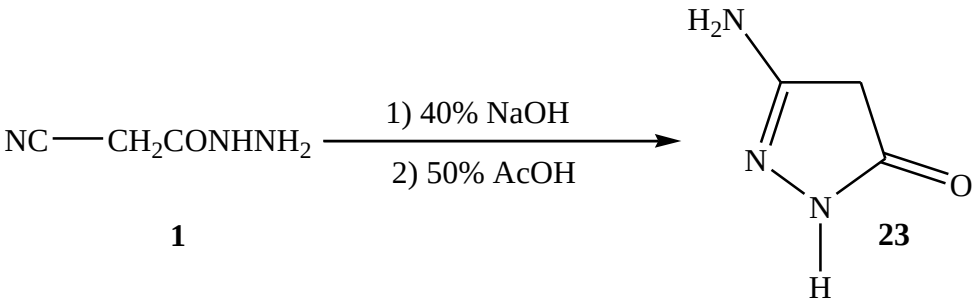


Scheme 8

b - Heterocycles obtained via the utility of functional groups No. 1,5 (The cyano and hydrazino groups .)

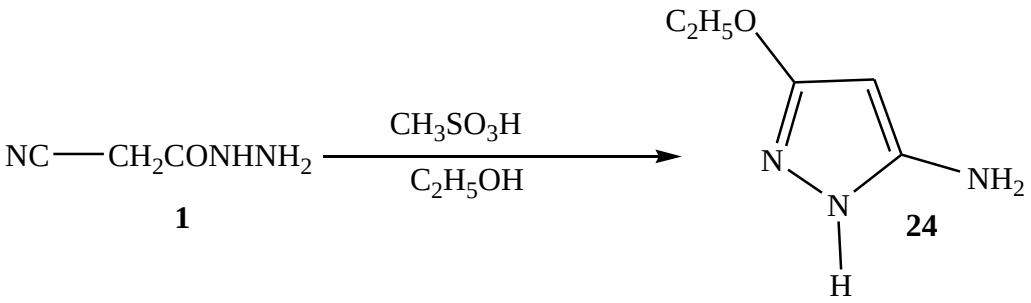
There are several reactions in which cyanoacetohydrazide undergoes first self - cyclization involving the cyano and amino - groups to give 3-amino-5- pyrazolone **23**, then the latter compound reacts with the available reagent present in the reaction mixture. Due to the presence of more than one reactive center in compound **23**, the center (or centers) involved in the reaction course depends on the other reactant and the experimental conditions used. Its worthy to mention that

compound **23** could be obtained by treatment of **1** with 40 % NaOH followed by neutralization with 50% AcOH[1] as shown in Scheme 9.



Scheme 9

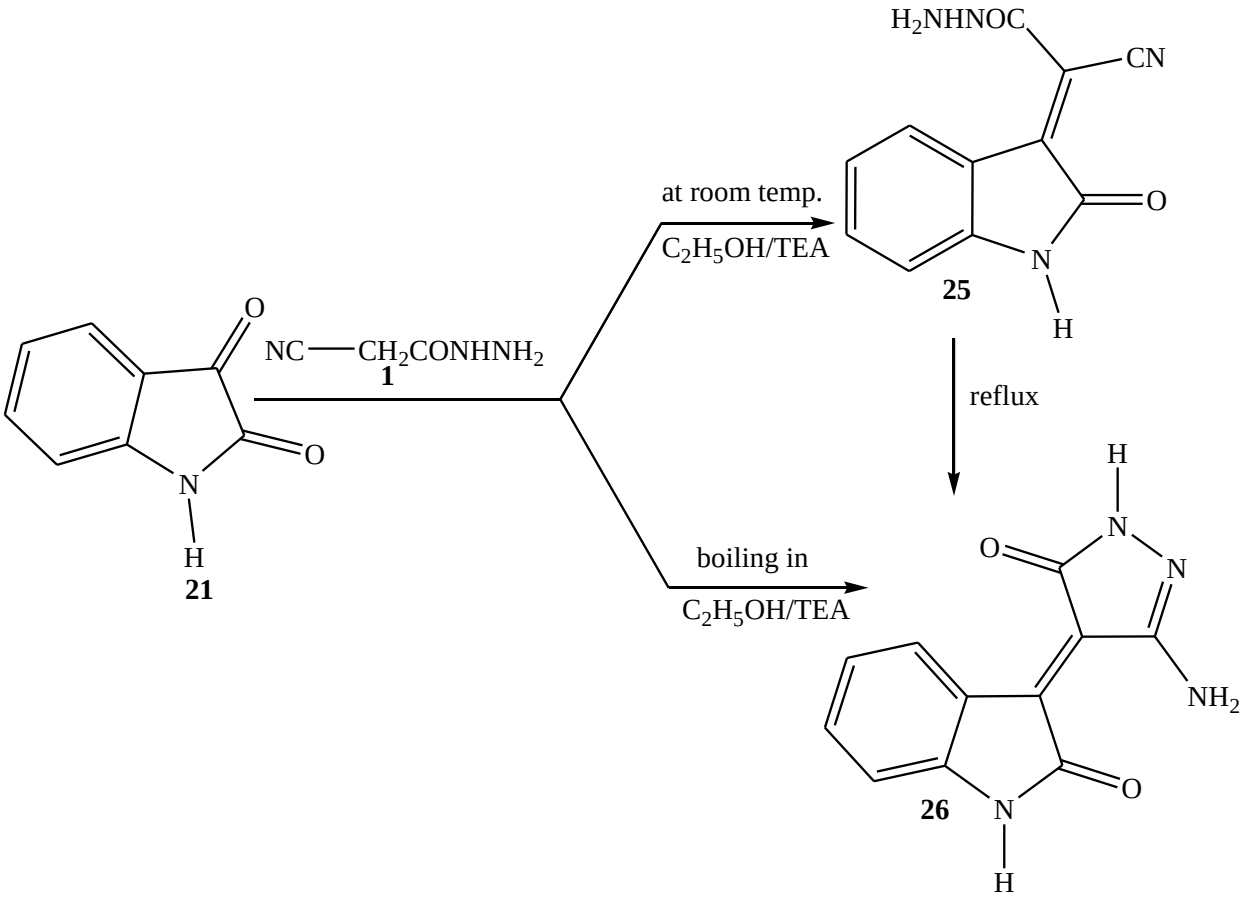
Thus, It has been reported that reflux of an ethanolic solution of cyanoaceto-hydrazide **1** in presence of CH_3SO_3H yield 5- amino-3-ethoxypyrazole **24**[10] (Scheme 10) .



Scheme 10

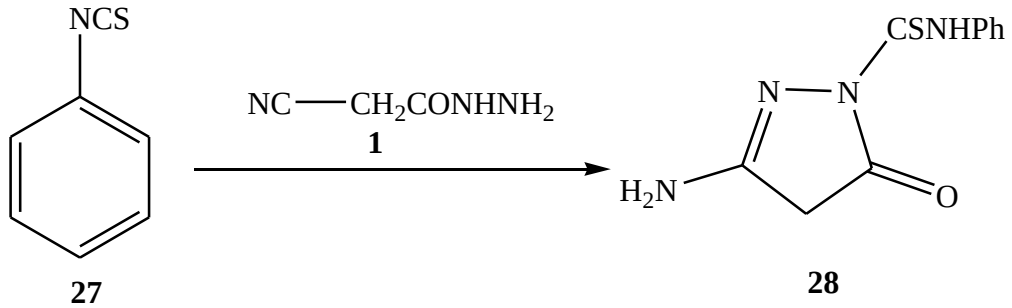
Regaila et al.[11] reacted **1** with isatin **21** in boiling ethanol containing catalytic amount of triethylamine and the obtained product was interpreted as 3-amino-4 -(oxindol - 3- ylidene) -5- pyrazolone **26** (Scheme 11).

On the other hand, when the above reaction was carried out at room temperature, the compound **25** was obtained which could be converted into the corresponding cyclized analogue on boiling its solution in ethanol and triethylamine (Scheme 11).



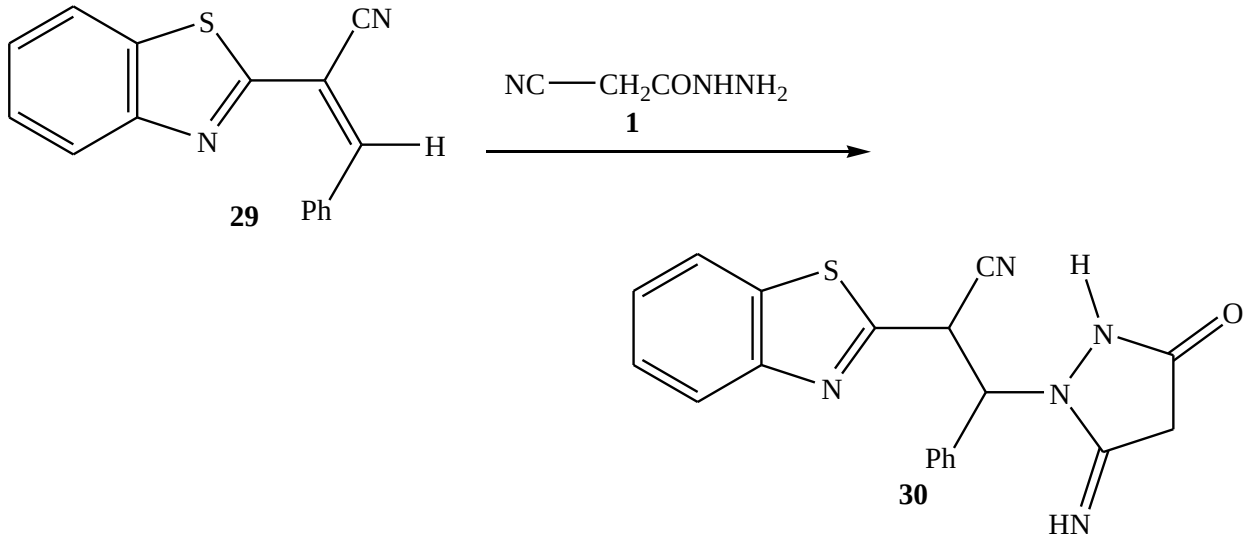
Scheme 11

In some other cases, the addition to the activated double bond can take place by the amido NH group of the pyrazolone ring, for example the reaction of **1** with phenyl isothiocyanate **27** in refluxing dioxane and the separated product was defined as the 1- phenylthiocarbamoyl-3- amino-5- pyrazolone **28**[12] as shown in Scheme 12.



Scheme 12

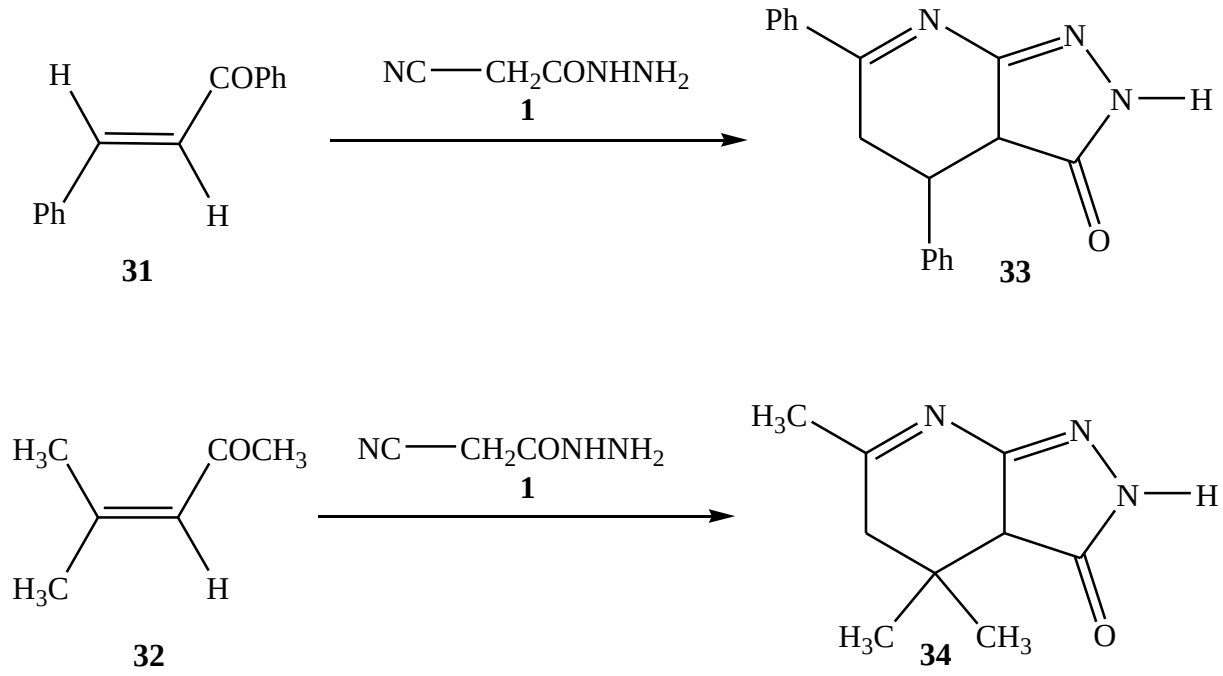
Also, it has been reported by Ghoneim et al.[13] that when **1** reacted with at α-benzylidene-2-cyanomethylbenzothiazole **29**, a product interpreted as 1:1 Michael adduct **30** was obtained (Scheme 13).



Scheme 13

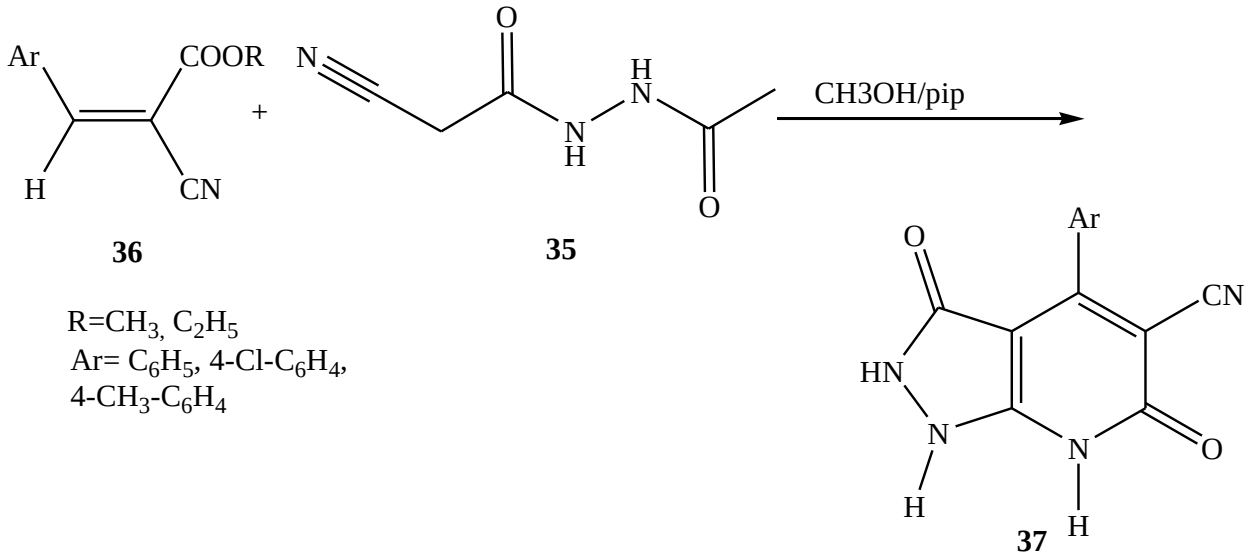
Some reactions involved the active centers, amino and active methylene groups of the pyrazolone ring and as aresult a number of Pyrazolopyridines were formed.

Thus, when El-Wassimy et al.[14] reacted **1** with the α,β-Unsaturated ketones **31** or **32**, they separated products which have been interpreted as the 4,6 - disubstituted - 2H - pyrazolo [4,3 – b] pyridin- 3- ones **33** or **34** , respectively . These reactions are believed to proceed via a Michael addition by the active methylene on the activated double bond of the chalcone giving the corresponding 1:1 Michael adducts which then undergo self - cyclization with elimination of water as shown in Scheme 14.



Scheme 14

Also, it has been reported that, the reaction of 2'- acetyl-2-cyanoacetohydrazide **35** with α-carboalkoxy cinnamonitriles **36** in methanol - piperidine gave products interpreted as the pyrazolo[3,4-b] pyridones **37**[15] (Scheme 15) .

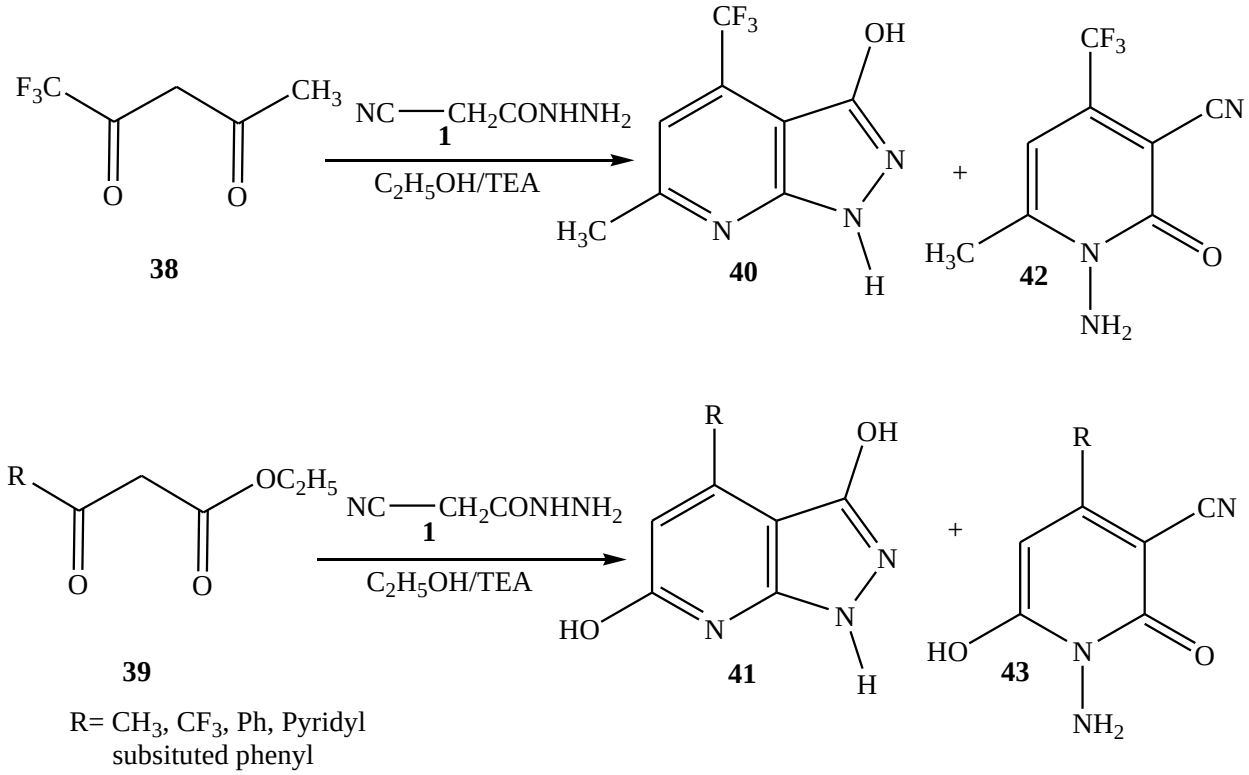


R=CH_3, C_2H_5
Ar= C_6H_5, 4-Cl-C_6H_4,
4-CH_3-C_6H_4

Scheme 15

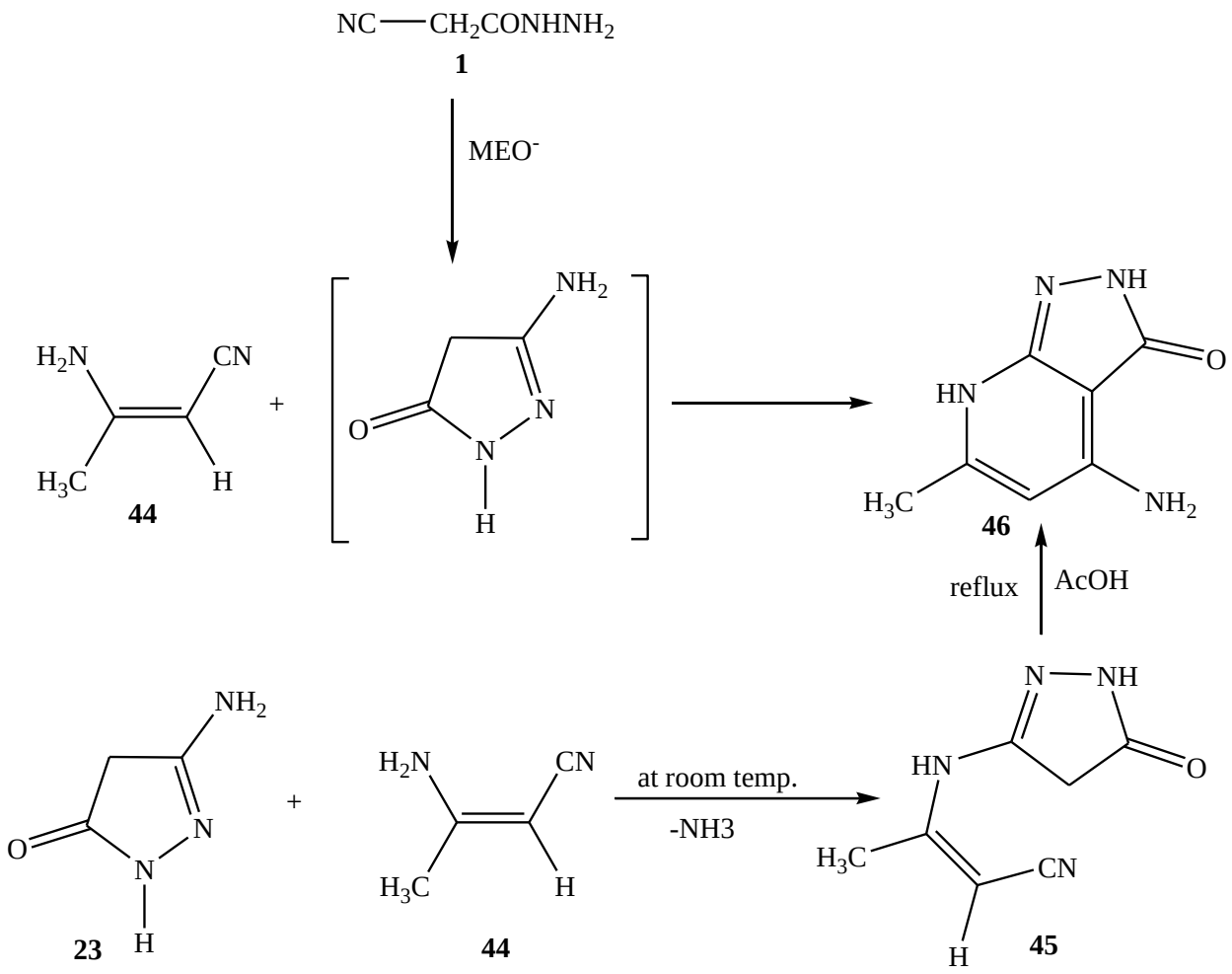
Moreover, pyrazolopyridines could be also obtained through the reaction of **1** with β-bifunctional reagents such as β- diketone , B- ketoesler or β-ketoaldehydes.

Thus. it has been reported that, the reaction of **1** with the β- diketo compounds **38** or **39** in refluxing ethyl alcohol and catalytic amount of triethylamine gave in each case mixtures of two products identified as pyrazolo [3, 4 – b] pyrldines (**40**, **41**) and N-aminopyridine derivatives (**42** and **43**)[16,17] as shown in Scheme 16.



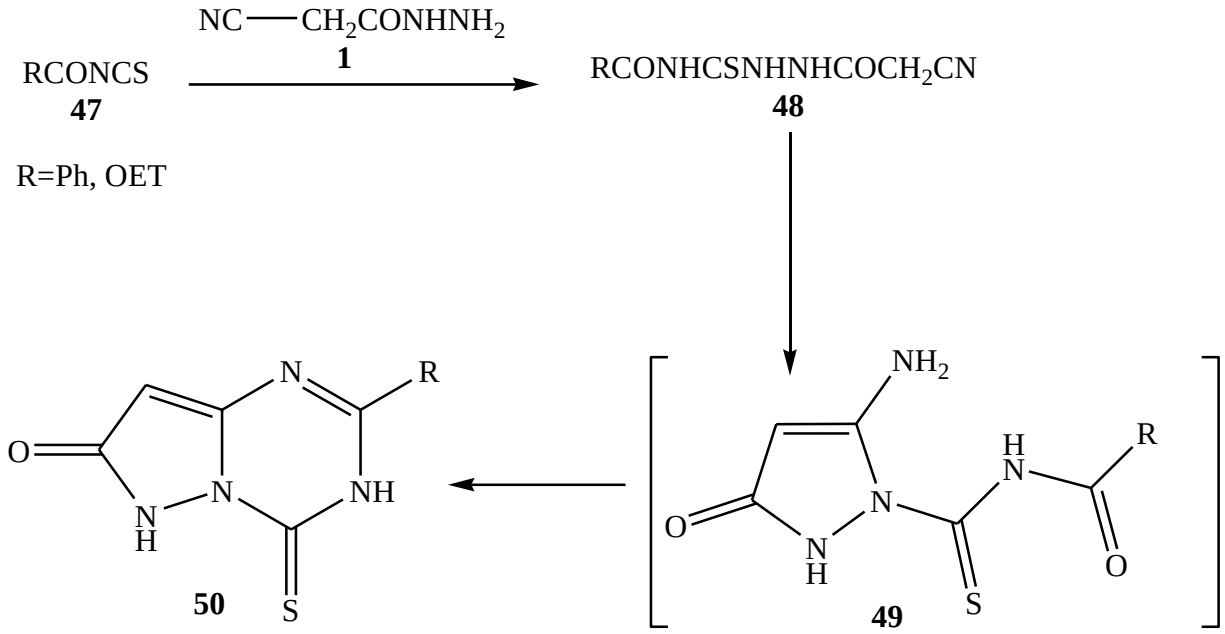
Scheme 16

The reaction of β- aminocrotononitrile **44** with cyanoacetohydrazide **1** in presence of sodium methoxide, gave a condensation product which has been identified as the pyrazolo[3, 4 - b] pyridine derivative **46**. The reaction is assumed to proceed via the intermediate **45** which could be separated when **44** was stirred with 3-amino pyrazolone **23** at room temperature . This intermediate when refluxed in acetic acid gave the final isolable product **46**[18] (Scheme 17).



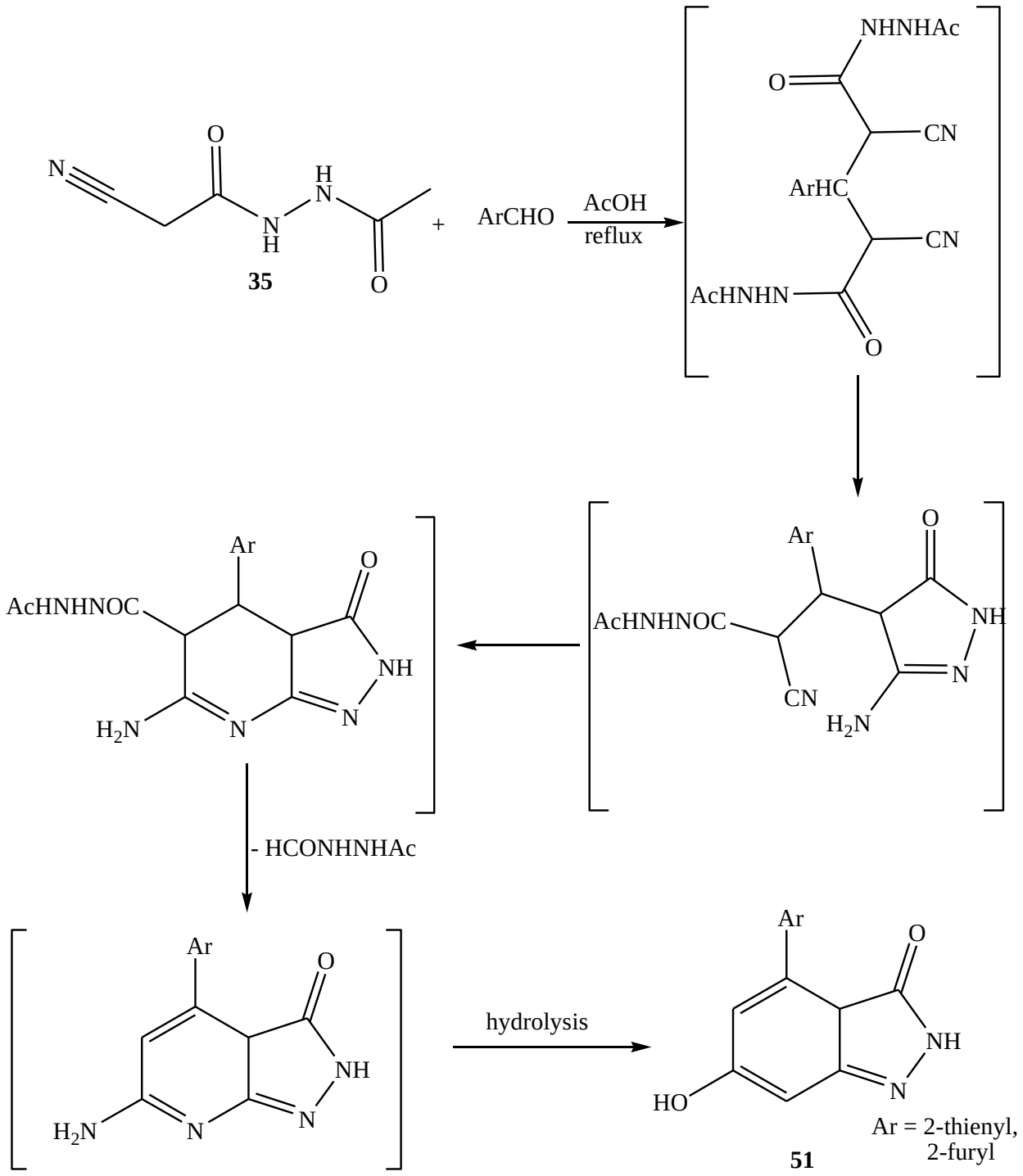
Scheme 17

The pyrazolo[1,5-a]- s-triazine derivative **50** was obtained when 1- cyanoacetyl -4-substituted thiosemicarbazide **48** (prepared from **1**and **47**) was refluxed in ethanolic potassium hydroxide or ethanolic sodium ethoxide. The formation of **50** is assumed to proceed via the intermediate **49** which self-cyclized with loss of water to give the final isolable product[19] (Scheme 18).



Scheme 18

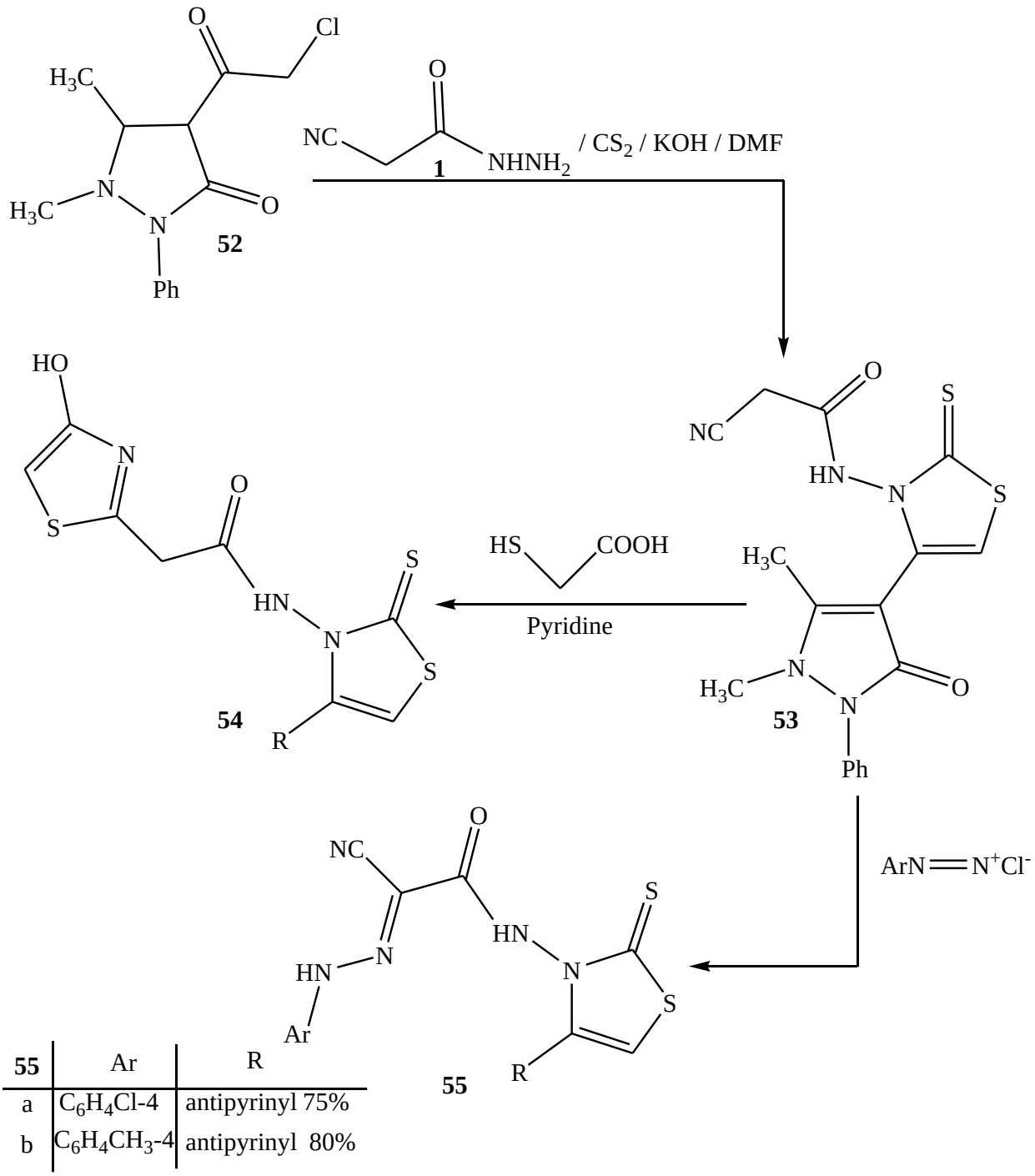
It has been reported that, the reaction of 2'-acetyl-2-cyanoacetohydrazide **35** with aromatic aldehydes in ethanol and triethylamine as a catalyst gave the corresponding c-arylidine derivatives. However. When the reaction of **35** with arylaldehyde was carried out in acetic acid instead of ethanol triethylamine. The pyrazolopyridines **51** were obtained. The reaction course is assumed to proceed via an ylidine bis intermediate as illustrated in the following Scheme 19[6].



Scheme 19

In addition, 2-Cyano-N-[4-(4-antipyrinyl)-2-thioxothiazol-3(2H)-yl]acetamide **53** was obtained through the reaction of a mixture of 4-chloroacetylantipyrine **52**[20] with 2-cyanoacetohydrazide **1** in dimethylformamide containing carbon disulfide

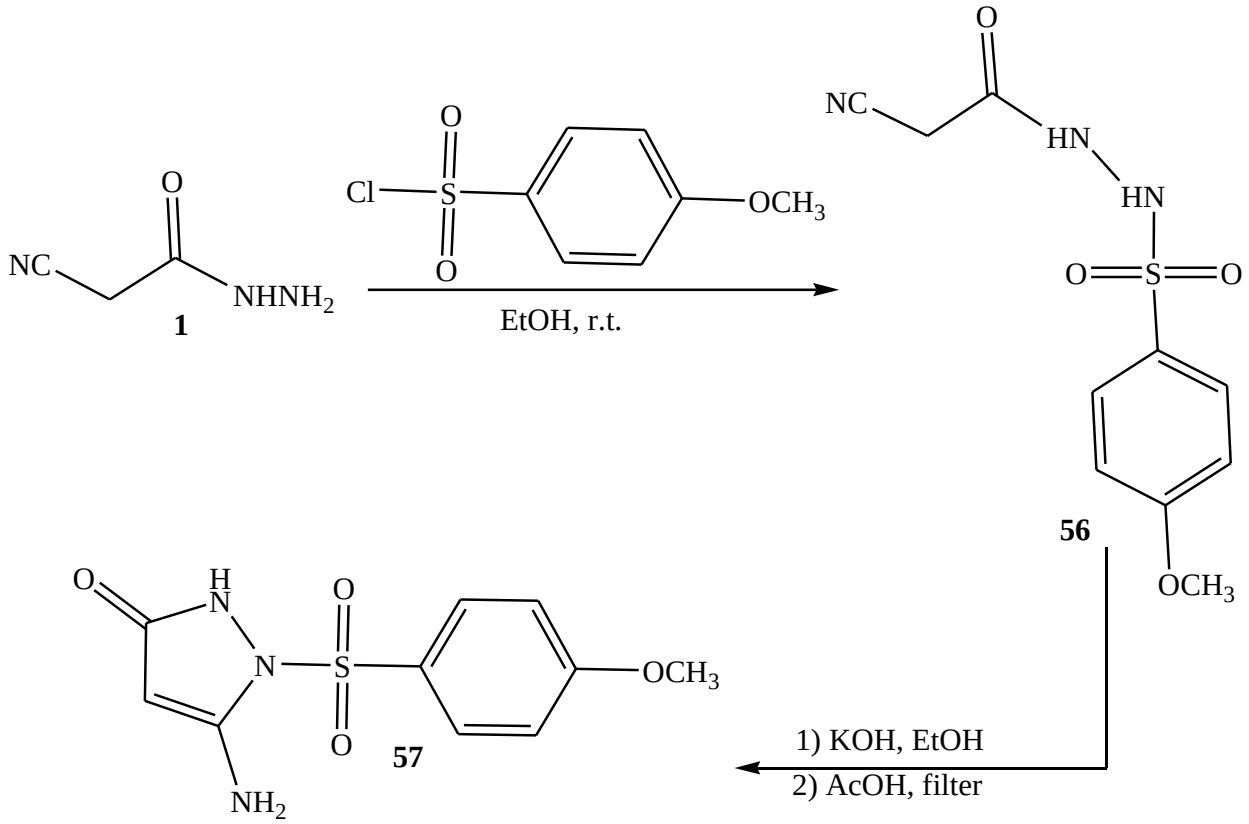
and potassium hydroxide. On the other hand, compound **53**[21] reacted with mercaptoacetic acid in dry pyridine to give N-[4-(4-antipyrinyl)-2-thioxothiazol-3(2H)-yl]-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide **54**. Coupling of **53** with aryl diazonium salts yields 2-arylhydrazone derivatives **55** [22,23] (Scheme 20).



55	Ar	R
a	C_6H_4Cl-4	antipyrinyl 75%
b	$C_6H_4CH_3$-4	antipyrinyl 80%

Scheme 20

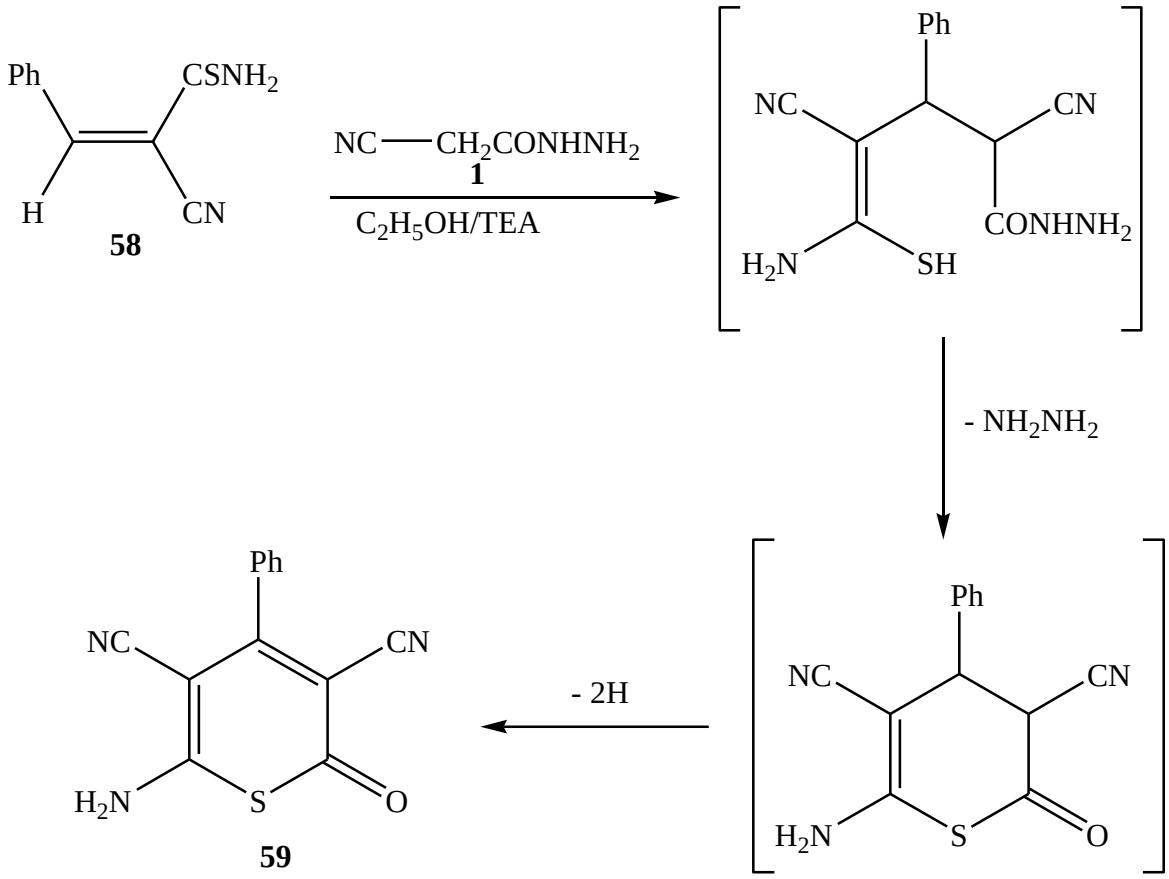
The reaction between commercially available cyanoacetohydrazide **1** and 4-methoxy- phenylsulfonyl chloride in ethanol resulted in the formation of the sulfonamide **56**, which precipitated from solution. Cyclization of sulfonamide **56** to pyrazolone **57** took place in an ethanolic solution of KOH, followed by neutralization with AcOH (Scheme 21)[24].



Scheme 21

c - Heterocycles obtained via the utility of functional groups No. 2, 3 (The methylene and carbonyl groups .)

Riad et al.[25] concluded that the reaction between cyanoacetohydrazide **1** and phenylmethylenecyanothioacetamide **58** in refluxing ethyl alcohol in the presence of triethylamine resulted in the formation of the 2-amino- 3,5- dicyano-4 -phenylthiopyran-6-one **59** according to the following mechanism (Scheme 22) :



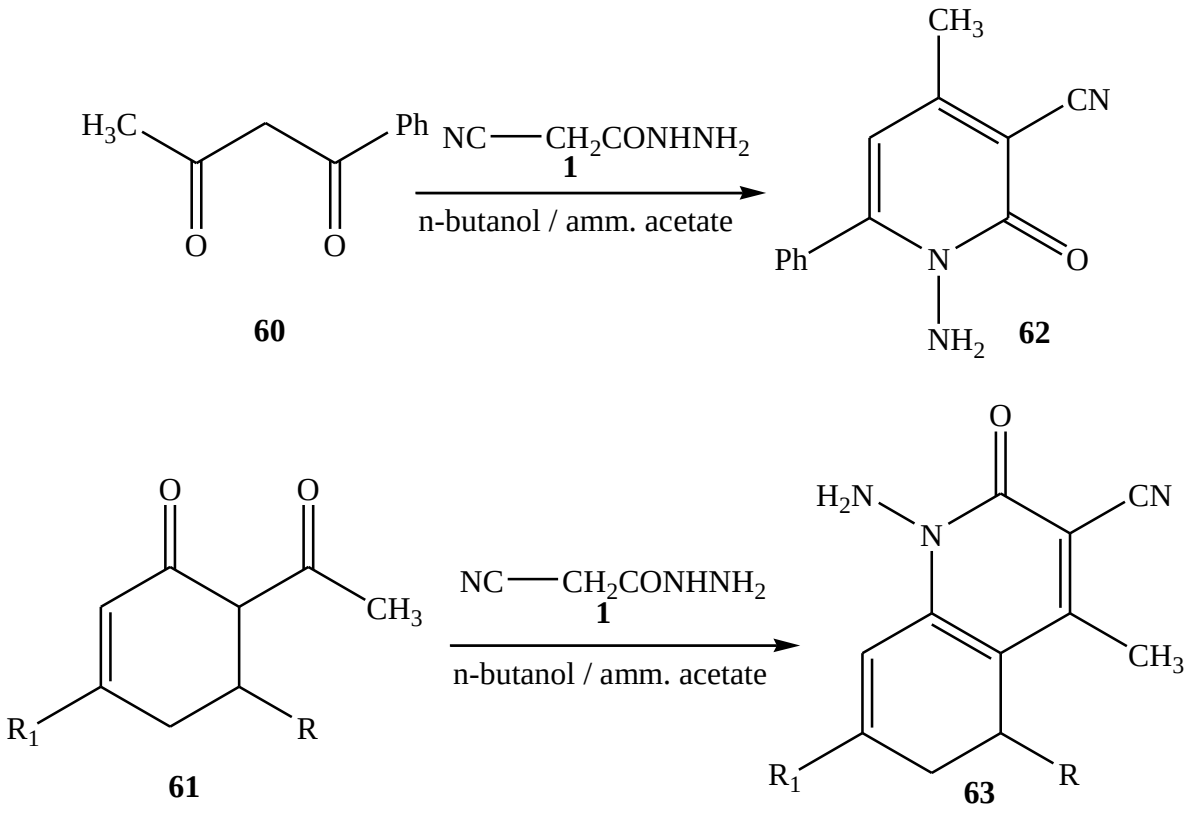
Scheme 22

d - Heterocycles obtained via the utility of functional groups No. 2,4 (The methylene and amido groups .)

Recently, N-amino-2-pyridones have proved to be useful synthetic intermediates. Few synthetic procedures are reported for their Preparations, among which we may mention the reaction of hydrazine with 2-pyrones, which are in turn prepared in low yields from the open chain compounds[26-28]. However, the condensation reaction of cyanoacetohydrazide via its methylene and amido groups with β-diketo compounds represent a facile and a general approach for the preparation of such compounds through one step reaction.

Thus, it has been reported that the reaction of **1** with benzoylacetone **60** or 2 -acetylcyclohexanones **61** in refluxing n.butanol in presence of ammonium acetate gave products which have been identified as 1-amino-3-cyano-4-methyl-5-

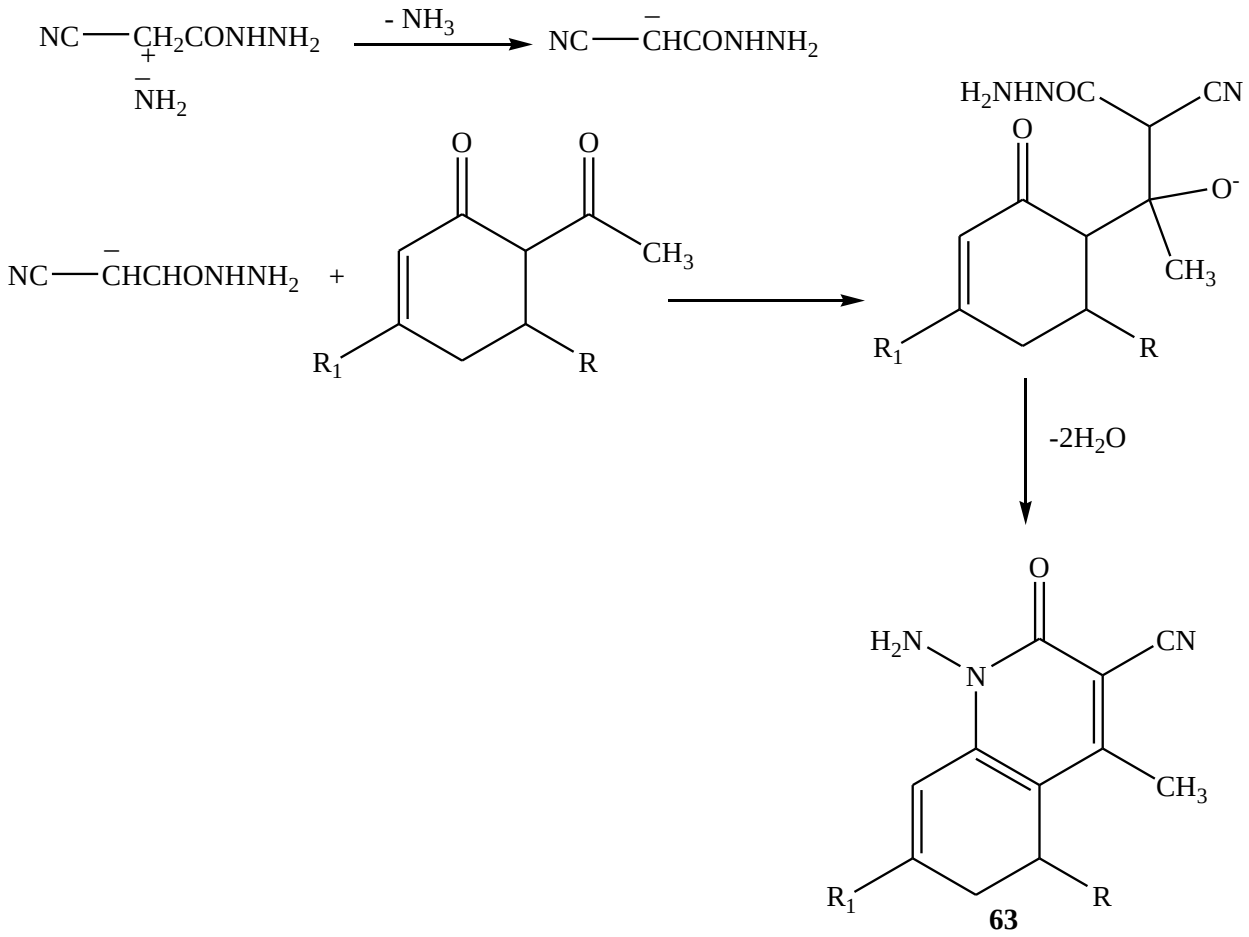
phenylpyridin-2-one **62** and 1-amino-3-cyano-5,7-diaryl-3-methyl- 5,6- dihydro-2-oxo - quinolines **63**, respectively [29,30] (Scheme 23).



a, R,R_1 = Ph
b, R=C_6H_4-$N(CH_3)_2$, R_1 = Ph

Scheme 23

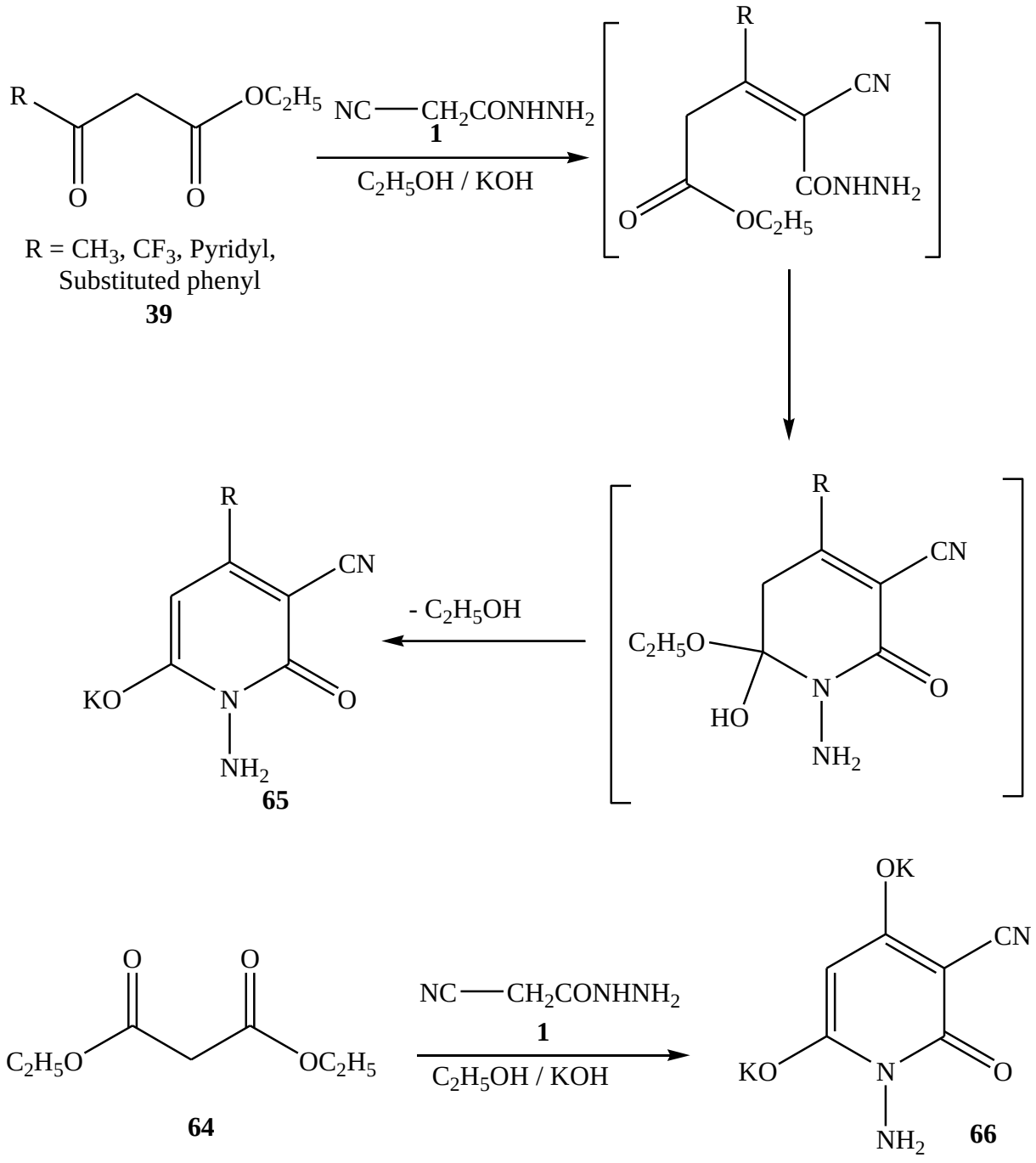
The reaction proceeds according to the following mechanism Scheme 24:



Scheme 24

The reaction of **1** with β-ketoester and β-diester in ethanolic potassium hydroxide have been reported to yield N-aminopyridone derivatives via Michael type reaction with its active methylene nucleophile and subsequent cyclization involving its nitrogen nucleophile amido group[31].

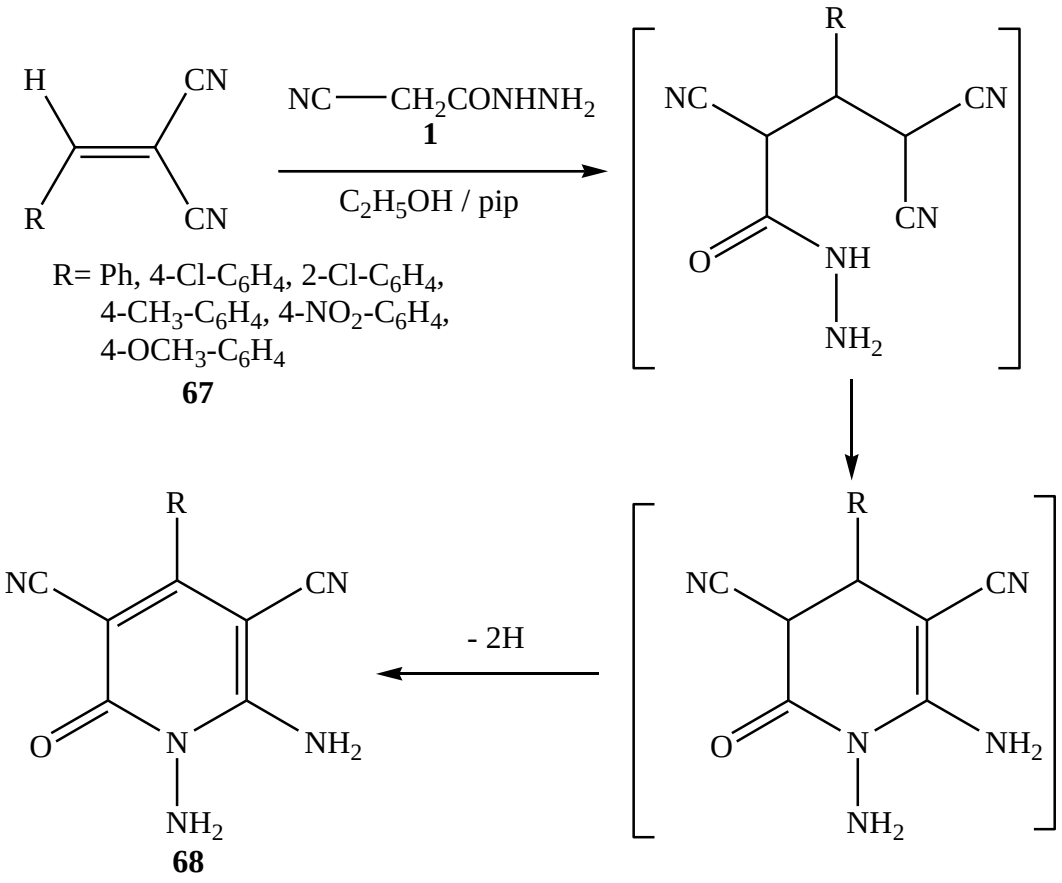
For example, when **1** reacted with ethyl acetoacetate derivatives **39** or diethyl malonate **64** in ethyl alcohol in presence of potassium hydroxide, the reaction gave N - aminopyridone derivatives **65** and **66**, respectively (Scheme 25).



Scheme 25

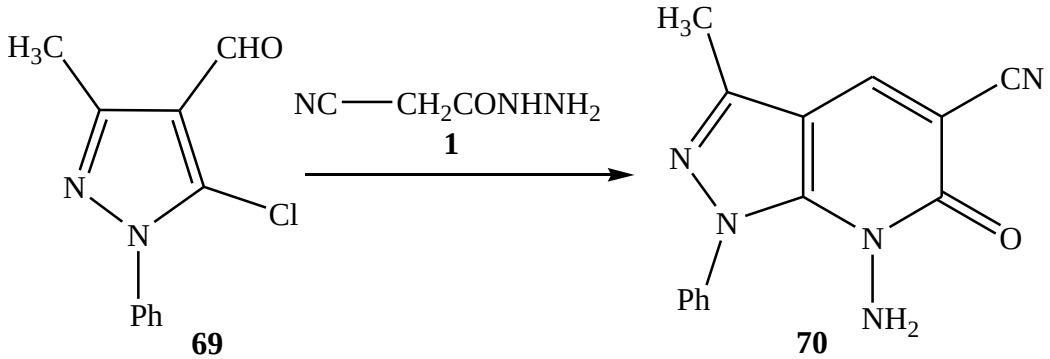
N - aminopyridones were also prepared via the reaction of cyanoacetohydrazide **1** with arylidene derivatives. This route has been utilized frequently in recent literature for the synthesis of such ring systems . Thus, it has been shown that cyanoacetohydrazide **1** reacted with the arylidene malononitrile derivatives **67** in ethyl alcohol and piperidine at room temperature to give the corresponding N-

aminopyridones **68**, these products were assumed to be formed via the Michael adduct intermediates which then undergo self- cyclization[32-35] (Scheme 26).



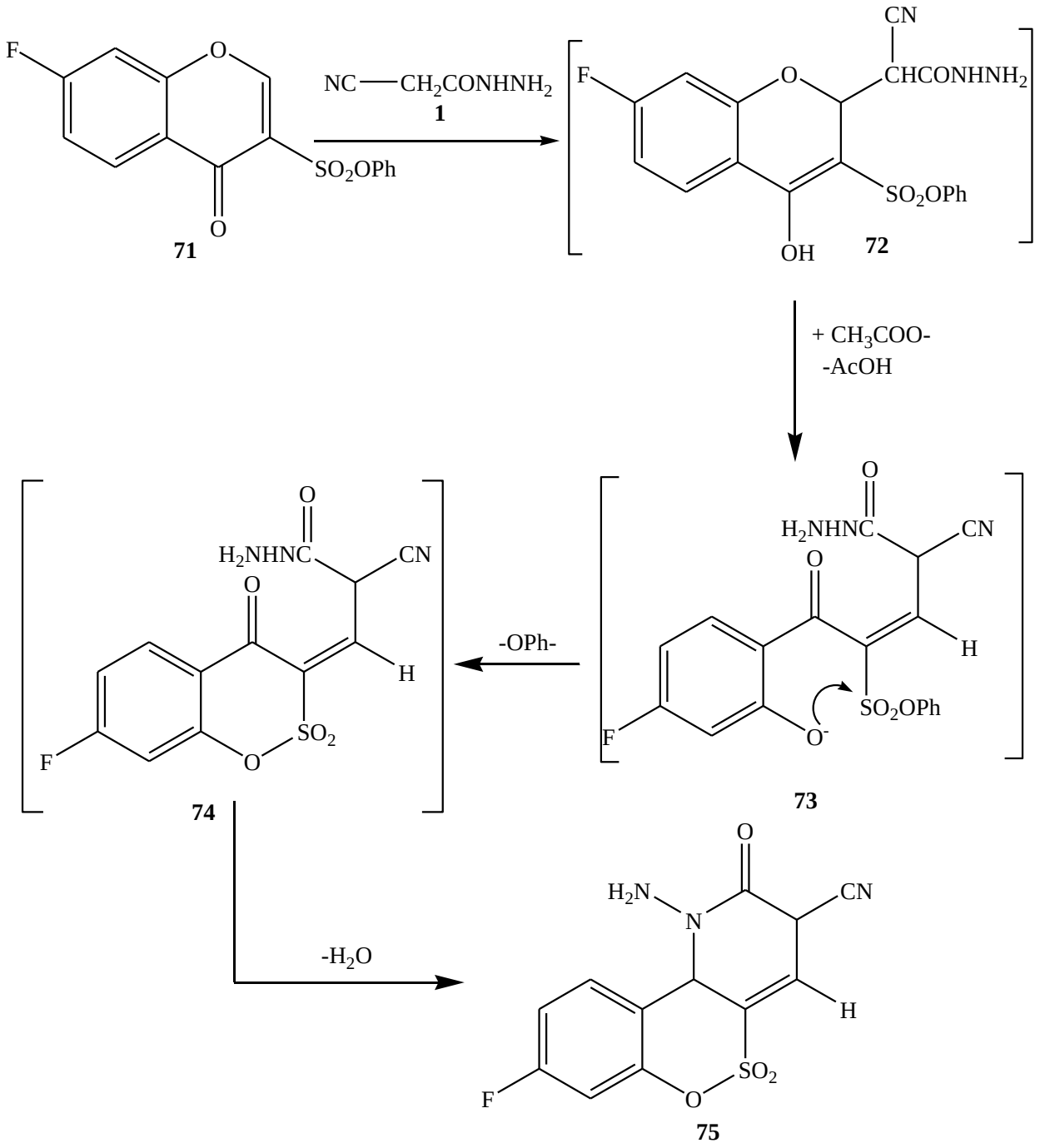
Scheme 26

The pyrazolopyridone **70**[36] was obtained from the reaction of **1** with 1-phenyl -3- methyl -4- formyl -5- chloropyrazole **69** (Scheme 27).



Scheme 27

It's important to mention that, cyanoacetohydrazide **1** may act as an ambident nucleophile, i.e. N - and C- nucleophile, as observed in its reaction with phenyl -7-fluoro-4- chromone -3- sulphonate **71** in the presence of sodium acetate. Two new compounds were obtained from the reaction[37] and interpreted as 1-amino -3-cyano-8-fluoro-1,2-dihydro-2-oxo[1,2]benzoxathiino[4,3-b1 pyridine- 5,5- dioxide **75** and 7-fluoro-2H-[1,2]benzoxathiino[4,3-c]pyrazole- 4, 4- dioxide mono hydrate **80** as shown in Scheme 28, 29.

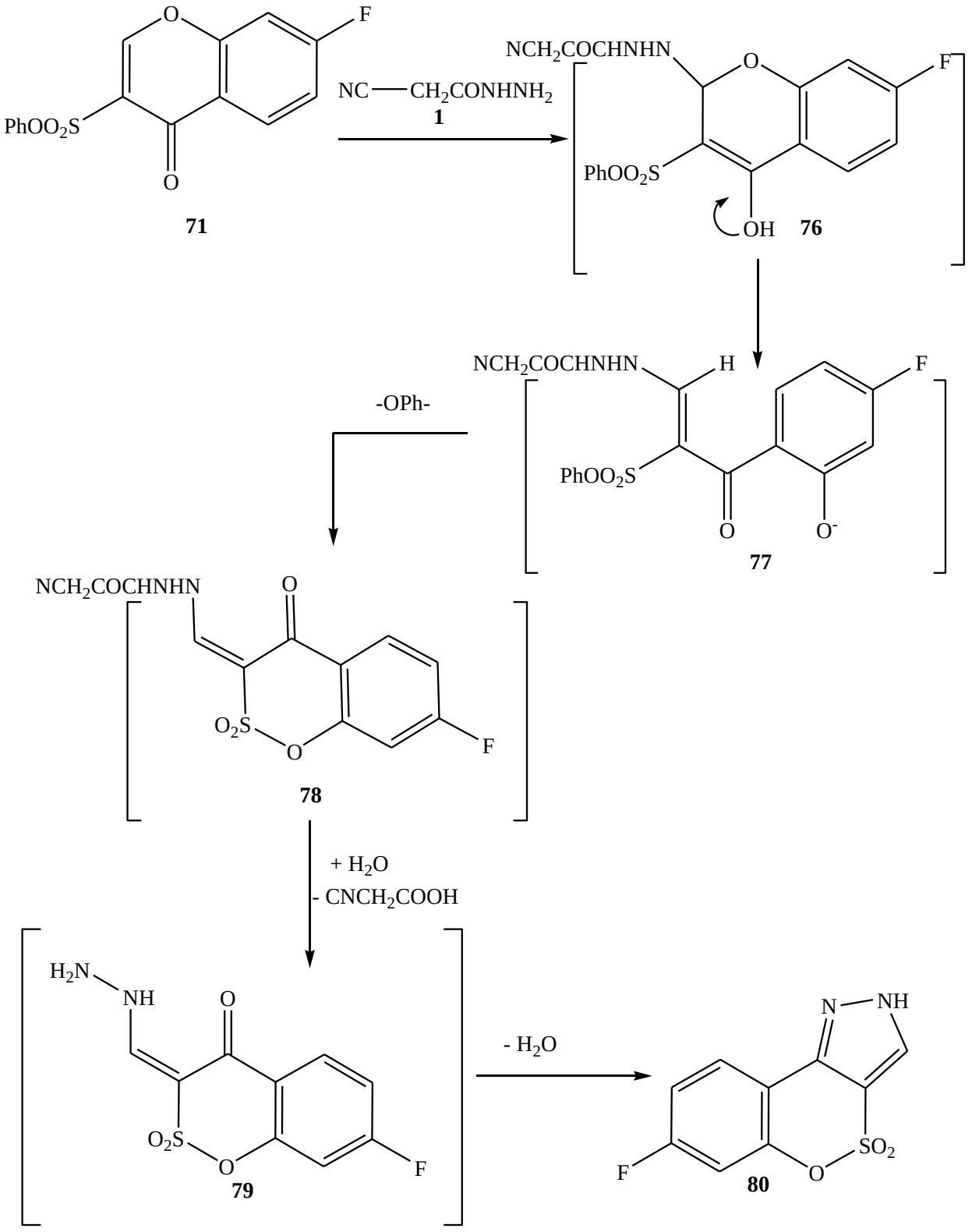


Scheme 28

During the course of benzoxathiinodihydropyridine **75** synthesis, the nucleophilic methylene group of **1** adds to the activated electrophile C – 2 atom of the chromone **71,** This gives the intermediate **72** from which the open - ringed form **73** develops after sodium acetate – induced deprotonation.The sultone **74** was

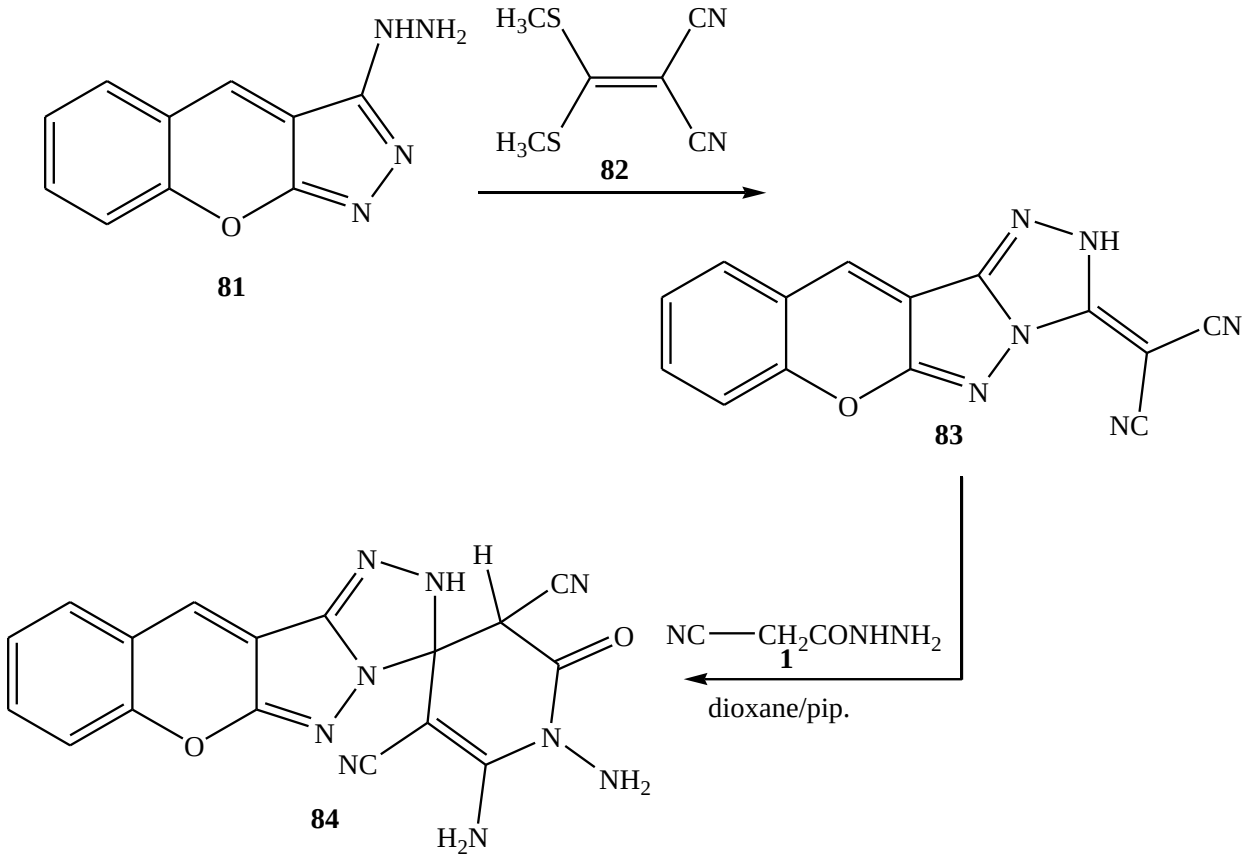
formed after the elimination of the phenolate group and subsequent dehydration leads to the production of the end isolable product **75** (Scheme 28)[37].

On the other hand, the reaction path leading to **80** is assumed to proceed as follows: first. the hydrazino nitrogen atom of **1** nucleophilically attacks the positive C-2 atom of compound **71** producing the intermediate **76**. After sodium acetate - induced deprotonation, the ring opens, thereby forming the intermediate **77**, followed by phenolate group elimination to give sultone **78** and subsequent hydrolytic cleavage of cyano acetic acid to **79**. Finally, the ring closes, thereby producing the final isotable product **80** (Scheme 29)[37].


O
F
PhOO2S
O
71
NC—CH2CONHNH2
1
NCH2COCHNHN
O
F
PhOO2S
OH
76
NCH2COCHNHN
H
F
PhOO2S
O
O-
77
-OPh-
NCH2COCHNHN
O
O2S
O
F
78
+ H2O
- CNCH2COOH
H2N
NH
O
O2S
O
F
79
- H2O
N
NH
F
O
SO2
80

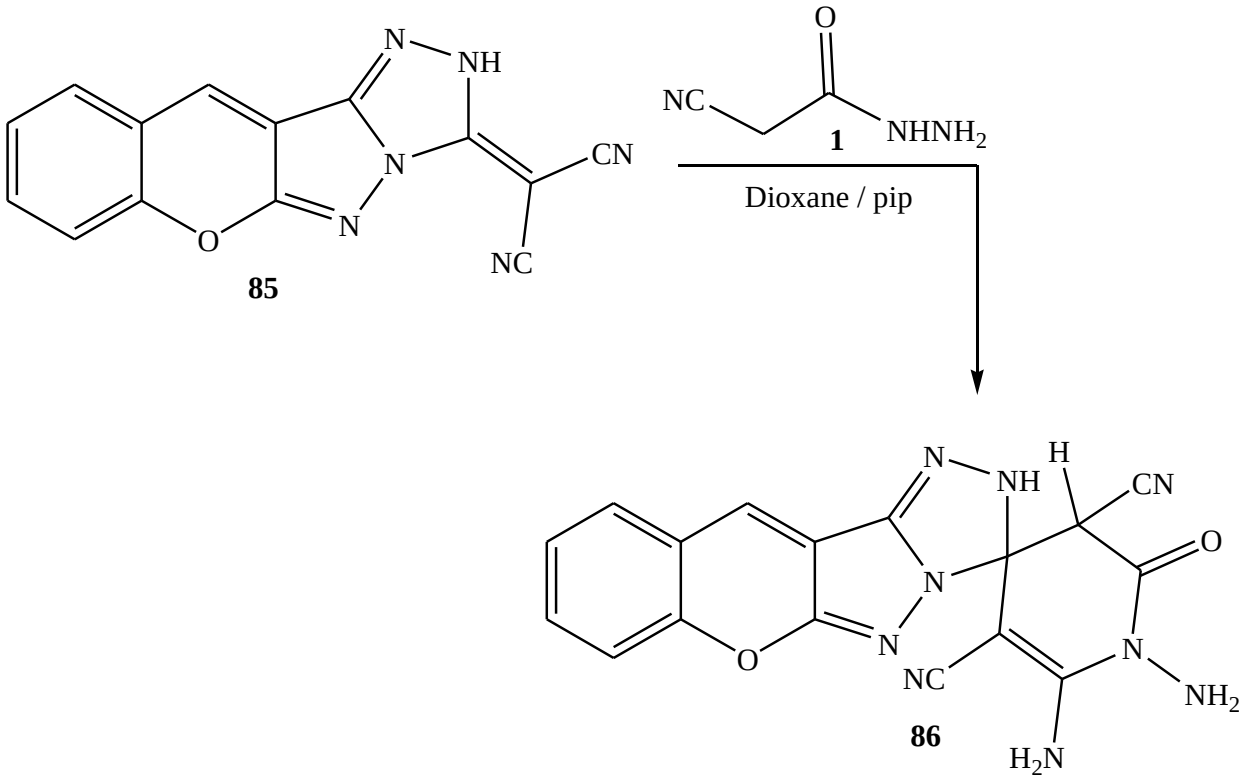
Scheme 29

Moreover, compound, 3-hydrazinoben-zopyrano[2,3-*c*]pyrazole (**81**) was reacted with 1,1-dicyano-2,2-dimethylthioethylene **82** to give compounds **83**, compound **83** was reacted with cyanoacetohydrazide **1** in refluxing dioxane containing piperidine as a catalyst, to afford compounds **84**, Scheme 30[38].



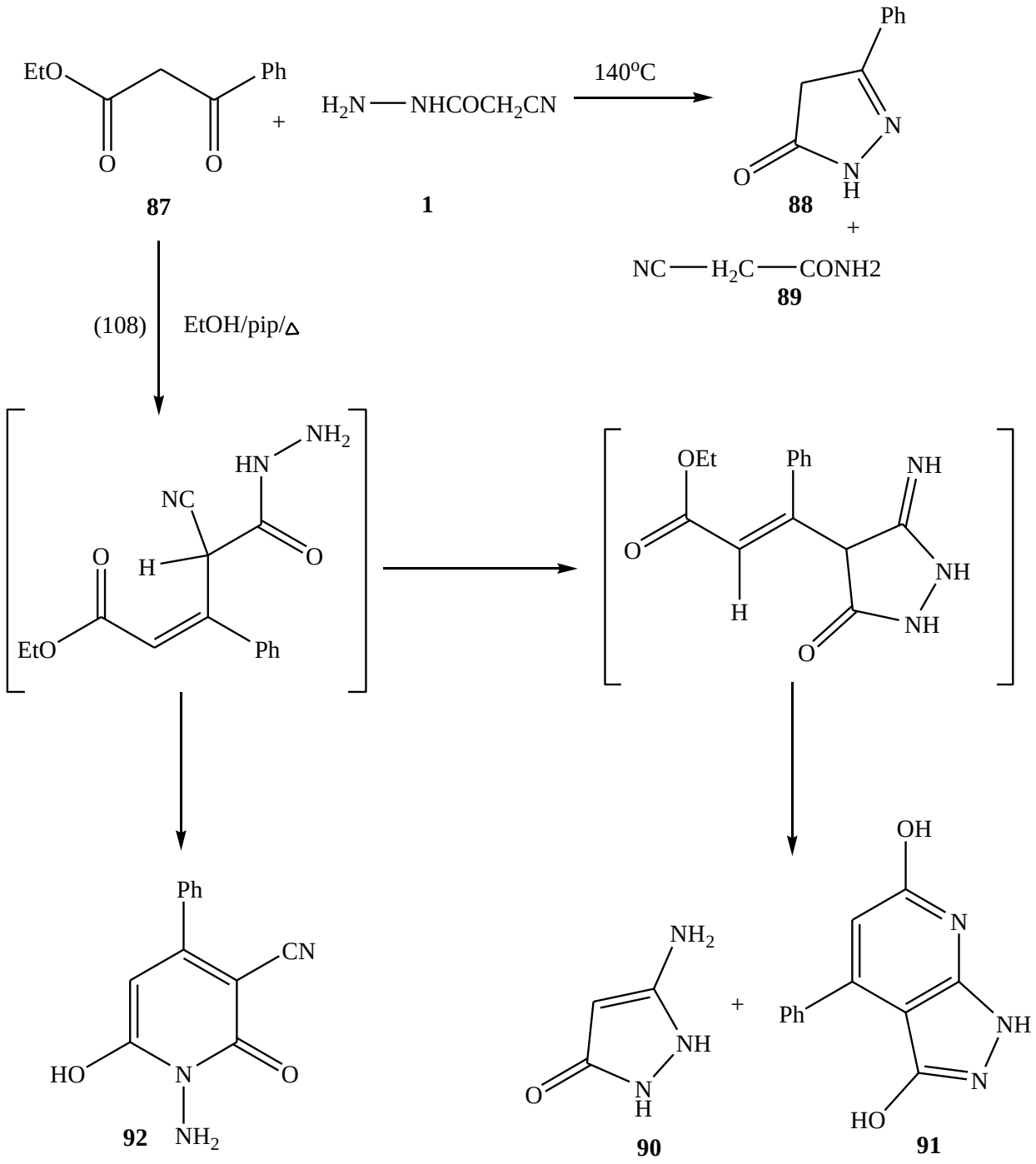
Scheme 30

Also compound **85** reacts with cyanoacetohydrazide **1** in refluxing dioxane in the presence of piperidine, leading to the spiro-2-pyridone **86** (Scheme 31)[39] .



Scheme 31

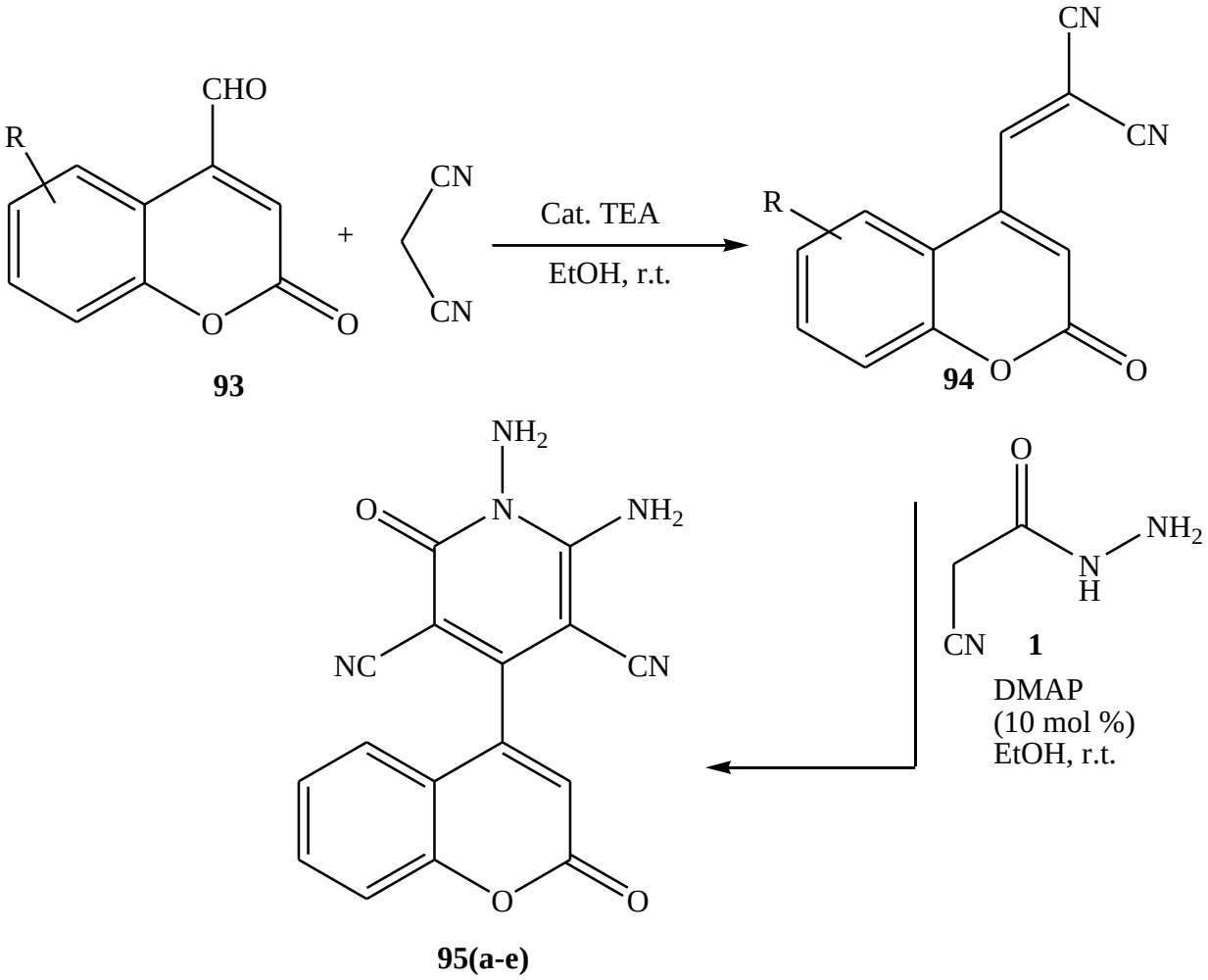
The reaction between ethyl 3-oxo-3-phenylpropanoate **87** and cyanomethylhydrazide **1** resulted in the formation of various outputs, depending on the reaction conditions. As a consequence, fusion at 140°C yielded pyrazol-3-one **88** and N,.N'-bis(cyanoacetyl) hydmzine **89**, on the other side, heating in ethanol-containing piperidine yielded a mixture containing pyrazol-3-one **90**, pyrazolo[3,4-b]pyridin-3-one **91**, and pyridine **92**, Scheme 32[40,41].



Scheme 32

The sequence of synthetic reactions resulting in the title compound **95 (a-e)** was initiated with coumarinmethylene malononitriles **94 (a-e)**[42] as a alkene intermediate which is, in turn, obtained by a Knoevenagel reaction between 4-formylcoumarins[43] **93** and malononitrile. moreover, 1,6-diamino-dihydropyridino-

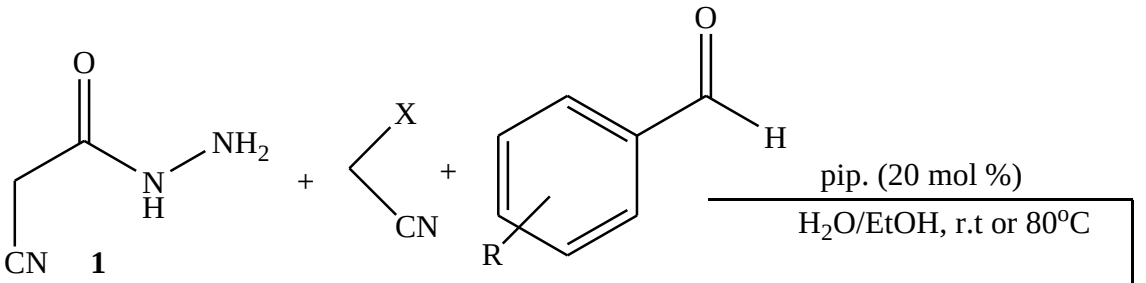
coumarins **95 (a-e)** were obtained through the reaction between intermediate **94** and 2-cyanoacetohydrazide **1** in the presence of catalytic amount of DMAP in excellent yields (Scheme 33)[44].



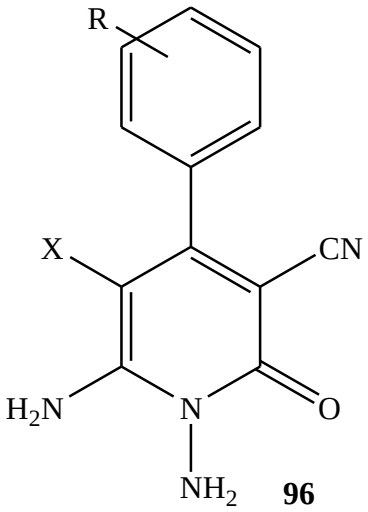
R = 6-CH_3, 6-OCH_3, 6-Cl, 7-CH_3, 7,8-Benzo

Scheme 33

In addition, the reaction of cyanoaceto hydrazide **1** and aromatic aldehyde with malononitrile was accomplished by piperidine in water at room temperature to afford N-amino-3-cyano-2-pyridones **96** (Scheme 34)[45].



R, X	R, X	R, X
4-Cl, CN	4-Br, CN	4-NO_2, CN
4-OMe, CN	3-OMe, CN	H, CN
2-Cl, CN	3-Cl, CN	4-CF_3, CN
3,4-$(OMe)_2$, CN	4-F, CN	3-F, CN
4-Cl, COOEt	4-Br, COOEt	2-Cl, COOEt
3-F, COOEt	4-F, COOEt	4-Br, $CONH_2$
4-Cl, $CONH_2$	3-Cl, $CONH_2$	2-Cl, $CONH_2$
4-F, $CONH_2$		

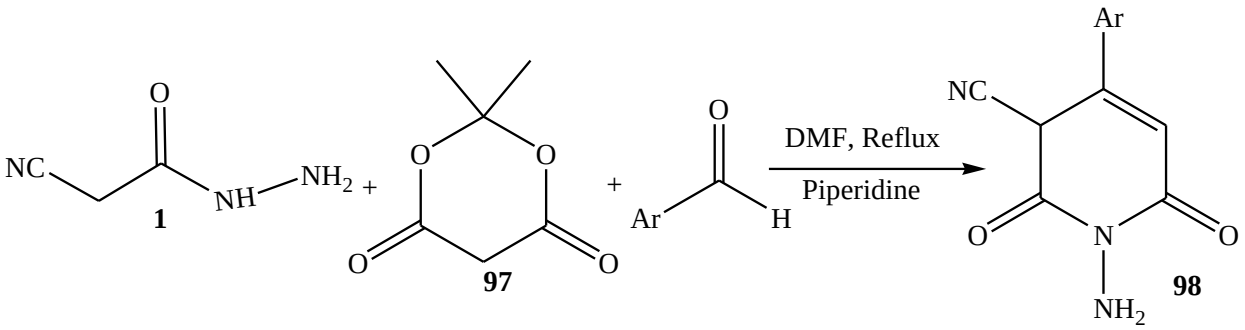


96

Scheme 34

The reaction between 2-cyanoacetohydrazide **1** (1.0 mmol), Meldrum's acid **97** (1.0 mmol), and aryl aldehyde (1.0 mmol) was conducted[46] in the presence of four drops of piperidine under different reaction conditions for the synthesis of 1-amino-2,6-dioxo-4-(p-tolyl)-1,2,3,6- tetrahydropyridine-3-carbonitrile **98** (Scheme 35).

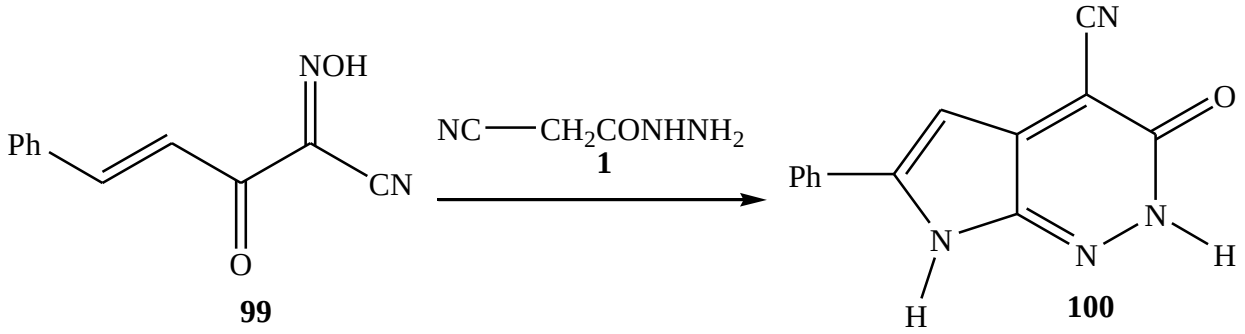
Furthermore, Aryl aldehydes with electron-withdrawing and electron-donating groups, under typical reaction conditions, also yielded[46] good to excellent output of the products. As for the aryl aldehyde, nature was very important. When the aldehyde derivatives, especially with electron-withdrawing groups such as halide, were deployed, a larger output was obtained accordingly (Scheme 35).



Scheme 35

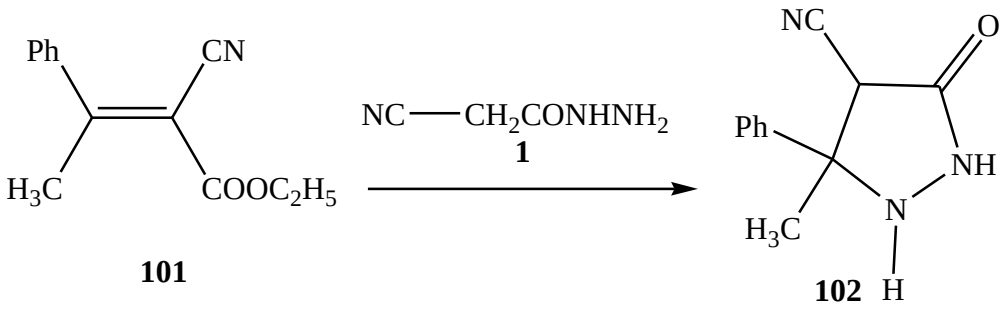
<u>e - Heterocycles obtained via the utility of functional groups No. 2,5 (The methylene and hydrazino groups .)</u>

Nawwar et al.[47] reported the isolation of the pyrrolopyridazinone **100** from the reaction of cyanoacetohydrazide **1** with cinnamoylacetonitrile oxime **99**. The formation of this product is assumed to proceed via a Michael type addition by the active methylene to the activated oximino double bond giving the 1:1 Michael adduct which then cyclized to the final product **100** (Scheme 36) .



Scheme 36

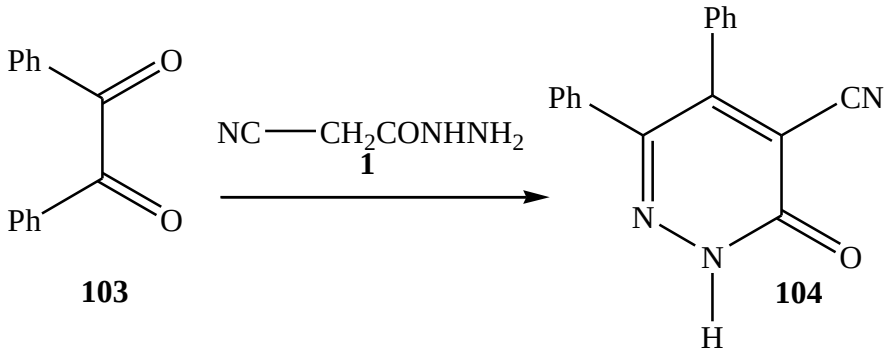
The reaction of **1** with ethyl β- phenyl -β- methylmethylene cyanoacetate **101** occured with the formation of 3- methyl - 3- phenyl -4-cyanopyrazolin -5-one **102** which was formed via ylidene exchange with elimination of ethyl cyanoacetate and subsequent cyclization to the final isolable product **102**[48] (Scheme 37) .



101 **102**

Scheme 37

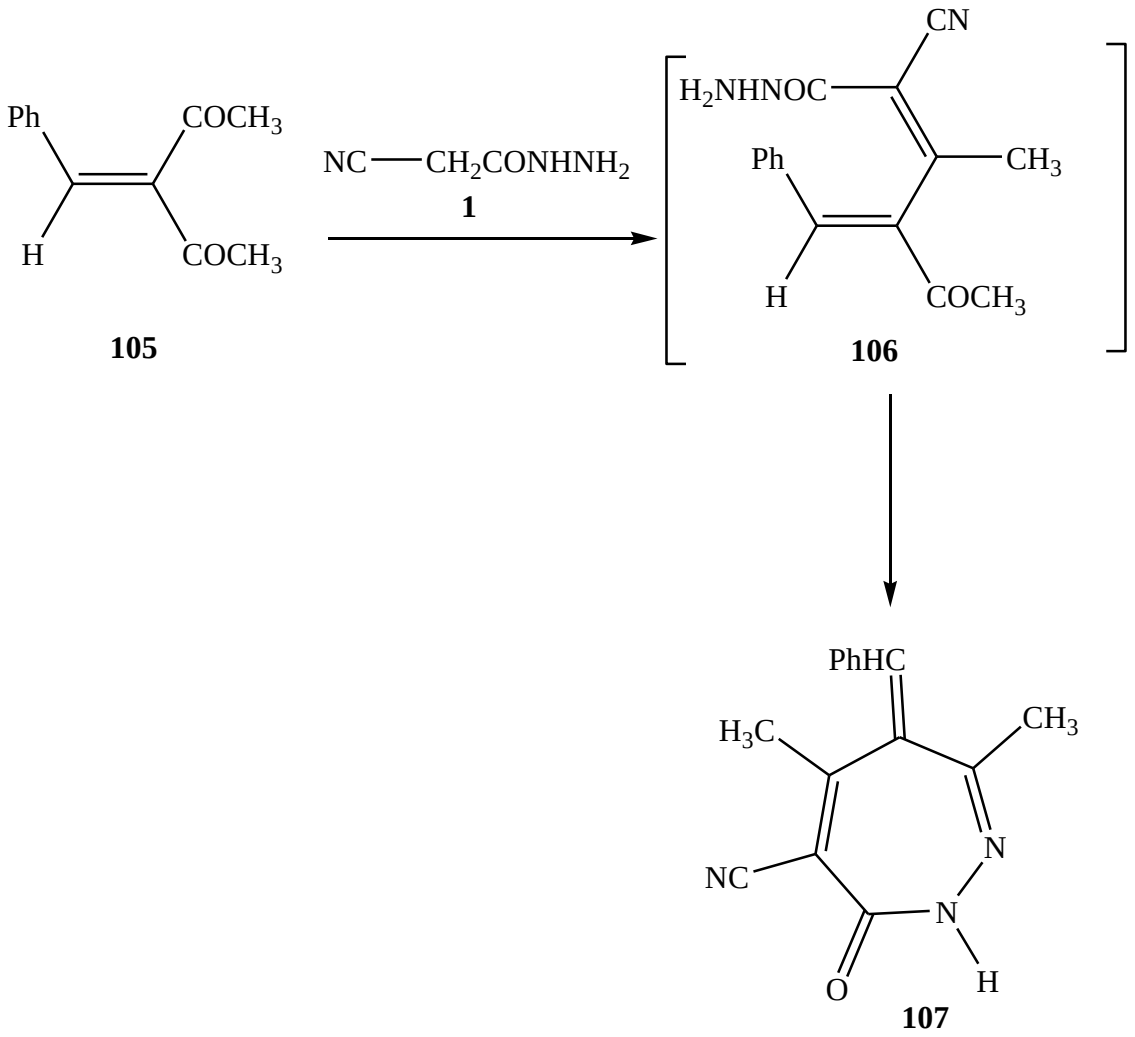
It was also reported that, cyanoacetohydrazide **1** condensed readily with benzyl **103** to give the 3,4-diphenyl -5- cyanopyridazin-6- one **104**[49] as shown Scheme 38.



103 **104**

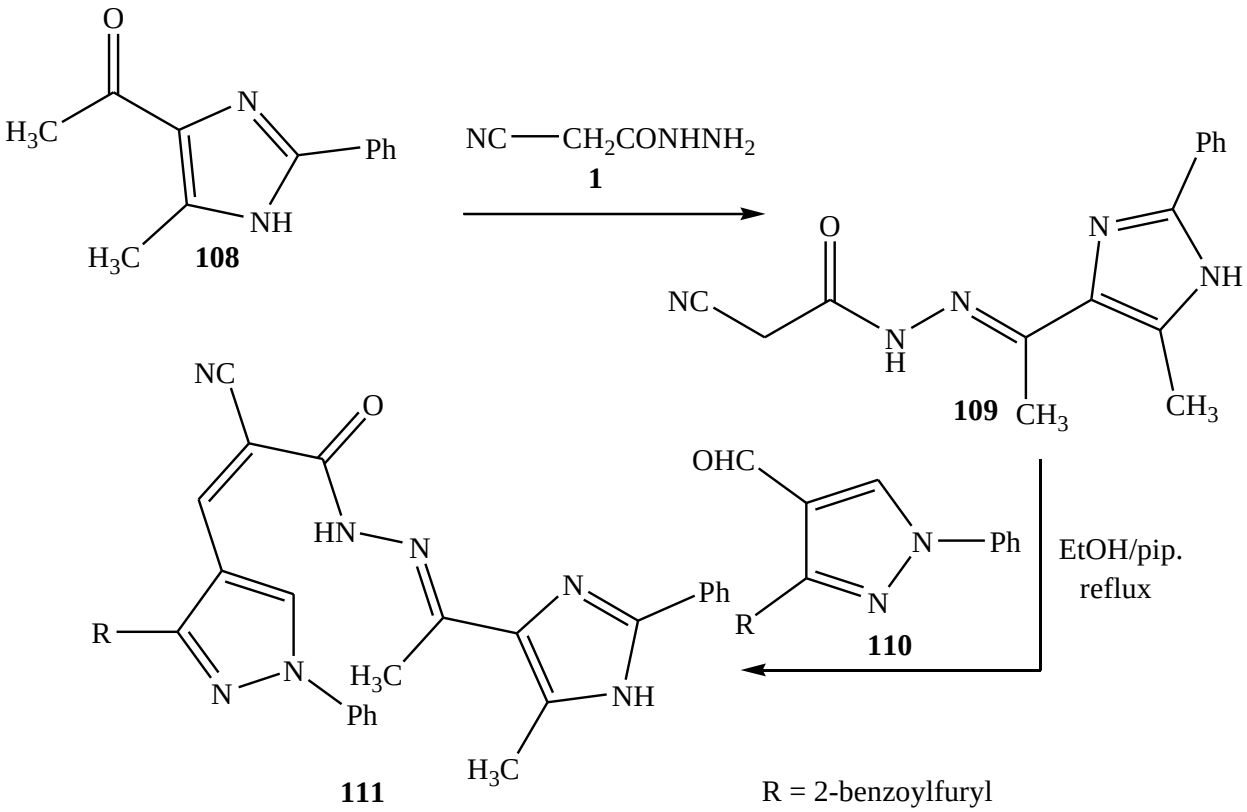
Scheme 38

Seven membered ring with two hetero atoms could be obtained from the reaction of cyanoacetohydrazide **1** with the unsaturated 1,3-diketone **105**. The reaction is assumed to proceed via the intermediacy of **106**, resulting from the Knoevenagel condensation which then undergoes intra-cyclization to give the 1, 2-diazepinone **107**[50] (Scheme 39).



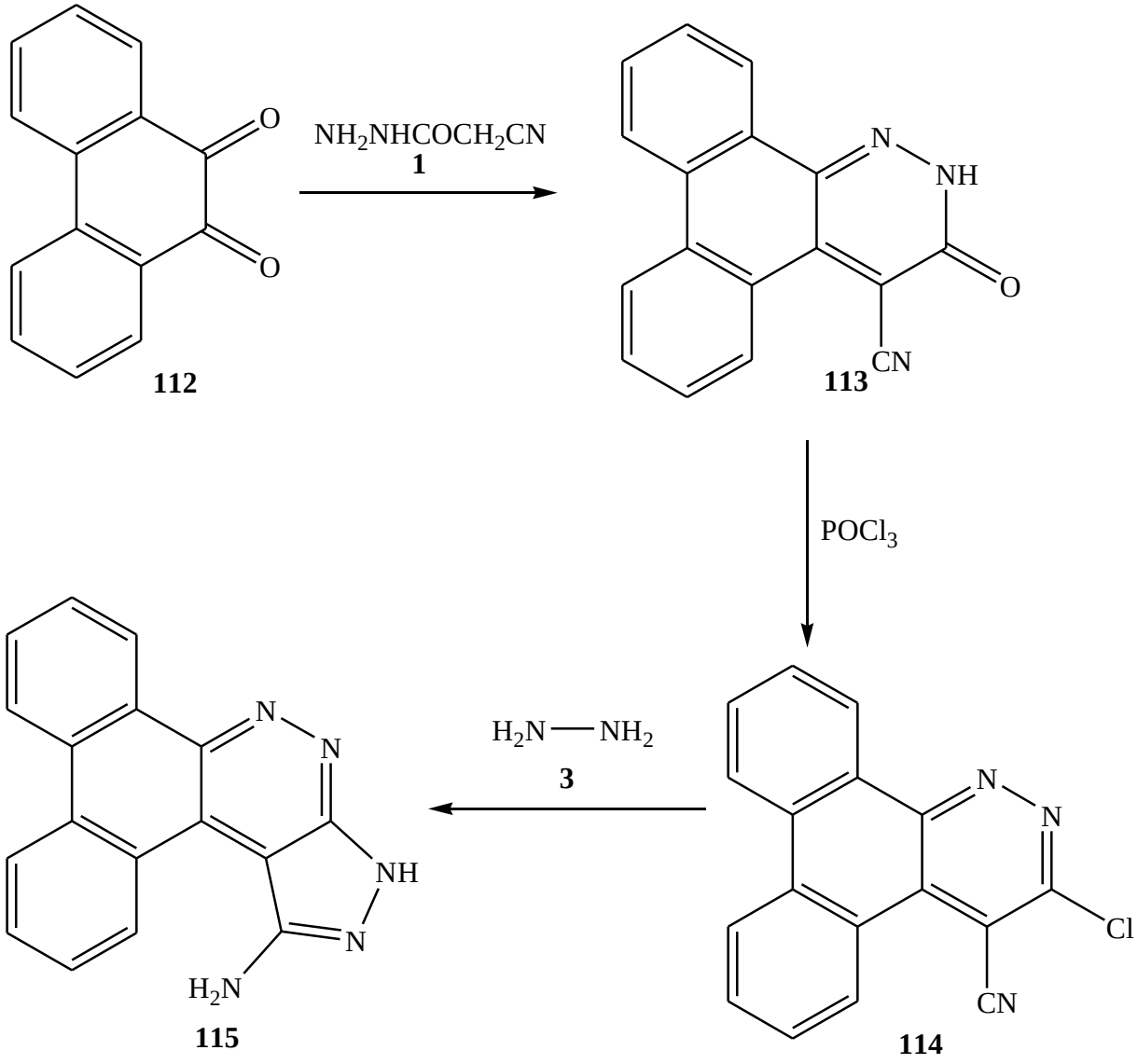
Scheme 39

Moreover, cyanoacetylhydrazine **1** reacts with 4-acetyl-5-methyl-2-phenylimdazole[51] **108** to give the hydrazidehydrazone derivative **109**. The reaction of **109** with pyrazole-aldehyde **110** gave the benzalidene derivative **111** (Scheme 40)[52].



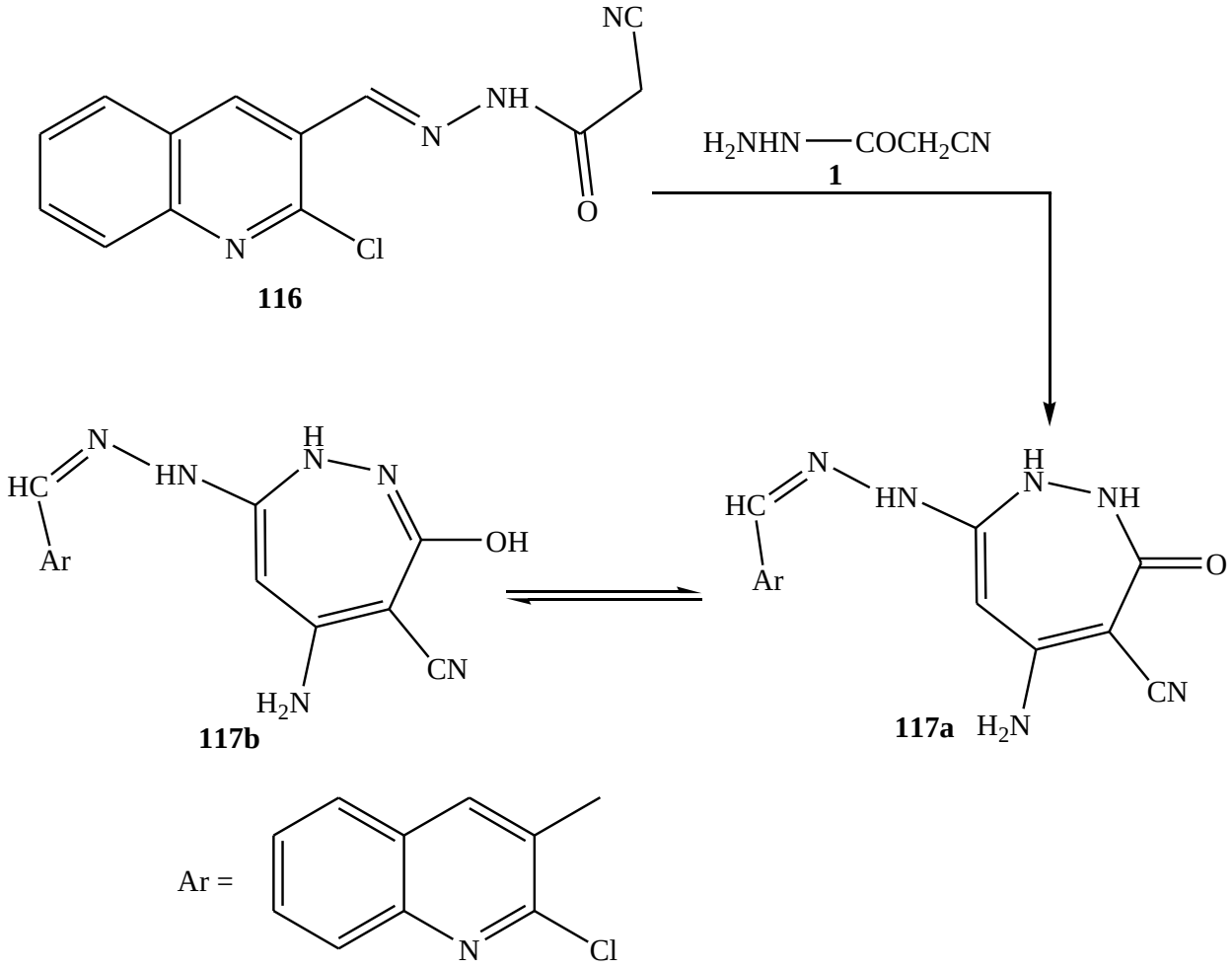
Scheme 40

We also conclude that the reaction of compound **112** with 2-cyanoacetohydrazide **1** supplied the corresponding cyanopyridazone derivative **113**, which was treated with phosphorus oxychloride to give the corresponding chloro derivative **114**. The latter compound was cyclized with hydrazine hydrate **3** to produce the amino pyrazole derivative **115**, Scheme 41[53].



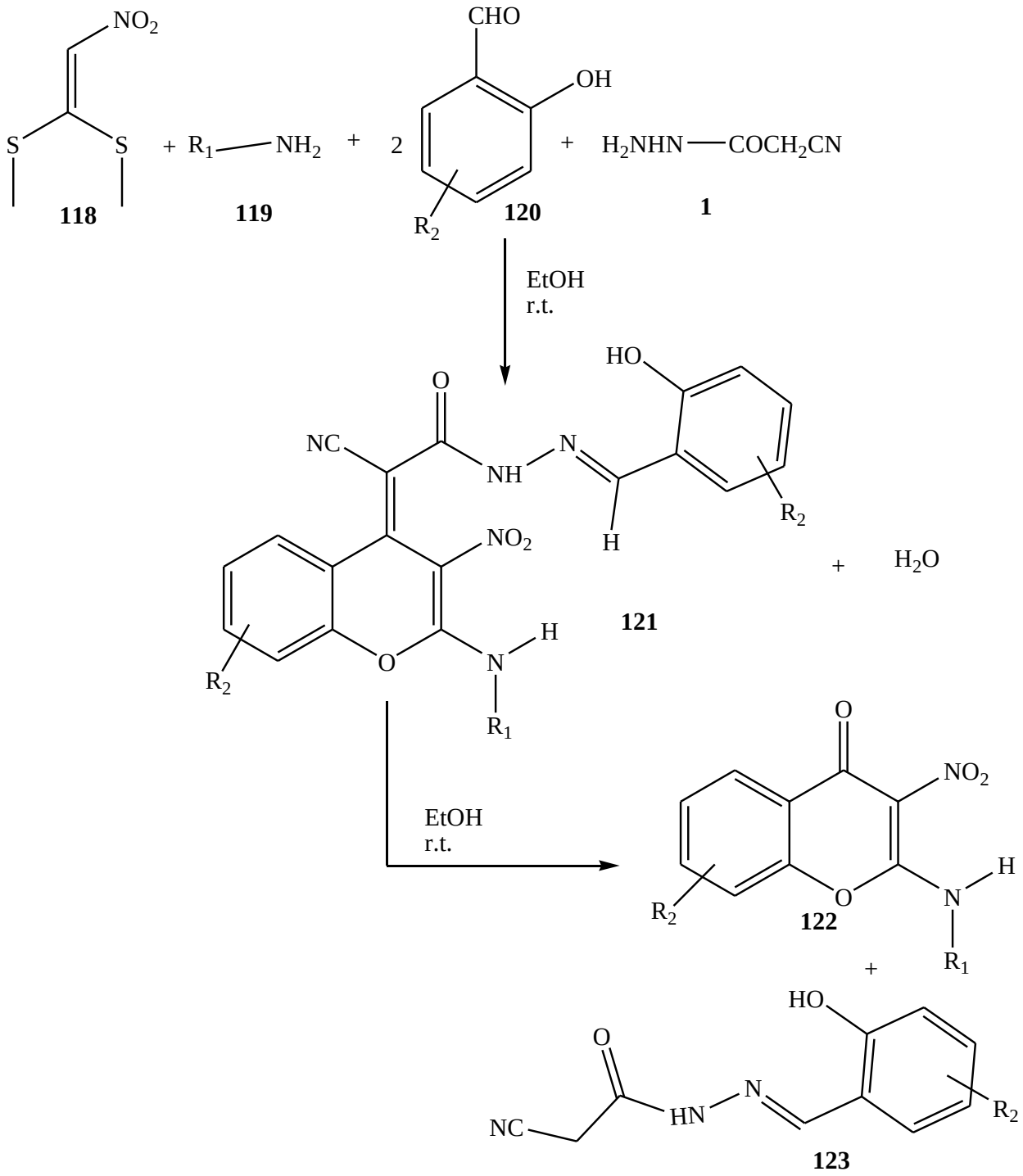
Scheme 41

N'-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide **116** was synthesized from 2-choloroquinoline-3-carbaldehyde[54,55] and 2-cyanoaceto-hydrazide **1** as described in literature[56,57]. When compound **116** was boiled with 2-cyanoacetohydrazide **1** afforded 1,2-diazepine derivatives **117a**, **117b**, as shown in Scheme 42[58].



Scheme 42

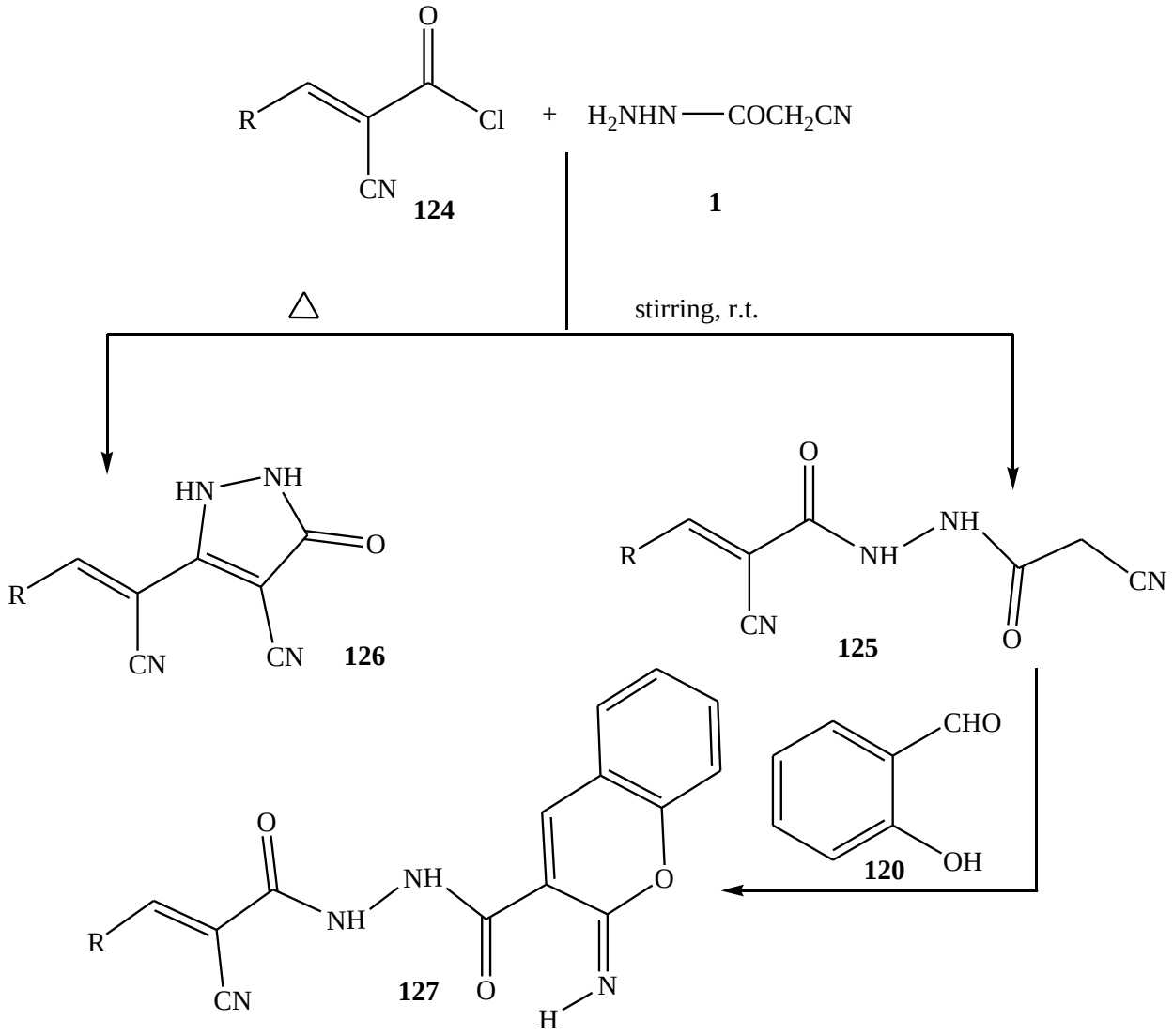
Moreover, the reaction of 1,1-bis(methylthio)-2-nitroethene **118**, diverse amines **119**, salicylaldehydes **120**, and cyanoacetohydrazide **1** in ethanol as solvent at ambient temperature resulted in functionalized chromene derivatives **121** in good to high yields. The product **121** then did undergo a smooth reaction with moisture in air or H_2O in ethanol, to produce compound **122** upon longer reaction time (Scheme 43)[59].



Scheme 43

Moreover, the requisite acid chloride namely 2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl) acryloyl chloride **124** was synthesized[60]. Luckily, the reaction of the acid chloride **124** with 2-cyanoacetohydrazide **1** was predominantly capatalizing

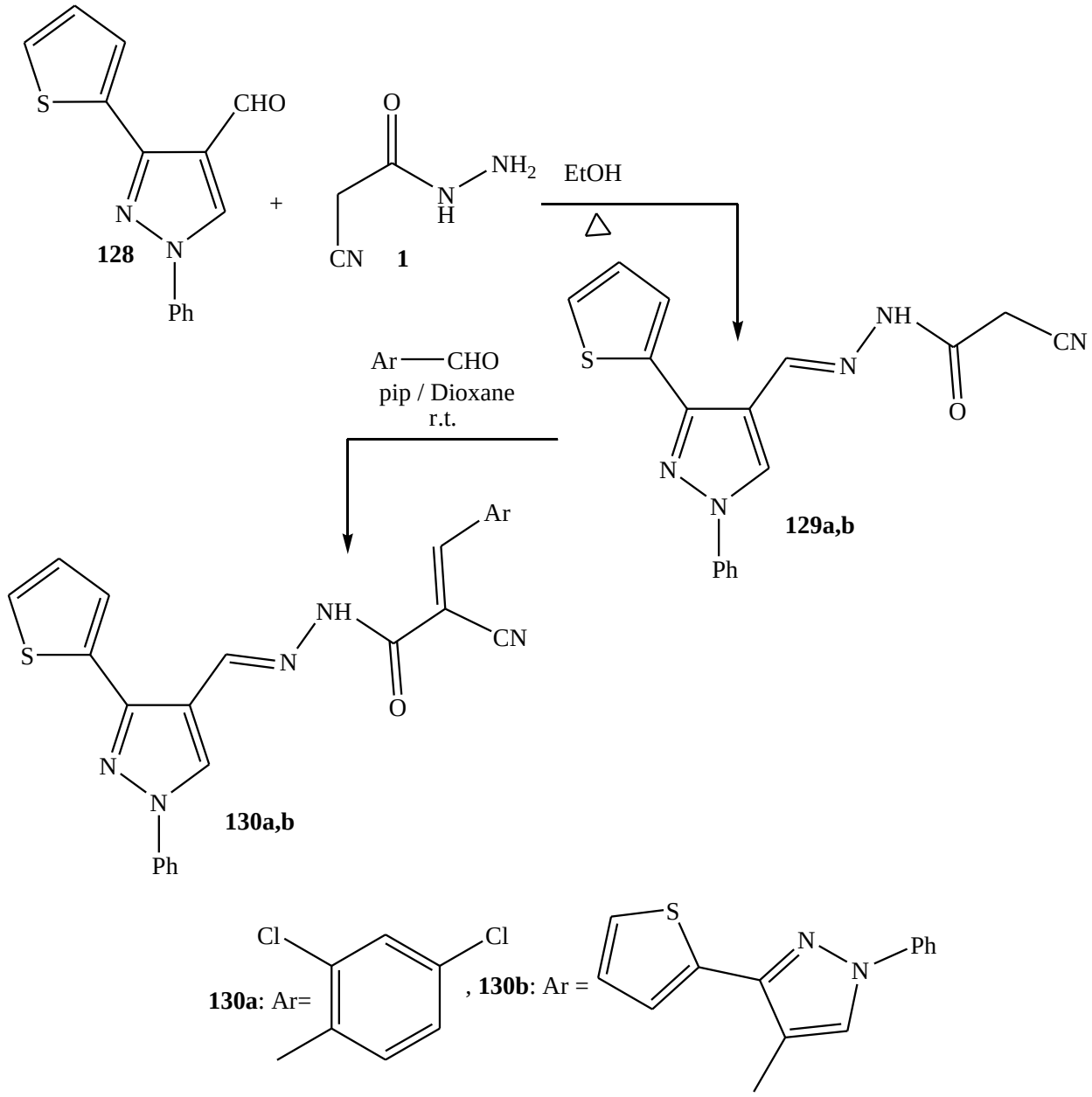
on the reaction conditions. Therefore, conducting the reaction at ambient temperature furnished the hydrazide derivative **125**. Moreover, while at refluxing conditions, the pyrazolone derivative **126** was produced. It was also noted that, the iminochromene derivative **127** was obtained through treating the nitrile derivative **125** with salicylaldehyde **120** in the presence of a catalytic amount of piperidine (Scheme 44)[61].



Scheme 44

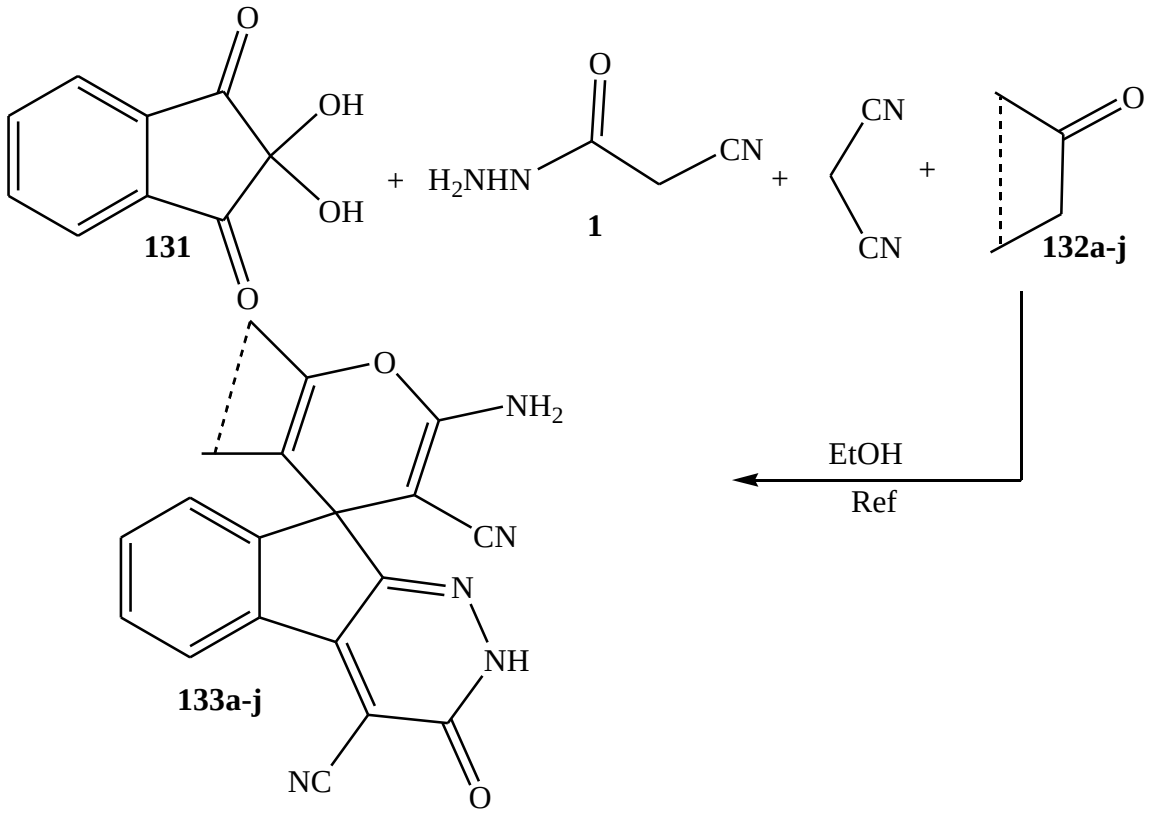
In addition, condensation of 1-phenyl-3-(thiophen-2-yl)-pyrazole4-carboxaldehyde[62] **128** with 2-cyanoacetohydrazide **1** in refluxing ethanol for 2 hours resulted in the formation of the corresponding N-condensation product **129**

in a good yield as yellow crystals[63] (Scheme 45). Moreover, Knoevenagel condensation of the active methylene compound **129** with aromatic aldehydes namely, 2,4-dichlorobenzaldehyde and pyrazole aldehyde **128** in dioxane containing piperidine as a base at ambient temperature yielded the α,β-unsaturated carbonyl compounds **130a,b**, respectively[64] (Scheme 45).

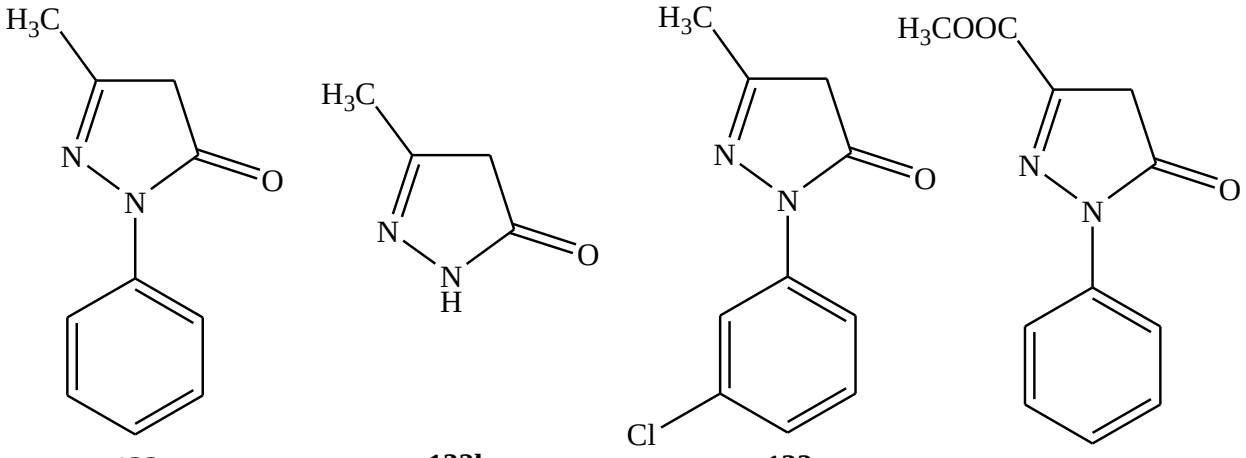


Scheme 45

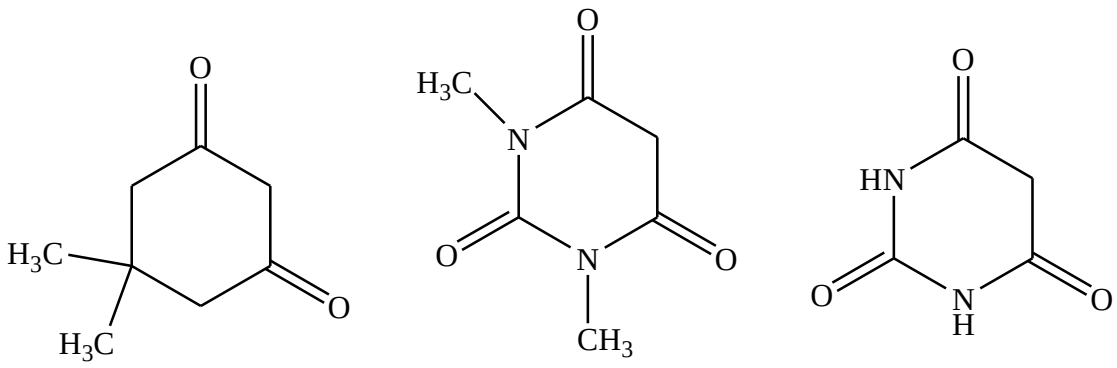
In addition, Bayat et al.[65] explained the efficient synthesis of novel spiroindenopyridazine-4*H*-pyran derivatives, where they used ninhydrin **131**, cyanoacetohydrazide **1**, malononitrile , and various cyclic CH–acids **132a**–**j** as substrates to synthesize the target compounds **133a**–**j** (Scheme 46).



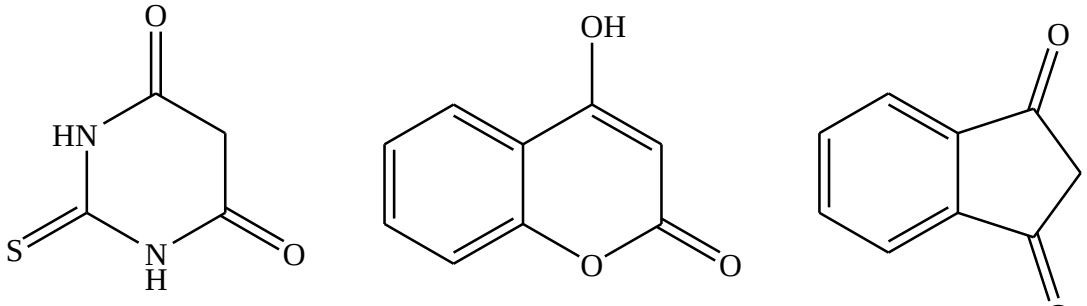
Scheme 46



132a **132b** **132c** **132d**



132e **132f** **132g**

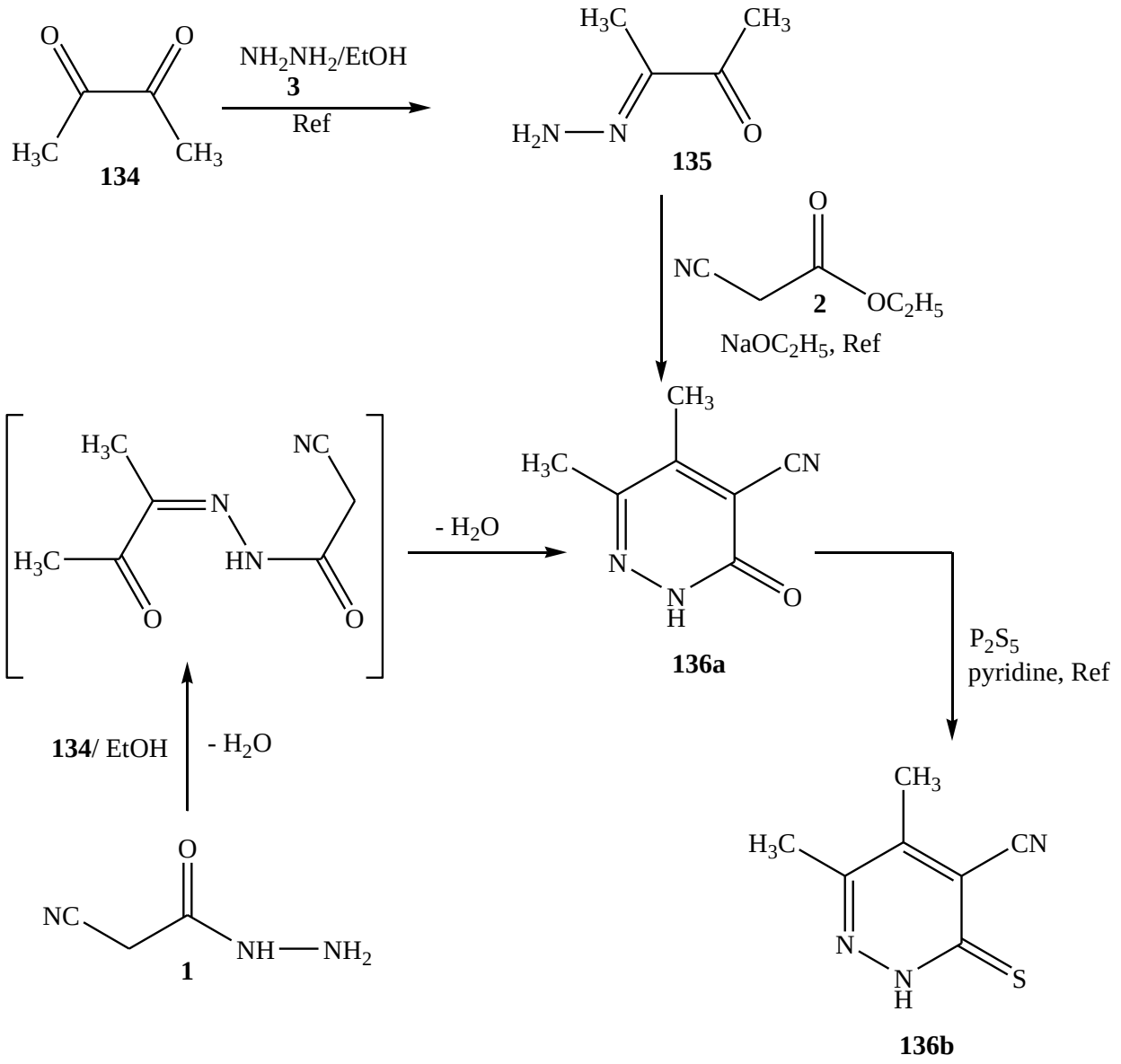


132h **132i** **132j**

132a–j

Also, Gaber et al.[66] explained the synthesis of 4-cyano-5,6-dimethylpyridazin-3(2*H*)-one **136a** by treatment of diacetyl **134** with hydrazine hydrate **3** in refluxing ethanol to produce monohydrazone **135**, followed by cyclocondensation with ethyl cyanoacetate **2** in presence of sodium ethoxide. Moreover, their research yielded the synthesis of pyridazinone **136a** through one-pot reaction of diacetyl **134** and

cyanoacetic acid hydrazide **1** in ethanol at room temperature. Also, thiation of compound **136a** with phosphorus pentasulfide under reflux in pyridine resulted in the formation of the pyridazinethione **136b** (Scheme 47).

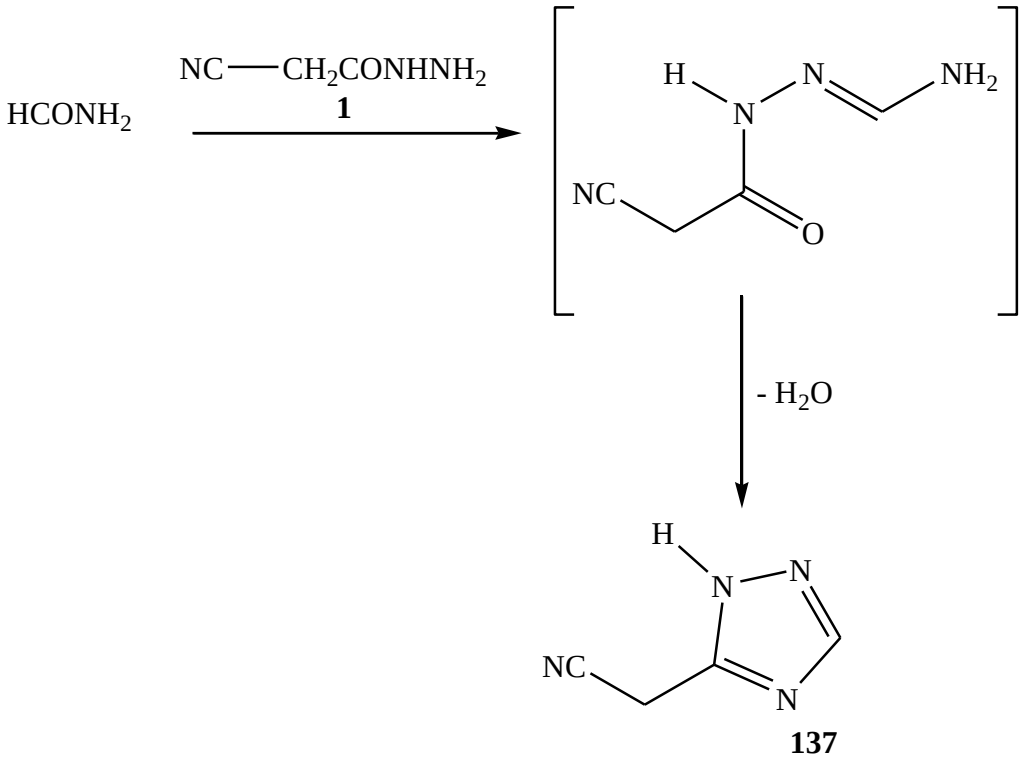


Scheme 47

f- Heterocycles obtained via the utility of functional groups No. 3,5 (The carbonyl and hydrazino groups .)

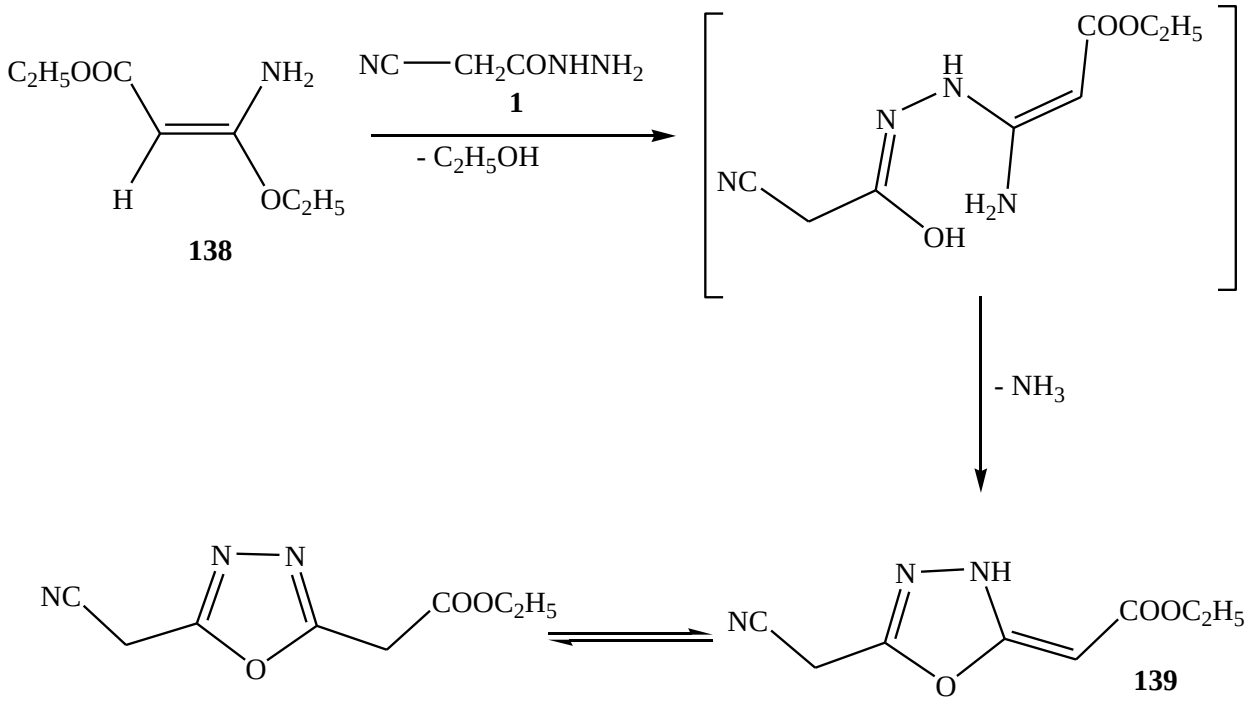
The presence of the carbonyl and amino groups led to the formation of five membered rings with three heteroatoms.

Thus, it has been reported that 5-cyanomethyl-1,2,4- triazole **137** can be formed by heating cyanoacetohydrazide **1** with formamide for several hours on a steam bath, followed by cooling and dilution with ethyl alcohols[67] as shown in Scheme 48.



Scheme 48

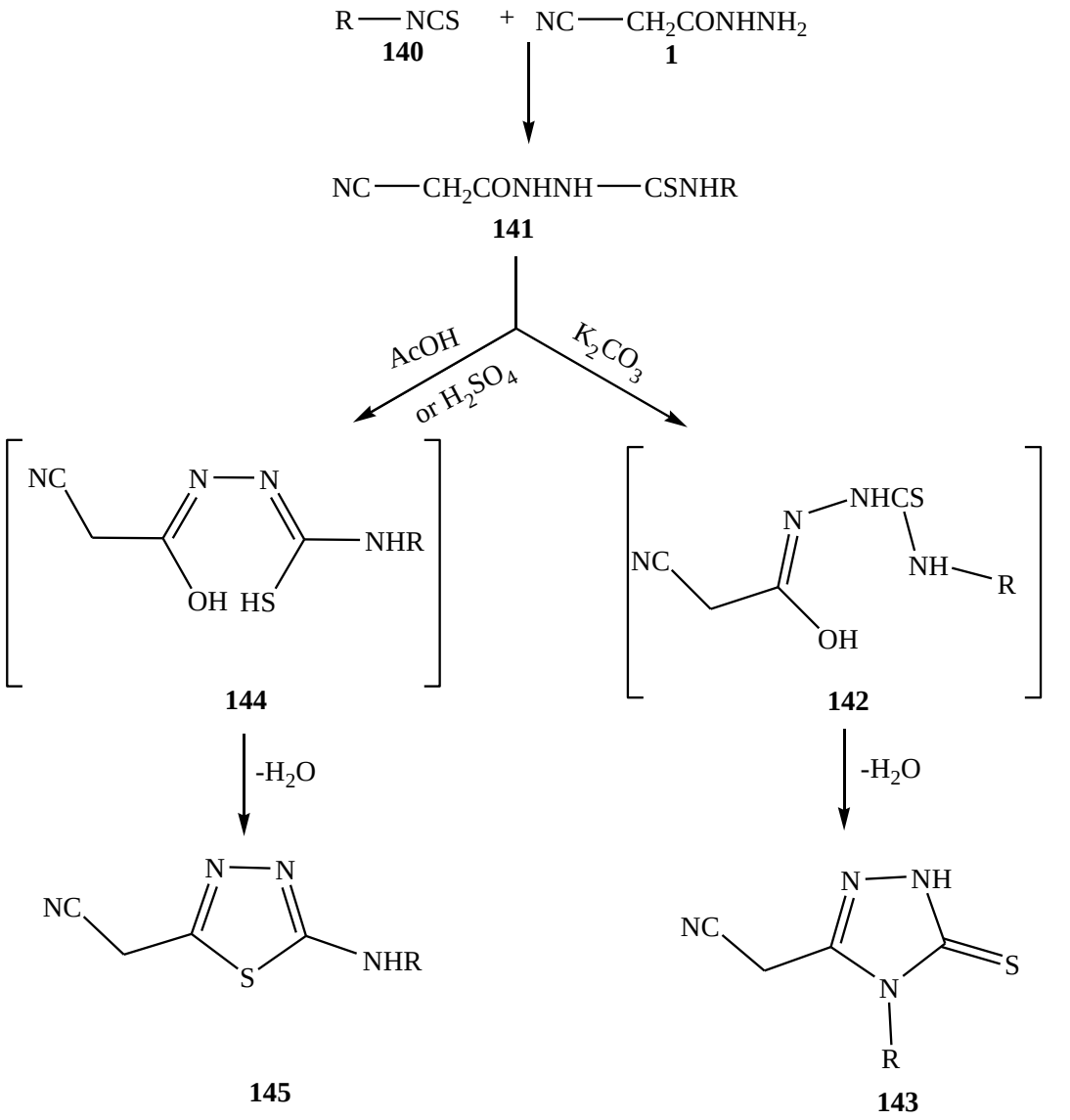
Moreover, treatment of cyanoacetohydrazide **1** with ethyl β-ethoxy-β-aminomethylene acetate **138** gave a product which had been interpreted as ethyl (5-cyanomethyl -1,3,4-oxadiazol-2-yl)acetate **139**. A mechanistic pathway for its formation was suggested[68] (Scheme 49).



Scheme 49

Five-membered rings with three hetero atoms could be also obtained by refluxing cyanoacetohydrazide **1** with acyl or aryl isothiocyanate **140** to give 1-cyanoacetyl-4-aryl thiosemicarbazides **141**, these could be cyclized by two different ways as follows[69-71] (Scheme 50).

Refluxing **141** in aqueous potassium carbonate give the triazole derivatives **143** which are formed by dehydration of the enol form of the thiosemicarbazide derivative **142**; whereas refluxing **141** in acetic acid or heating with concentrated sulphuric acid gave the thiadiazole derivatives **145** which are formed by dehydration of the enol form **144** (Scheme 50).



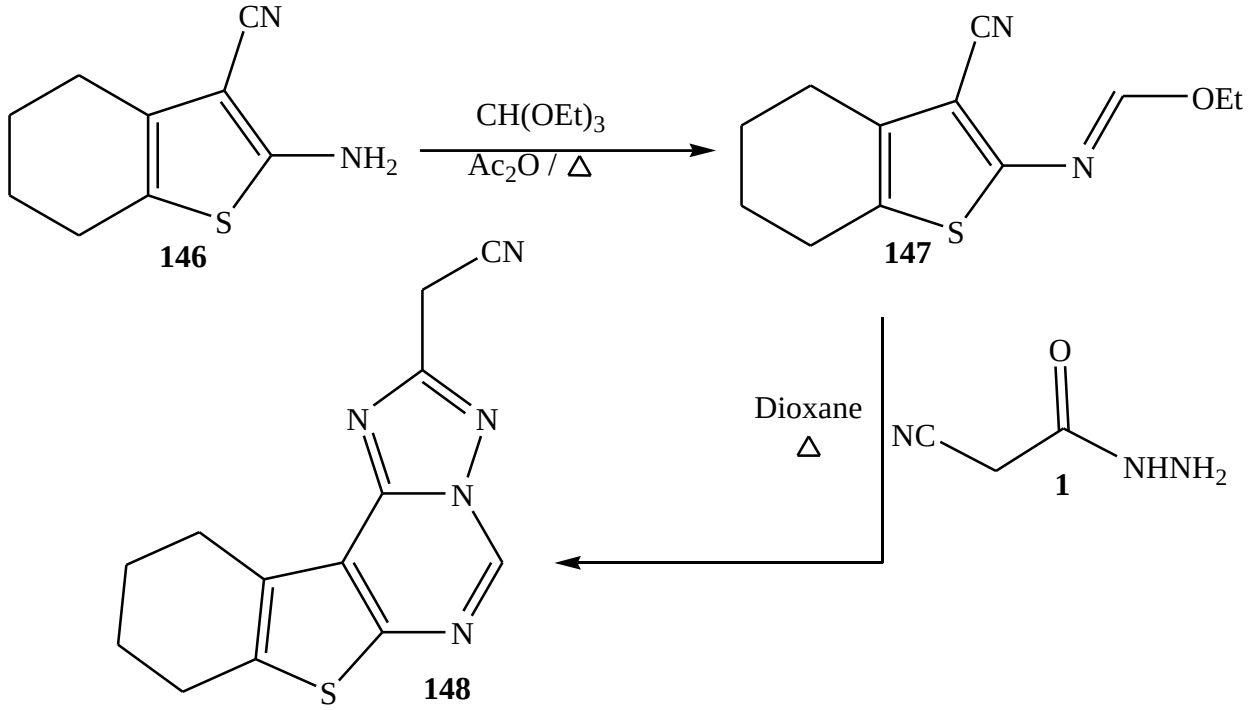
R= $COCH_3$, COPh, $COOC_2H_5Ph$, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 1- or 2-naphthyl

3-Br-C_6H_4, 3,4-dimethyl-C_6H_3 4-Cl-C_6H_4, 4-Br-C_6H_4

Scheme 50

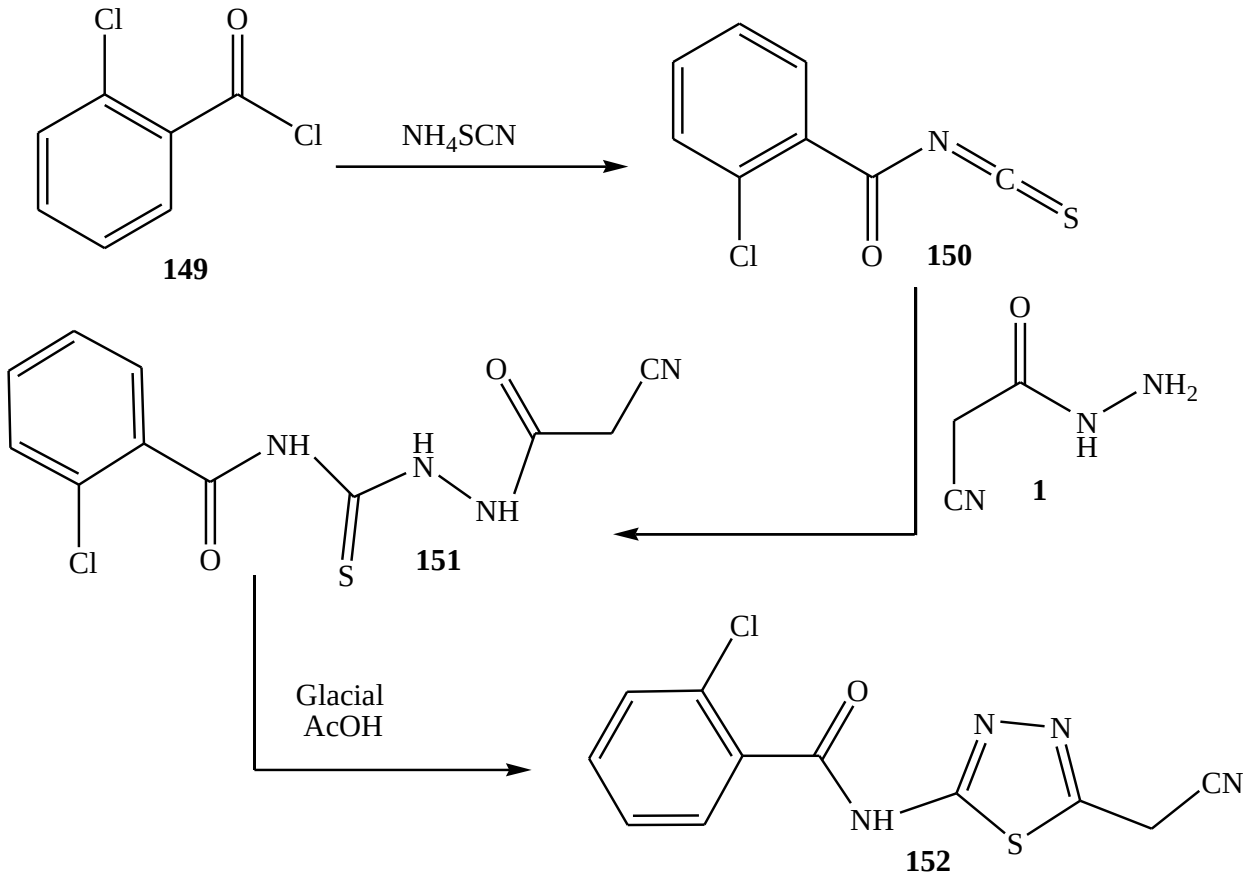
Interestingly, 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile[72] **146** has been a research focus for decades. Where, the reaction of **146** with triethylorthoformate in the presence of freshly distilled acetic anhydride (drops) resulted in ethyl N-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylformimidate **147**, which reacting with 2-cyanoacetohydrazide **1** in refluxing dioxane produced

2-cyanomethyl-8,9,10,11-tetrahydrobenzothieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine**148** (Scheme 51)[73].



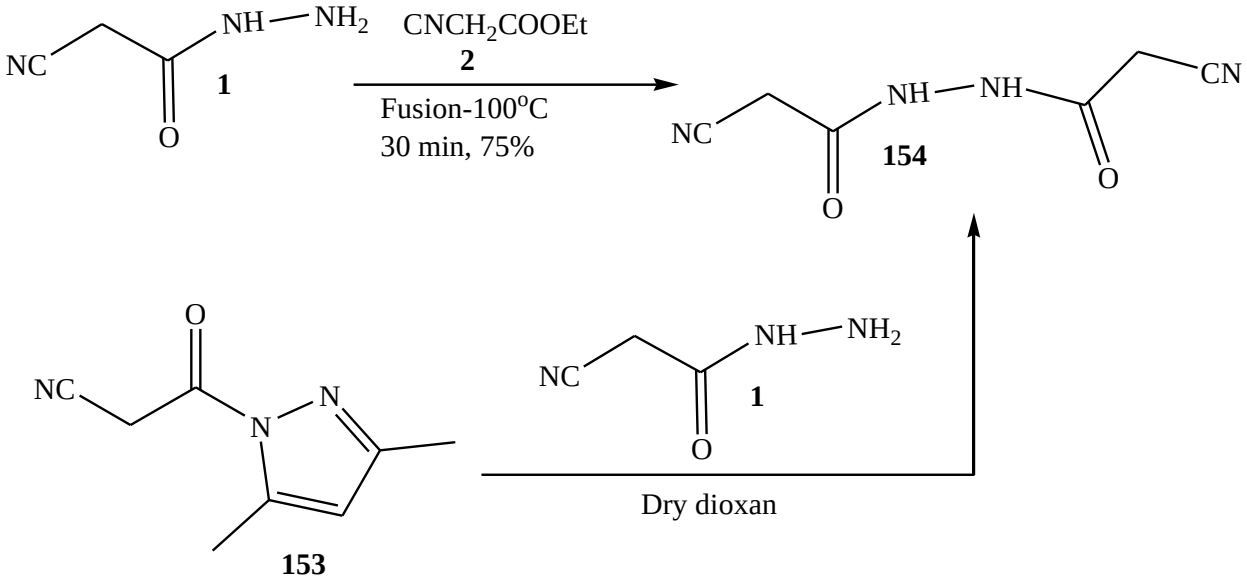
Scheme 51

This synthetic approach was applied in the synthesis of hitherto undocumented title compound as exemplified in Scheme 52. Where, the stirring of 2-chlorobenzoyl chloride **149** with ammonium thiocyanate in dry acetonitrile yielded the 2-chlorobenzoyl isothiocyanate **150**, in situ cyanoacetohydrazide **1** was supplied on the later under stirring at ambient temperature, succeeded by refluxing of the engendered 2-chloro-N-(2-(2-cyanoacetyl)hydrazine-1-carbonothioyl)-benzamide **151** in glacial acetic acid to generate 1,3,4-thiadiazole derivative **152** (Scheme 52)[74].



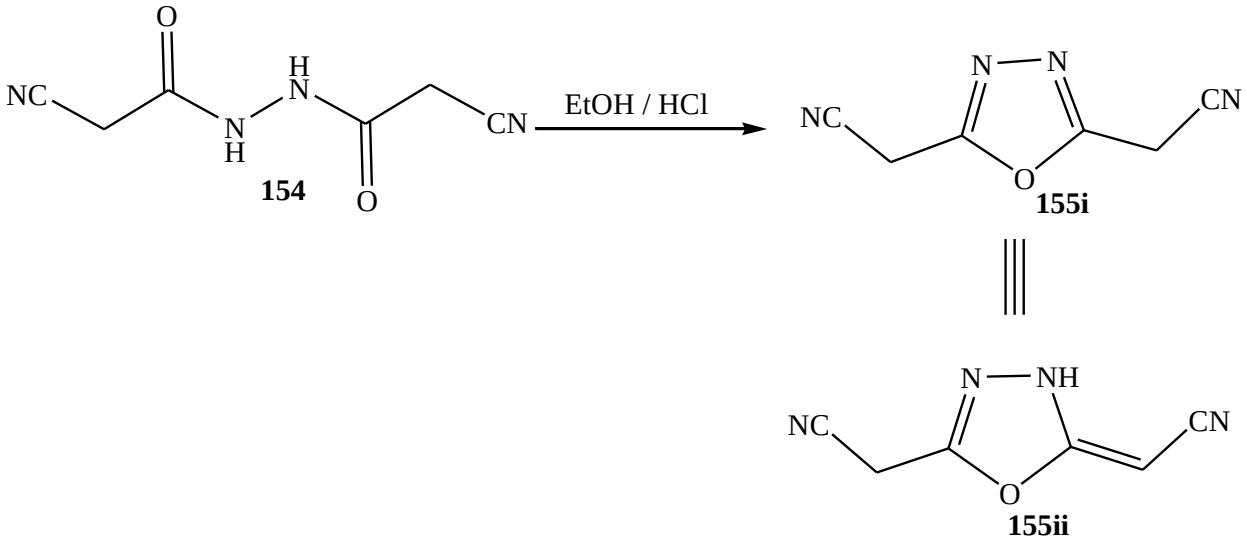
Scheme 52

Also, the fundamental intermediate 2-cyano-N'-(2- cyanoacetyl) acetohydrazide **154** was easily available from the solvent-free reaction of cyanoacetic acid hydrazide **1** with ethyl cyanoacetate **2** or from the reaction of cyanoacetichydrazide **1** with 3-(3,5-dimethyl-1H-pyrazol-1- yl)-3-oxopropanenitrile **153** in dry dioxan[75], Scheme 53.



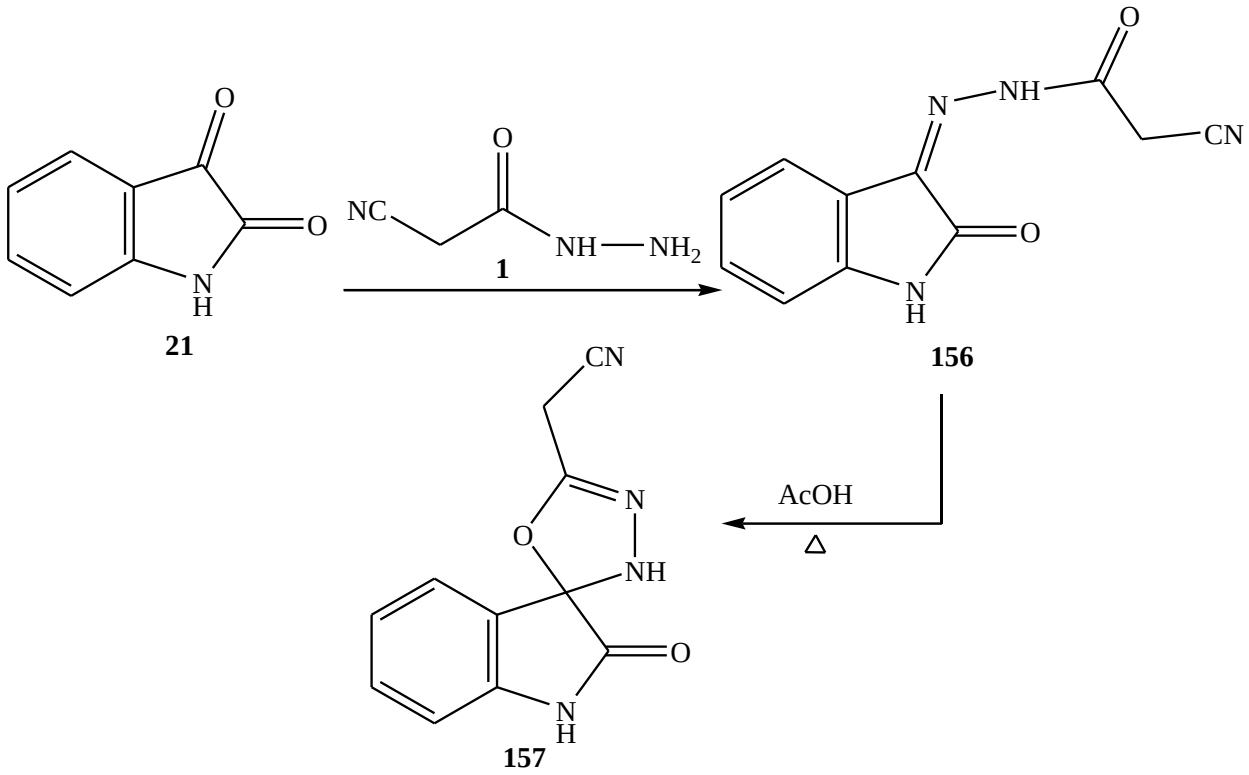
Scheme 53

Moreover, when compound **154** was heated to boiling point in ethanol containing few drops of conc. hydrochloric acid, 2,2'-(1,3,4-oxadiazole-2,5- diyl) diacetonitrile **155** was generated as the only product[75], Scheme 54.



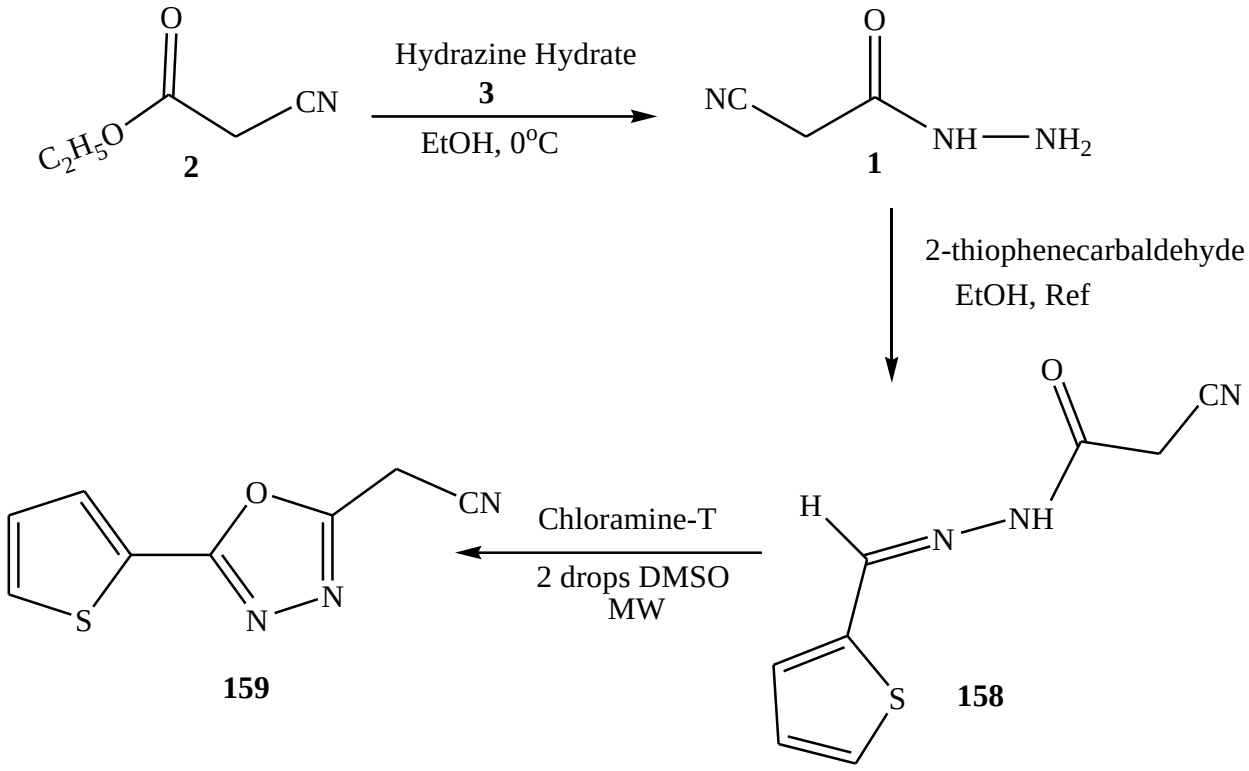
Scheme 54

It is noteworthy that Allam and Nawwar conducted the synthesis of cyanomethyloxadiazole-spiroindoline **157**. They concluded that the condensation product of cyanoacetohydrazide **1** with isatin **21** could be cyclized in acidic medium to yield the oxadiazolo-2-spiroindoline structure **157** (Scheme 55)[76].



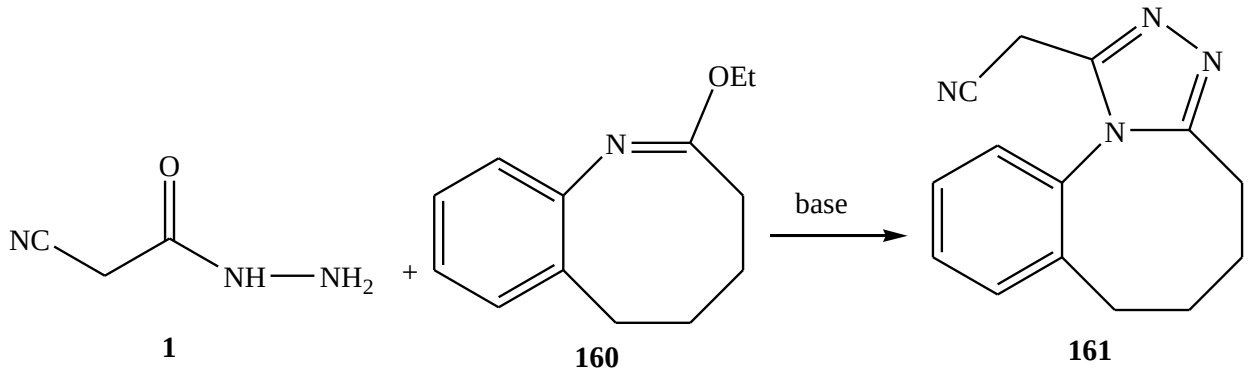
Scheme 55

Also, Thorat synthesized 2-substituted-5-(2′-thiophene)-1,3,4-Oxadiazole **159** using microwave irradiation. At first, cyanoacetic acid hydrazide **1** was generated via addition of hydrazine hydrate **3** to ethyl cyanoacetate **2** in ethanol with stirring at 0 °C. Upon condensation with 2-thiophenecarbaldehyde, the hydrazide resulted in the corresponding hydrazone **158**, which upon oxidative cyclization with chloramine-T under microwave irradiation resulted in the corresponding 2,5-disubstituted-1,3,4-oxadiazole **159**. Two drops of dimethylsulfoxide (DMSO) were added to the mixture of hydrazone **158** and chloramine-T in molar ratio of 1:1, and the resulting clear liquid was heated under microwave irradiation for 12 s, succeeded by addition of alcohol to yield solid product (Scheme 56)[77].



Scheme 56

Golovko and coworkers published the reaction of **1** with lactim ether **160**, which furnished the 5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1]benzazepin-1-ylacetonitrile **161** (Scheme 57)[78].



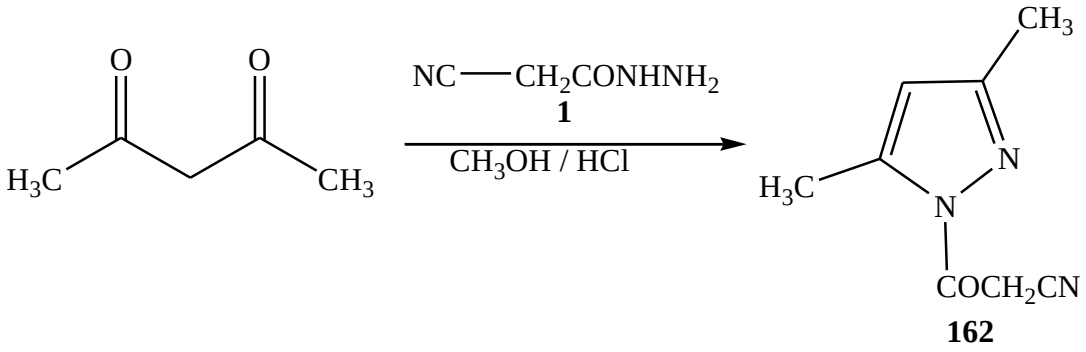
Scheme 57

g- Heterocycles obtained via the utility of functional groups No. 4,5 (The amido and hydrazino groups .)

There are some reactions in which cyanoacetohydrazide behaves as a Hydrazine, meaning that the NH and NH_2 active centers are involved in these

reactions . One of the well known approaches for the synthesis of substituted pyrazoles is the condensation of 1,3- bidentate reagents such as β-diketones and β-ketoesters with cyanoacetohydrazide in acidic medium .

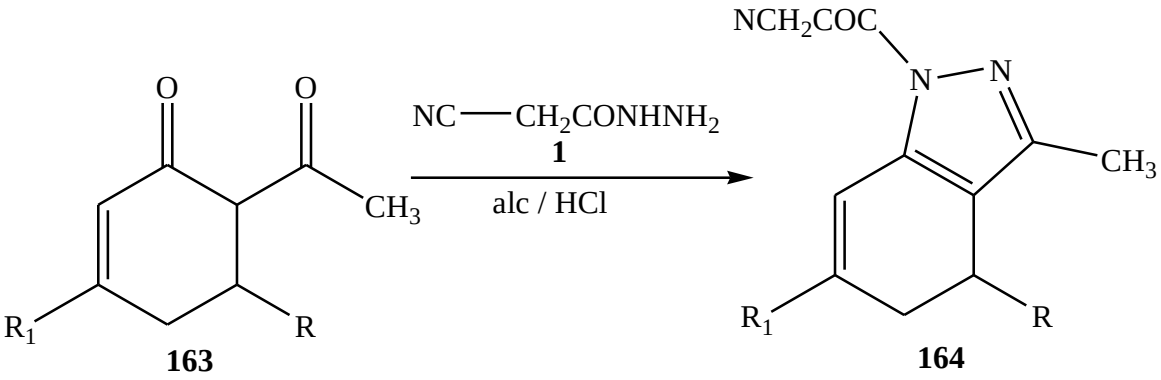
Thus, when Balicki et al.[79] reacted **1** with acetylacetone in acidic medium, they separated a product which was interpreted as the 1-cyanoacetyl-3,5-dimethyl-pyrazole **162** as shown in Scheme 58.



162

Scheme 58

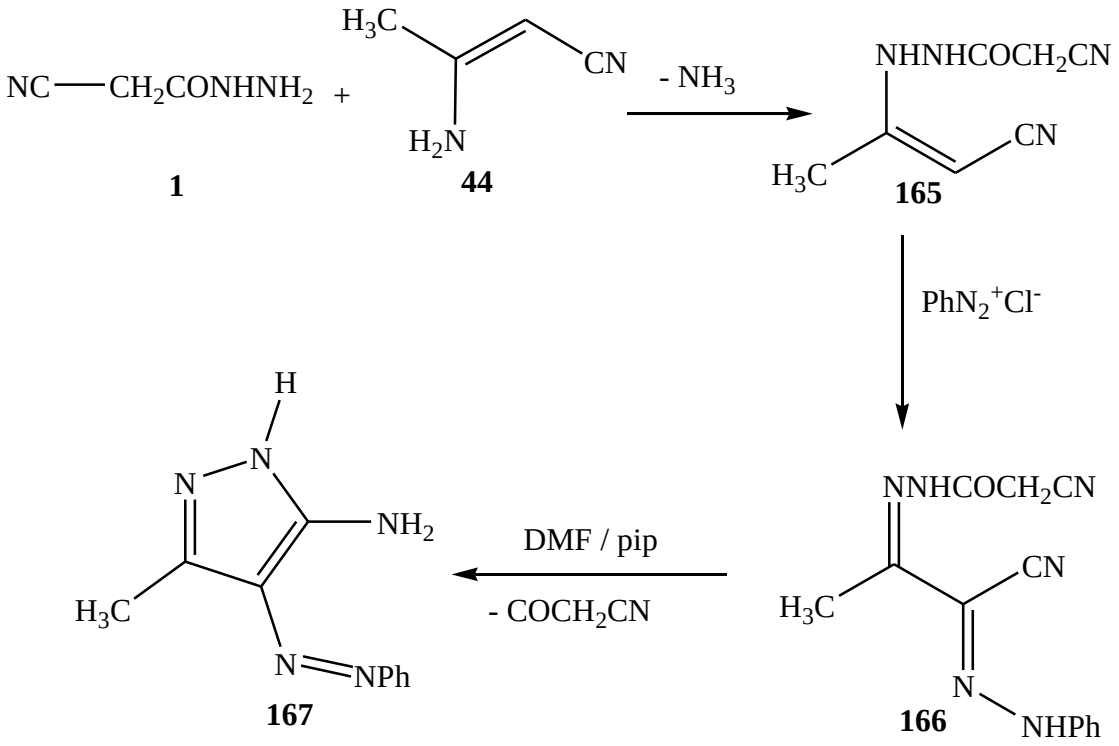
Similarly, cyanoacetohydrazide **1** reacted with 2-acetyl-3,5-disubstituted cyclohexanones **163** in presence of HCI with the formation of the condensed pyrazoles **164**[80]. It's worthy to mention that, when El - Hashash et al[30] carried out the same reaction in alkaline medium instead of acidic medium, the quinoline derivatives were only obtained (Scheme 59).



R = Ph, 2-Furanylvinyl,
4-OCH_3-C_6H_4
R_1 = Ph, 4-OCH_3-C_6H_4, 2-furyl

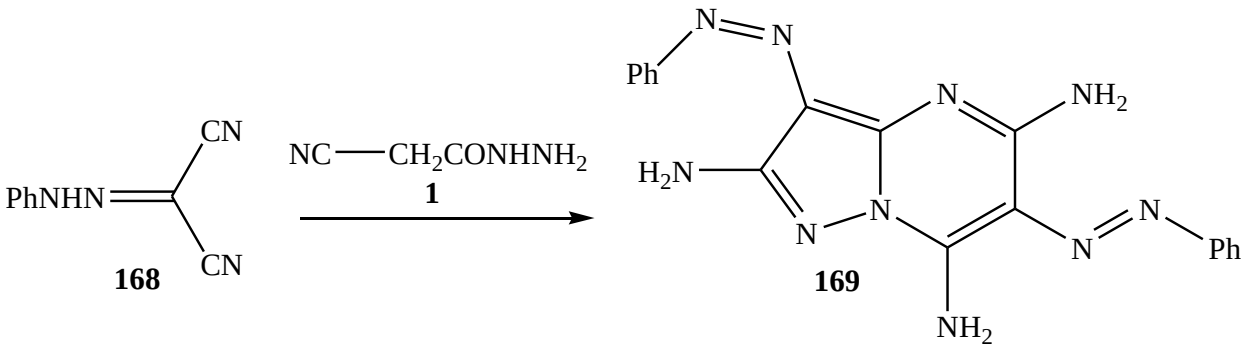
Scheme 59

The reaction of cyanoacetohydrazide **1** with β-aminocrotonitrile **44** gave the condensation product **165** which was formed by elimination of ammonia. This compound was readily coupled with benzenediazonium chloride to yield a product which was formulated as the hydrazone derivative **166**. The latter when refluxed in dimethyl fomamide - piperidine gave a product identified as 5-amino-3-methyl-4-phenylazopyrazole **167**[18] (Scheme 60).



Scheme 60

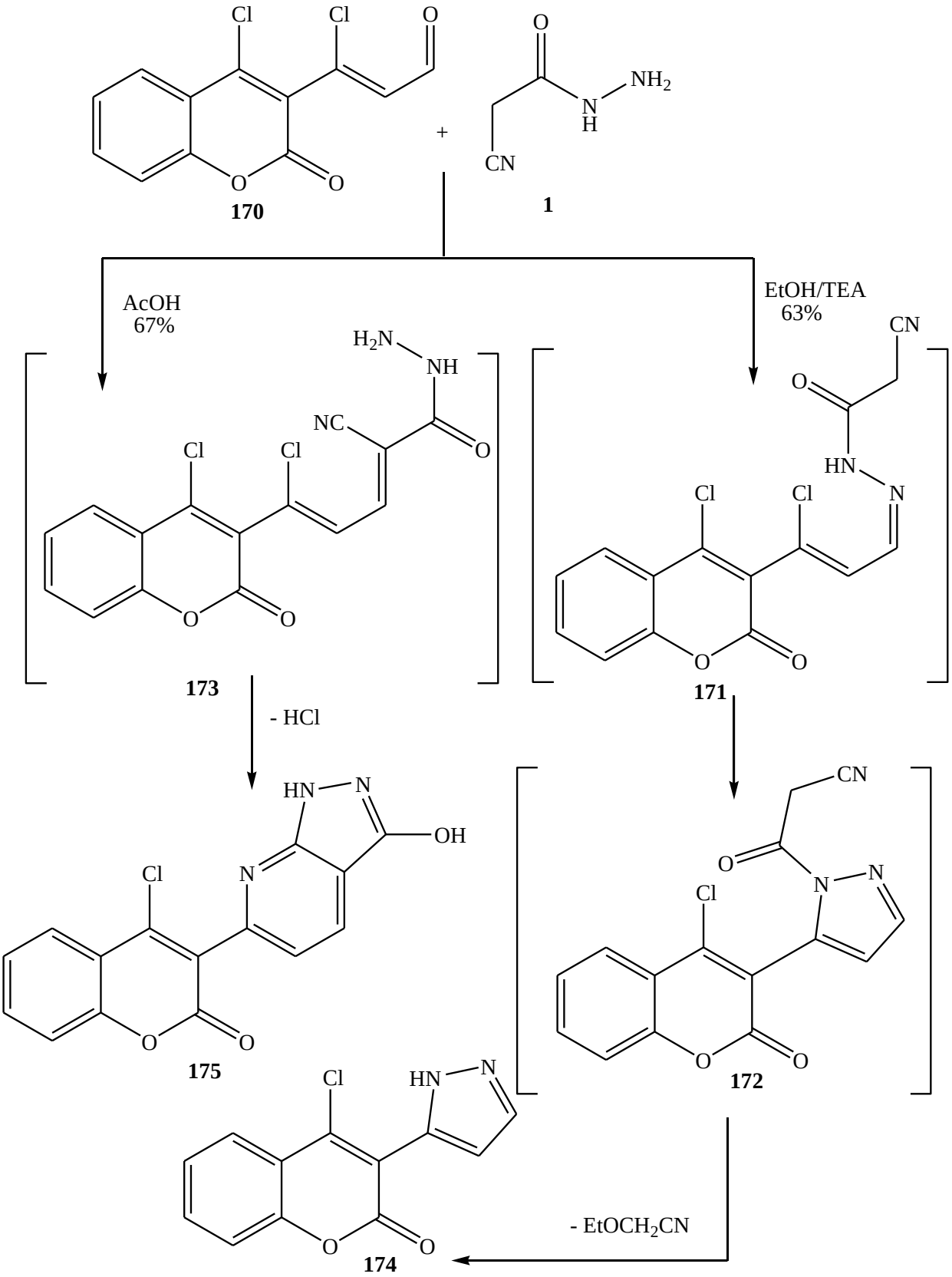
Cyanoacetohydrazide **1** behaves also as a hydrazine in its reaction with 2-phenyl-hyclrazonopropane dinitrile **168** ; as a result, the 3,6- diphenylhydrazono-2,5,7- triaminopyrazolo[2,3- a] pyrimidine **169** was obtained[81] as shown in Scheme 61.



Scheme 61

In addition, treatment of dichloro-aldehyde **170**[82] with cyanoacetohydrazide **1** in boiling ethanol yielded pyrazolylcoumarin **174** as demonstrated in Scheme 62. The latter reaction took place through elimination of H_2O (intermediate **171**) followed by losing HCl molecule, yielding the non-isolable intermediate **172**, which did

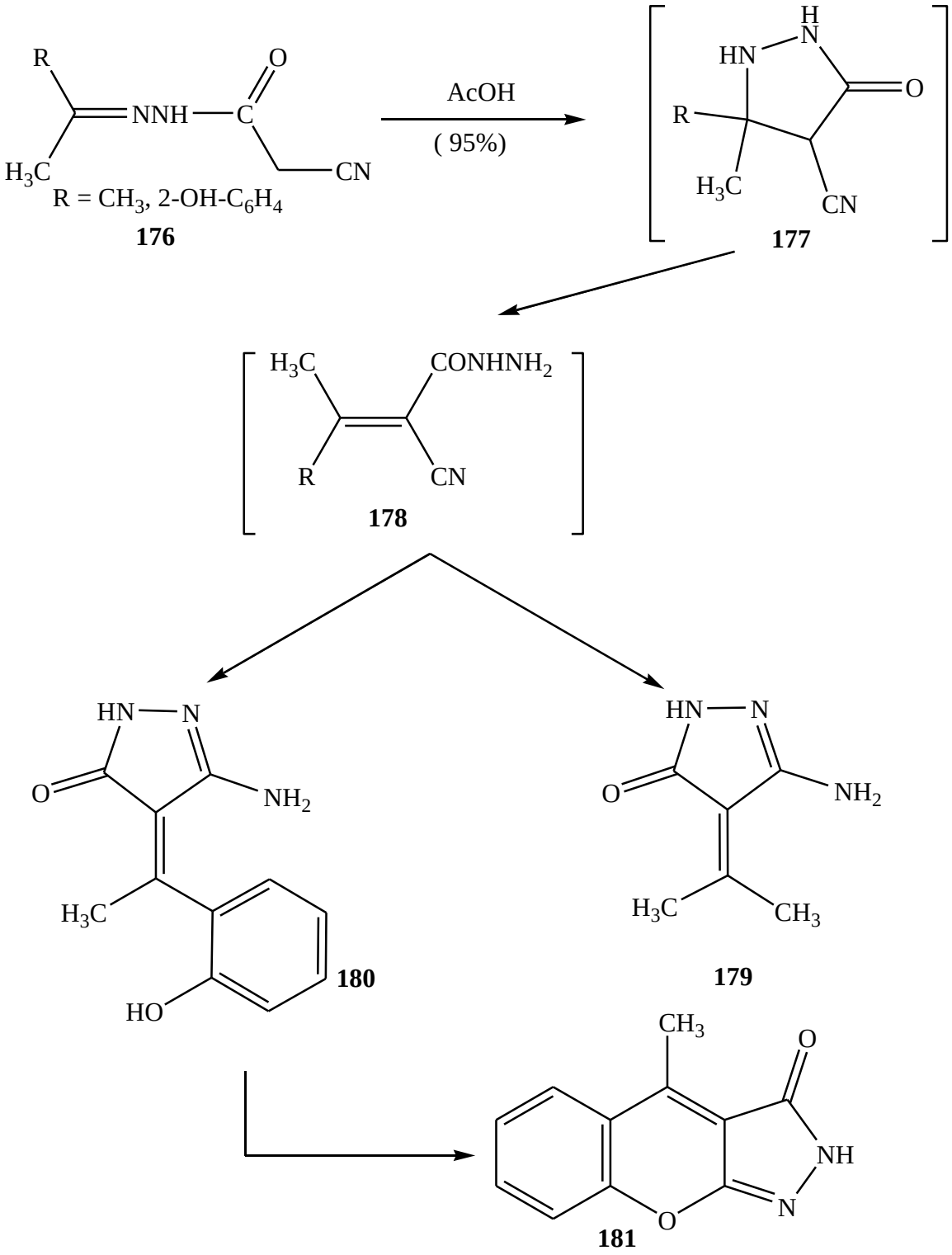
undergo elimination of cyanoacetyl group by ethanol, resulting in the final product **174**. Reconducting the previous reaction in boiling acetic acid furnished the pyrazolopyridinyl- coumarin derivative **175**. Where, the cyanoacetohydrazide started as carbon nucleophile and later condensed with the aldehyde group in compound **170** yielding intermediate **173**, which, in turn, did undergo cycloaddition followed by cyclocondensation, resulting in the final product **175**, as illustrated in Scheme 62[83].


Cl
Cl
O
O
O
NH2
N
H
CN
+
170
1
AcOH
67%
EtOH/TEA
63%
H2N
NH
NC
O
Cl
Cl
O
O
173
CN
O
HN
N
Cl
Cl
O
O
171
- HCl
HN
N
OH
Cl
N
O
O
175
CN
O
N
N
Cl
O
O
172
Cl
HN
N
O
O
174
- EtOCH2CN

Scheme 62

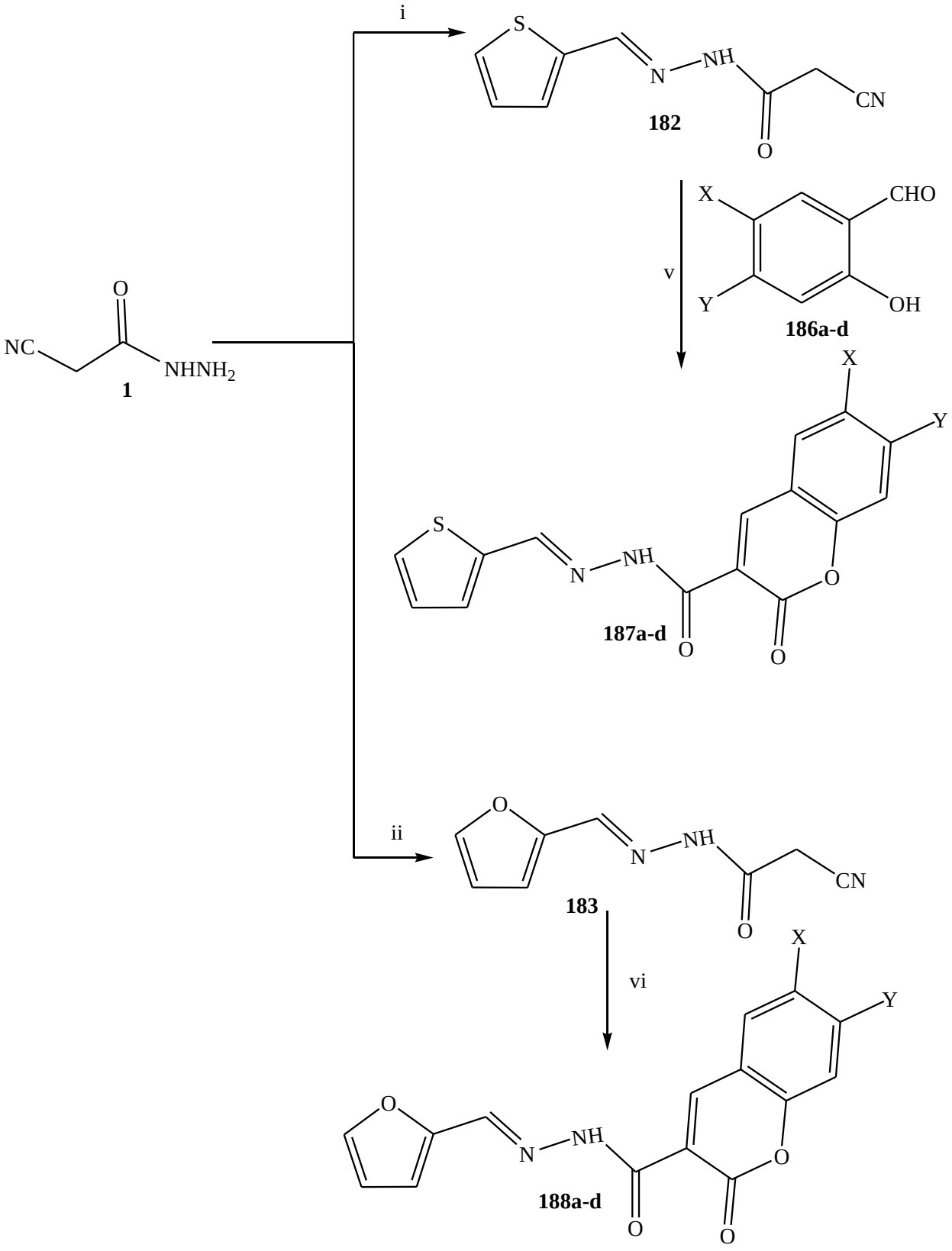
h- Heterocycles obtained via the utility of functional groups No. 1,2,5 (The cyano, methylene and hydrazino groups .)

When the hydrazones **176** (prepared from the reaction of **1** with acetone or 2-hydroxyacetophenone)[84,85] were refluxed in acetic acid, the reaction product was influenced by the substituent present in the hydrazone. Thus, the reaction is assumed to proceed via the pyrazoline intermediates **177** which undergo aryl transfer to the thermostable C-arylidene condensate intermediate **178** with subsequent intracyclization to the corresponding aminopyrazolones **179** and **180**. In case of the acetone derivative, the reaction terminated at this step and the aminopyrazolone derivative **179** was isolated, whereas in case of the 2-hydroxyphenyl derivative **180** further cyclization involving the NH_2 and OH groups occured and the chromenopyrazolone **181** was the end isolable product[4] (Scheme 63).

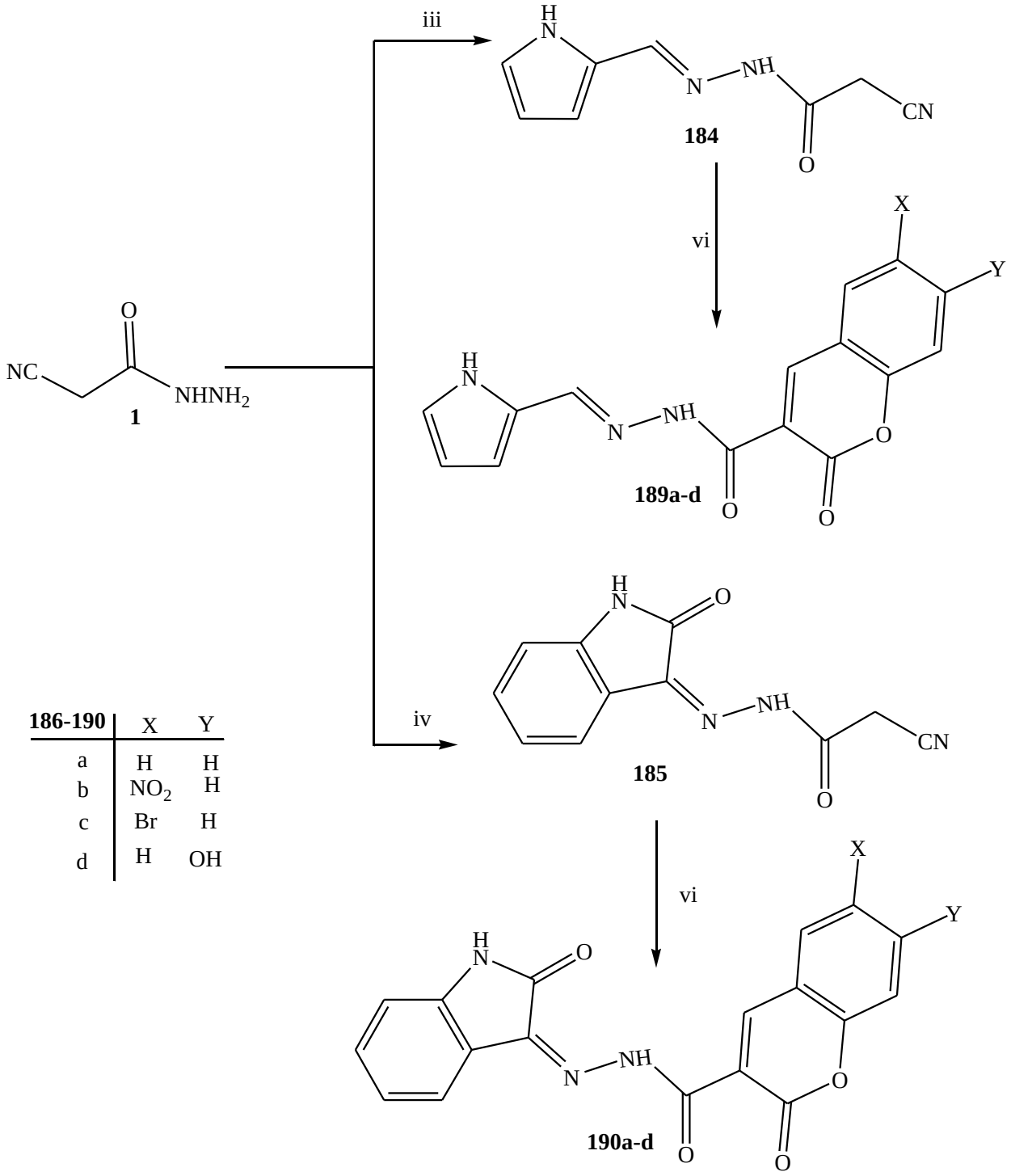

R
O
NNH
C
H3C
CN
R = CH3, 2-OH-C6H4
176
AcOH
(95%)
H
N
HN
O
R
H3C
CN
177
H3C
CONHNH2
R
CN
178
HN
N
O
NH2
H3C
HO
180
HN
N
O
NH2
H3C
CH3
179
CH3
O
NH
N
O
181

Scheme 63

Several 2-cyanoacetohydrazones **182-185** were prepared by condensing 2-hetaryl aldehydes with 2-cyanoacetohydrazide (**1)** or by combining isatin with 2-cyanoacetohydrazide (**1)**[76,86-88]. The Knoevenagel condensation of 2-hydroxy-benzaldehydes **186a-d** with 2-cyanoacetohydrazones **182-185** in refluxing ethanol containing a catalytic amount of piperidine followed by treating the product with dilute HCl afforded coumarin hydrazide-hydrazone derivatives CHHD's **187-190** in high chemical yield (Scheme 64a,b)[89].


i
S
N
NH
CN
O
182
X
CHO
v
Y
OH
186a-d
O
NC
NHNH2
1
X
Y
S
N
NH
O
O
O
187a-d
ii
O
N
NH
CN
O
183
vi
X
Y
O
N
NH
O
O
O
188a-d

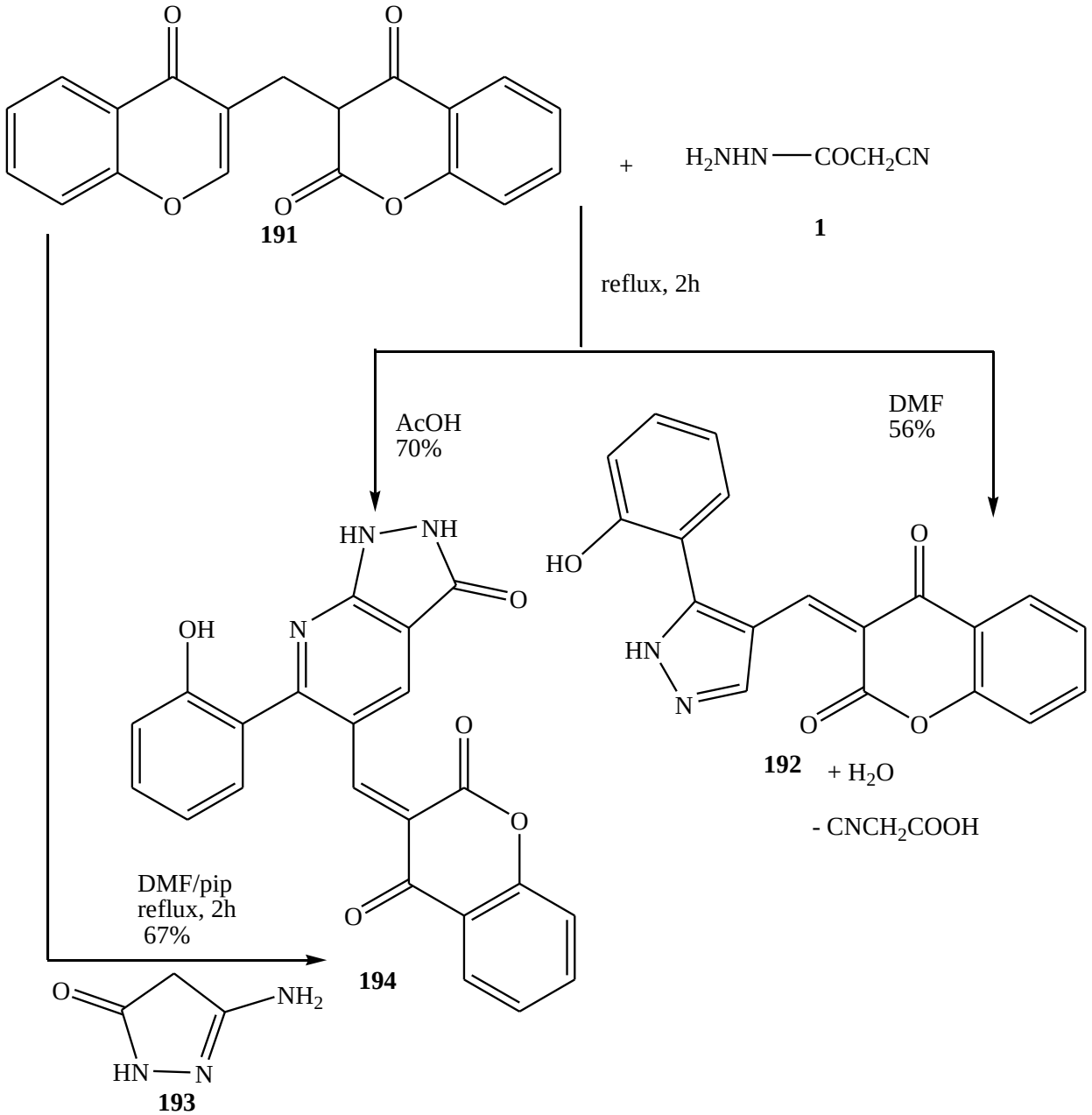
Scheme 64a



Scheme 64b

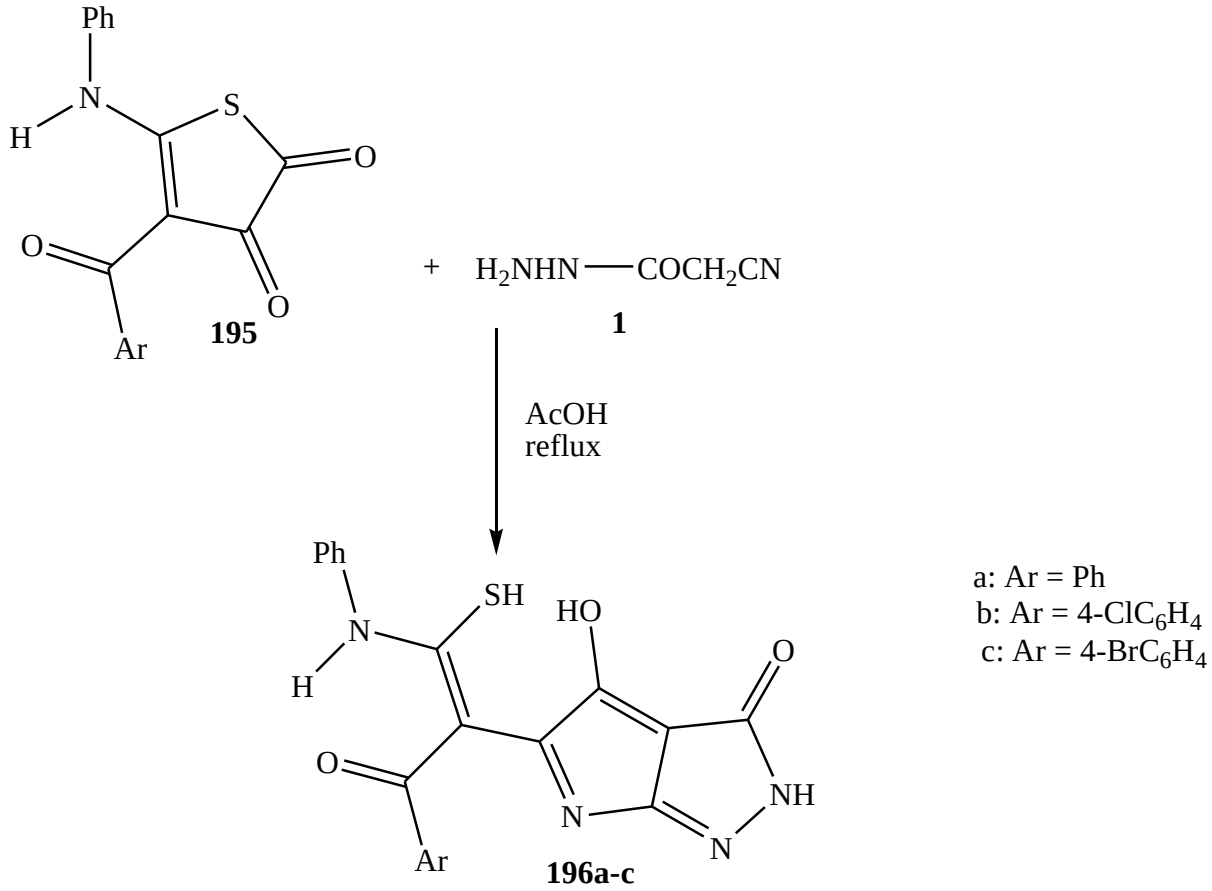
i) Thiophene -2-carbaldehyde, ethanol, acetic acid, reflux, 30 min.; ii) furan -2-carbaldehyde, ethanol, acetic acid, reflux, 15 min; iii) *1H*-Pyrrole -2-carbaldehyde, ethanol, acetic acid, reflux, 30 min; iv) isatin, ethanol, acetic acid, reflux, 30 min; v) ethanol, piperidine, reflux, 6 h; vi) compound **186a-d**, ethanol, piperidine, reflux, 6 h.

It is noteworthy that the treatment of compound **191** with cyanoacetohydrazide **1** in boiling DMF yielded pyrazole derivative **192**, which is the final product **192**, as demonstrated in Scheme 65. Moreover, the reaction of compound **191** with cyanoacetohydrazide **1** was conducted in glacial acetic acid and resulted in pyrazolo[3,4-b]pyridine derivative **194**.[90] Also, compound **194** was also generated authentically from the reaction of compound **191** with 5-amino-2,4-dihydro-3H-pyrazol-3-one **193**, in boiling DMF containing piperidine[91] (Scheme 65).



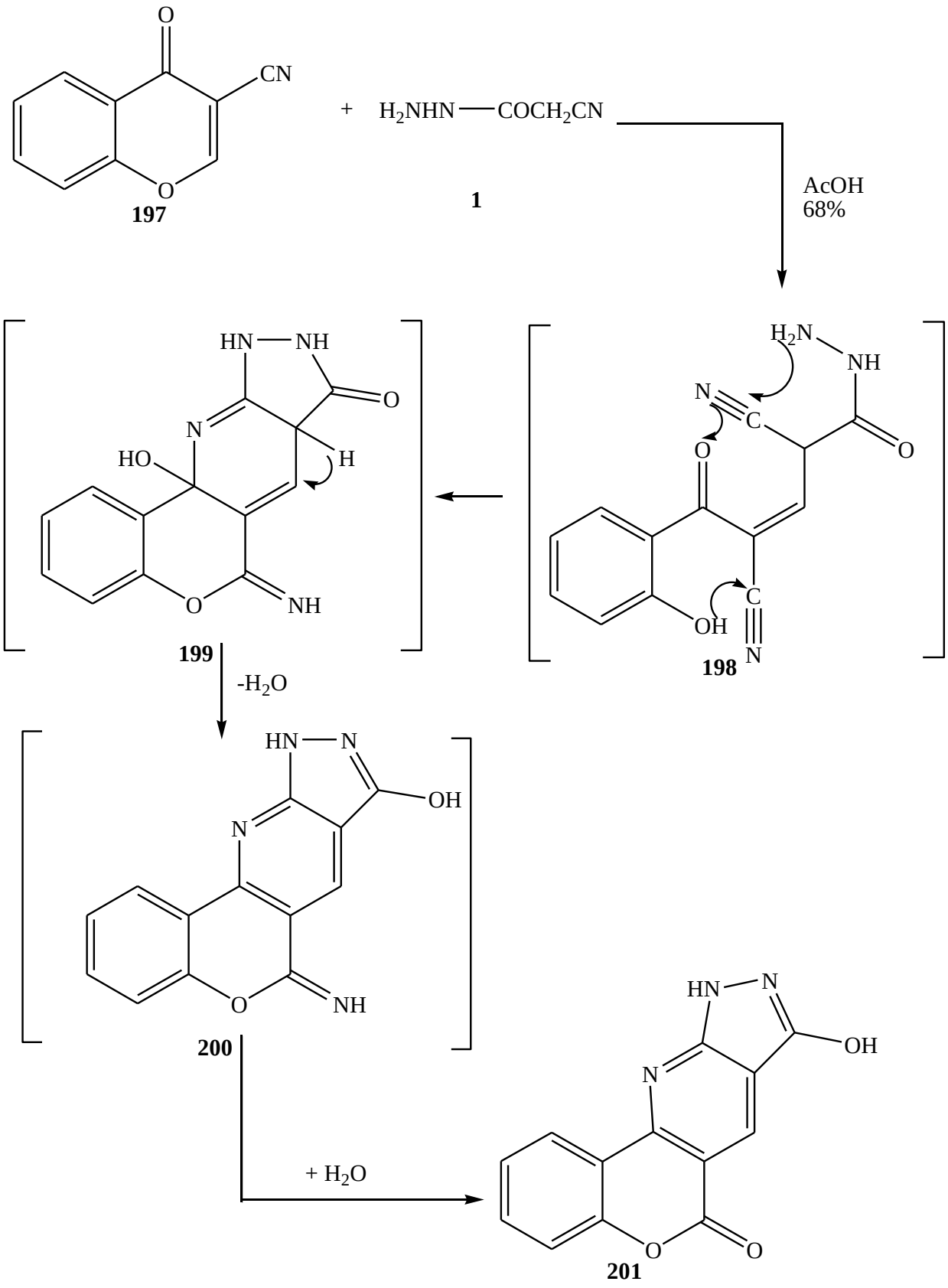
Scheme 65

In addition, the condensation reaction of 4-aroyl-5-phenylamino-2,3-dihydro-thiophene-2,3-diones **195** with cyanoacetohydrazide **1** under reflux condition in glacial acetic acid yielded pyrrolo[2,3-c]pyrazol-3(2H)-one 2 derivatives **196** (Scheme 66)[92].



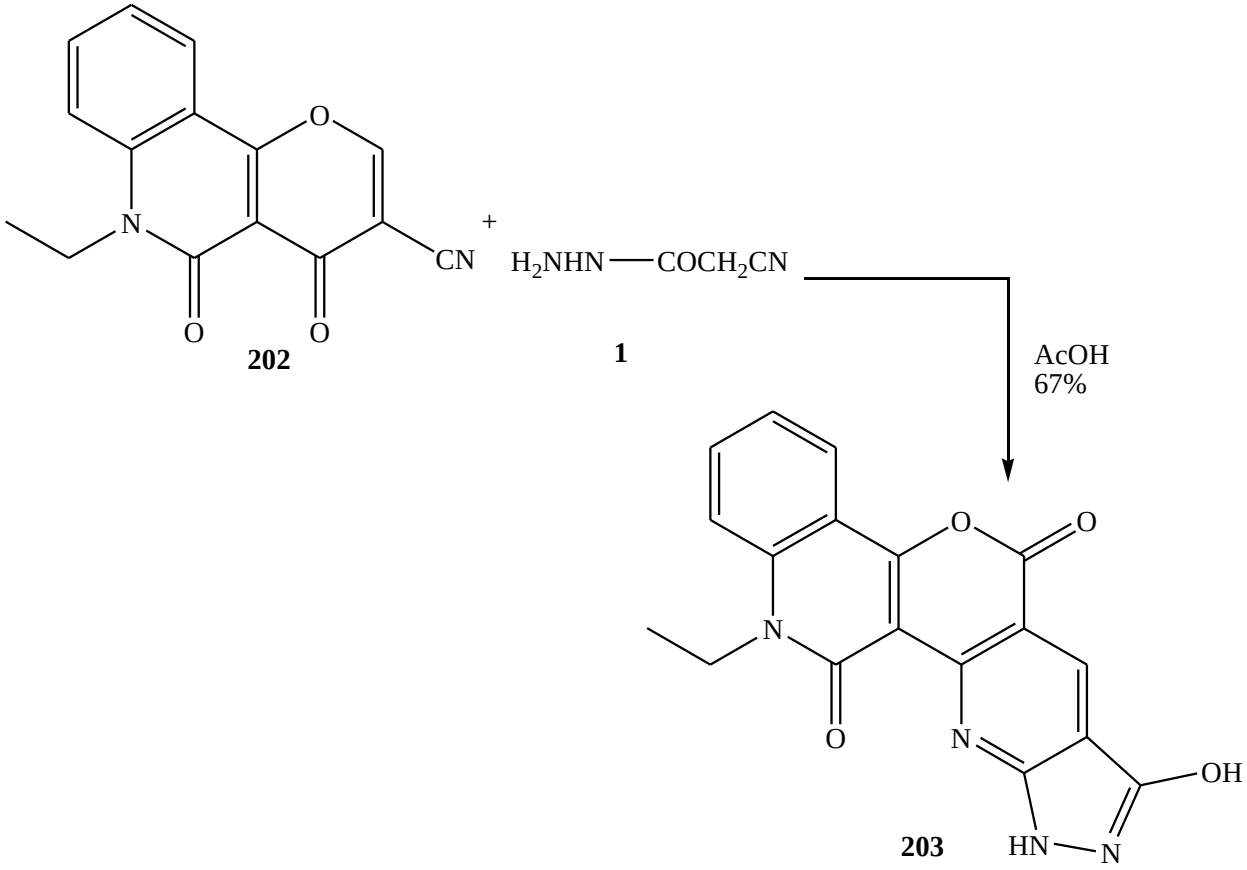
Scheme 66

Moreover, the novel chromeno[4,3-b]pyrazolo[4,3-e] pyridine **201** was obtained through the chemical transformation of carbonitrile **197** with cyanoacetohydrazide **1** in acetic acid (Scheme 67)[93]. This reaction could take place through nucleophilic attack at C-2 position by active methylene group in cyanoacetohydrazide with γ-pyrone ring opening, producing intermediate **198**, which did undergo cycloaddition reactions, resulting in intermediate **199**. Where the dehydration of the latter intermediate yielded intermediate **200**, which hydrolyzed under the reaction conditions, resulting in the final product **201**, as demonstrated in Scheme 67.


O
CN
O
197
+ H2NHN—COCH2CN
1
AcOH
68%
H2N
NH
N
C
O
O
C
OH
N
198
HN—NH
O
N
HO
H
O
NH
199
-H2O
HN—N
OH
N
O
NH
200
+ H2O
HN
N
OH
N
O
O
201

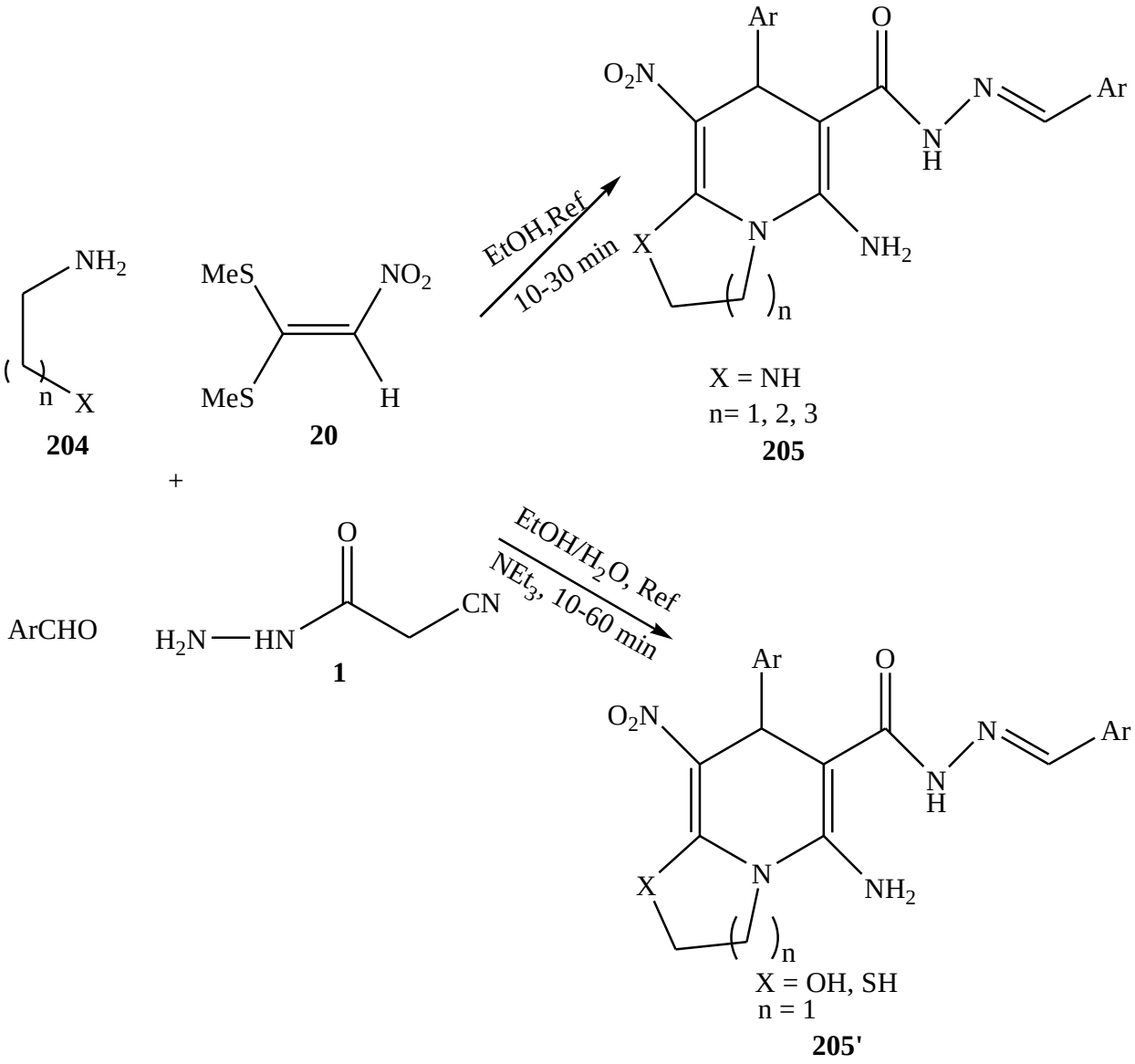
Scheme 67

Similarly, reaction of carbonitrile **202** with cyanoacetohydrazide **1** in boiling acetic acid take place via a domino process, resulting in heteroannulated quinolino[3",4":5',6']pyrano[4',3'-b]pyrazolo[4,3-e]pyridine derivative **203** (Scheme 68)[94].



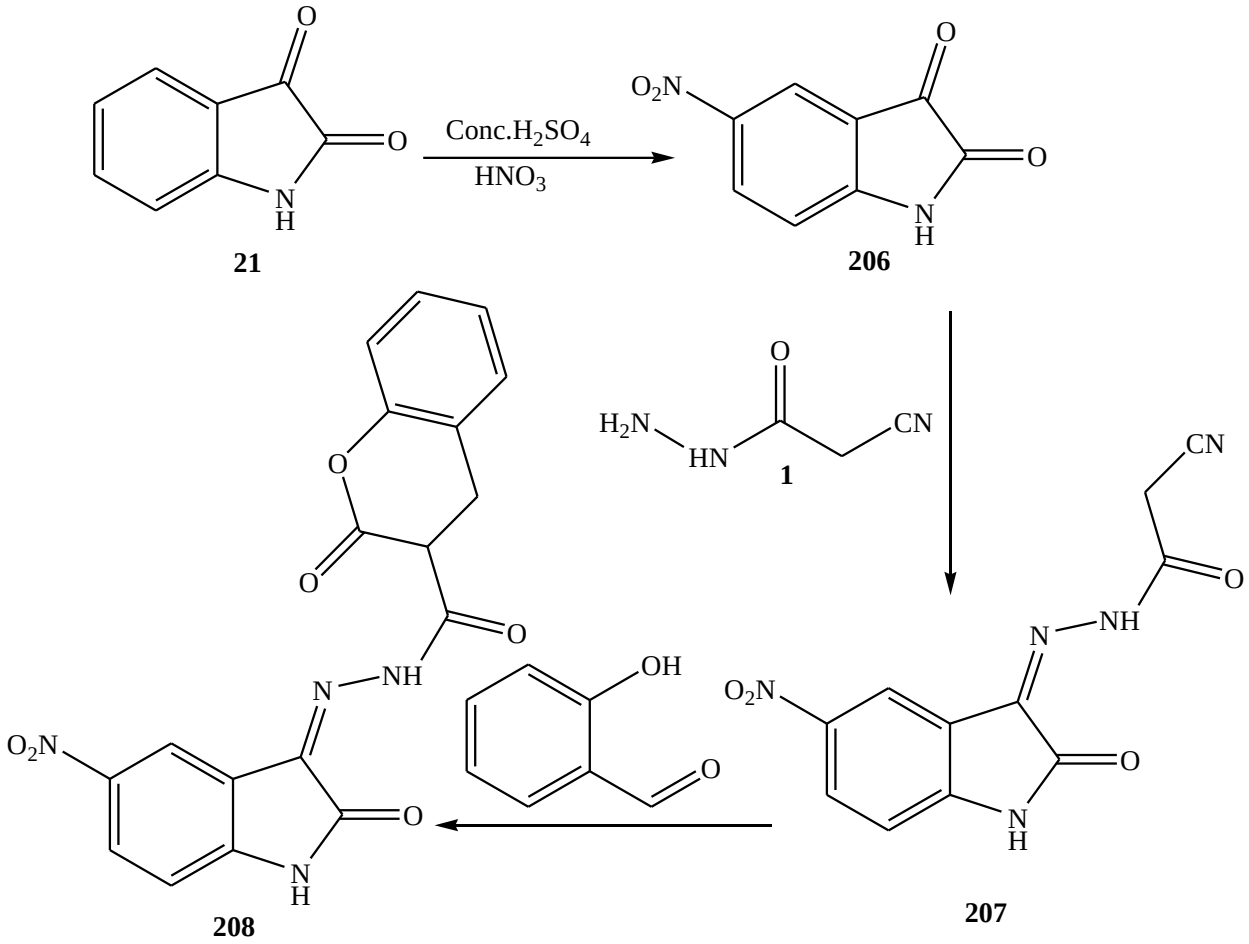
Scheme 68

Moreover, Bayat and coworker synthesized carbohydrazide derivatives **205**, **205′**. Where, the reactions of various amines **204**, 1,1-bis(methylthio)-2-nitroethene **20**, aromatic aldehydes, and cyanoacetohydrazide **1** in EtOH and EtOH/H_2O at reflux yielded the corresponding fused heterocyclic systems **205** and **205′**, respectively (Scheme 69)[95,96].



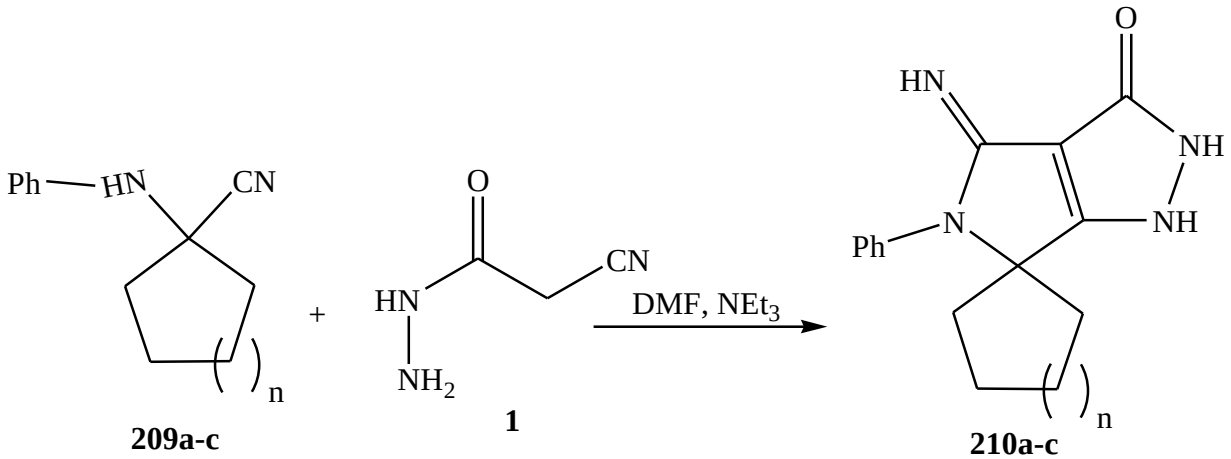
Scheme 69

Moreover, Compound 2-cyano-*N'*-(5-nitro-2-oxoindolin-3-ylidene)aceto-hydrazide[98] **207** was synthesized by the reaction of nitro-isatin **206** with cyanoaceto- hydrazide **1** in 1,4-dioxane which then reacted with salicylaldehyde to give *N'*-(5-nitro-2-oxoindolin-3-ylidene)-2-oxochromane-3-carbohydrazide **208** (Scheme 70)[97].



Scheme 70

Also, Soliman et al. studied the reaction of compounds **209a**–**c** with cyanoacetohydrazide **1**. This reaction took place through nucleophilic attack of the –NH group of the substrate at the cyano function of the reagent, followed by another nucleophilic attack of the CH_2 group in the reagent at the cyano group and cyclization, then removal of NH_3 molecule and cyclization produced the desired spiro heterocycles **210a**–**c** (Scheme 71)[98].



209a-c

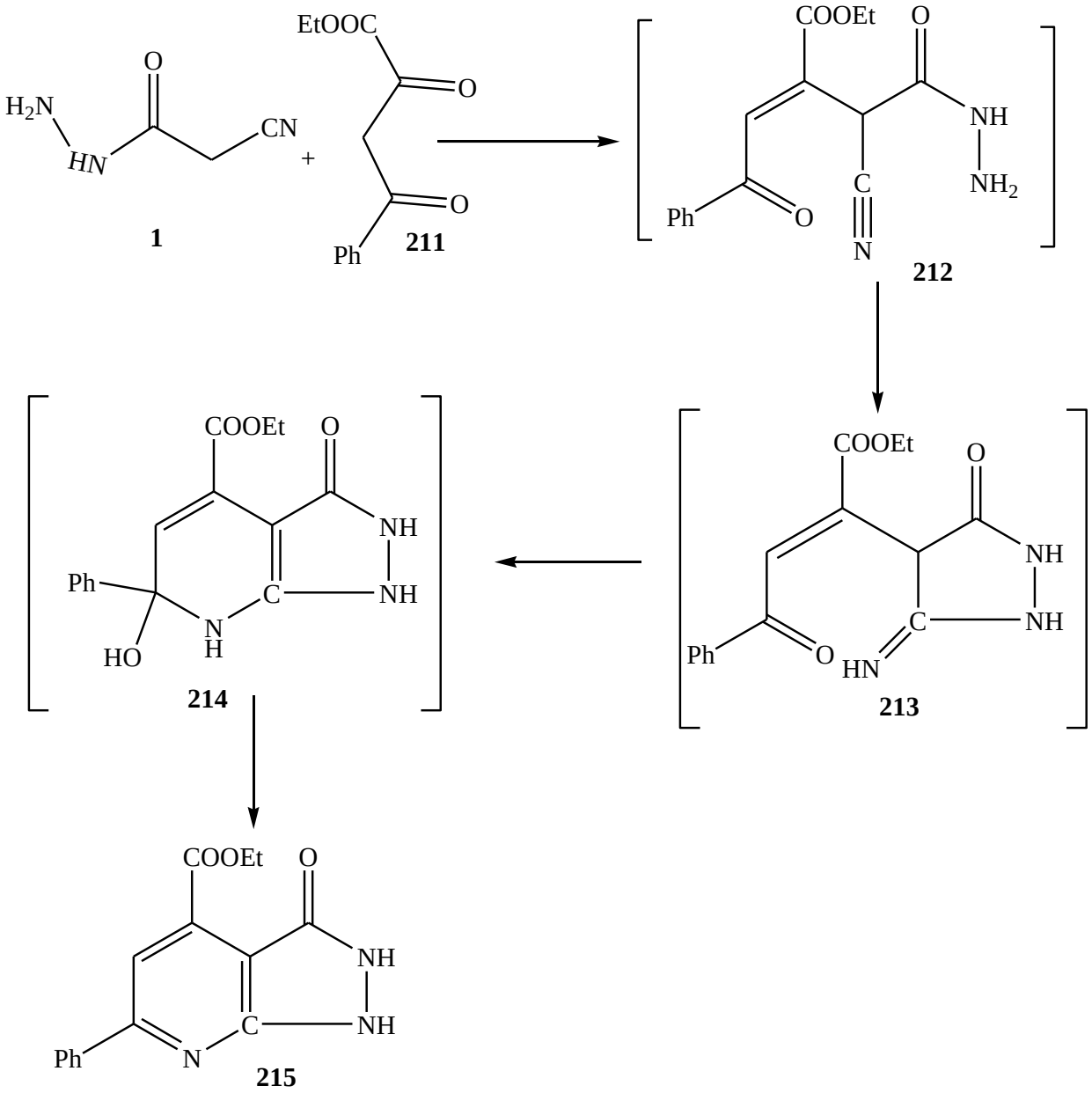
a: n=1
b: n=2
c: n=3

1

210a-c

Scheme 71

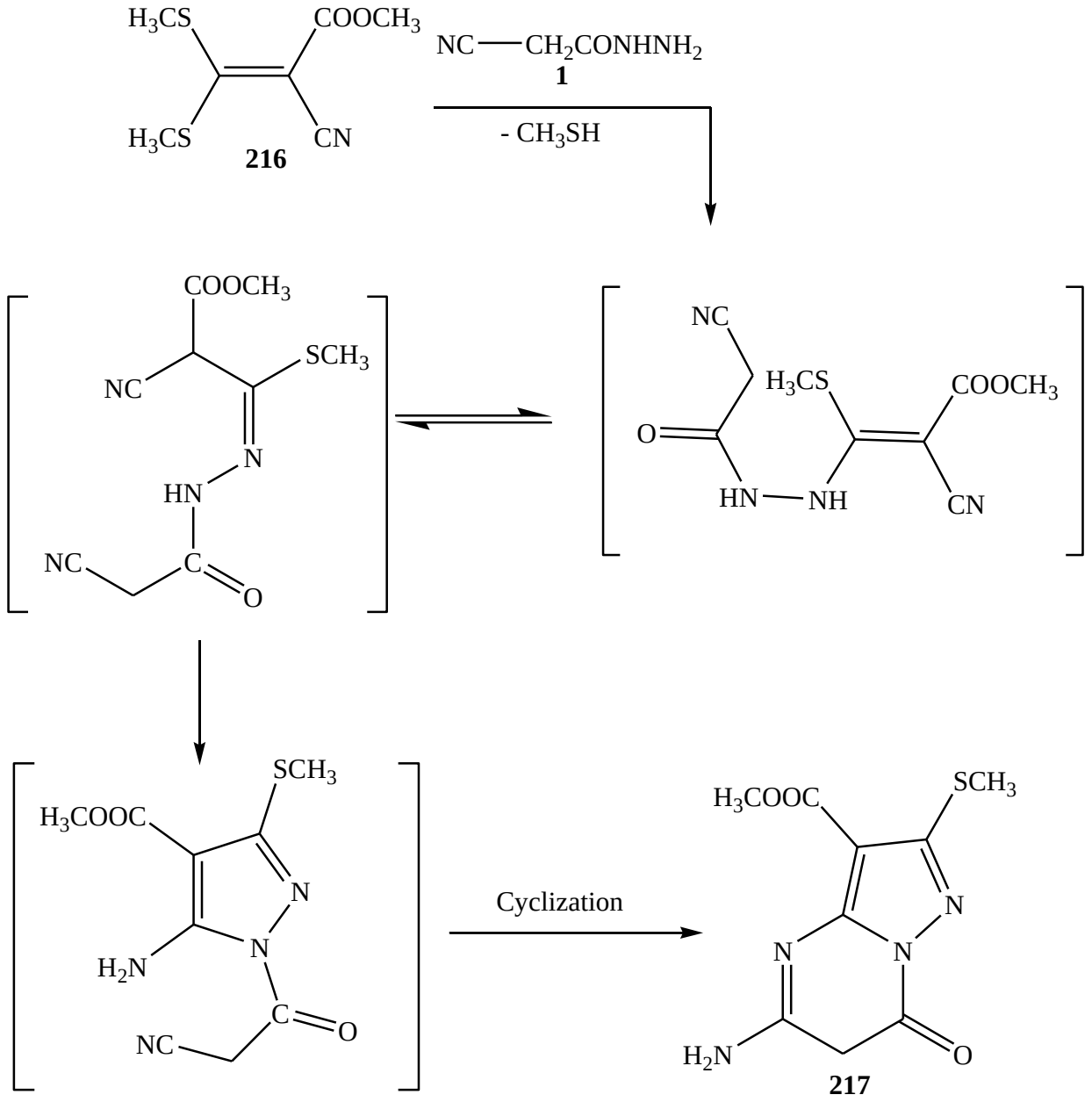
In addition, Kabirifard et al.[99] synthesized pyrazolo[3,4-*b*]pyridine-4-carboxylate **215** by condensation of the cyanoacetic acid hydrazide **1** with ethyl Benzoylpyruvate **211** in glacial acetic acid at 70–80 °C. Theoretically, the reaction mechanism implies the formation of ethyl 2-benzoylmethylene-3-cyano-4-oxo-4-hydrazinobutanoate **212** from cyanoacetohydrazide **1** and ethyl benzoylpyruvate **211**, which, in turn, undergoes intramolecular ring closure by attack of NH_2 group on nitrile group to give intermediate **213**. Furthermore, another cyclization yields 6-hydroxy-pyrazolopyridine **214**, which produces the final product **215** (Scheme 72).



Scheme 72

i- Heterocycles obtained via the utility of functional groups No. 1,4,5 (The cyano, amido and hydrazino groups .)

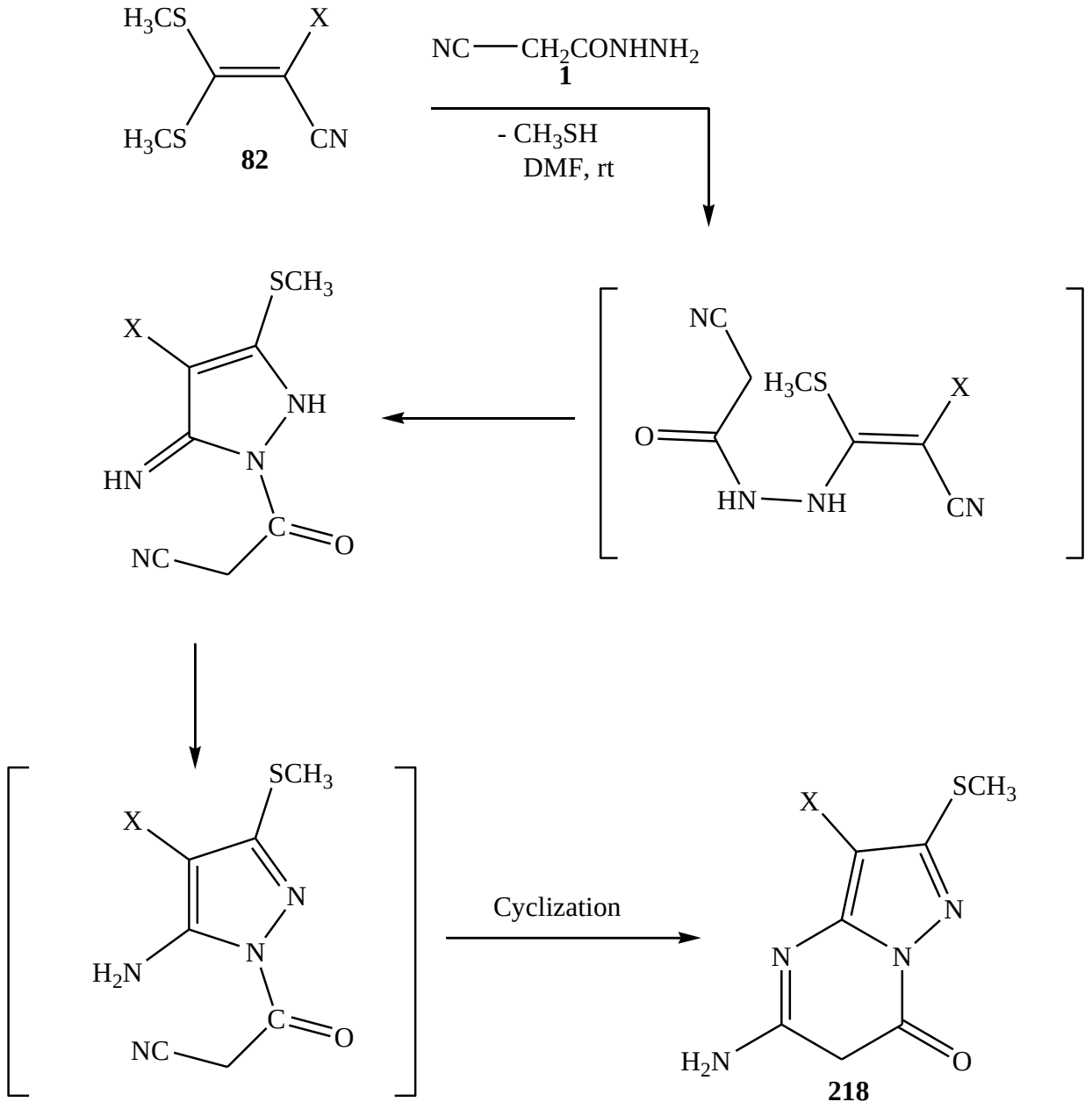
Recently, it has been reported that, cyanoacetohydrazide **1** reacted via its cyano, amido and hydrazino groups with the ketene dithio-acetal derivative **216**, and the isolated product was identified as the 2-methylthio-3-methoxycarbonyl-5-aminopyrazolo[2,3-a]pyrimidin-7-one **217**. A mechanistic pathway for this product formation was suggested as follow (Scheme 73):[100]



Scheme 73

In anaology, Napoles et al. synthesized pyrazolo[1,5-*a*]pyrimidines **218** from cyanoacetohydrazide **1** and push–pull systems. Beginning with cyanoacetohydrazide **1** and cinnamonitrile derivatives **82** in DMF, the target compounds could be generated in only one step, but with low yield, because of the formation of multiple byproducts. Furthermore, when the reactions of polarized ethylenes with other nucleophiles are conducted, two steps are necessary, and the reaction mixture must be heated for a few hours. Hypothetically, the presence of the

appropriate reactive centerin, the ketene-*S*,*S*-acetals and 1,3-dithiethanes used as push–pull systems, facilitates the necessary intramolecular cyclizations after the initial nucleophilic attack of the cyanoacetohydrazide **1** (Scheme 74)[101].

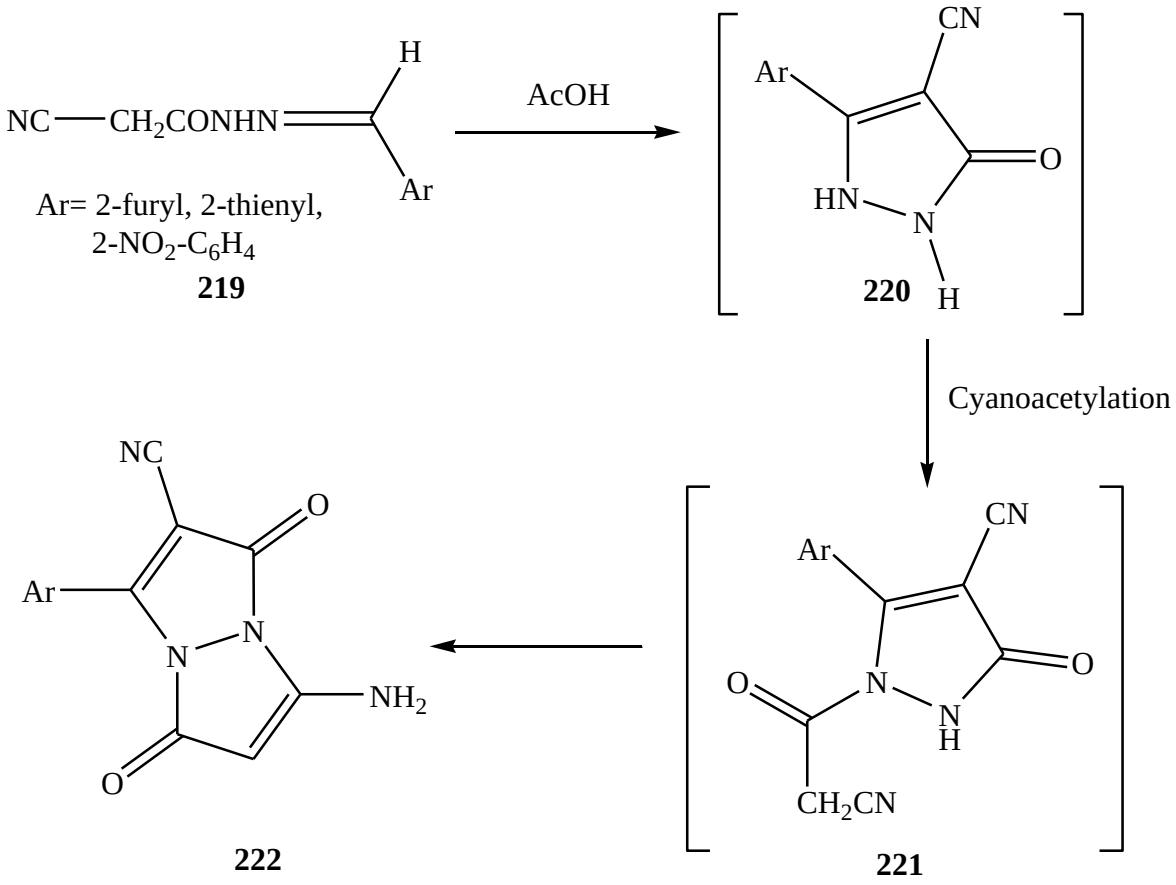


X = COOEt, CN, $CONHCH_2Fu$

Scheme 74

j- Heterocycles obtained via the utility of functional groups No. 2,4,5 (The methylene, amido and hydrazino groups .)

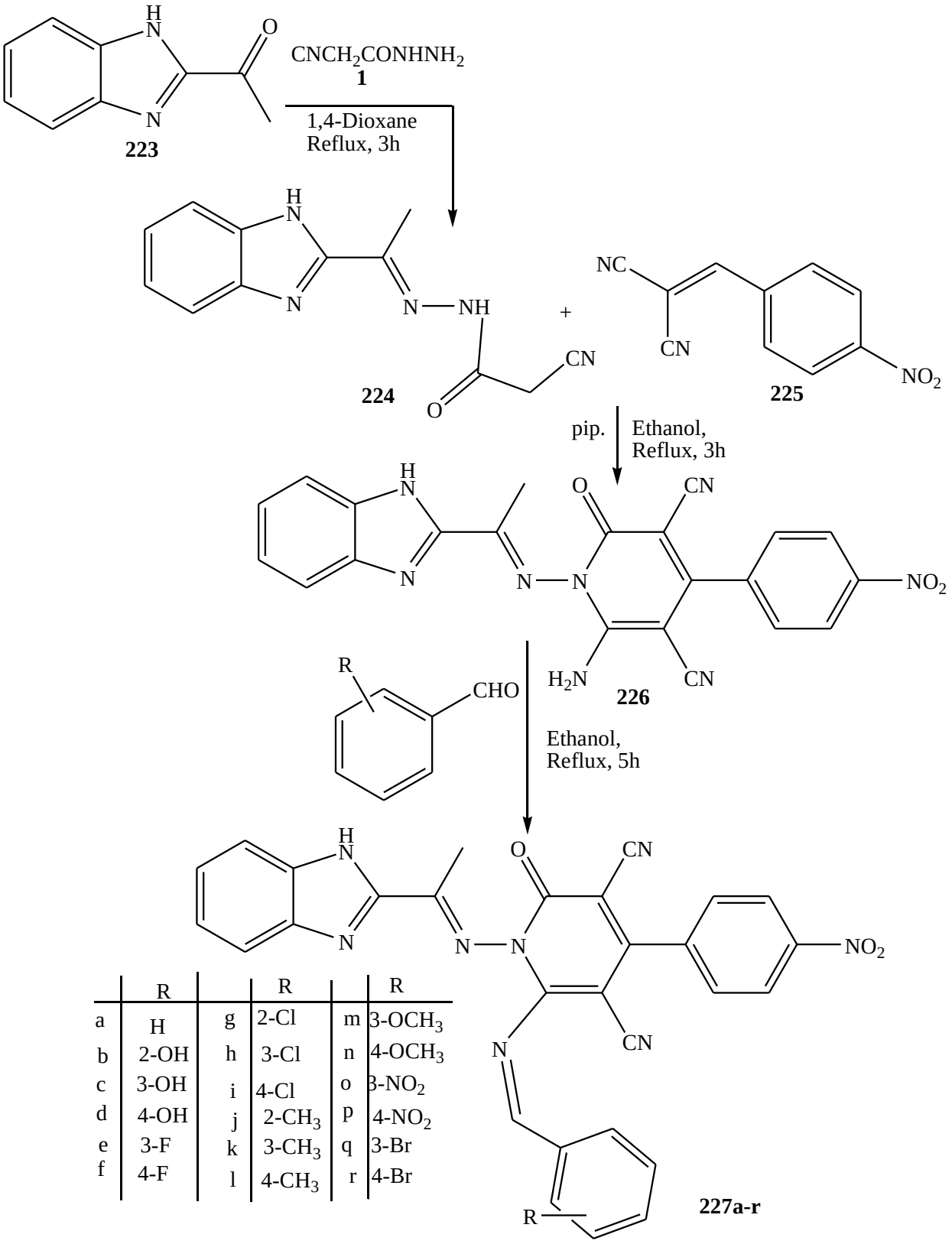
When the hydrazones **219** (obtained from the reaction of cyanoacetohydrazide **1** with the corresponding aldehyde)[102] were refluxed in glacial acetic acid, new products were isolated which have been identified as the condensed pyrazoles **222** . The formation of these products is assumed to proceed through a reaction involving the nucleophilic (CH_2) and the electrophilic (C=N) centers to afford the intermediates, **220** which subsequently cyanoacetylated at its nitrogen nucleophilic center by its open form hydrazone and finally self-cyclized via the CN and NH groups to form the final isolabie product **222**[102] as shown in Scheme 75.



Scheme 75

On the other hand, condensation of 1-(1*H*-benzo[*d*]imidazol-2-yl)ethanone **223** with equimolar quantity of cyanoacetic acid hydrazide **1** in refluxing 1,4-dioxane afforded a single product, that was identified as *N'*-(1-(1*H*benzo[*d*]imidazol-2-

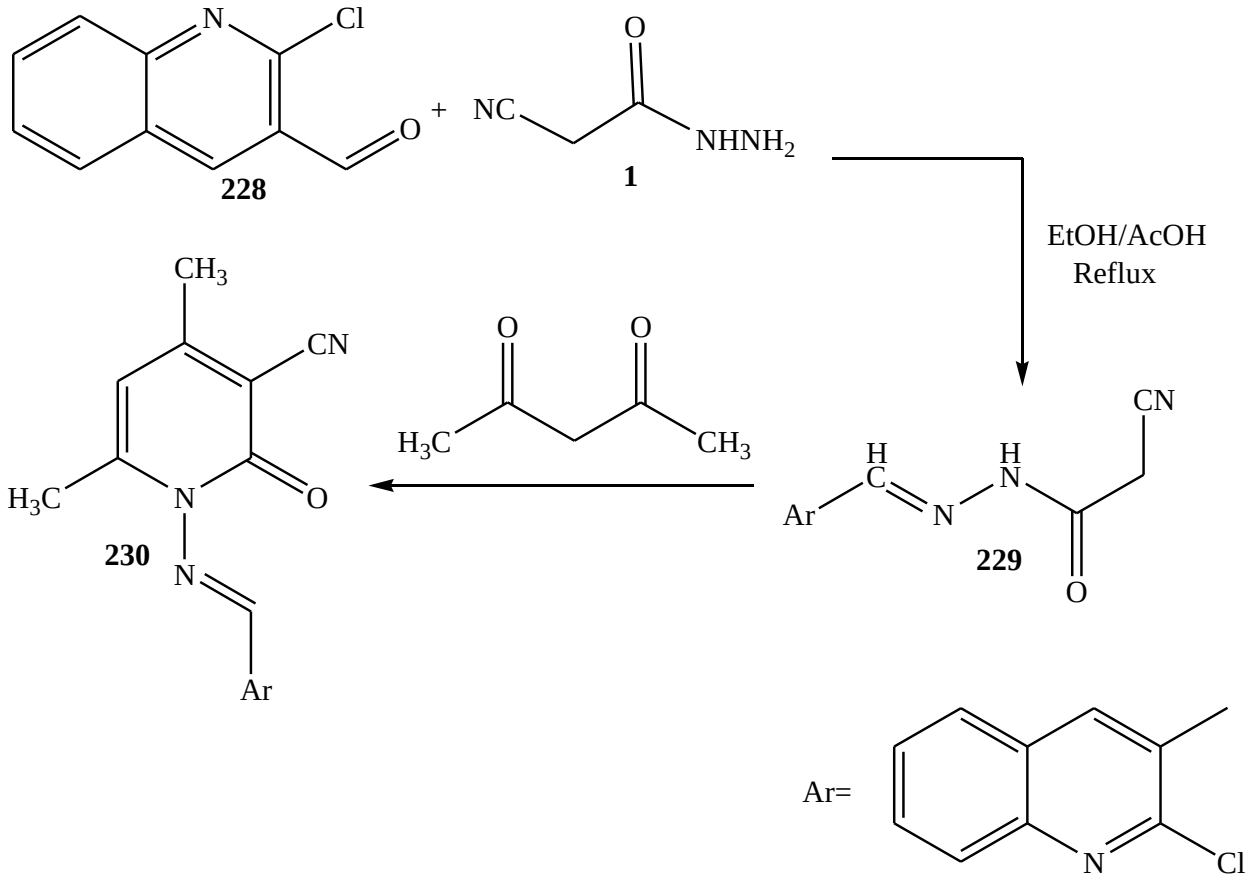
yl)ethylidene)-2-cyanoacetohydrazide **224**. Additionally, the reactive methylene group in the hydrazide **224** is crucial for the Michael-type condensation with Knoevenagel product *p*-nitrobenzaldehyde and malononitrile compound **225** in the presence of catalytic amount of piperidine. Also, utilizing ethanol (95%) as a solvent furnished 2-pyridone derivative identified as 1-((1-(1*H*-benzo[*d*]imidazol-2-yl)ethylidene)amino)-6-amino-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **226**. Furthermore, condensation of 2-pyridone derivative **226** with appropriate aromatic aldehydes in boiling ethanol resulted in the respective targeted benzimidazole-bearing 2-pyridones, acknowledged as 1-((1-(1*H*-benzo[*d*]imidazol-2-yl)ethylidene)amino)-6-((arylbenzylidene)amino)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **227a-r**, Scheme 76[103].



	R		R		R
a	H	g	2-Cl	m	3-OCH_3
b	2-OH	h	3-Cl	n	4-OCH_3
c	3-OH	i	4-Cl	o	3-NO_2
d	4-OH	j	2-CH_3	p	4-NO_2
e	3-F	k	3-CH_3	q	3-Br
f	4-F	l	4-CH_3	r	4-Br

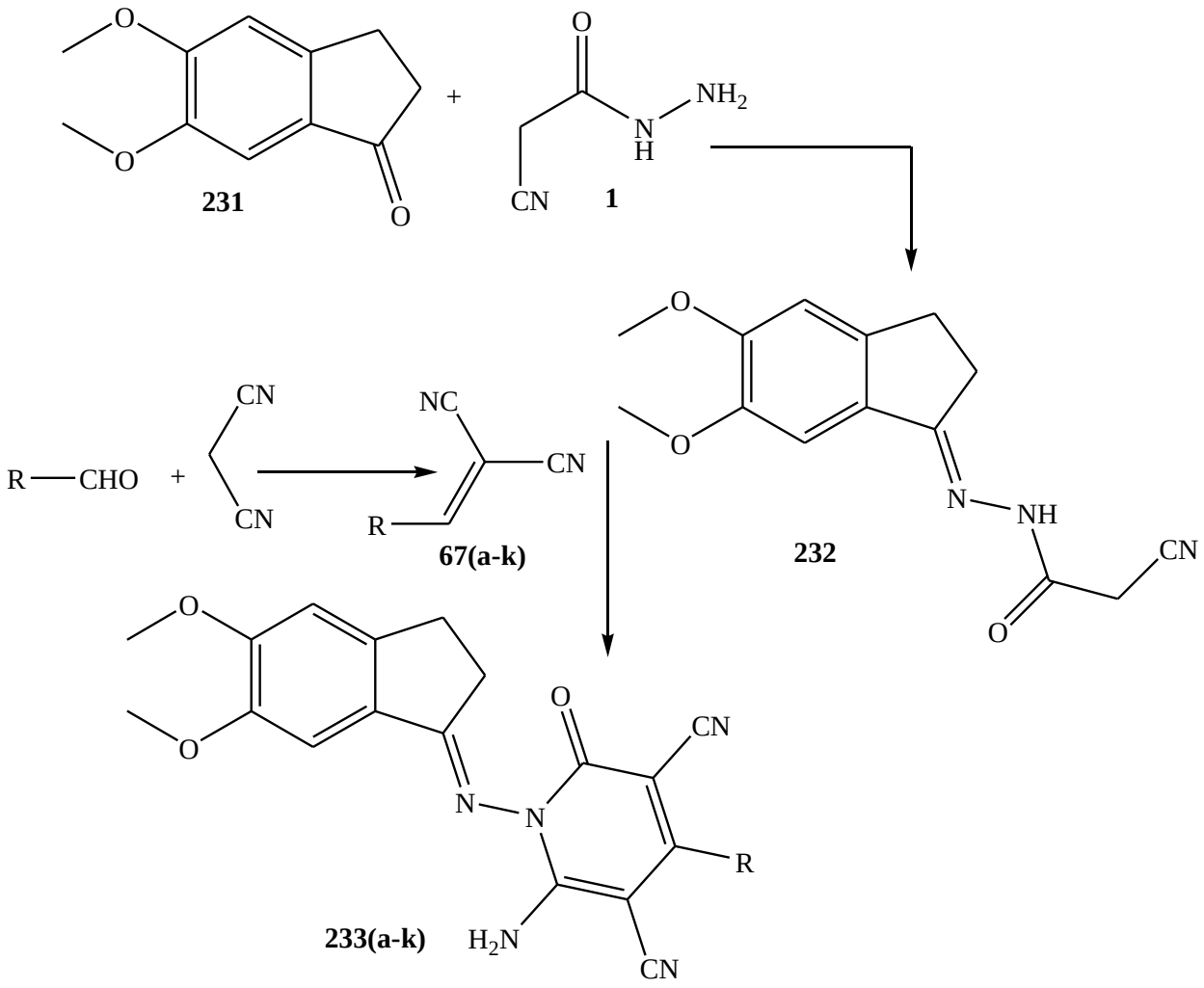
Scheme 76

The synthesis of Hydrazide hydrazone **230** was reported from the reaction of cyanoacetyl- hydrazone, which, in turn, was prepared via the reaction of cyanoacetyl hydrazide **1** with aldehydes, and acetyl acetone[104] e.g. 2-chloroquinoline-3-carbaldehyde **228**. Also, the reaction of **228** with cyanoacetyl hydrazide **1** yielded the formation of N'-((2-chloroquinolin-3-yl) methylene)-2-cyanoacetohydrazide **229**, which reacted with acetyl acetone in refluxed ethanol to produce[105] **230** (Scheme 77).



Scheme 77

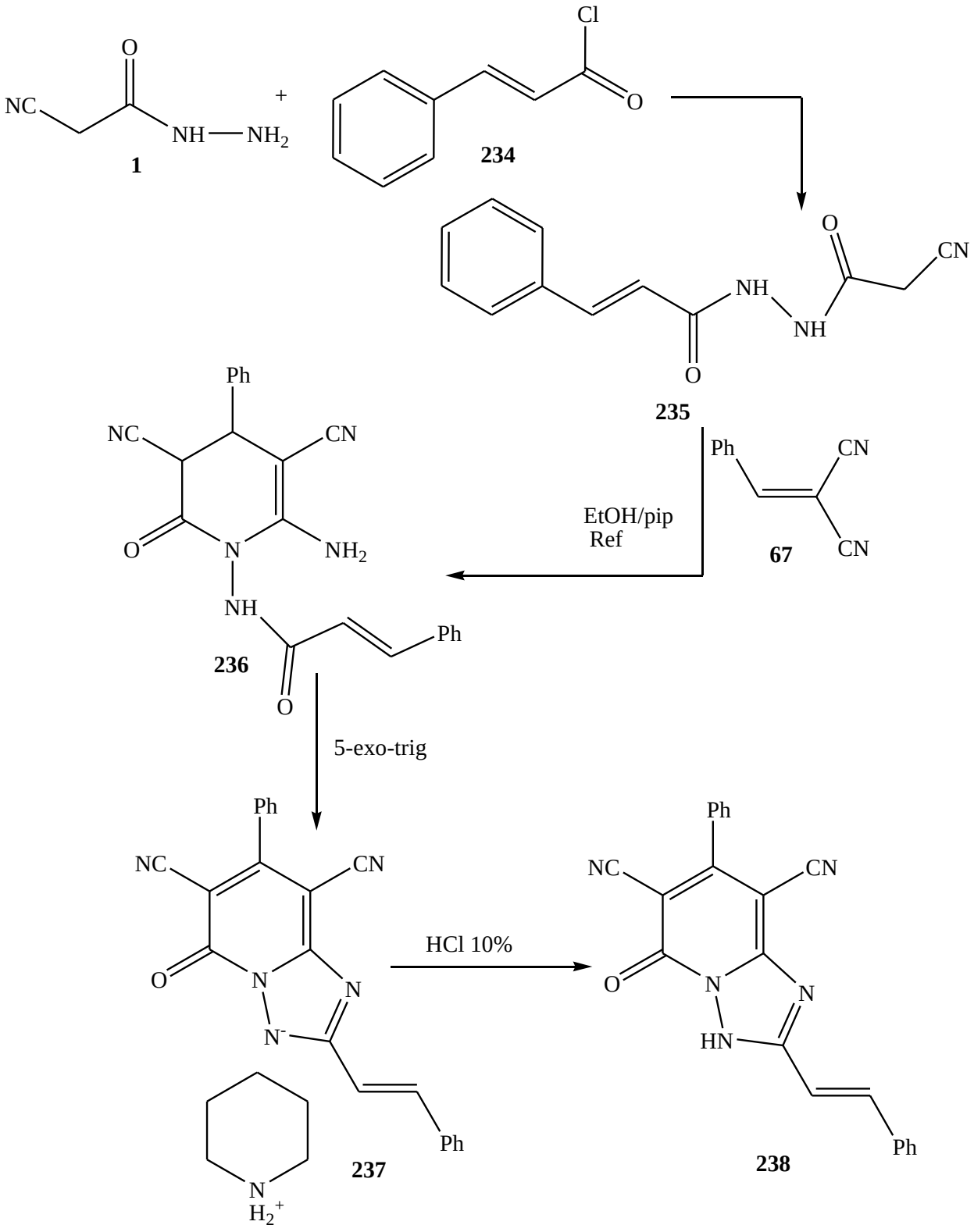
Furthermore, a group of 6-amino-1-(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylideneamino)-2-oxo-4-aryl-1,2-dihydropyridine-3,5-dicarbonitrile derivatives **233**(**a**–**k**) was obtained from the reaction of 2-Cyano-*N*′-(5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ylidene) aceto-hydrazide **232** with 2-arylidenemalononitrile **67**(a-k)[106] in the presence of a piperidine catalyst to supply the title compounds (Scheme 78)[107].



Scheme 78

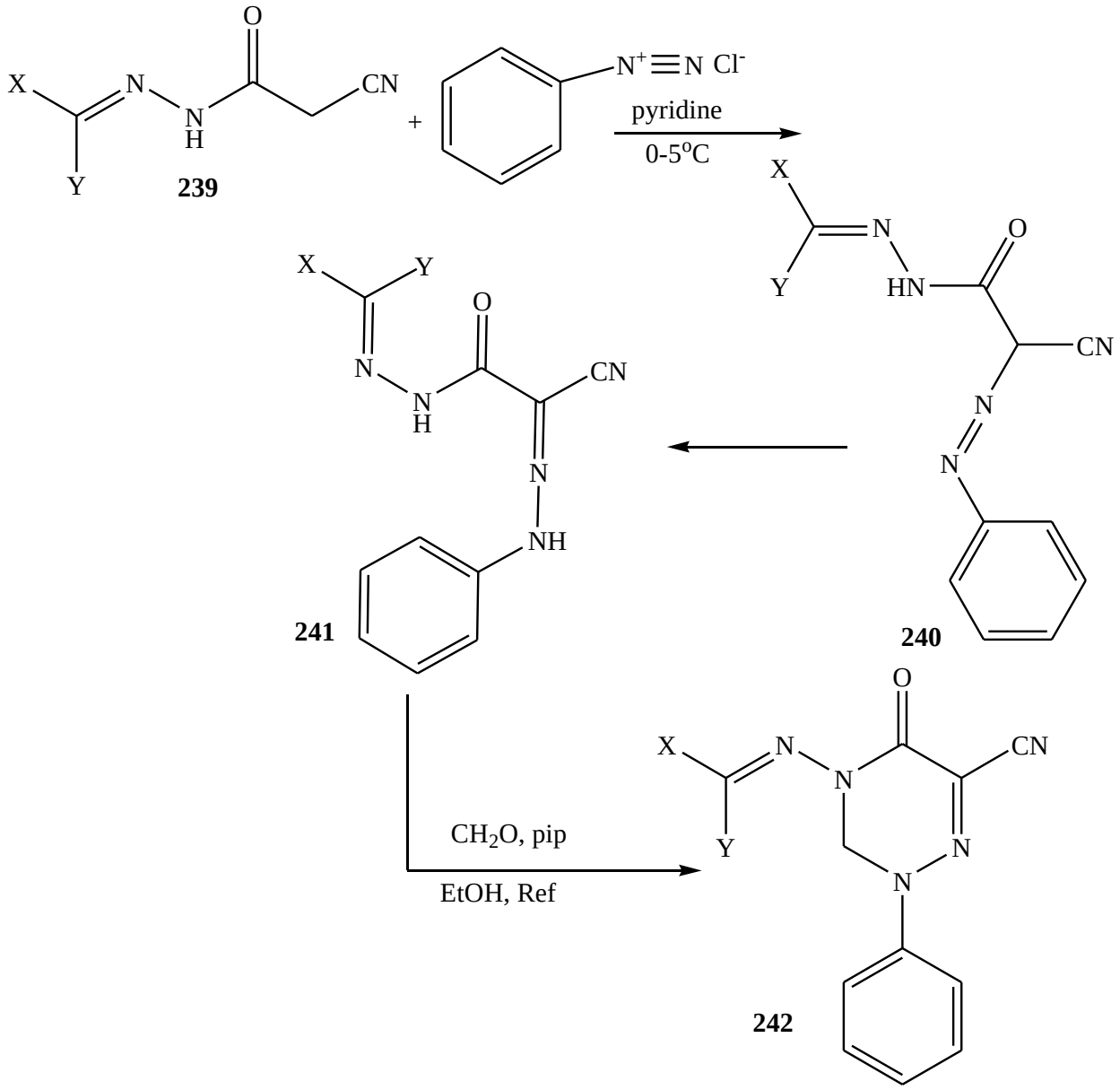
Moreover, Hadi illustrated[108] the synthesis of [1,2,4]triazolo[1,5-*a*]pyridines via concerted reactions between 2′-cinnamoyl-2-cyanoacetohydrazide and α-cyanocinna- monitriles. At first, through the reaction of cyanoacetohydrazide **1** with 3-phenylpropenoyl chloride **234** at 0 °C, the corresponding *N*-substituted 2-cyanoacetohydrazides **235** were formed. Then, reaction of compound **235** with α-substituted cinnamonitriles **67** and piperidine in alcoholic solution resulted in 6-*exo-dig* cyclization to produce the intermediate *N*-cinnamoylamino-3,4-dihydro-2-pyridones **236**. After that, subsequent 5-*exo-trig* cyclization by attack of the primary amino group on the lower reactive amide carbonyl group resulted in the

[1,2,4]triazolo[1,5-*a*]pyridones that were separated as piperidinium salts due to the high acidity of the ring proton, in moderate to good yield. Furthermore, production of the piperidinium salt in the triazolo[1,5-*a*]pyridinone is due to the stability of the anions, originating from charge delocalization in the two fused heterocyclic rings, triazolo nitrogens, and the pyridone oxygen in compounds **237**. Lastly, the neutral compounds **238** could be generated from the piperidinium salt **237** by treatment with hydrochloric acid (Scheme 79)[108].


NC
O
NH
NH2
1
Cl
O
234
O
CN
NH
NH
O
235
Ph
NC
CN
O
N
NH2
NH
Ph
O
236
EtOH/pip
Ref
Ph
CN
CN
67
5-exo-trig
Ph
NC
CN
O
N
N
N-
Ph
N
H2+
237
HCl 10%
Ph
NC
CN
O
N
N
HN
Ph
238

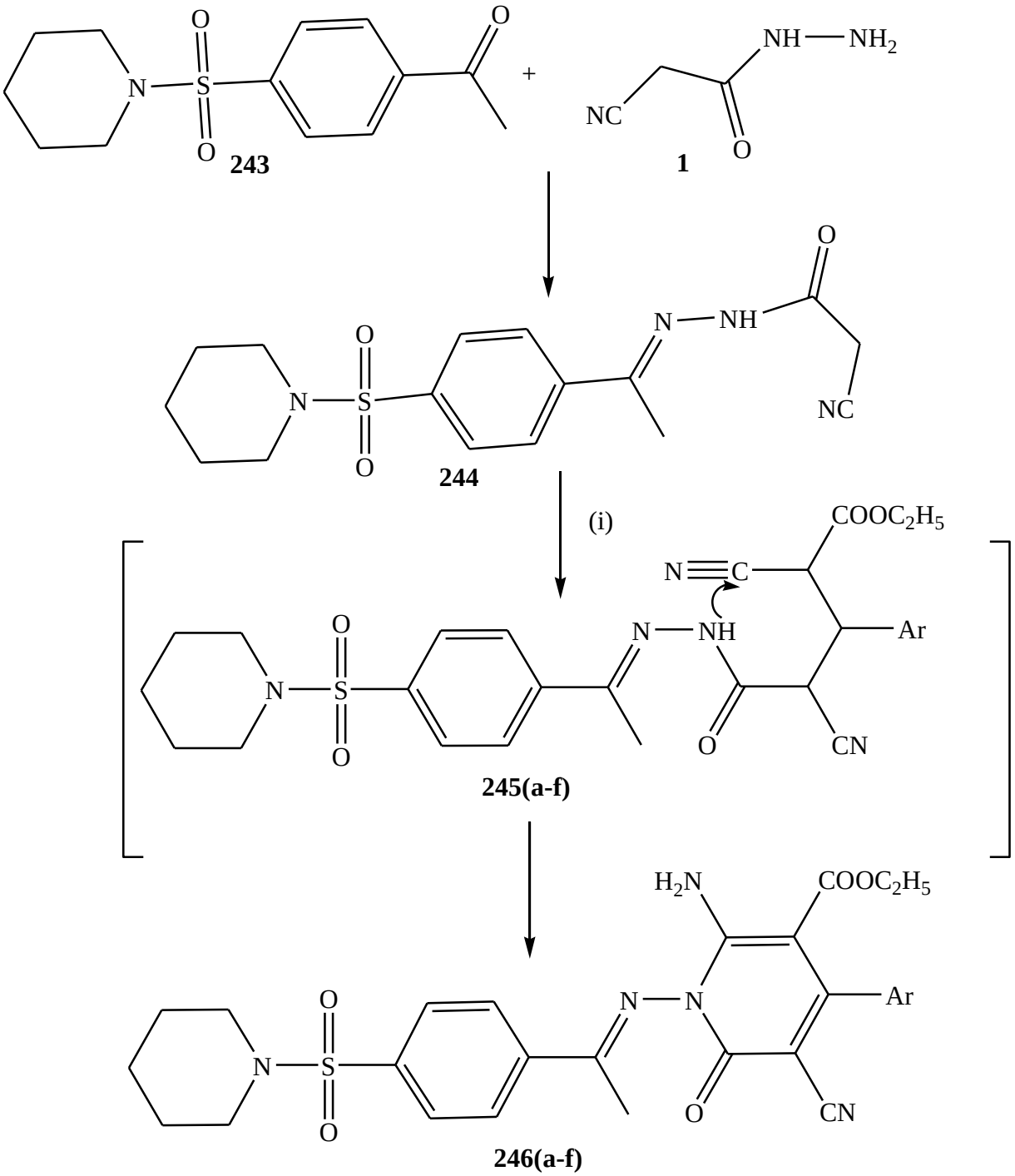
Scheme 79

It is noteworthy that cyanoacetohydrazide derivatives **239** react with diazonium salts in pyridine in an ice bath. After that, the product reacted with formaldehyde to yield triazine derivatives **242** (Scheme 80)[109].



Scheme 80

Moreover, 2-cyanoacetohydrazide **1** reacts with 1-[4-(piperidin-1-ylsulfonyl)phenyl] ethanone **243**[110], yielding hydrazide hydrazone derivative **244**. Also, the reaction of **244** with ethyl α-cyanocinnamate resulted in the pyridine derivatives **246(a-f)**, respectively. Note that the reaction proceeded through the intermediate formation of **245(a-f)**, as shown in Scheme 81[111].



246a, Ar= $C_6H_4CH_3$-4
246b, Ar= C_6H_4OH-4
246c, Ar= $C_6H_4OCH_3$-4
246d, Ar= $C_6H_3OCH_3$-3,OH-4
246e, Ar= $C_6H_4N(CH_3)_2$-4
246f, Ar= C_6H_4Cl-4

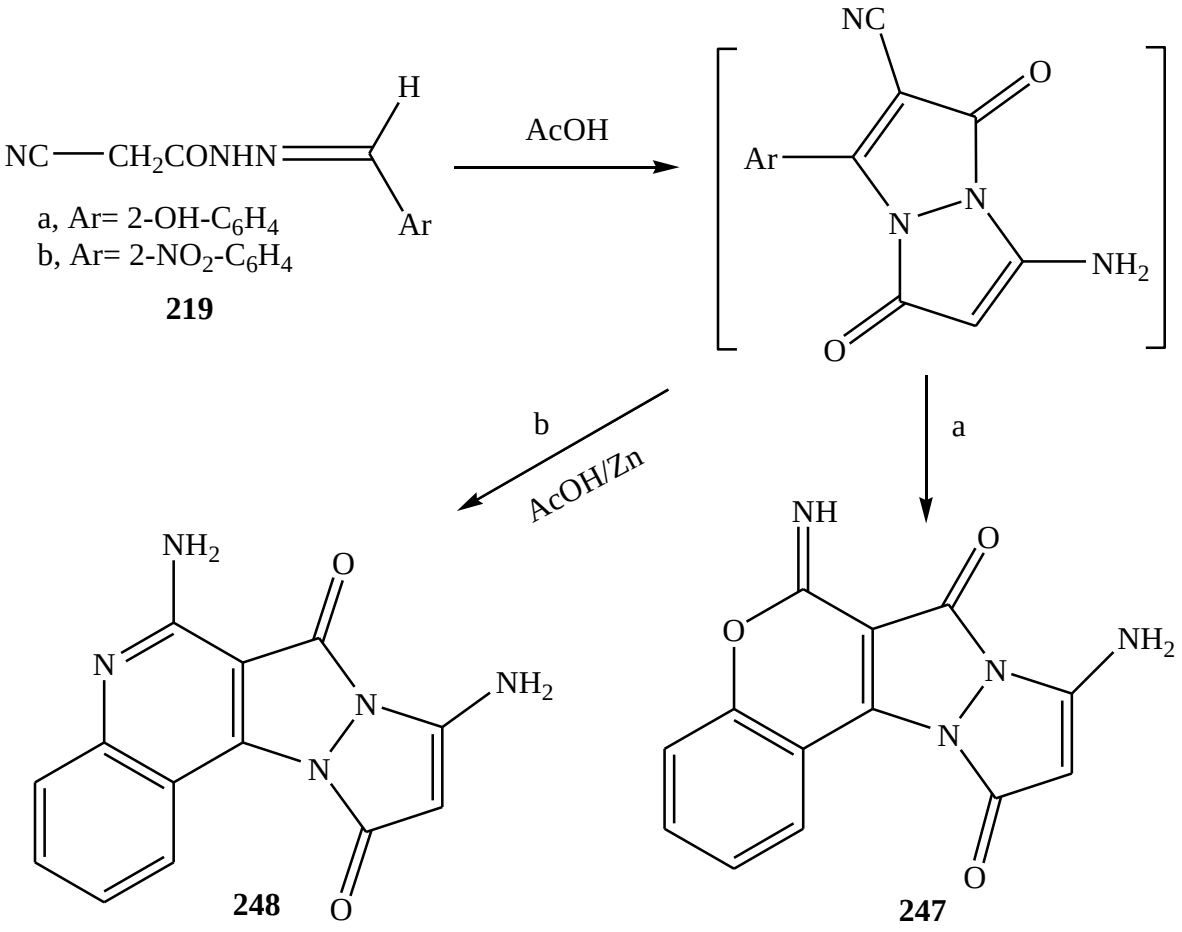
Reagent and conditions: i, ethyl α-cyanocinnamate derivatives/1,4-dioxane/TEA.

Scheme 81

k- Heterocycles obtained via the utility of functional groups No. 1,2,4,5 (The cyano, methylene, amido and hydrazino groups .)

Four reactive centers from cyanoacetohydrazide **1** may be involved in heterocyclic synthesis as observed in the following reaction. The condensed α-iminocoumarin **247** was obtained when the α-cyanoacetylsalicylaldehyde hydrazone **219a** was refluxed in glacial acetic acid (Scheme 82), the reaction is assumed to proceed by the same mechanistic pathway disscussed before[6] .

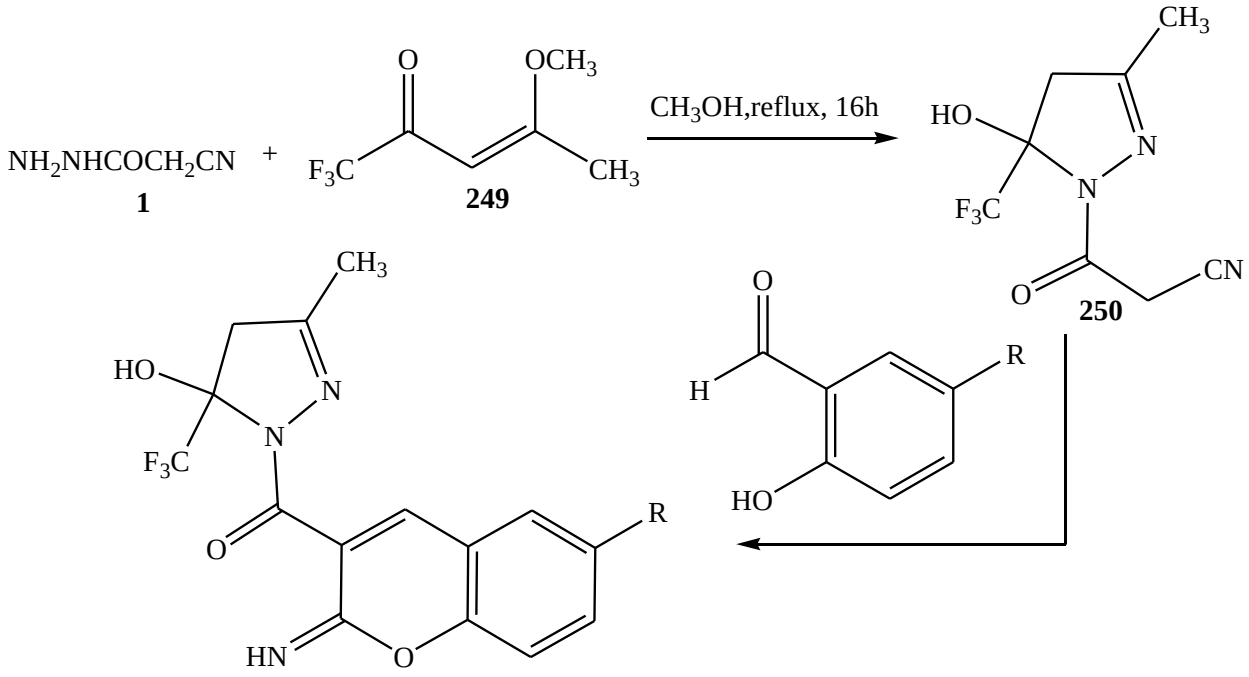
Similarly, α-cyanoacetyl-2-nitrobenzaldehyde **219b** when refluxed in glacial acetic acid containing zinc dust, the condensed quinoline **248** derivative was obtained[6] as shown in Scheme 82.



Scheme 82

In addition, 1-cyanoacetyl-4,5-dihydro-1H-pyrazole **250** was generated from the cyclocondensation of cyanoacetic hydrazide **1** and 4-methoxy-1,1,1-trifluoropent-3- en-2-one **249**[112,113] (Scheme 83).

After that, when pure 4,5-dihydropyrazole **250** reacted with substituted salicylic aldehydes, regiospeci-fically and in a one-step reaction, pyrazolinyl-iminochromenes **251(a-d)** were generated via a typical Knoevenagel condensation reaction, as a result of the existence of an active methylenic center in the precursor **250** (Scheme 83)[114].

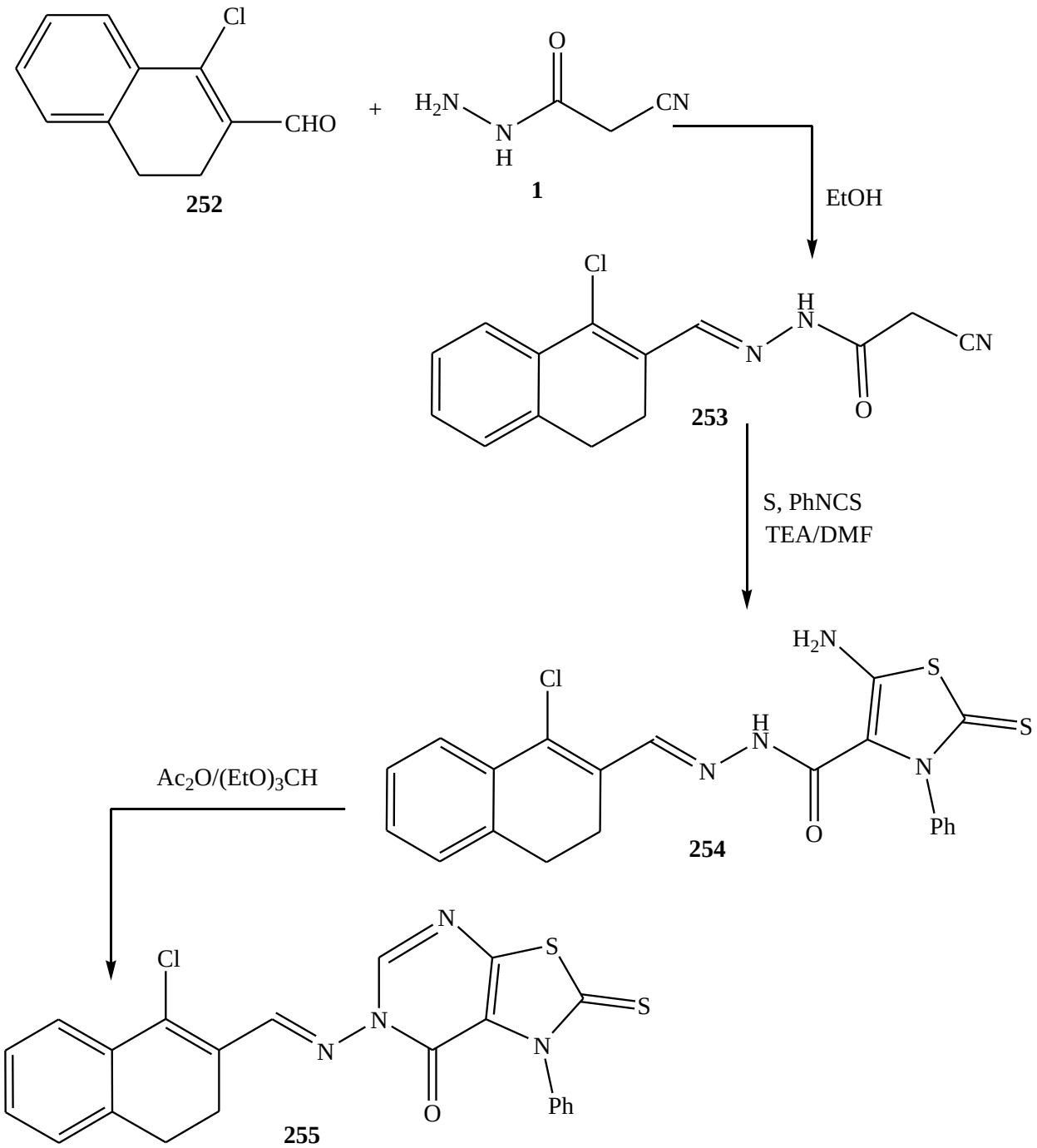


251	a	b	c	d
R	H	NO_2	Br	OCH_3

Scheme 83

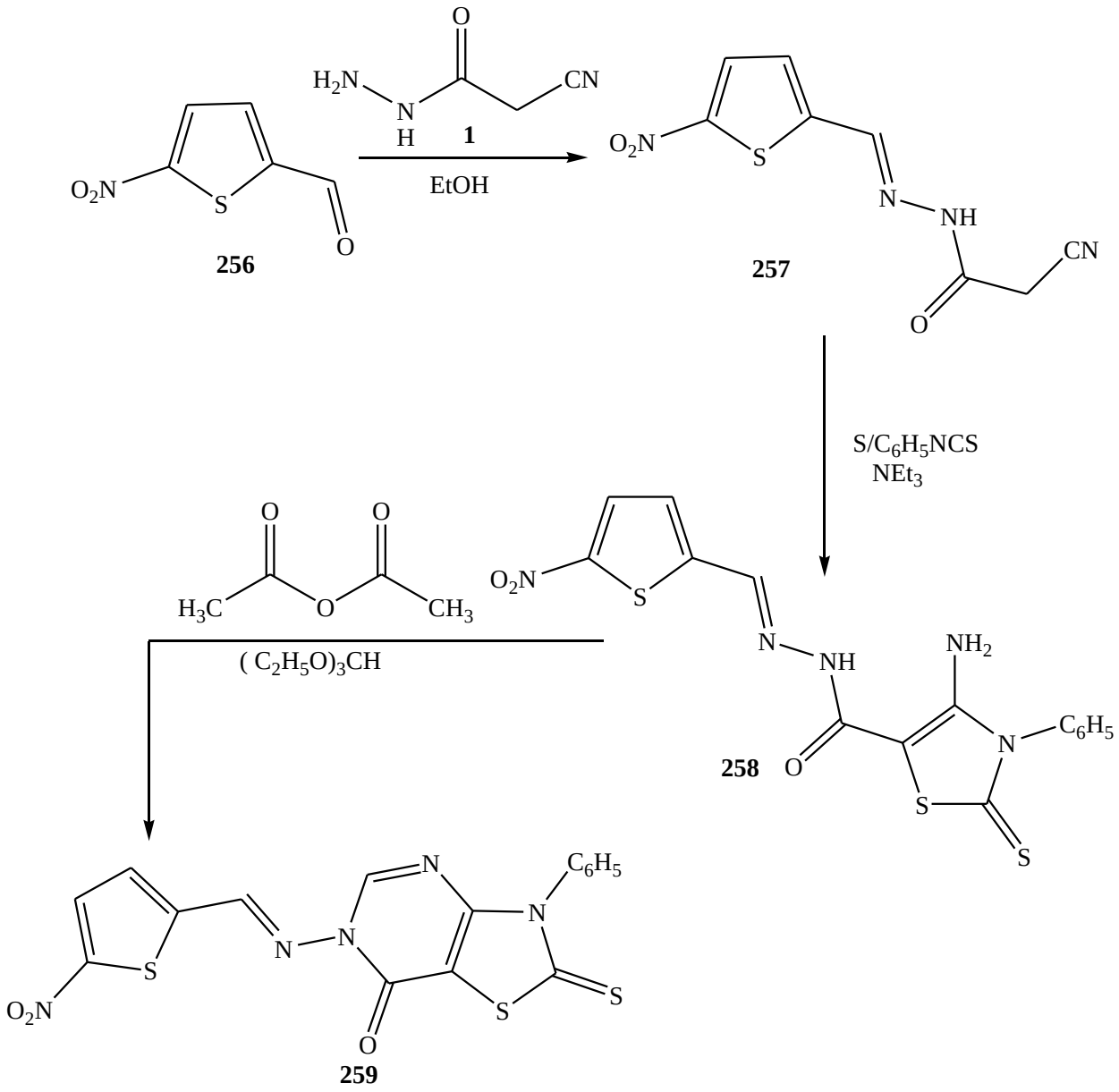
Importantly, the fundamental intermediate **253** was prepared[115] in a considerable yield by condensing **252** with cyanoacetic acid hydrazide **1**. Utilizing both the Gewald reaction[116] and the Schiff's base of cyanoacetic acid hydrazide **253**, as the nitrile containing active methylene moiety, 5-amino-N0-[1-chloro-3,4-dihydronaphthalen-2-yl)- methylene]-3-phenyl-2-thioxo-2,3-dihydro-1,3-thiazole-

4-carbohydrazide **254** was obtained via the reaction of **253** with sulfur and phenyl isothiocyanate in the presence of triethylamine as a primary catalyst. The thiazolo[5,4-d]pyrimidinone derivative **255** was obtained through heating **254** with a mixture of triethylorthoformate and acetic anhydride (1:1), (Scheme 84)[117].



Scheme 84

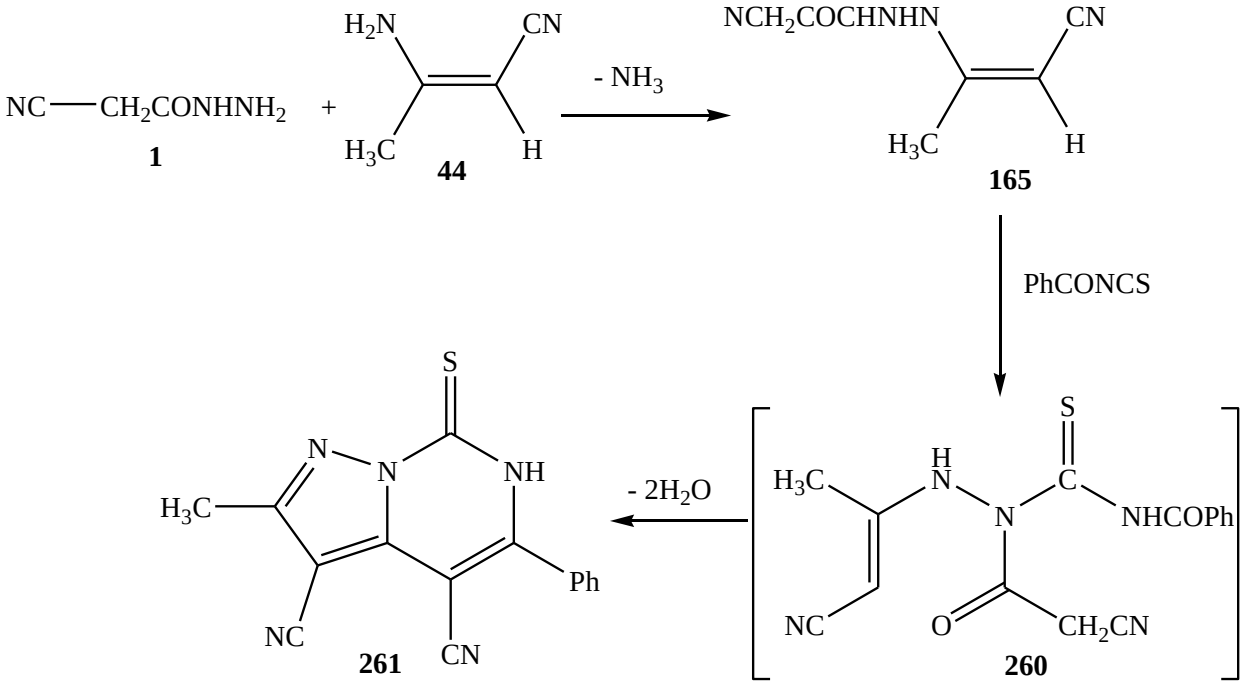
Furthermore, Badr proposed the synthesis of thiazolo[4,5-*d*]pyrimidinone **259**. Where, in this reaction, condensation of 5-nitro-2-thiophene carboxaldehyde **256** with cyanoacetic acid hydrazide **1** yielded *N*′-arylidene cyanoacetic acid hydrazide **257**, which, upon treatment with sulfur and phenyl isothiocyanate, resulted in the formation of thiazolocarbohydrazide **258**. Eventually, thiazolo[4,5-*d*]pyrimidinone **259** was generated via heating compound **258** with a mixture of triethyl orthoformate and acetic anhydride (Scheme 85)[118].



Scheme 85

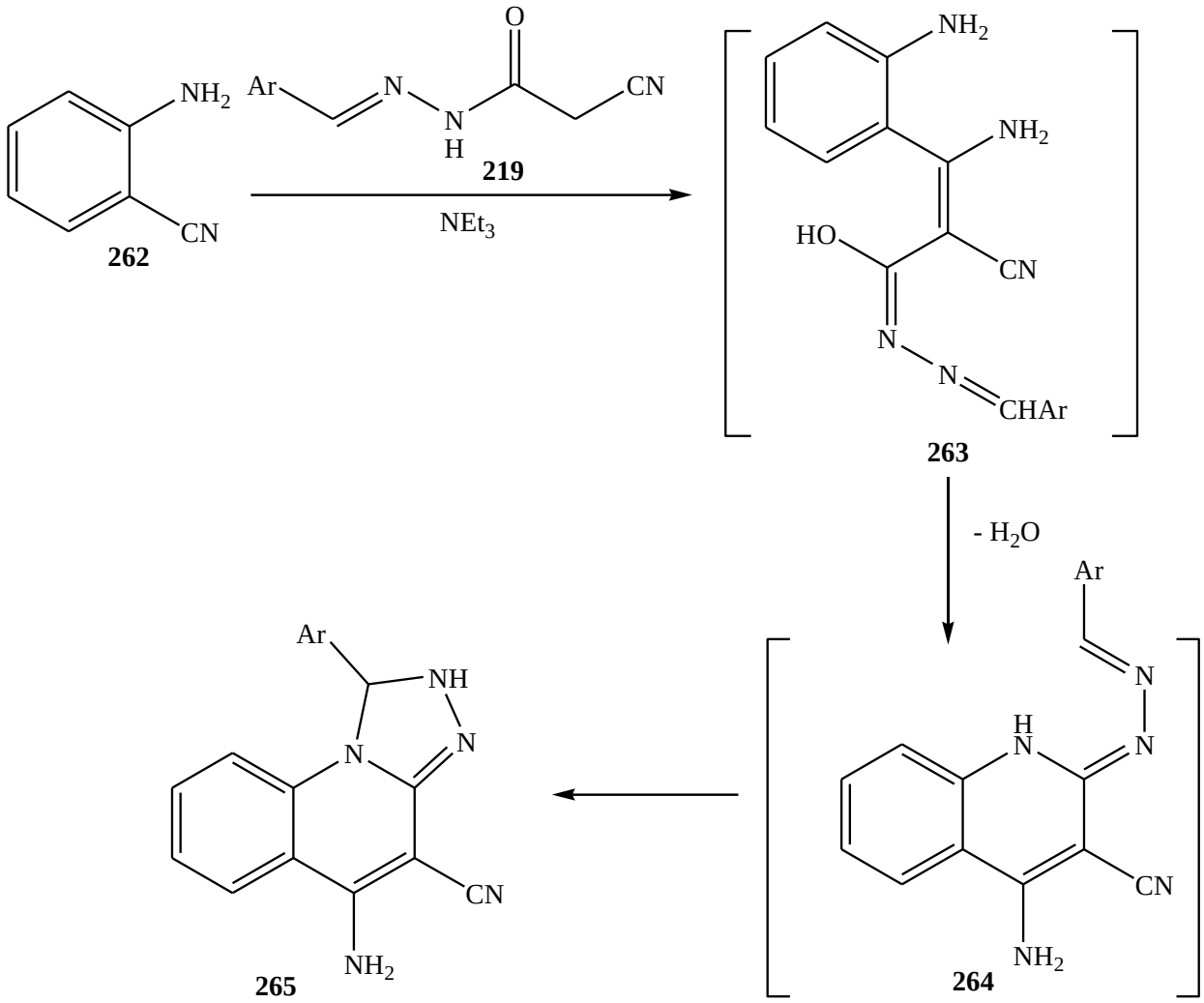
l- Heterocycles obtained via the utility of functional groups No. 2,3,45 (The methylene, carbonyl, amido and hydrazino groups .)

Also, it has been reported that the pyrazolo[1,5-c]pyrimidin-7-thione derivative **261** was obtained when **165** was allowed to react with benzoyl isothiocyanate. This reaction is believed to proceed via an initial attack of the nitrogen nucleophile in **165** on the electrophilic center (C = S) in the benzoyl isothiocyanate to yield the intermediate **260** which then cyclized under the reaction conditions to give the final isolable product1 **261**[18] as described in Scheme 86.



Scheme 86

In addition, compounds **265** are generated via initial Thorpe–Ziegler addition of the methylene group of **219** to the CN group of **262** in order to yield the acyclic intermediates **263**, followed by the removal of a water molecule to produce intermediates **264**, which, in turn, undergo a further cyclization via addition of NH to the activated C=N to yield the final products **265** (Scheme 87)[119].



Scheme 87

Conclusion

From the findings of the present study, it can be concluded that: A variety of heterocyclic compounds were synthesized from cyanoacetohydrazide and its derivatives, as it contains five different functional groups (cyano, active methylene, carbonyl, amido and hydrazino groups) . Some of them could act as a nucleophile or as an electrophile. The reviewed reactions were classified according to the active centers of cyanoacetohydrazide involved. They are divided into the 12 classes, the behavior of cyanoacetohydrazide in the reaction mechanism depends on the reaction conditions and the other reactants. Moreover, the versatility of this reagent could be extended to form condensed heterocycles via the involvement of more than two centers in the reaction course.

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