

Synthesis, and synthetic applications of cyanoacetamides

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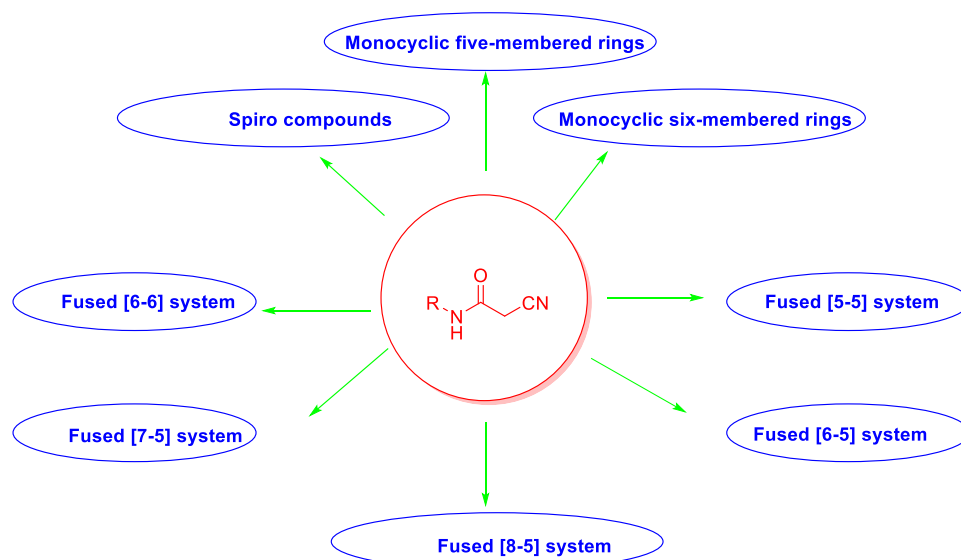
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Abstract

Approaches for the preparation of cyanoacetamide derivatives as well as the chemical reactivity profiles and structures of these substances are reviewed. The utility of these compounds as precursors is emphasized in the synthesis of five- and six-membered heterocycles and their fused heterocycles. The reported heterocyclic compounds in this review article are classified according to the kind of the heterocyclic systems.



Keywords: Cyanoacetamides; synthesis; chemical reactivity; five membered heterocycles and their fused heterocycles; six membered heterocycles and their fused heterocycles

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1. Introduction

Cyanoacetamides are versatile precursors in the synthesis of a set of pharmacologically active organic compounds and agrochemicals.¹ The cyano and carbonyl groups of these compounds react efficiently with common bidentate reagents to afford a variety of heterocycles. Additionally, the methylene group of these compounds can participate in a group of condensation and substitution reactions. Thus, these compounds are versatile intermediates for the synthesis of wide variety of various nitrogen-containing heterocycles.²⁻⁸

The present review of literature is expected to provide a comprehensive survey of the synthetic utility of cyanoacetamides as precursors for a variety of monocyclic five-membered, six-membered and fused heterocycles and to supplement the information available in two earlier reviews that have appeared in 1999 by Litvinov⁹ and in 2008 by Fadda *et al*.¹ A brief survey of the methods for the synthesis of cyanoacetamides that have recently appeared is also included. The literature is presently covered upto 2019.

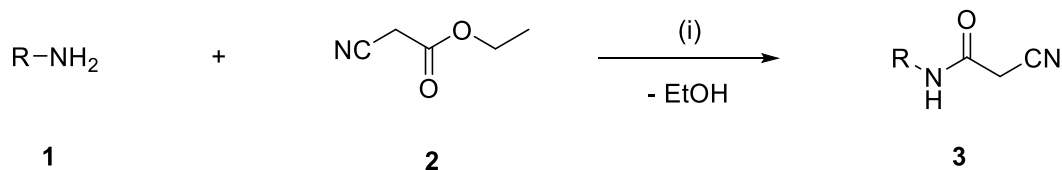
2. Synthesis of Cyanoacetamide Derivatives

The different synthetic approaches of cyanoacetamides include reaction of different substituted aryl or heteroaryl amines with alkyl cyanoacetates, cyanoacetic acid and/or 3-oxopropanenitriles in different reaction conditions. In addition, cyanoacetamides can also be obtained *via* treatment of amines with chloroacetyl

chloride and subsequent treatment with potassium cyanide and *via* condensation of butylamine and potassium cyanate in different conditions; followed by reaction with cyanoacetic acid and acetic anhydride.

2.1 Reaction of amine with ethyl cyanoacetate in different conditions

Cyanoacetamides **3a-aa** were produced *via* the condensation of amines **1a-aa** with ethyl cyanoacetate **2** in different reaction conditions (Scheme 1, Table 1).^{10,11}



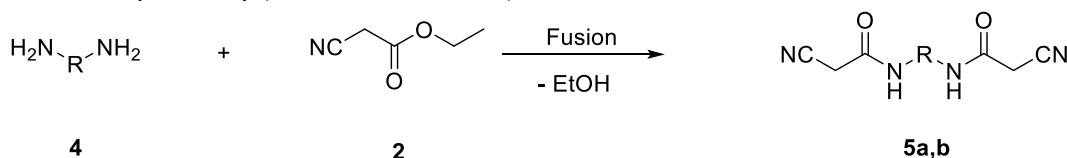
Scheme 1

Table 1: Synthesis and % yields of **3a-aa**

Product	R	Reaction condition (i)	Yield (%)	Ref.
3a	X = H Y = H	Fusion or Solvent free	91-93	12,13
3b	X = Et Y = H	Fusion	88	14,15
3c	X = Cl Y = H	Solvent free	69	13
3d	X = H Y = CO ₂ Me	Fusion, xylene	80	11,16
3e	X =	Fusion	80	17
3f	X = H	m-Xylene, reflux	92	18
3g	X = NH	EtOH	80	19
3h	X = O	EtOH or DMF, reflux	86	19,20
3i	X = S		82	
3j		EtOH, reflux	78	21
3k	Ar = Ph	EtOH, reflux	75	22
3l	Ar = 4-MeC ₆ H ₄		80	
3m	Ar = 2-MeC ₆ H ₄		84	
3n	Ar = 4-MeOC ₆ H ₄		74	
3o	Ar = 4-ClC ₆ H ₄		78	
3p	Ar = 2-ClC ₆ H ₄		80	
3q		EtOH, reflux	70	23
3r		DMF, reflux	75	24
3s		DMF, reflux, 5 h	73	25

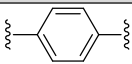
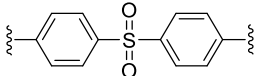
3t			Ac ₂ O, 60-70 °C, 1 h	60	26
3u		X = 4-Nitrophenoxy Y = Me Z = CO ₂ Et	Dioxane, reflux, 3 h	69	27
3v		X = Ph-NH=N Y = Ph Z = CO ₂ Et	EtONa, EtOH, reflux, 6 h	31	28
3w	<i>n</i> -Butyl <i>n</i> -Hexyl		heat US (40°C) or M. W or M.W at 300 W for 7 min	67-89 88-91	29,2
3x		X = Me X = Thiophene X = 2-Indol X = Ph X = 4-MeOC ₆ H ₄ X = 2-ClC ₆ H ₄ X = 2-MeOC ₆ H ₄ X = 4-MeOC ₆ H ₄ CH ₂ X = 1-methylnaphthyl X = Benzyl X = 4-FC ₆ H ₄ CH ₂ X = 3-FC ₆ H ₄ CH ₂ X = 4-ClC ₆ H ₄ CH ₂ X = 4-MeC₆H₄CH₂	MeONa, MeOH, reflux, 5 h	not reported	3
3y	Cyclohexyl		heat US (40°C) or M.W EtONa, EtOH or Al ₂ O ₃ , KF r.t (1 h)	80-90 90	29,30
3z	Benzyl		Stirring at r.t for 1 h heat US (40°C) or M.W EtONa, EtOH or Al ₂ O ₃ , KF, r.t, 1 h DMF, Reflux, 8 h	72 89 37	29-32
3aa	Tetrahydrofurfuryl		EtONa, EtOH or Al ₂ O ₃ , KF, r.t	90	30

Similarly, *N,N*-(1,4-phenylene)bis(2-cyanoacetamide) **5a**³³ and *N,N'*-(4,4'-sulfonylbis(4,1-phenylene))bis(2-cyanoacetamid) **5b**^{10,34} were also obtained *via* condensation of phenylene-1,4-diamine **4a** and Dapson **4b** with ethyl cyanoacetate **2** respectively (Scheme 2, Table 2).



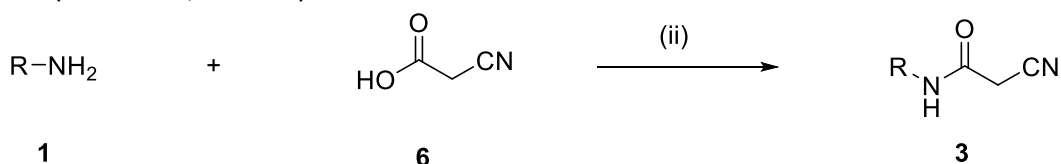
Scheme 2

Table 2. Synthesis and % yields of 5a,b

Product	R	Yield (%)	Ref.
5a		60	33
5b		92	10,34

2.2 Reaction of amine with cyanoacetic acid in different conditions

The reaction of arylamines **1ab-bc** with cyanoacetic acid **6** in variety of conditions gives 2-cyanoacetamide derivatives **3ab-bc** (Scheme 3, Table 3).^{35,36}



Scheme 3

Table 3. Synthesis and % yields of 3ab-bc

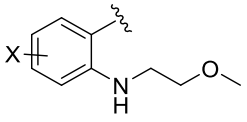
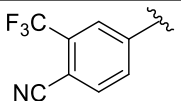
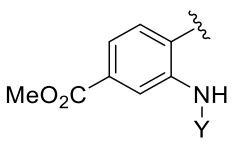
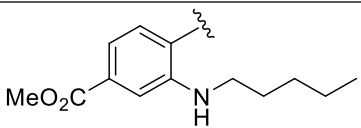
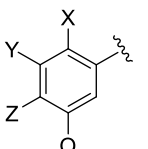
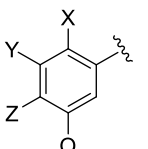
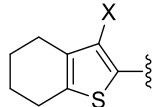
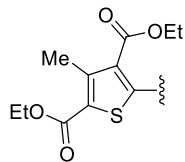
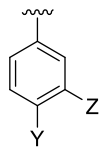
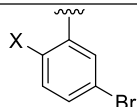
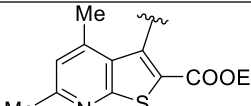
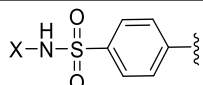
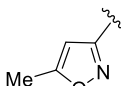
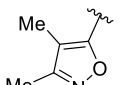
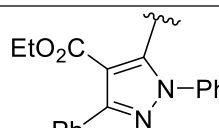
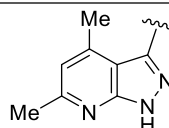
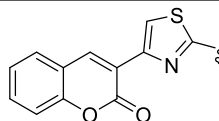
Product	R	Reaction condition (ii)	Yield (%)	Ref.
3ab1 3ab2	 X = H X = 5-Cl	EDCI, HOBt, CH ₂ Cl ₂ , 0°C, 30 min, r.t, 12 h	65-70	36
3ac		PCl ₅ , CH ₂ Cl ₂ , 40°C, 2 h	80	37
3ad 3ae 3af 3ag 3ah 3ai 3aj 3ak	 Y = Benzyl Y = Cyclohexyl Y = Cyclopentyl Y = Furan-2-ylmethyl Y = n-Propyl Y = CH ₂ CH ₂ OH Y = CH ₂ CH ₂ OAc Y = CH(CH ₃) ₂	EDCI, HOBt, CH ₂ Cl ₂ , 0°C, 30 min, r.t, 12 h	65-70	36
3al		DCC, DMAP, MeCN, r.t, 16 h	not reported	35
3am	 X = H Y = OC ₁₂ H ₂₅ Z = H Q = OC ₁₂ H ₂₅	DCC, THF, 60°C, 1 h	75	38
3an	 X = H Y = H	Ac ₂ O, 85°C, 25 min	78	39

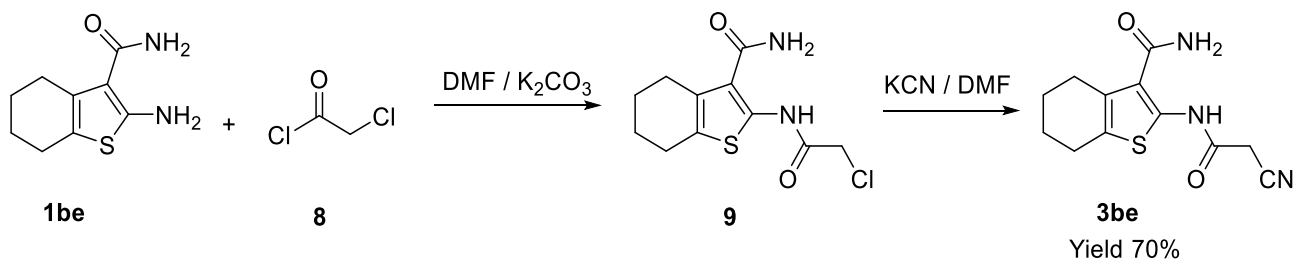
Table 4: Synthesis and % yields of **3bd-bv**

Product	R	Reaction condition (iii)	Yield (%)	Ref.
3bd 3be	 X = CO ₂ Et X = CONH ₂	Benzene, reflux, 5 h	90 90	47-49
3bf		Toluene, reflux, 3 h	80	50,4
3bg 3a 3bh 3bi 3bj 3bk 3bl 3bm 3bn 3bo	 Y = COMe, Z = H Y = H, Z = H Y = H, Z = NO ₂ Y = Br, Z = H Y = NO ₂ , Z = H Y = Cl, Z = Cl Y = F, Z = H Y = H, Z = CF ₃ Y = MeO, Z = MeO Y = H, Z = NH ₂	Toluene, r.t, overnight or reflux, 10-15 min Toluene or DMF, 80°C, 6-12 h Toluene, reflux, 10-15 min	65-93	51-55
3bp1 3bp2	 X = Benzyl piperazine X = N-Boc-piperazine	Toluene, r.t, overnight or reflux, 10-15 min	75 81	56
3bq		Toluene, reflux, 5 h	71	57
3f 3br1 3br2	 X = H X =  X = 	Dioxane, reflux, 5 h or Toluene, reflux, 2 h Dioxane, reflux, 3 h Toluene, reflux, 2h dioxane, reflux	70 80 90 82	58,59 60 5 61
3bs		Toluene, reflux, 3 h	88	62
3bt		Toluene, reflux, 30 min	65	63
3bu		Dioxane, reflux 3 h	85	64

3bv1		Benzene, reflux, 8 h	80	65
3bv2		Heat at 50-55 °C or 70-80 °C, 15-20 min	57	66

2.4. Treatment of amine with chloroacetyl chloride and subsequent treatment with potassium cyanide

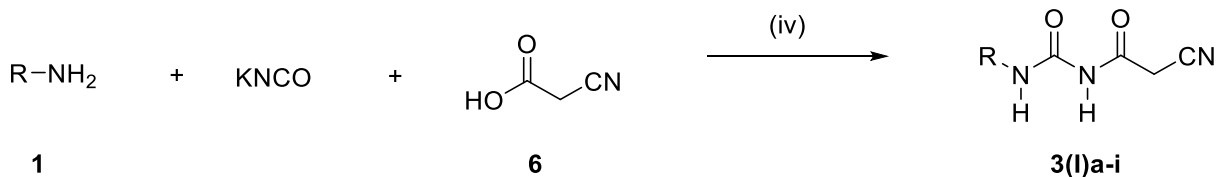
The compound 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **3be** was obtained by treatment of **1be** with chloroacetyl chloride **8** and subsequent treatment with potassium cyanide in dimethylformamide (DMF) (Scheme 5).⁶⁷



Scheme 5

2.5. Condensation of amines and potassium cyanate in different conditions; followed by reaction with cyanoacetic acid and acetic anhydride

The condensation of alkylamine **1** and potassium cyanate in presence of acetic acid resulted in the formation of alkylurea, which on reaction with cyanoacetic acid **6** and acetic anhydride afforded *N*-alkylcyanoacetylurea derivatives **3(I)a-i** (Scheme 6, Table 5).⁶⁸



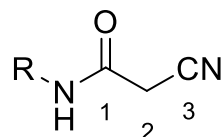
Scheme 6

Table 5. Synthesis and % yields of **3**

Product	R	Reaction condition (iv)	Yield (%)	Ref.
3(I)a	Ph	AcOH, Ac ₂ O, 60°C	83	68
3(I)b	<i>n</i> -Butyl		91	
3(I)c	Cyclohexyl		78	
3(I)d	Benzyl		88	
3(I)e	4-NO ₂ C ₆ H ₄		76	
3(I)f	<i>n</i> -Propyl,		90	
3(I)g	<i>i</i> -Propyl		91	
3(I)h	4-MeOC ₆ H ₄ CH ₂		90	
3(I)i	4-MeC ₆ H ₄		85	
3(I)d	Benzyl		[TMG][Ac], Ac ₂ O, 60°C, 5 h	

3. Reactivity of cyanoacetamide derivatives

Cyanoacetamides have both electrophilic and nucleophilic characteristics. The nucleophilic positions are NH and C-2 with the nucleophilicity order: C-2 > NH. These chemical characteristics have been used to design a variety of heterocyclic compounds with various ring sizes such as triazine, pyrimidine, pyrazole, thiophene, pyrrole, thiazole, imidazole, pyridine, thiadiazole, pyridazine, pyrane and azirine. In the same time, cyanoacetamide have electrophilic positions, especially at C-3, C-1 with the electrophilicity order: C-3 > C-1.



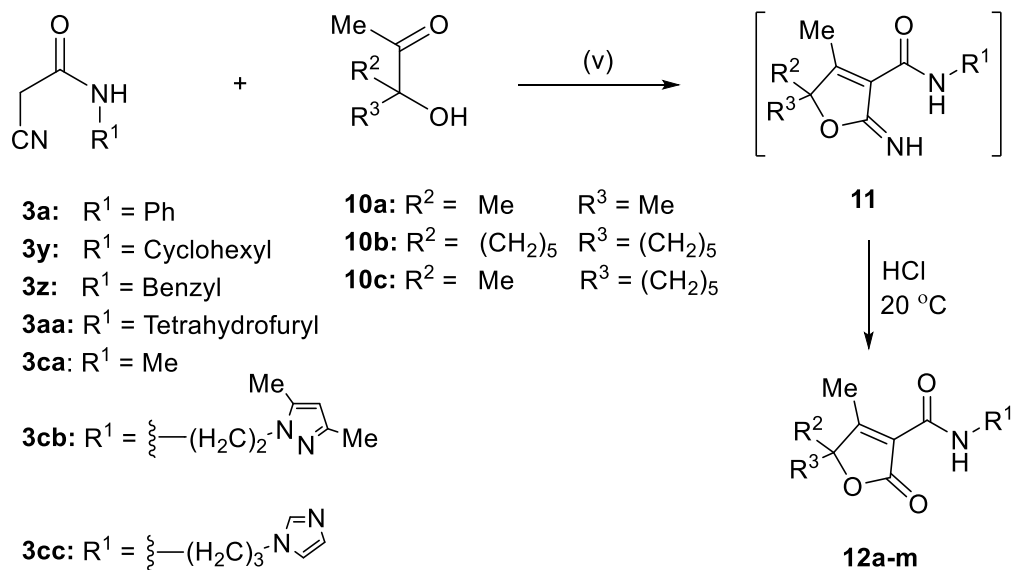
Reactions of cyanoacetamides are classified depending on the number of the rings, the ring size, the number of heteroatoms, and finally, the type of heteroatoms of the produced compound.

3.1. Monocyclic compounds:

3.1.1. Monocyclic five-membered rings with one hetero atom:

3.1.1.1. Furan derivatives:

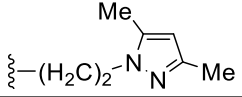
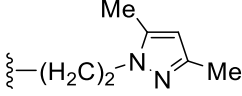
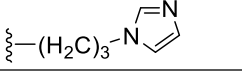
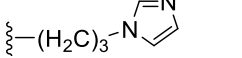
The condensation of α -hydroxyketones **10a-c** with cyanoacetamides **3** in the presence of catalytic amount of sodium methoxide in methanol⁷⁰ or sodium ethoxide in ethanol³⁰ afforded 2-imino-2,5-dihydrofuran-3-carboxamides **11** that hydrolyzed *in situ* to 2,5-dihydro-2-oxofuran-3-carboxamides **12a-m** in good yields (Scheme 7, Table 6).⁷⁰



Scheme 7

Table 6. Synthesis and % yields of **12a-m**

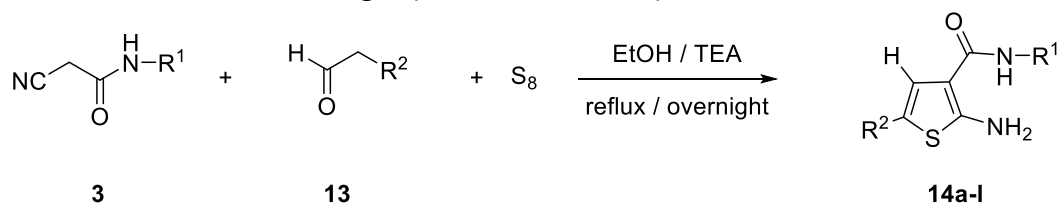
Product	R ¹	R ²	R ³	Reaction condition (v)	Yield (%)	Ref.
12a	Me	Me	Me	MeOH / MeONa / 35-40 °C	79	70
12b	Benzyl	Me	Me	MeOH / MeONa / 35-40 °C	76	70
12c	Ph	Me	Me	MeOH / MeONa / 35-40 °C	75	70
12d	Me	(CH ₂) ₅	(CH ₂) ₅	MeOH / MeONa / 35-40 °C	79	70

12e	Cyclohexyl	Me	Me	EtOH / EtONa / r.t or MeOH / MeONa / 40 °C	99 92	30 71
12f	Benzyl	Me	Me	EtOH / EtONa / r.t	94	30
12g	Tetrahydrofurfuryl	Me	Me	EtOH / EtONa / r.t	75	30
12h	Cyclohexyl	Me	(CH ₂) ₅	MeOH / MeONa / 40 °C	98	71
12i	Cyclohexyl	(CH ₂) ₅	(CH ₂) ₅	MeOH / MeONa / 40 °C	95	71
12j		Me	Me	MeOH / MeONa / 40 °C	72	72
12k		(CH ₂) ₅	(CH ₂) ₅	MeOH / MeONa / 40 °C	70	72
12l		Me	Me	MeOH / MeONa / 40 °C	72	72
12m		(CH ₂) ₅	(CH ₂) ₅	MeOH / MeONa / 40 °C	70	72

3.1.1.2. Thiophene derivatives

3.1.1.2.1. Synthesis *via* Gewald reactions

The cyanoacetamides **3** and elemental sulfur were used as essential reactants in Gewald reaction with different aldehydes **13**. The desired substituted 2-aminothiophenes **14a-l** were synthesized in ethanolic triethylamine solution under reflux overnight (Scheme 8, Table 7).⁷³

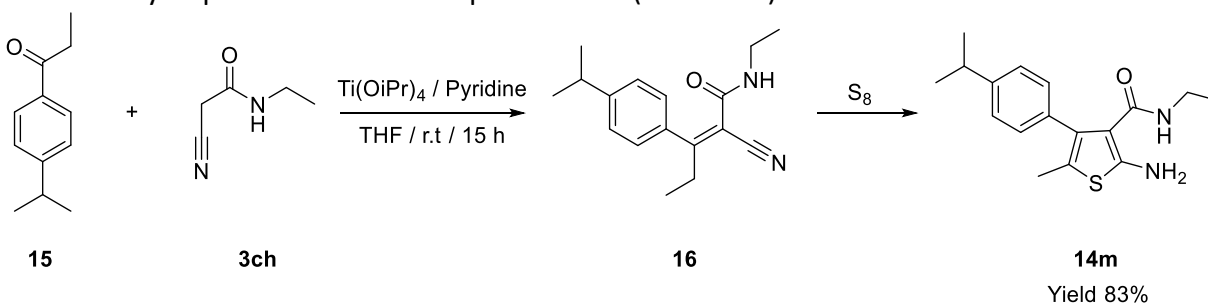


Scheme 8

Table 7. Synthesis and % yields of **14a-l**

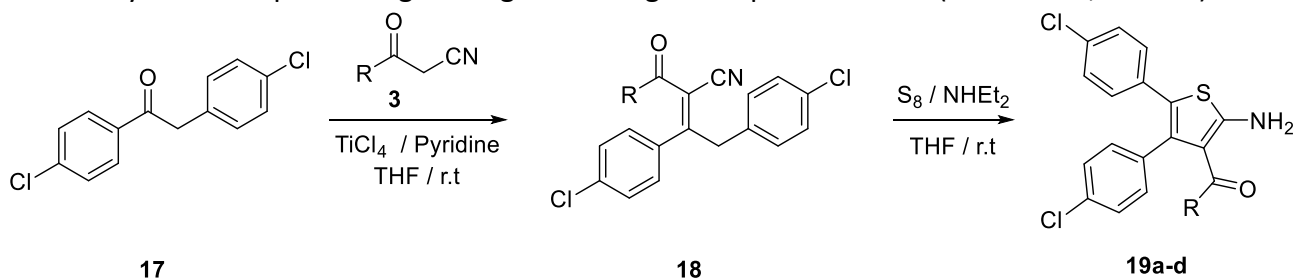
3w	<i>n</i> -Butyl	13f	Ph	14a	73
3cd	<i>n</i> -Pentyl	13f	Ph	14b	40
3ce	<i>n</i> -Octyl	13f	Ph	14c	20
3cf	<i>n</i> -Dodecyl	13f	Ph	14d	30
3cg	Ph(CH ₂) ₄	13f	Ph	14e	29
3w	<i>n</i> -Butyl	13a	Me	14f	20
3w	<i>n</i> -Butyl	13b	Et	14g	30
3w	<i>n</i> -Butyl	13c	<i>n</i> -Propyl	14h	29
3w	<i>n</i> -Butyl	13e	<i>n</i> -Pentyl	14i	30
3w	<i>n</i> -Butyl	13g	4-ClC ₆ H ₄	14j	23
3w	<i>n</i> -Butyl	13h	4-BrC ₆ H ₄	14k	74
3w	<i>n</i> -Butyl	13d	<i>n</i> -Butyl	14l	56

Condensation of **15** with **3ch** in the presence of $\text{Ti}(\text{OiPr})_4$ and pyridine in THF at room temperature for 15 hours has afforded the desired product **16** with 36% conversion. The reaction of **16** and elemental sulfur was performed smoothly to provide 2-aminothiophene **14 m** (Scheme 9).⁷⁴



Scheme 9

The condensation of compound **17** with 2-cyanoacetamide derivatives **3** in the presence of TiCl_4 afforded the olefin intermediates **18**. Treatment of olefin intermediates **18** with elemental sulfur and diethyl amine furnished the cyclized thiophene ring leading to the target compounds **19a-d** (Scheme 10, Table 8).⁷⁵

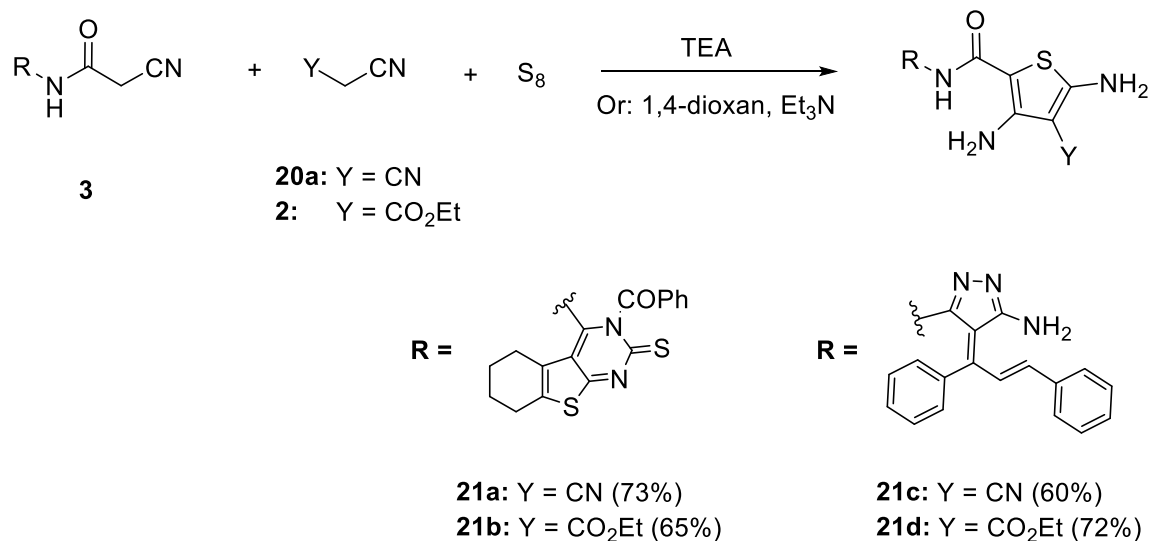


Scheme 10

Table 8. Synthesis and % yields of **19a-d**

Entry	Product	R	Yield (%)
3ci	19a		54
3cj	19b		80
3y	19c		70
3a	19d		54

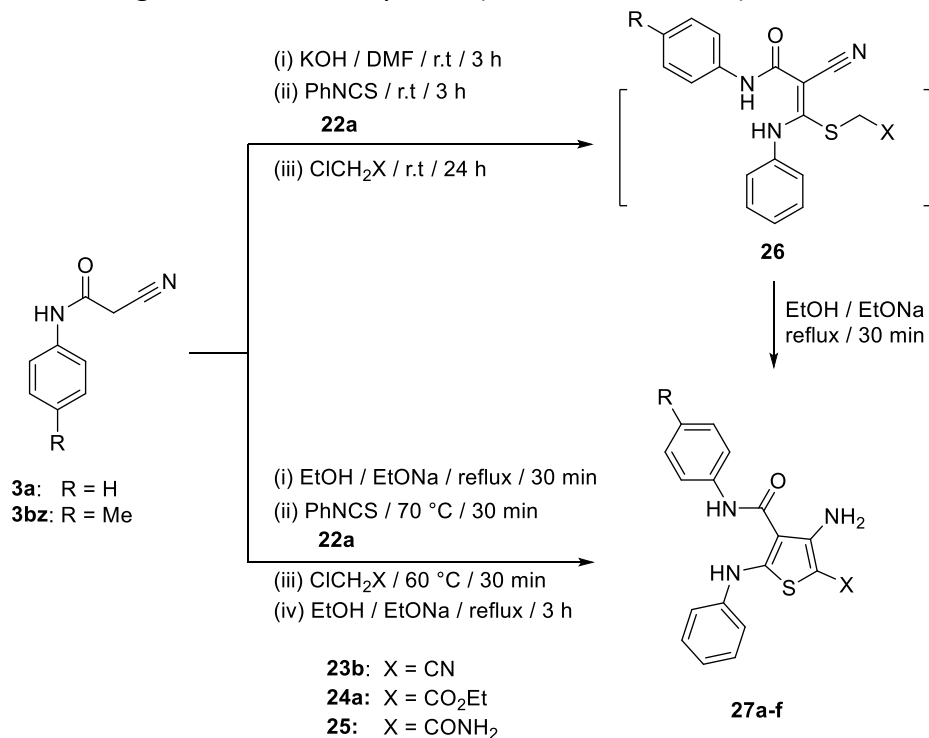
The reaction of compound **3** with sulfur and malononitrile **20a** or ethyl cyanoacetate **2** gave different thiophene derivatives **21a-f** (Scheme 11).^{76,77}



Scheme 11

3.1.1.2.2. Synthesis *via* Michael addition reactions

The thiophene derivatives **27a-f** were produced from the cyanoacetamides **3** through the addition of their anions to phenyl isothiocyanate **22a**, followed by treatment with halogenated compounds (chloroacetonitrile **23b**, ethyl chloroacetate **24a** or chloroacetamide **25**) and finally, base-induced cyclization to form aminothiophenes **27a-f** through the intermediacy of **26** (Scheme 12, Table 9).⁷⁸



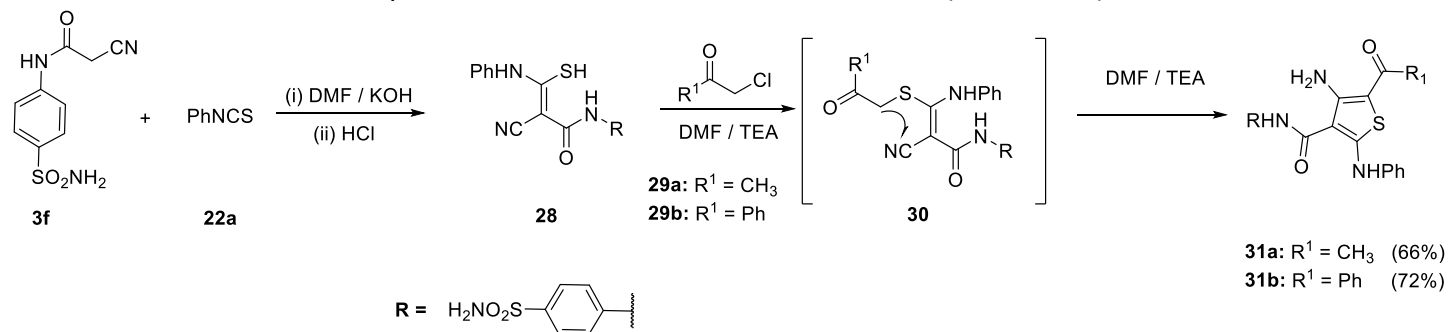
Scheme 12

Table 9. Synthesis and % yields of **27a-f**

Product	R	X	Yield (%)
27a	H	CN	84

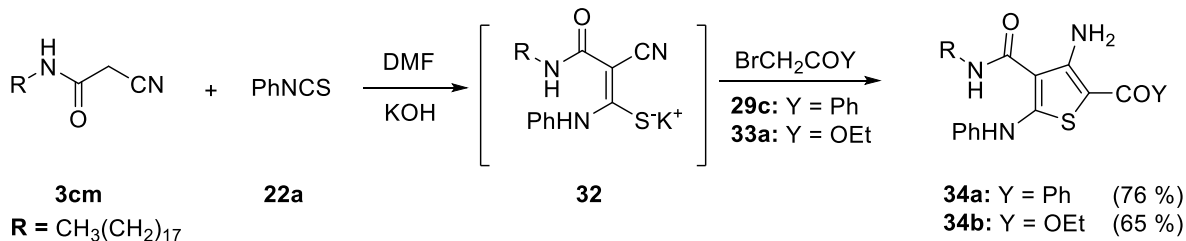
27b	H	CO ₂ Et	63
27c	H	CONH ₂	71
27d	Me	CN	92
27e	Me	CO ₂ Et	61
27f	Me	CONH ₂	75

The reaction of compound **3f** with phenyl isothiocyanate **22a** in DMF, in presence of KOH, at room temperature, followed by acidification, afforded the thiocarbamoyl **28**. The reaction of the intermediate **28** with chloroacetone **29a** or 2-chloro-1-phenylethanone **29b** under reflux in DMF/TEA furnished the thiophene derivatives **31a,b** as the final products via intermediate formation of **30** (Scheme 13).⁵⁸



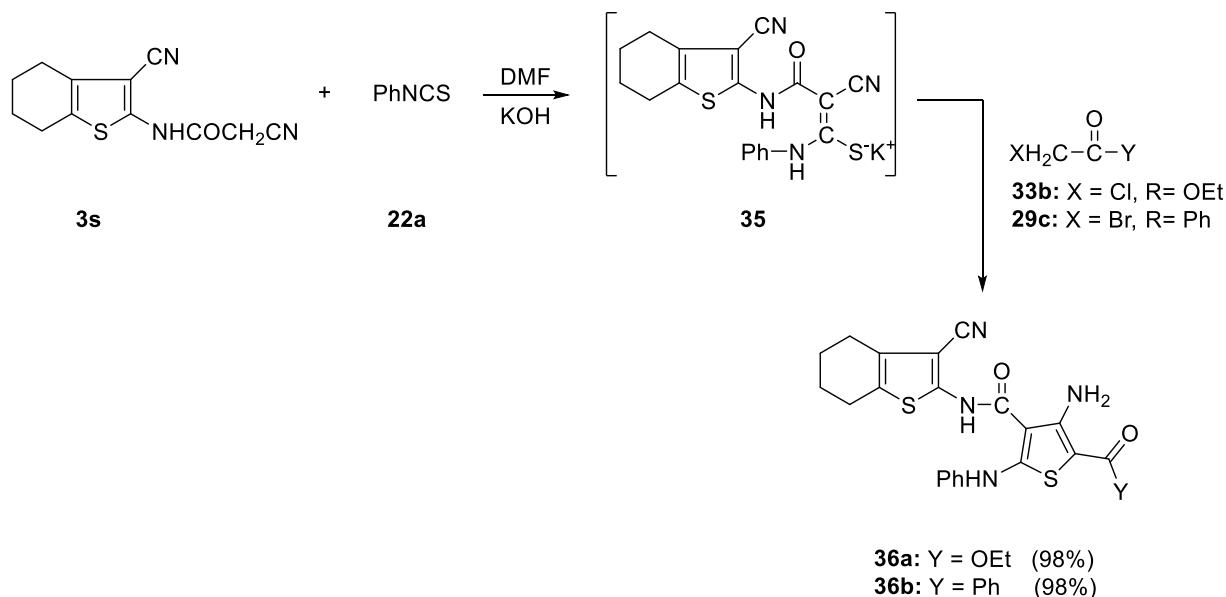
Scheme 13

The reaction of cyanoacetamide derivative **3cm** with phenyl isothiocyanate **22a** in DMF in the presence of potassium hydroxide has afforded the nonisolable enaminonitrile **32** which undergoes cyclization when treated with α -halocarbonyl compounds **29c** and **33a** to afford the thiophene derivatives **34** (Scheme 14).⁷⁹



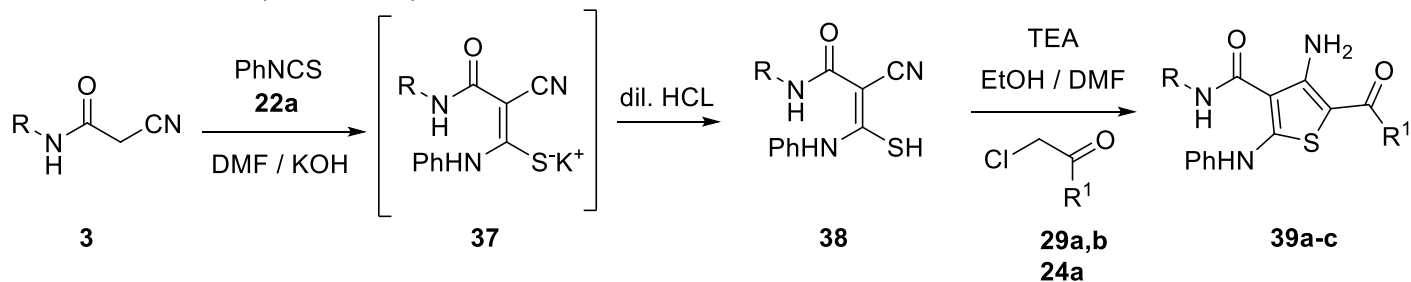
Scheme 14

Subjecting the active methylene precursor **3s** to the aforementioned reaction using α -halocarbonyl reagents **33b** and **29c** afforded the functionalized thiophene derivatives **36** through the intermediacy of the potassium sulfide salt **35** (Scheme 15).²⁵



Scheme 15

Treatment of cyanoacetamide **3** with phenyl isothiocyanate **22a**, in dry DMF in the presence of potassium hydroxide, afforded the potassium thiolate **37**. Acidification of the potassium salt **37** liberated the β -sulfonylacetamide **38**. Heating of compound **38** with **29a,b** or **24a** in DMF/EtOH at reflux in the presence of triethylamine, resulted in the formation of 5-acetyl(or-benzoyl)-4-amino-2-phenylaminothiophene-3-carboxamides **39a-c** (Scheme 16).^{80,81}

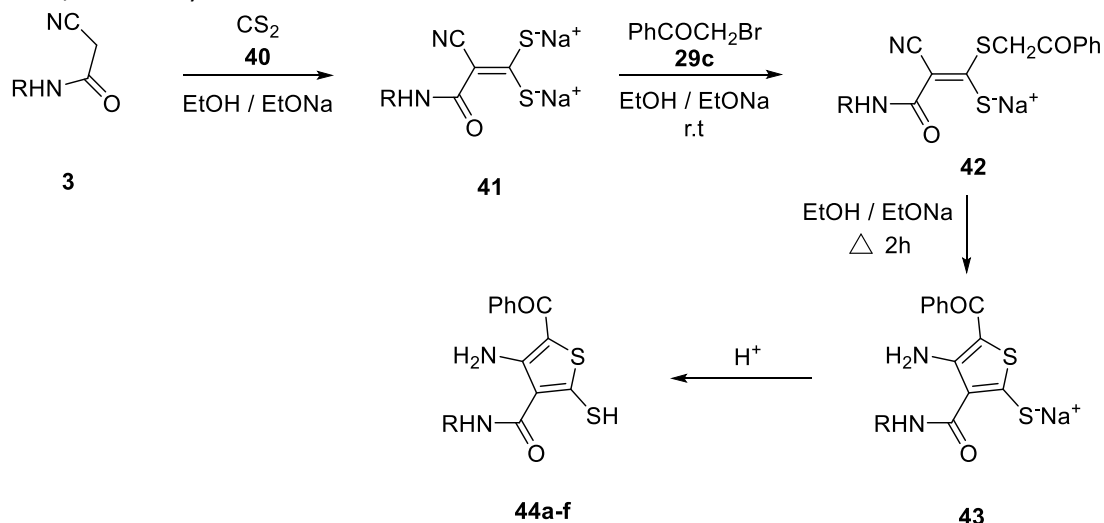


	R =	R ¹ =	Yield
39a		Me	60%
39b		Ph	65%
39c		OEt	20%

Scheme 16

Reaction of substituted acetanilide derivatives **3** with carbon disulfide **40** in the presence of sodium ethoxide gives the sodium dithiolate salts **41**. Compounds **41** are easily monoalkylated to give the stable sodium salts of monoalkylthio derivatives. Thus, one equivalent of phenacyl bromide **29c** gave the

corresponding sodium salts of monoalkylated products **42** in good yields. The sodium α -cyanoketene dithiolates **42** were cyclized on heating in sodium ethoxide at reflux to give the corresponding sodium thiophenethiolates **43**, which were acidified with hydrochloric acid to give the novel 2-mercaptothiophenes **44a-f** (Scheme 17, Table 10).⁸²



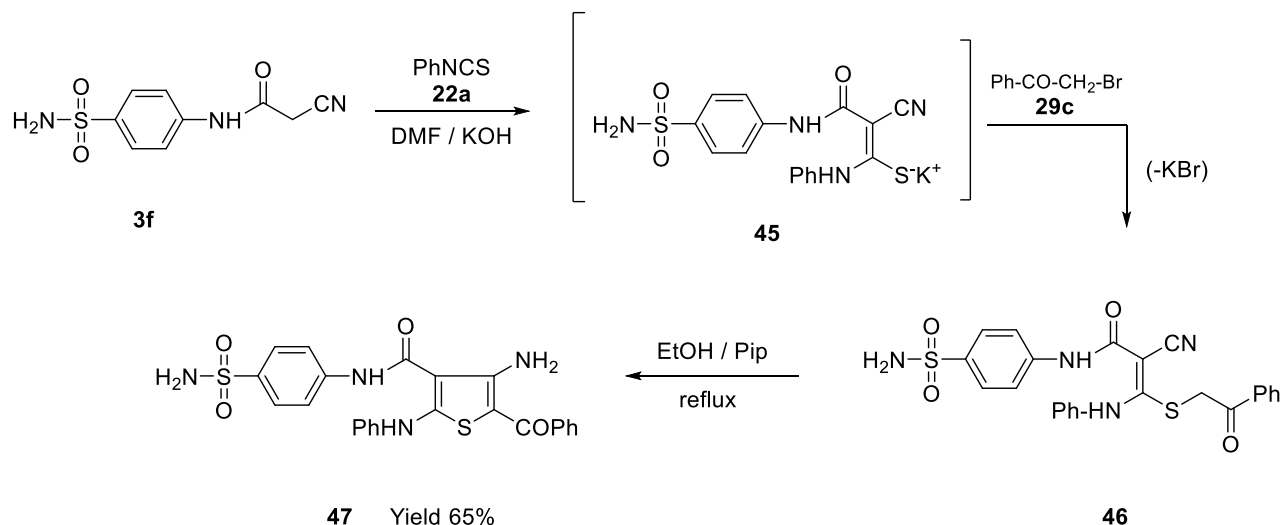
Scheme 17

Table 10. Synthesis and % yields of **44a-f**

Entry	Product	R	Yield (%)
3a	44a	Ph	70
3cn	44b	4-ClC ₆ H ₄	80
3co	44c	2-ClC ₆ H ₄	81
3bz	44d	4-MeC ₆ H ₄	78
3bi	44e	4-BrC ₆ H ₄	80
3by	44f	4-MeOC ₆ H ₅	75

3.1.1.2.3. Synthesis *via* Thorpe-Ziegler reactions

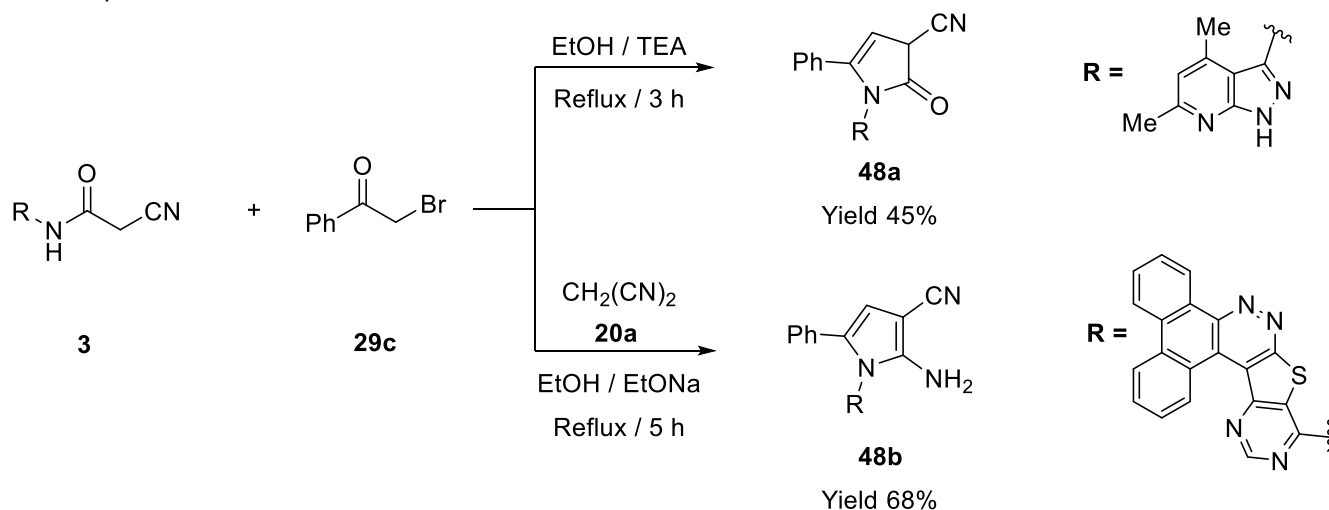
The potassium sulfide salt **45** was obtained by the nucleophilic addition of compound **3f** to phenyl isothiocyanate **22a** in DMF at the room temperature in presence of KOH. Treatment of compound **45** with phenacyl bromide **29c** gave the thioether derivative **46**, *via* elimination of potassium bromide. Cyclization of **46** by refluxing in ethanolic/piperidine solution afforded the novel aminothiophene derivative **47** *via* Thorpe-Ziegler reaction. Compound **47** was assumed to be formed *via* nucleophilic attack of the active methylene to the cyano group followed by tautomerization (Scheme 18).⁸³



Scheme 18

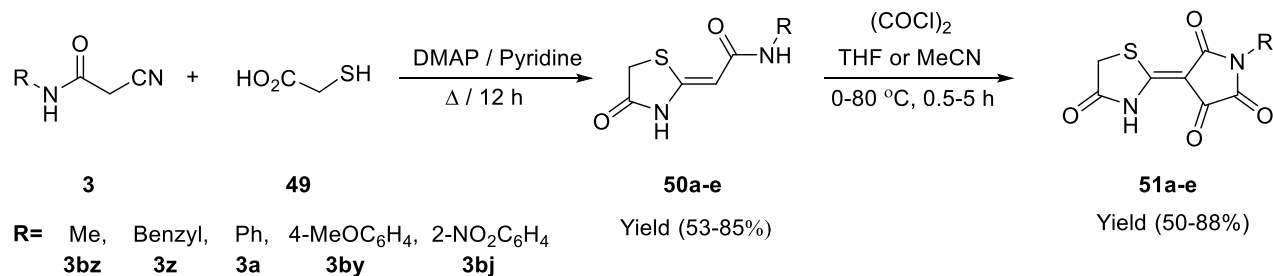
3.1.1.3. Pyrrole derivatives:

The condensation of cyanoacetamide **3** with phenacyl bromide **29c** in boiling ethanol in the presence of triethylamine as a basic catalyst produced the pyrrole derivative **48a**.⁶³ While condensation of **3** with phenacyl bromide **29c** and malononitrile **20a** in presence of sodium ethoxide produced the pyrrol derivative **48b**.⁸⁴ (Scheme 19).



Scheme 19

Cyanoacetamides **3** react with 2-mercaptoacetic acid **49** to produce 2-(1,3-thiazolidin-2-ylidene)acetamides **50** that undergo cyclocondensation reactions with oxalyl chloride to form 4-(4-oxo-1,3-thiazolidin-2-ylidene)pyrrolidine-2,3,5-triones **51a-e** (Scheme 20).⁸⁵



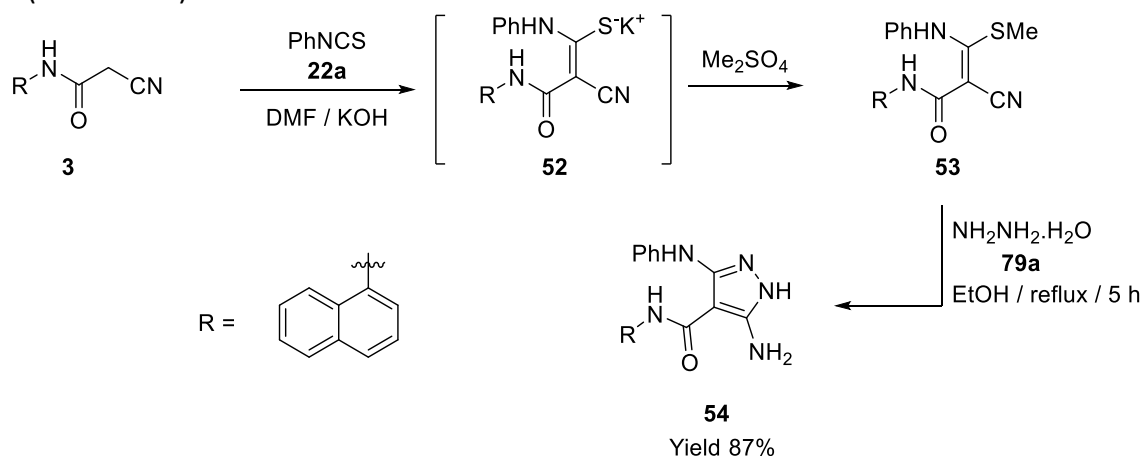
Scheme 20

3.1.2. Mono cyclic five-membered rings with two hetero atoms

3.1.2.1. Pyrazole derivatives

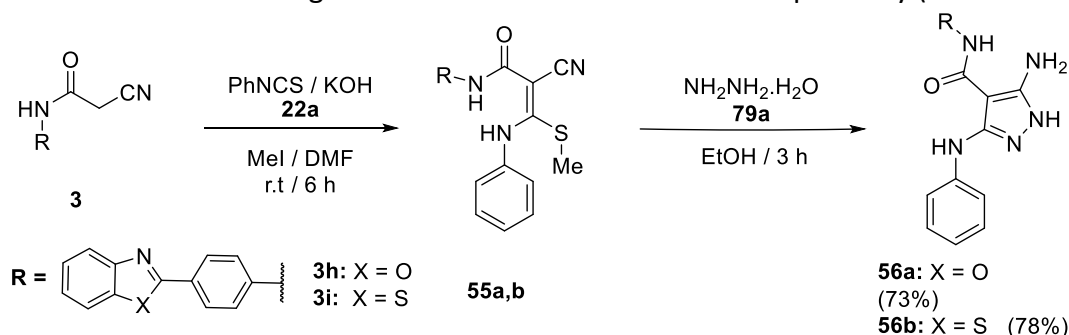
3.1.2.1.1. Synthesis *via* Michael addition reactions

The base prompted reaction of cyanoacetamide **3** with phenyl isothiocyanate **22a** in DMF affords the intermediate **52**. Treatment of non-isolable thiocarbamoyl **52** with dimethyl sulfate yielded the ketene *N,S*-acetal **53**. Treatment of **53** with hydrazine hydrate **79a** in ethanol resulted in the formation of 5-aminopyrazole derivative **54** (Scheme 21).⁸⁶



Scheme 21

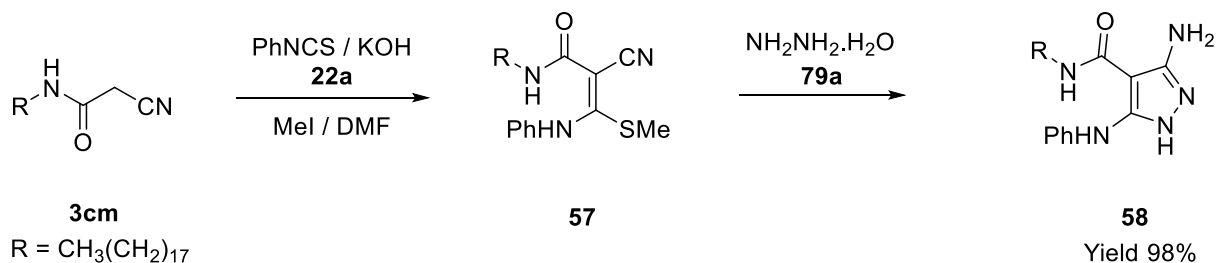
Cyanoacetamides **3h** and **3i** were reacted with phenyl isothiocyanate **22a** and methyl iodide in presence of KOH giving the *N,S*-ketene acetal derivatives **55a** and **55b**. These ketene acetals were cyclized upon reaction with hydrazine **79a** in ethanol resulting in the formation of **56a** and **56b** respectively (Scheme 22).⁸⁷



Scheme 22

Moreover, 2-cyano-3-(methylthio)-Noctadecyl-3-(phenylamino)acrylamide **57** was established by the reaction of **3cm** with phenyl isothiocyanate **22a** in DMF containing KOH followed by addition of methyl iodide.

The reaction of **57** with hydrazine hydrate **79a** resulted in the formation of pyrazole derivatives **58** (Scheme 23).⁷⁹



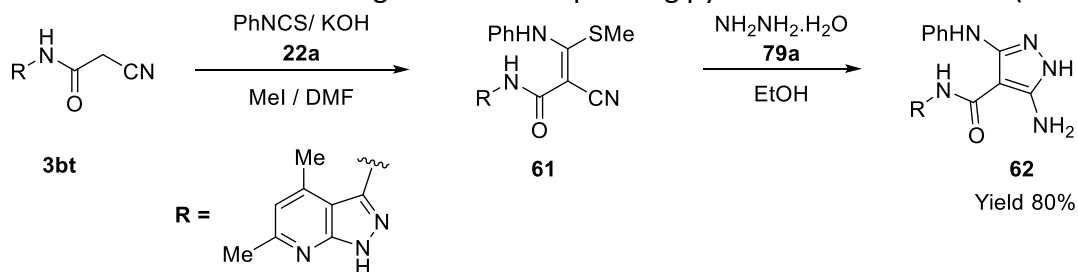
Scheme 23

N-(4-Phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide **60** was obtained in good yields in two consecutive steps *via* the base-catalysed nucleophilic addition of phenyl isothiocyanate **22a** to 2-cyanoacetamide **3cq** followed by *in situ* addition of methyl iodide to give the ketene *N,S*-acetal **59**. Heating the latter product with excess of hydrazine hydrate **79a** in ethanol at reflux afforded compound **60** (Scheme 24).⁸⁸



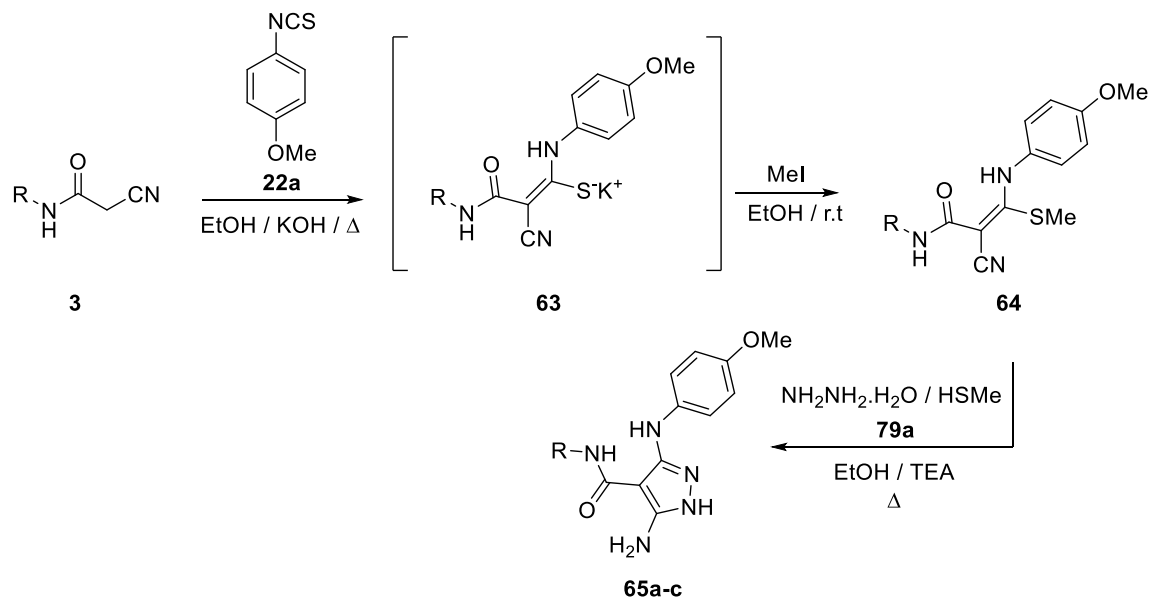
Scheme 24

Treatment of compound **3bt** with phenyl isothiocyanate **22a** in DMF, and in the presence of KOH at room temperature, followed by addition of methyl iodide afforded the ketene *N,S*-acetal **61**. Reaction of **61** with hydrazine hydrate **79a** in ethanol at reflux gave the corresponding pyrazole derivative **62** in (Scheme 25).⁵⁹



Scheme 25

Cyanoacetamide derivatives **3** were reacted with 4-methoxyphenyl isothiocyanate **22b** in absolute ethanol in the presence of potassium hydroxide to give the corresponding intermediates **63**. When the latter was alkylated with methyl iodide in ethanol, it afforded the ketene *N,S*-acetals **64** which react with hydrazine **79a** to give amino pyrazole **65a-c** (Scheme 26, Table 11).⁸⁹

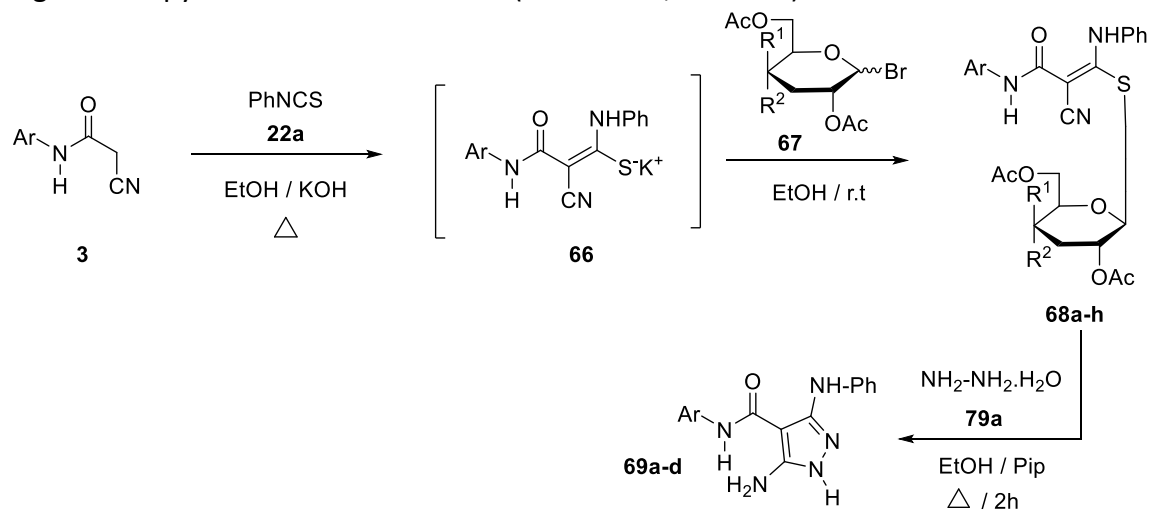


Scheme 26

Table 11. Synthesis and % yields of **65a-c**

Entry	Product	R	Yield (%)
3a	65a	Ph	79
3bz	65b	4-MeC ₆ H ₄	82
3co	65c	4-ClC ₆ H ₄	80

Heating the acetanilide derivatives **3** with phenyl isothiocyanate **22a** in EtOH-KOH affords the stable 2-cyano-ethylene-1-thiolate potassium salts **66**. The latter compounds react with *α*-D-gluco- and galactopyranosyl bromides **67** in ethanol at room temperature to give the corresponding *S*-glucosides **68a-d** or *S*-galactosides **68e-h**. Attempted removal of protecting groups in **68a-h** by methanolic ammonia did not afford the free glycosides. The reaction of compound **68** with hydrazine **79a** in ethanol at reflux affords the corresponding 5-aminopyrazole derivatives **69a-d** (Scheme 27, Table 12).⁹⁰



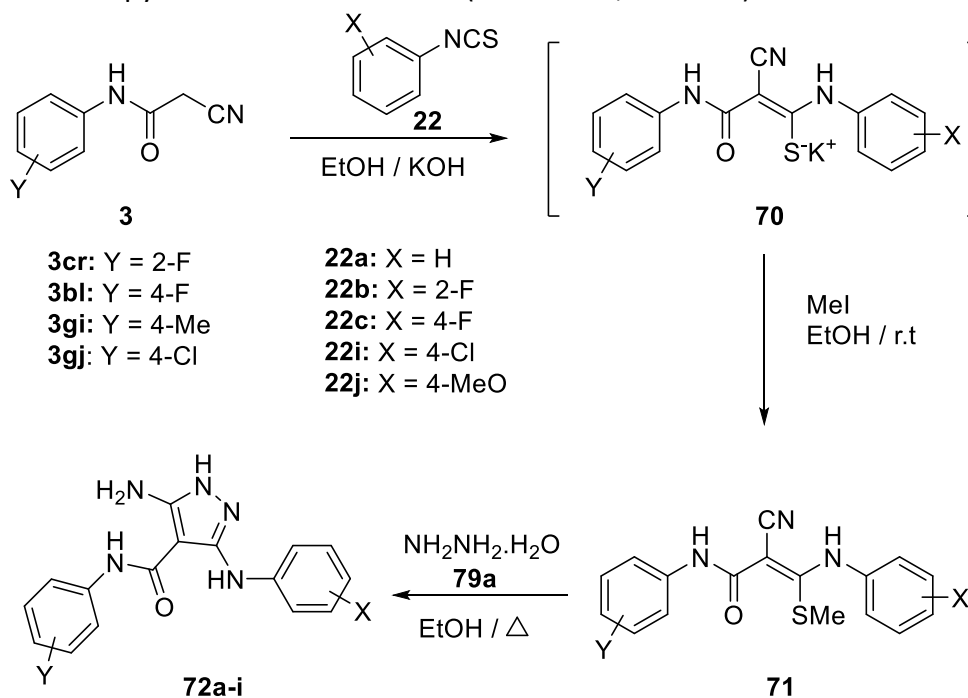
Scheme 27

Table 12: Synthesis and % yields of **68a-h** and **69a-d**:

Entry	Product	Ar	R ¹	R ²	Yield (%)
-------	---------	----	----------------	----------------	-----------

3a	68a	Ph	H	OAc	87
3bz	68b	4-MeC ₆ H ₄	H	OAc	86
3by	68c	4-MeOC ₆ H ₄	H	OAc	77
3co	68d	4-ClC ₆ H ₄	H	OAc	77
3a	68e	Ph	OAc	H	85
3bz	68f	4-MeC ₆ H ₄	OAc	H	86
3by	68g	4-MeOC ₆ H ₄	OAc	H	76
3co	68h	4-ClC ₆ H ₄	OAc	H	87
3a	69a	Ph	-	-	not reported
3bz	69b	4-MeC ₆ H ₄	-	-	not reported
3by	69c	4-MeOC ₆ H ₄	-	-	not reported
3co	69d	4-ClC ₆ H ₄	-	-	not reported

The reaction of cyanoacetamides **3** under the effect of heat with aryl isothiocyanates **22** in KOH-EtOH affords the corresponding potassium 2-cyanoethylene-1-thiolate salts **70**. Alkylation with methyl iodide in ethanol resulted in the formation of the fluorinated ketene *N,S*-acetals **71**. Reaction of compounds **71** with hydrazine hydrate **79a** in ethanol at reflux in the presence of a catalytic amount of piperidine gave the corresponding substituted pyrazole derivatives **72a-i** (Scheme 28, Table 13).⁹¹



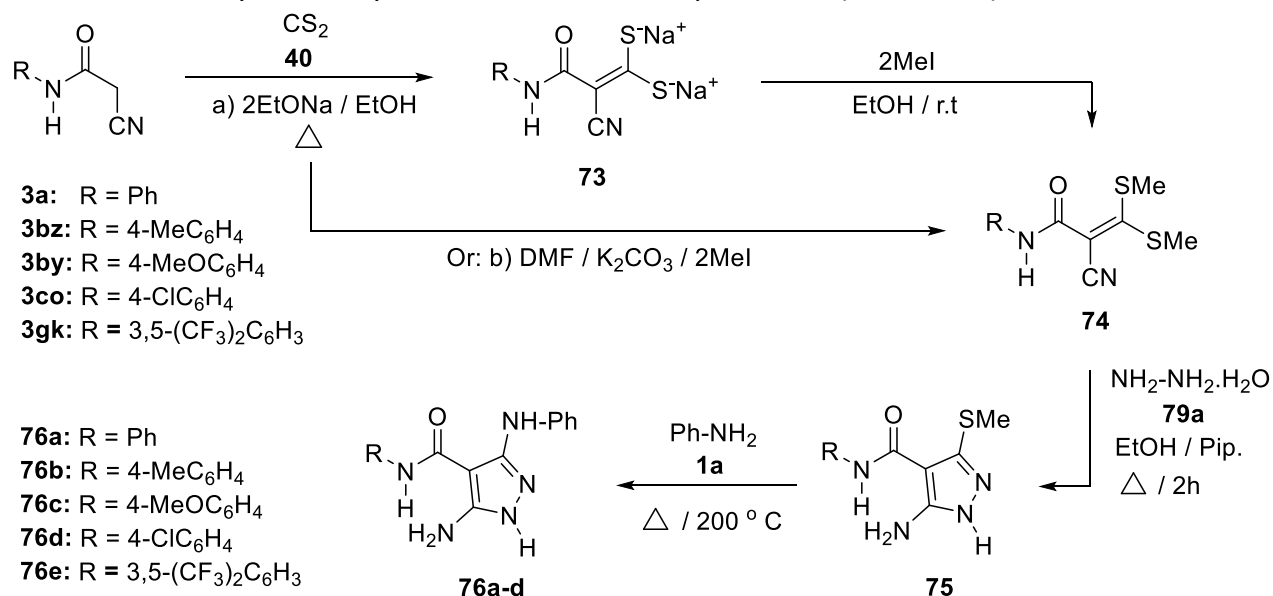
Scheme 28

Table 13. Synthesis and % yields of **72a-i**

Product	Y	X	Yield (%)	Ref.
72a	2-F	H	78	91
72b	4-F	H	85	
72c	4-F	2-F	80	
72d	2-F	4-F	85	
72e	4-F	4-F	84	

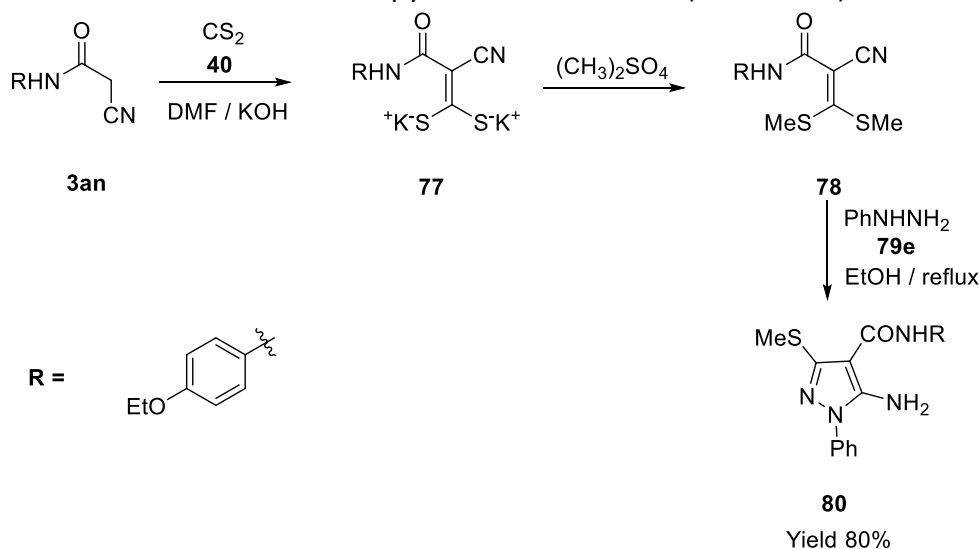
72f	2-F	4-Cl	79	92
72g	4-F	4-Cl	81	
72h	4-Me	4-MeO	not	
72i	4-Cl	4-MeO	reported	

Compounds **76a-d** were obtained by reaction of the 3-methylthiopyrazoles **75** with aniline **1a**. Compounds **75** were produced via the reaction of the acetanilide derivatives **3** with carbon disulfide **40** in EtOH/EtONa⁹⁰ or DMF/K₂CO₃⁴⁶ followed by its reaction with methyl iodide to give the ketene *S,S*-acetals **74**. The latter compounds react with hydrazine hydrate **79a** to afford compounds **75** (Scheme 29).



Scheme 29

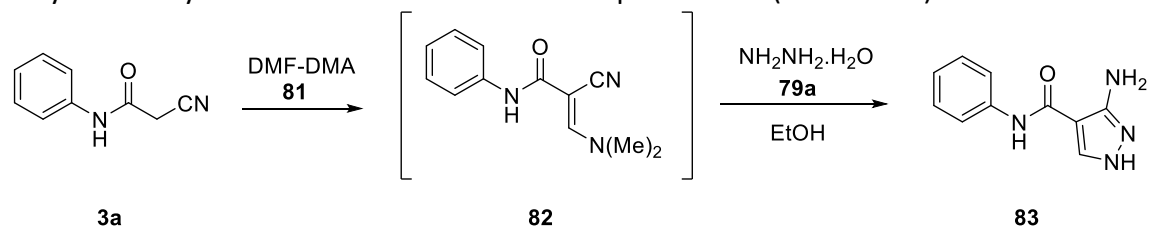
The reaction of **3an** with carbon disulfide **40** in DMF and in the presence of KOH furnished the non-isolable intermediate **77**. The latter compound was converted into 2-cyano-3,3-bis(methylsulfanyl) acrylamide **78** in good yield by treatment with dimethyl sulfate at room temperature. Cyclocondensation of compound **78** with phenyl hydrazine **79e** afforded the novel aminopyrazole derivative **80** (Scheme 30).⁹³



Scheme 30

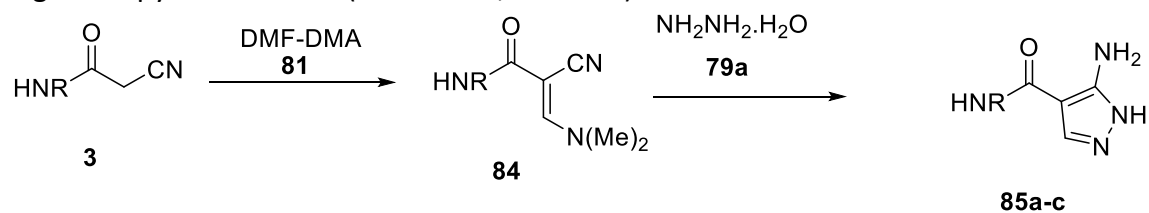
3.1.2.1.2. Synthesis *via* condensation reactions

The reaction of 2-cyano-N-phenylacetamide **3a** with DMF-DMA **81** afforded the enaminonitrile **82** that was reacted with hydrazine hydrate **79a** in ethanol at reflux to produce **83** (Scheme 31).¹²



Scheme 31

The cyanoacetamides **3** were reacted with dimethylformamide dimethylacetal (DMF-DMA) **81** to yield the enamines **84**. The enamines **84** react with hydrazine hydrate **79a** in dioxane at reflux to yield the corresponding aminopyrazoles **85a-c** (Scheme 32, Table 14).⁴²

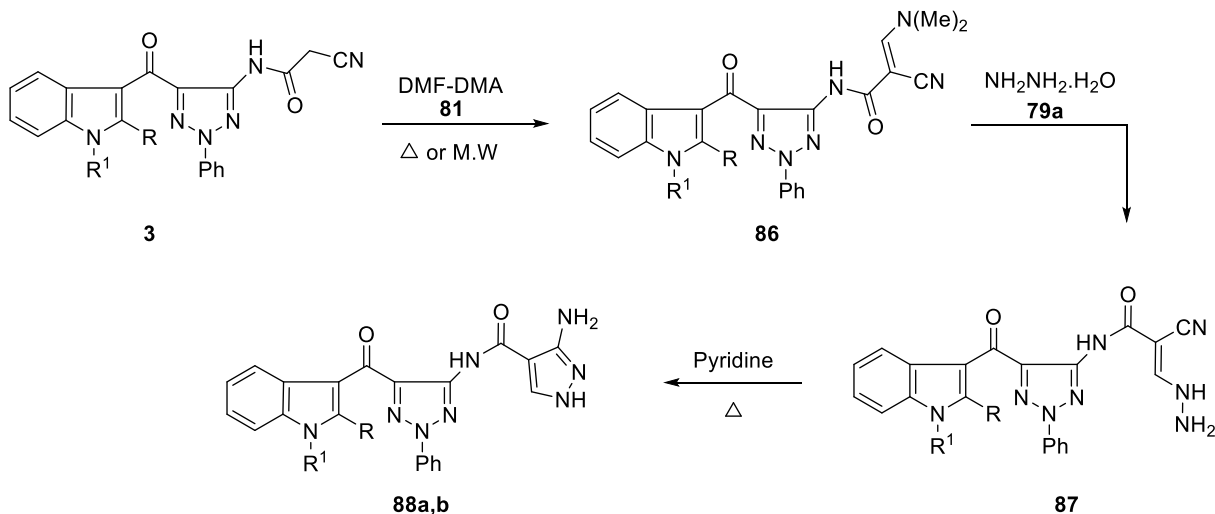


Scheme 32

Table 14. Synthesis and % yields of **85a-c**

Entry	Product	R	Yield (%)	Ref.
3aw	85a		70	42
3ax	85b		68	
3am	85c	CH ₃ (CH ₂) ₁₇	65	94

The cyanoacetamides **3** react with dimethylformamide dimethylacetal (DMF-DMA) **81** to yield the corresponding enamines **86**. The reaction of enamines **86** with hydrazine hydrate **79a** in ethanol at reflux affords the hydrazine derivatives **87** that undergo cyclization in pyridine at reflux to form the corresponding aminopyrazole **88a,b** (Scheme 33, Table 15).⁴⁵

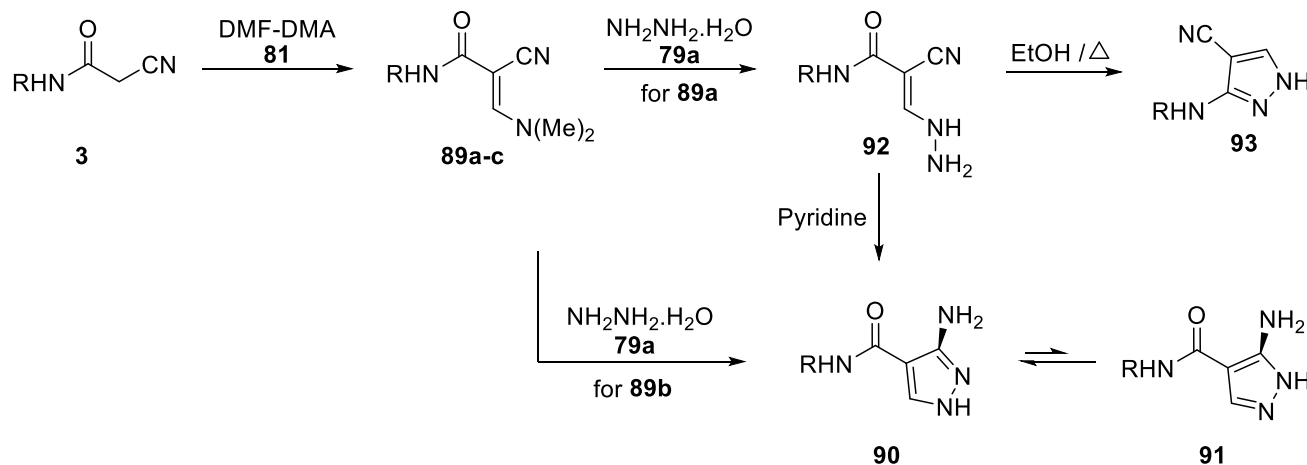


Scheme 33

Table 15. Synthesis and % yields of **88a,b**

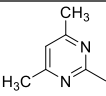
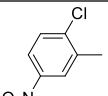
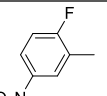
Entry	Product	R	R ¹	Yield (%)
3bb1	88a	H	Me	73
3bb2	88b	Me	H	68

Cyanoacetamide derivatives **3** undergo reaction with dimethylformamide dimethylacetal (DMF-DMA) **81** to yield the corresponding enamines **89**. Stirring a solution of **89b** in DMSO at reflux produces a mixture of **90** and the tautomer **91** in a 2 to 1 ratio. An ethanol solution of the cyano-enamine **89a** and hydrazine hydrate **79a** at room temperature undergoes reaction to form the acyclic hydrazine derivative **92**. Stirring a solution of **92** in ethanol afforded the cyanopyrazole **93** (Scheme 34, Table 16).⁴⁰

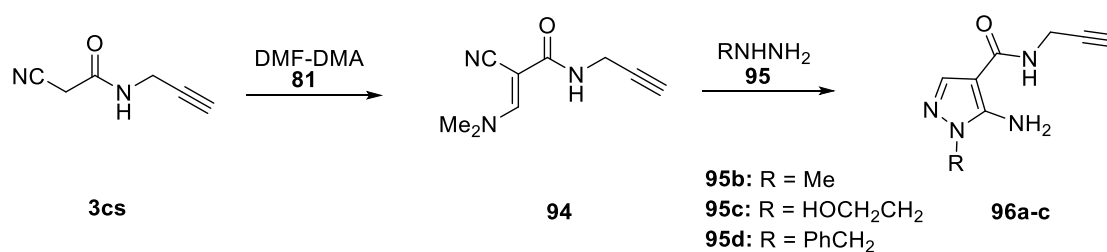


Scheme 34

Table 16: Synthesis and % yields of **89a-c**, **91** and **93**:

Compound	R				
	3av		3ao		3ap
Entry					
Products	89a	93	89b	91	89c
Ar					
Yield (%)	76	73	83	74	75

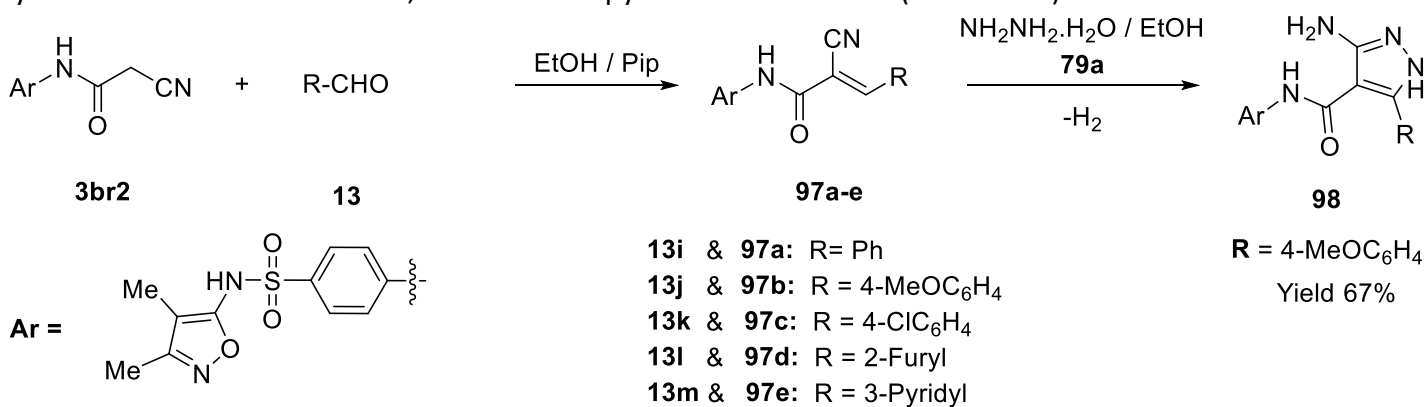
A convenient procedure for the synthesis of **96a-c** is based on the reaction of accessible *N*-propargylcyanoacetamide **3cs** with dimethylformamide dimethylacetal (DMF-DMA) **81**, followed by cyclocondensation of 2-cyano-3-(dimethylamino)acrylamide **94** with alkyhydrazines **95b-d** (Scheme 35, Table 17).⁹⁵

**Scheme 35****Table 17:** Synthesis and % yields of **96a-c**:

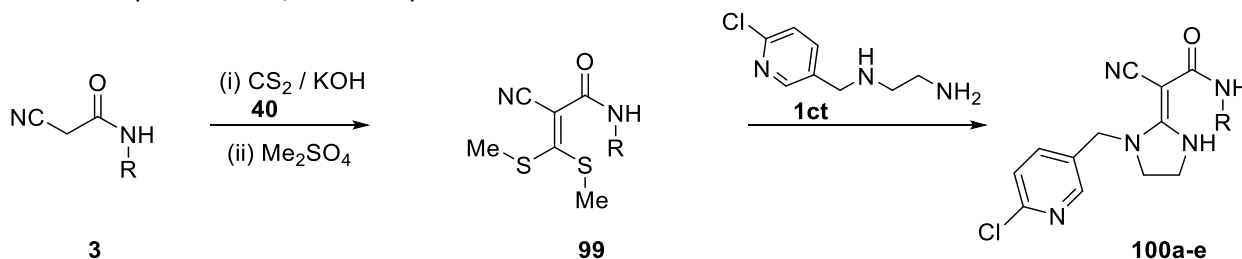
Product	R	Yield (%)
96a	Me	72
96b	HOCH ₂ CH ₂	69
96c	PhCH ₂	71

3.1.2.1.3. Synthesis via Knoevenagel condensation reactions:

Treatment of **3br2** with various types of aldehydes **13** in ethanol at reflux in the presence of piperidine leads to the formation of 2-cyano-3-aryl-acrylamides **97a-e**. Treatment of 2-cyanoacrylamide **97b** with hydrazine hydrate **79a** in ethanol at reflux, furnished the pyrazole derivative **98** (Scheme 36).⁶¹

**Scheme 36****3.1.2.2. Imidazole derivatives****A. Synthesis via Michael addition reactions**

The intermediates **99** were prepared by successive addition of carbon disulfide **40**, KOH and dimethyl sulfate to *N*-substituted-2-cyanoacetamides **3**. The neonicotinoids **100a-e** linked to an amide moiety were formed in good yields under mild conditions by the reaction of 2-cyano-*N*-substituted-acetamide **99** with amine **1ct** in ethanol at reflux (Scheme 37, Table 18).⁹⁶



Scheme 37

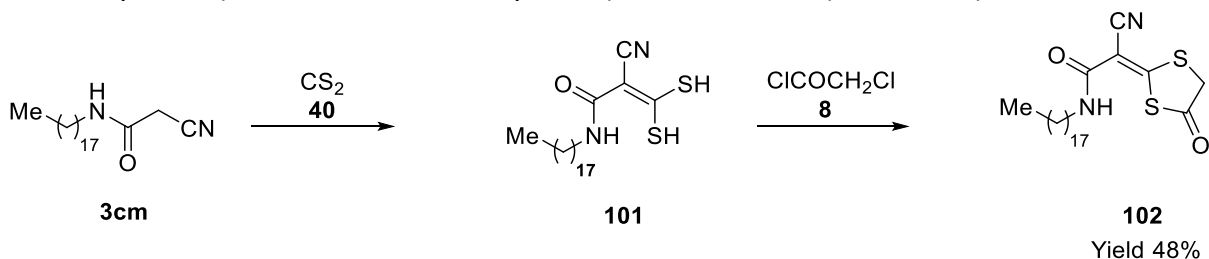
Table 18. Synthesis and % yields of **100a-e**

Entry	Product	R	Yield (%)
3z	100a	Benzyl	80
3a	100b	Ph	75
3co	100c	4-ClC ₆ H ₄	72
3cu	100d	2-MeC ₆ H ₄	70
3cv	100e	CH ₃ (Ph)CH	72

3.1.2.3. 1,3-Dithiolan derivatives

A. Synthesis *via* Michael addition reactions

The reaction of cyanoacetamide **3cm** with carbon disulfide **40** in DMF containing potassium hydroxide followed by acidification furnished the dithiol **101**. Subsequent reaction of **101** with chloroacetyl chloride **8** in DMF afforded 2-cyano-2-(4-oxo-1,3-dithiolan-2-ylidene) acetamide **102** (Scheme 38).⁷⁹

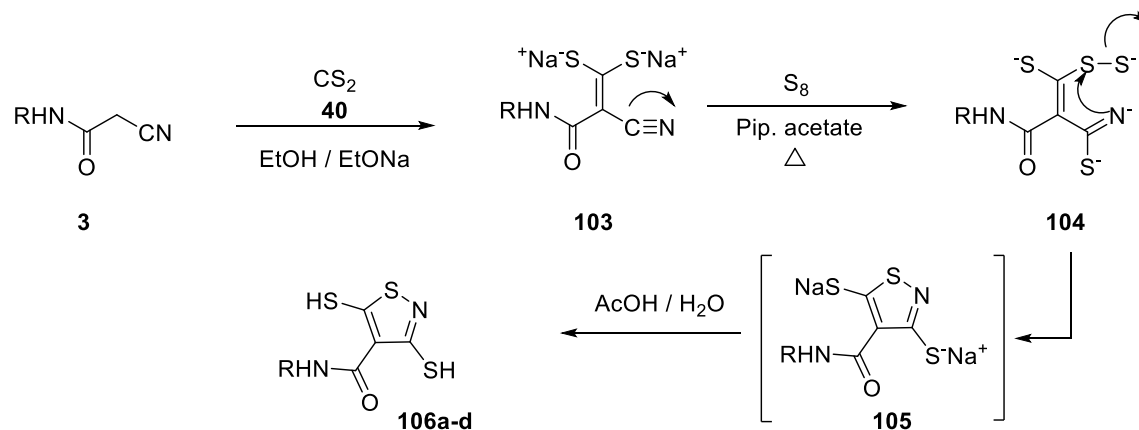


Scheme 38

3.1.2.4. 1,2-Thiazole derivatives

A. Synthesis *via* Gewald reactions

Sodium α -cyanoketene dithiolates **103**, was formed through the reaction of acetanilides **3** with carbon disulfide **40** in the presence of sodium ethoxide at room temperature. The reaction of sodium α -ketene dithiolates **103a-d** with sulfur in the presence of piperidine acetate afforded the corresponding sodium isothiazole-3,5-dithiolates **105**, which give the dimercapto isothiazole-4-carboxamides **106a-d** when acidified with acetic acid. (Scheme 39, Table 19).⁹⁷



Scheme 39

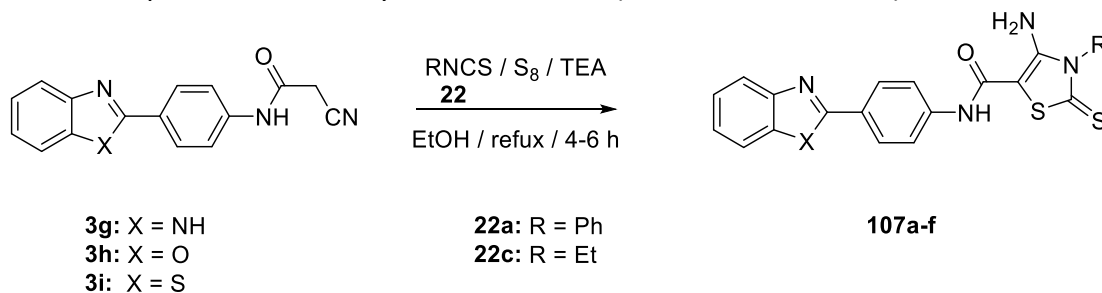
Table 19. Synthesis and % yields of 106a-d

Entry	Product	Ar	Yield (%)
3a	106a	Ph	70
3by	106b	4-MeOC ₆ H ₄	90
3bz	106c	4-MeC ₆ H ₄	90
3co	106d	4-ClC ₆ H ₄	90

3.1.2.5. Thiazole derivatives

3.1.2.5.1. Synthesis *via* Gewald reactions

2-Thioxothiazole derivatives **107** were obtained from the reaction of **3** with ethyl or phenyl isothiocyanates **22** and elemental sulfur in presence of triethylamine as a base (Scheme 40, Table 20).¹⁹

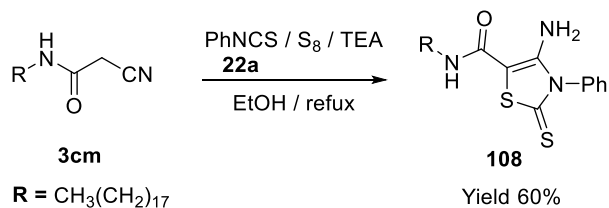


Scheme 40

Table 20. Synthesis and % yields of 107a-f

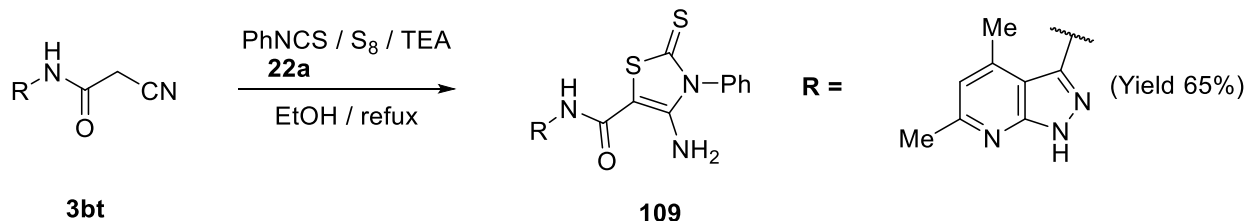
Product	X	R	Yield (%)	Product	X	R	Yield (%)
107a	NH	Et	58	107d	O	Ph	57
107b	NH	Ph	55	107e	S	Et	52
107c	O	Et	57	107f	S	Ph	48

When **3cm** was heated at reflux with elemental sulfur and phenyl isothiocyanate **22a** in ethanol in the presence of triethylamine, 4-aminothiazole-5-carboxamide **108** was produced (Scheme 41)⁷⁹



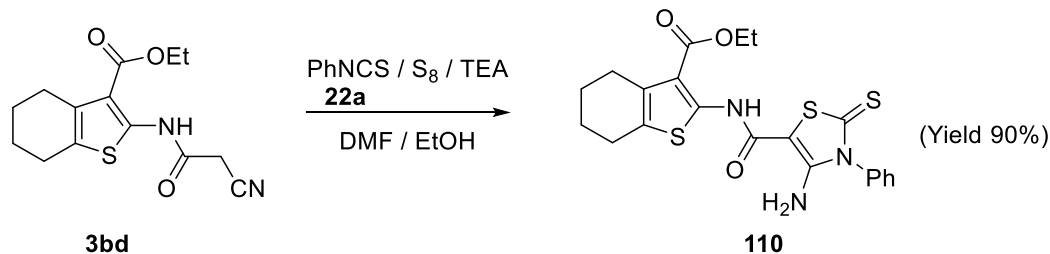
Scheme 41

The reaction of **3bt** with both elemental phenyl isothiocyanate **22a** and sulfur in boiling ethanol containing a catalytic amt of triethylamine afforded the thiazole derivative **109** (Scheme 42).⁵⁹



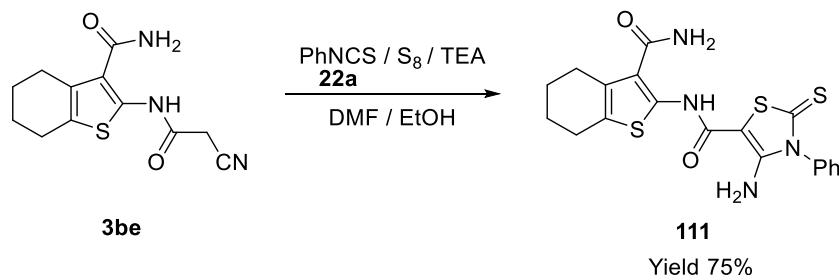
Scheme 42

Ethyl 2-(4-amino-2,3-dihydrothiazole-5-carboxamido)-tetrahydrobenzo[*b*]thiophene-3-carboxylate **110** was formed by the reaction of **3bd** with phenyl isothiocyanate **22a** and sulfur (Scheme 43).⁴⁷



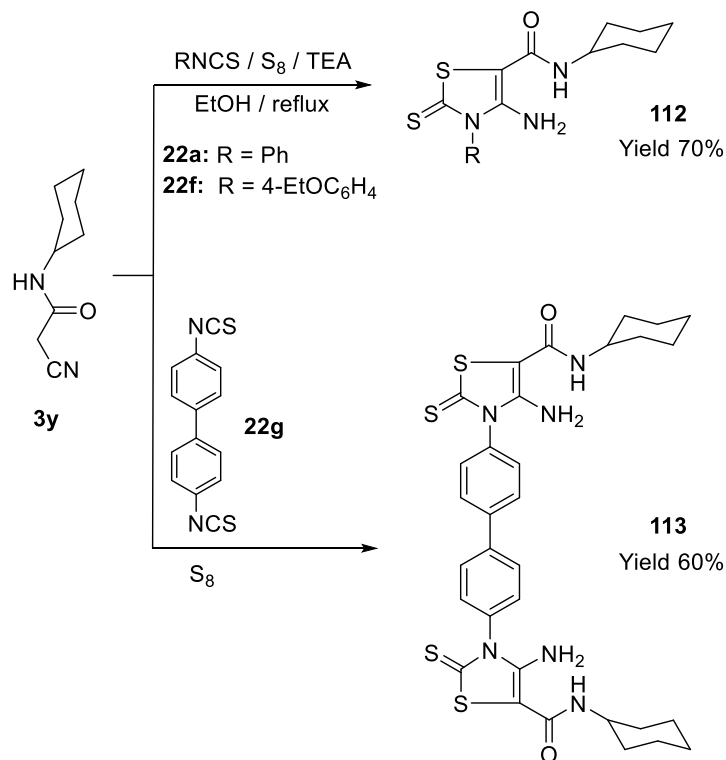
Scheme 43

Stirring **3be** with sulfur and phenyl isothiocyanate **22a** in DMF containing triethylamine at 60 °C afforded **111** (Scheme 44).⁶⁷



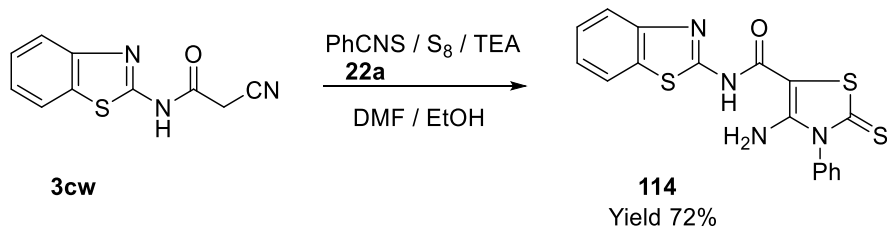
Scheme 44

The reaction of *N*-cyclohexyl-2-cyano-acetamide **3y** with isothiocyanate derivatives **22a,f** and/or biphenyl isothiocyanate **22g** and sulfur in ethanol catalysed with triethylamine gave thiazolidine **112** and bithiazolidine **113** derivatives (Scheme 45).⁹⁸



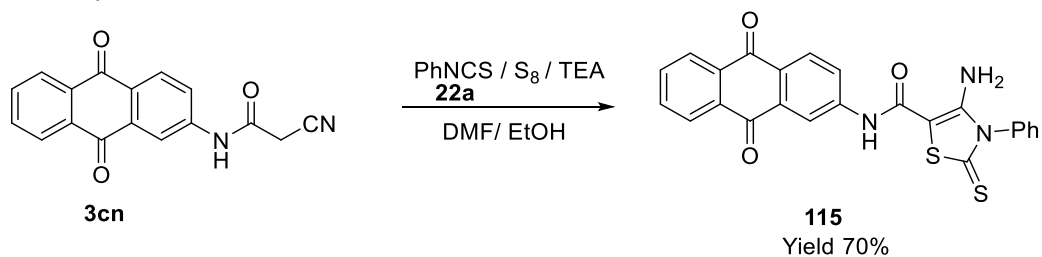
Scheme 45

The Gewald reaction of amide **3cw** with phenyl isothiocyanate **22a** and elemental sulfur in DMF / EtOH containing triethylamine as a basic catalyst furnished the functionalized thiazoline **114** (Scheme 46).⁹⁹



Scheme 46

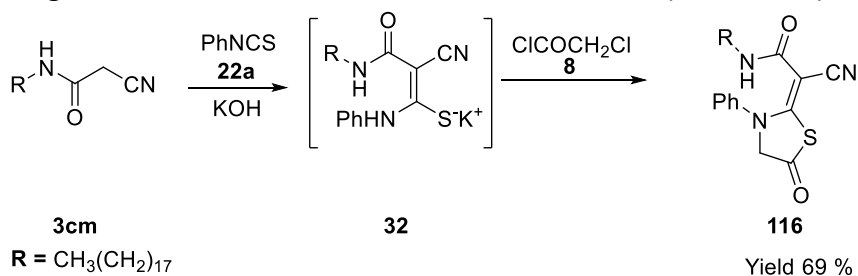
4-Aminothiazole-5-carboxamide **115** was obtained by the reaction of **3cn** with phenyl isothiocyanate **22a** and sulfur (Scheme 47).⁸⁰



Scheme 47

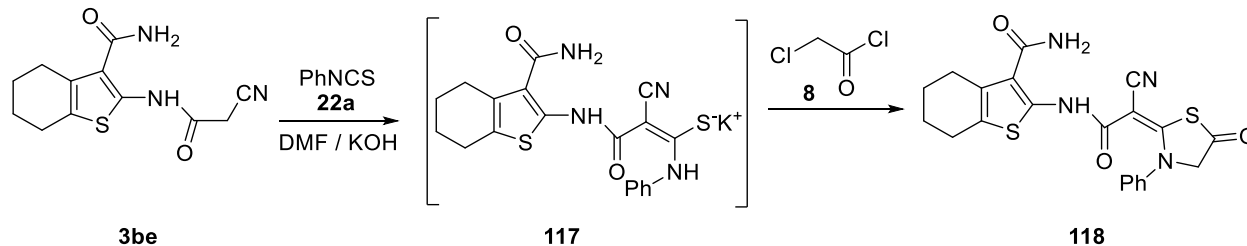
3.1.2.5.2. Synthesis *via* Michael addition reactions

The reaction of cyanoacetamide derivative **3cm** with phenyl isothiocyanate **22a** in DMF in the presence of KOH to afford the nonisolable enaminonitrile potassium salt **32** which undergoes cyclization when treated with chloroacetyl chloride **8** to give the functionalized thiazole derivatives **116** (Scheme 48).⁷⁹



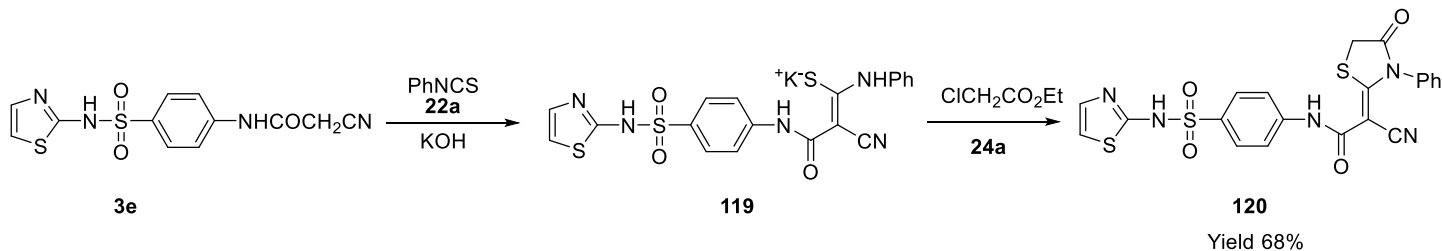
Scheme 48

The reaction of **3be** with phenyl isothiocyanate **22a** in DMF in presence of potassium hydroxide afforded **117**. When the intermediate **117** is reacted with 2-chloroacetyl chloride **8**, *N*-phenylthiazolone **118** is afforded (Scheme 49).⁴⁹



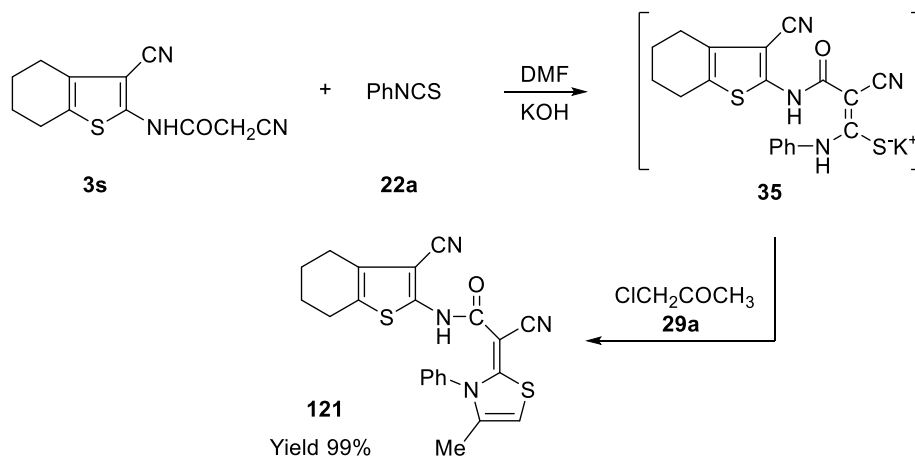
Scheme 49

Thiazolidinone **120** was prepared through the reaction of **3e** with phenyl isothiocyanate **22a** in the presence of KOH followed by reaction of the resulting adduct **119** with ethyl chloroacetate **24a** (Scheme 50).¹⁷



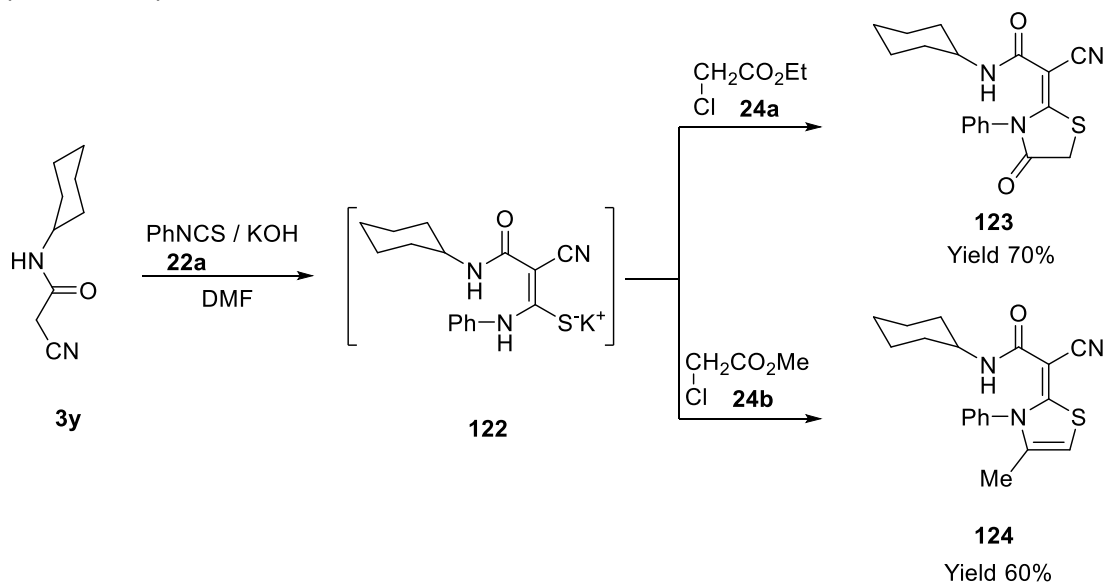
Scheme 50

Subjecting the active methylene precursor **3s** to the aforementioned reaction using chloroacetone **29a** furnished the thiazole derivative **121** through the intermediacy of the potassium sulfide salt **35** (Scheme 51).²⁵



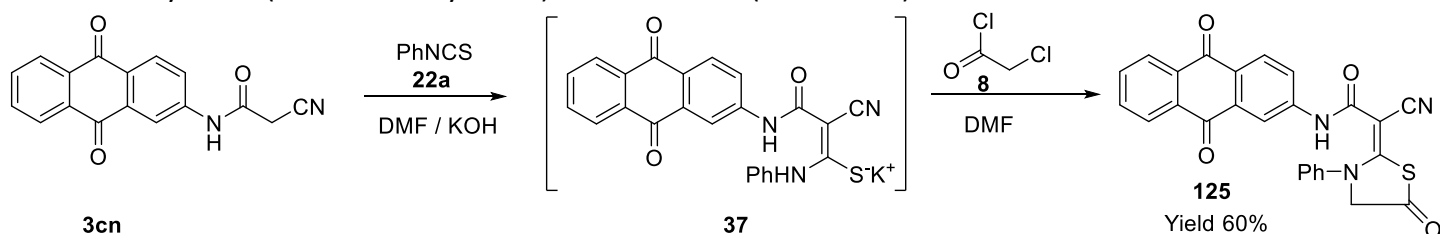
Scheme 51

The reaction of cyanoacetamide derivative **3y** with phenyl isothiocyanate **22a** in the presence of KOH at room temperature gave the non-isolable potassium salt **122**. On treatment with ethyl chloroacetate **24a** at room temperature afforded the novel 4-thiazolidinone derivative **123** in good yield. Cycloalkylation of the intermediate **122** with methylchloroacetate **24b** at room temperature gave the corresponding 4-methyl thiazole **124** (Scheme 52).⁹⁸



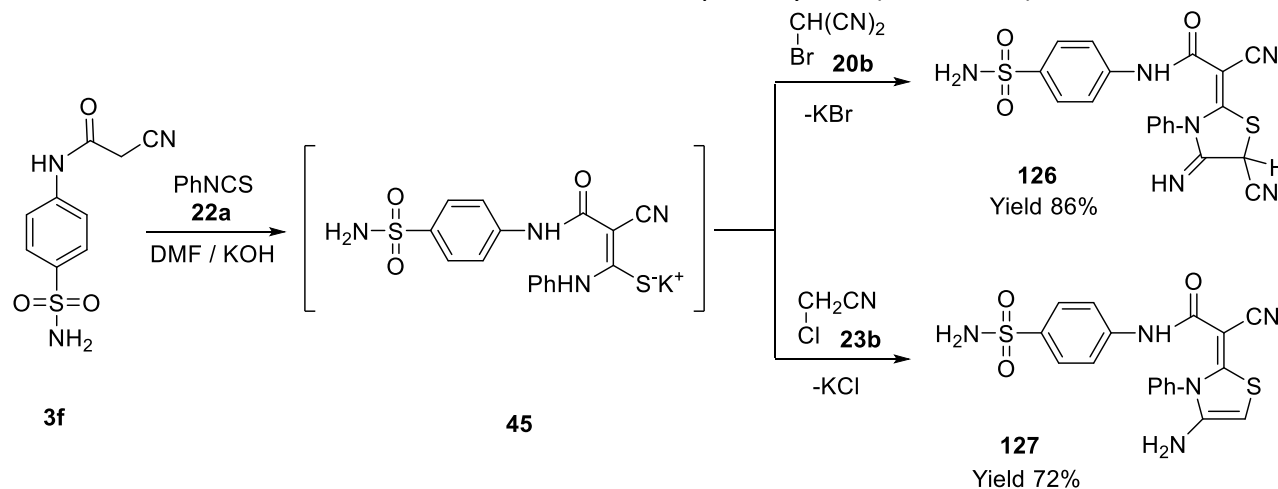
Scheme 52

Treatment of cyanoacetamide **3cn** with phenyl isothiocyanate **22a**, in dry DMF in presence of KOH, yielded the potassium thiolate **37**. Subsequent reaction of the potassium salt **37** with chloroacetyl chloride **8** in DMF afforded 2-cyano-2-(thiazolidin-2-ylidene)acetamide **125** (Scheme 53).⁸⁰



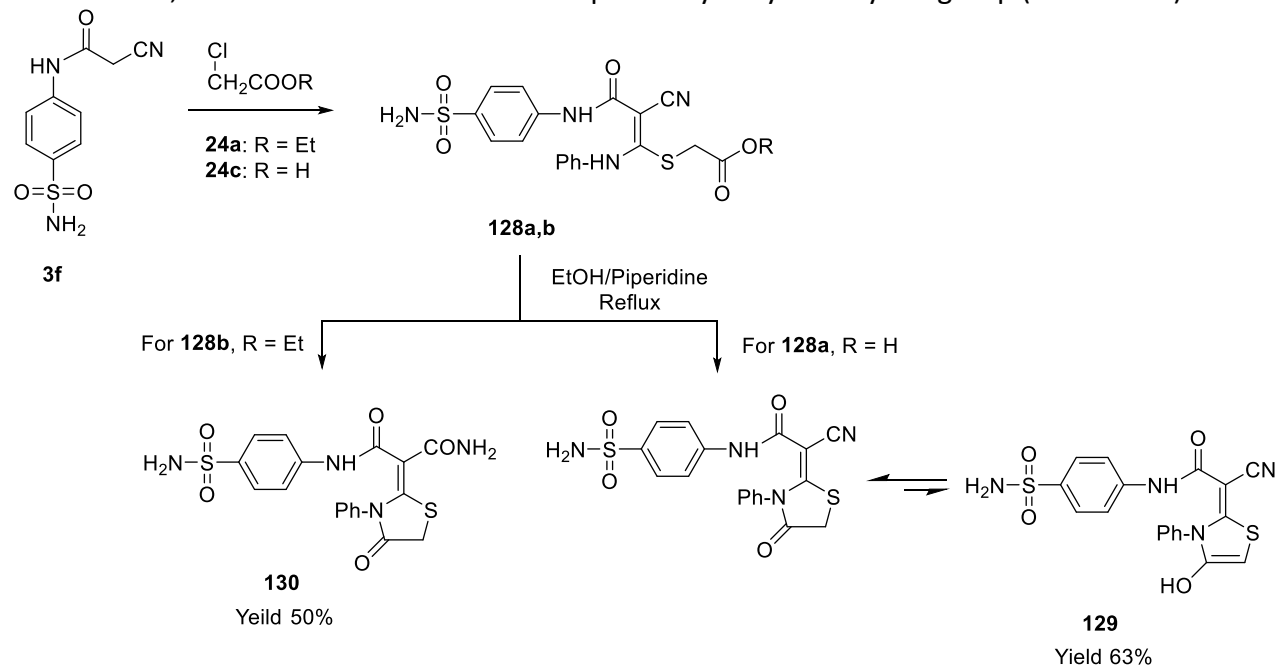
Scheme 53

It is reported that treatment of intermediate **45** with bromomalononitrile **20b** at room temperature gave iminothiazolidine derivative **126**, while, the cycloalkylation of the intermediate **45** with chloroacetonitrile **23b** afforded the novel aminothiazolidine derivative **127** in acceptable yields (Scheme 54).⁸³



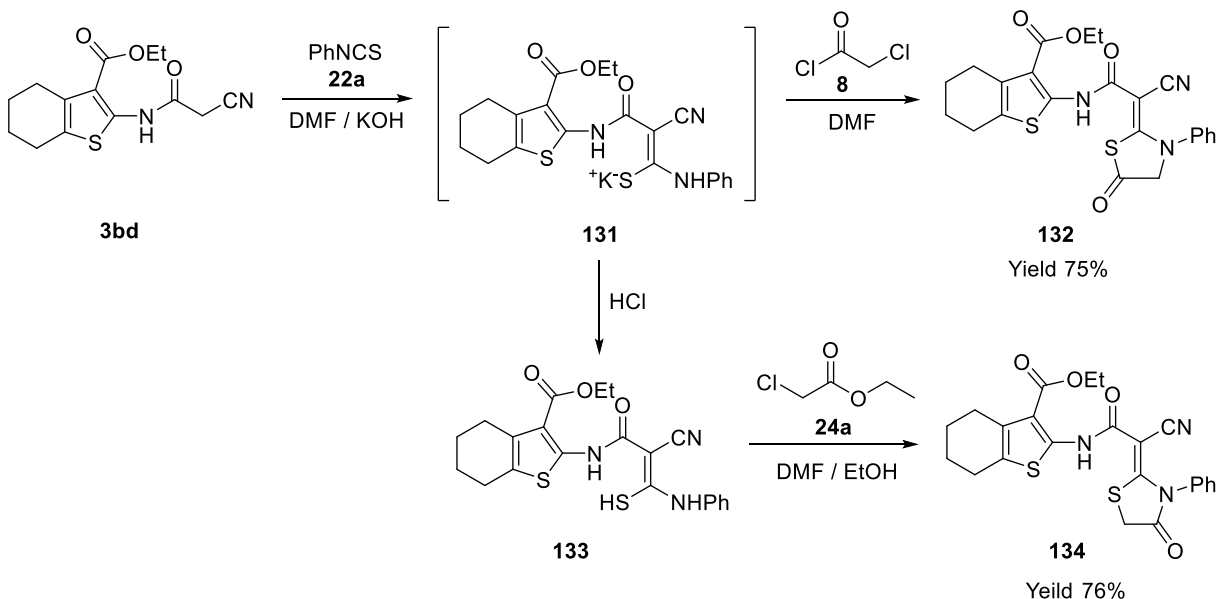
Scheme 54

The reaction of cyanoacetamide **3f** with ethyl chloroacetate **24a** and α -chloroacetic acid **24c** afforded the acyclic products **128a** and **128b**, respectively *via* loss of potassium chloride. Thiazolidine derivative **129** was obtained by cyclization of **128a** in ethanol at reflux in the presence of piperidine, through dehydration of water. On the other hand, heating of **128b** in ethanol at reflux in the presence of piperidine afforded the novel thiazolidinone **130**, via elimination of ethanol with partial hydrolysis of cyano group (Scheme 55).⁸³



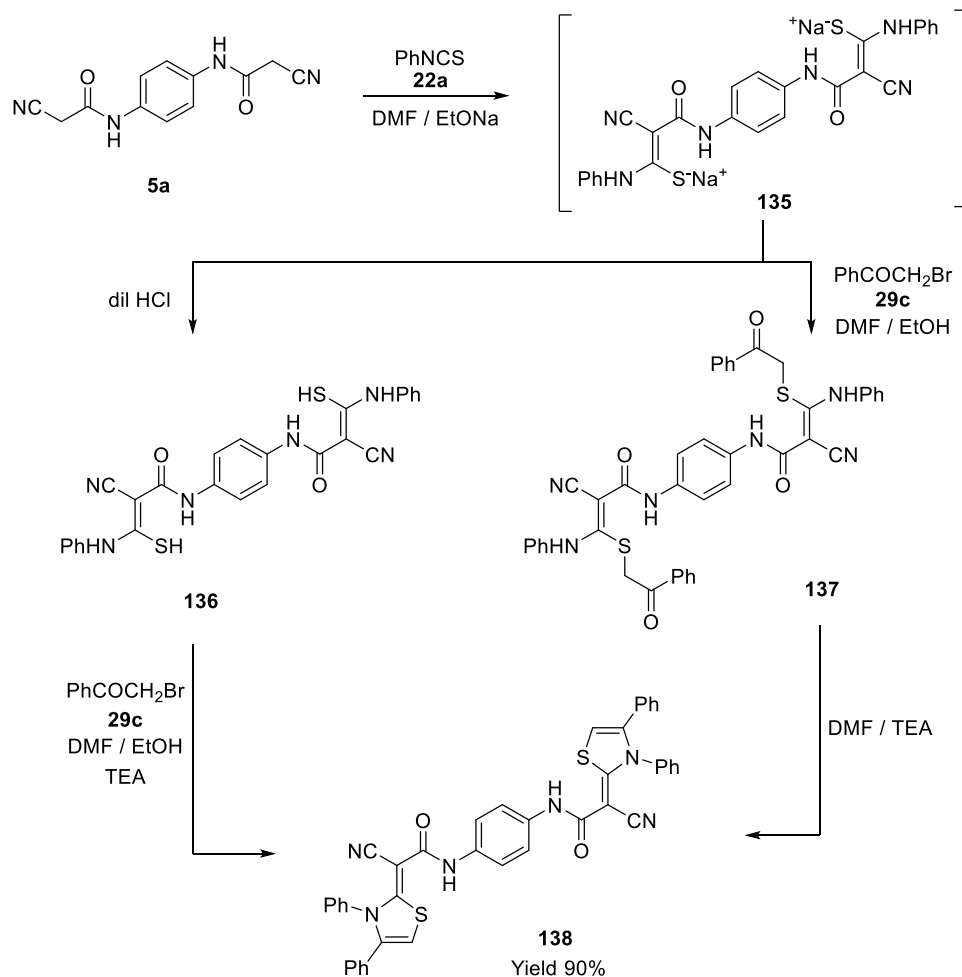
Scheme 55

Compound **3bd** reacted with phenyl isothiocyanate **22a** in dry DMF in the presence of KOH followed by addition of chloroacetyl chloride **8** to give 2-(5-oxothiazolidin-2-ylidene)cynoacetamido derivative **132** via the intermediate **131**. Acidification of the potassium salt **131** gave the corresponding thiocarbamoyl derivative **133**. Heating of compound **133** in dioxane at reflux with ethyl chloroacetate **24a** led to the formation of 4-oxo-3-phenyl-thiazolidin-2-ylidene derivative **134** (Scheme 56).⁴⁷



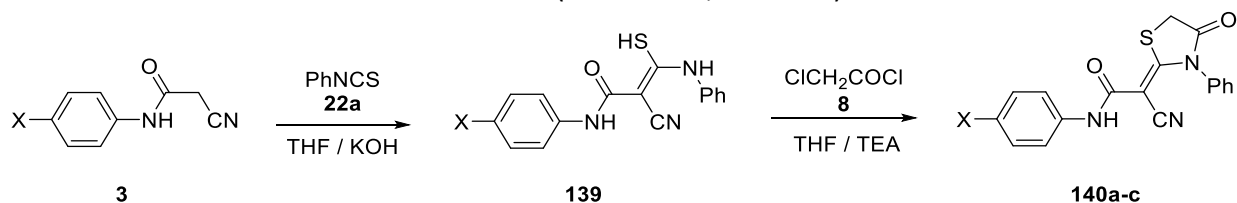
Scheme 56

Compound **5a** with phenyl isothiocyanate **22a** in DMF at room temperature in basic medium afforded of the non-isolable intermediate **135** which furnished thiocarbamoyl **136** upon treatment with HCl. Compound **136** yielded the product **138** upon reaction with phenacyl bromide **29c** in ethanol / DMF in presence of triethylamine. The reaction of **135** with phenacyl bromide **29c** in a mixture of ethanol and DMF (2:1) at room temperature afforded the acyclic intermediate **137** via HBr elimination. Heating of compound **137** in DMF at reflux with few drops of triethylamine afforded the product **138** (Scheme 57).¹⁰⁰



Scheme 57

2-Cyano-3-mercapto-3-phenylamino-*N*-arylacrylamides **139** were prepared *via* electrophilic attack of phenyl isothiocyanate **22a** on the active methylene of compounds **3**. The reaction was conducted in dry tetrahydrofuran in the presence of KOH. Reaction of **139** with chloroacetyl chloride **8** and catalytic amount of TEA afforded the 4-thiazolidinone derivatives **140** (Scheme 58, Table 21).¹⁰¹



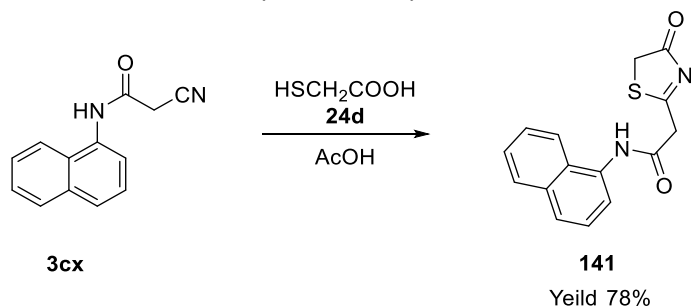
Scheme 58

Table 21. Synthesis and % yields of **140a-c**

Entry	Product	X	Yield (%)
3a	140a	H	73
3bz	140b	Me	67
3co	140c	Cl	65

C. Synthesis *via* cycloaddition reactions

Cyclocondensation of 1-naphthyl-2-cyanoacetamide **3cx** with sulfanylacetic acid **24d** in glacial acetic acid at reflux furnished the thiazolinone derivative **141** (Scheme 59).⁸⁶

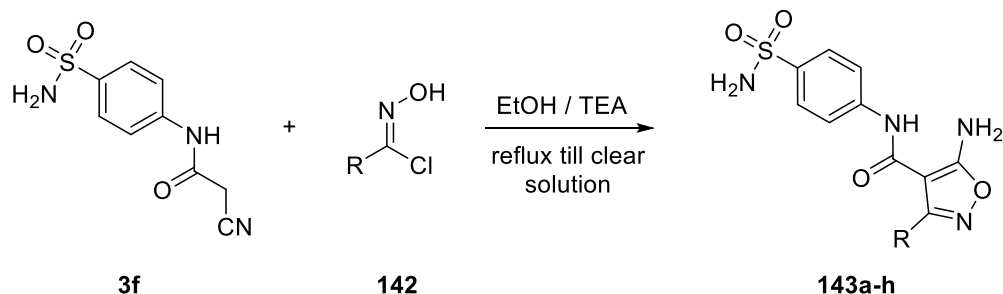


Scheme 59

3.1.2.6. Isoxazole derivatives

A. Synthesis *via* Michael addition reactions

N-(4-Sulfamoylphenyl)isoxazole-4-carboxamide compounds **143** were obtained through the reaction of hydroxymoyl chloride **142** with 2-cyano-*N*-(4-sulfamoylphenyl)acetamide **3f** in ethanol in the presence of triethylamine (Scheme 60, Table 22).¹⁰²



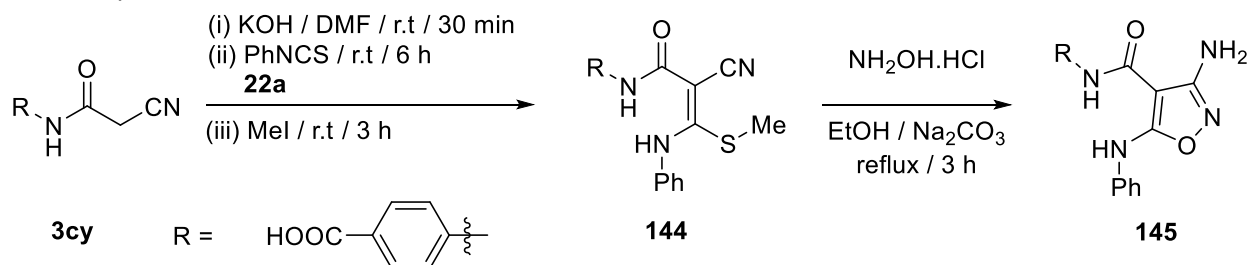
Scheme 60

Table 22. Synthesis and % yields of **143a-h**

Entry	Product	R	Yield (%)
142a	143a	2,6-Cl ₂ C ₆ H ₃	52
142b	143b	2,4-Cl ₂ C ₆ H ₃	27
142c	143c	4-ClC ₆ H ₄	24
142d	143d	4-BrC ₆ H ₄	26

Entry	Product	R	Yield (%)
142e	143e	Ph	35
142f	143f	2-NO ₂ C ₆ H ₄	64
142g	143g	5-Cl-2-furyl	53
142h	143h	5-Cl-2-thienyl	15

The reaction between compound **3cy** and phenyl isothiocyanate **22a** following by addition of methyl iodide gave compound **144** which reacted with hydroxylamine hydrochloride to produce isoxazole derivatives **145** (Scheme 61).¹⁰³

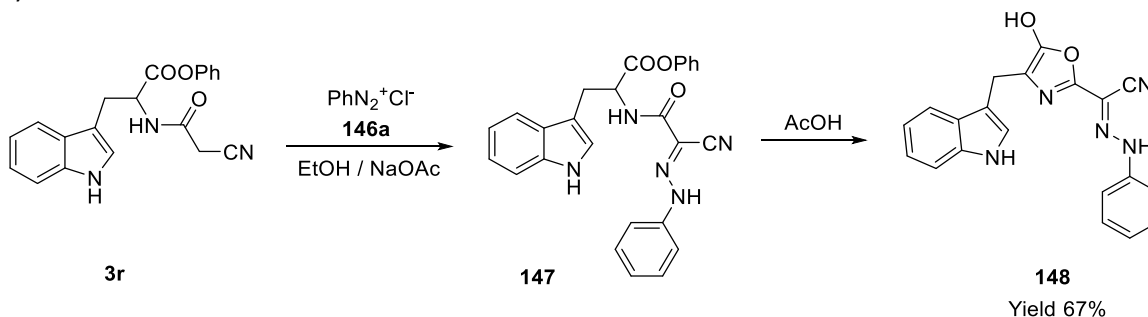


Scheme 61

3.1.2.7. Oxazole derivatives

A. Synthesis *via* coupling reactions

The reaction of **3r** with benzenediazonium chloride **146a** afforded the hydrazone **147**. Heating of compound **147** in acetic acid furnished the phenylhydrazonoindol-3-ylhydroxyoxazol-2-yl acetonitrile derivative **148** (Scheme 62).¹⁰⁴



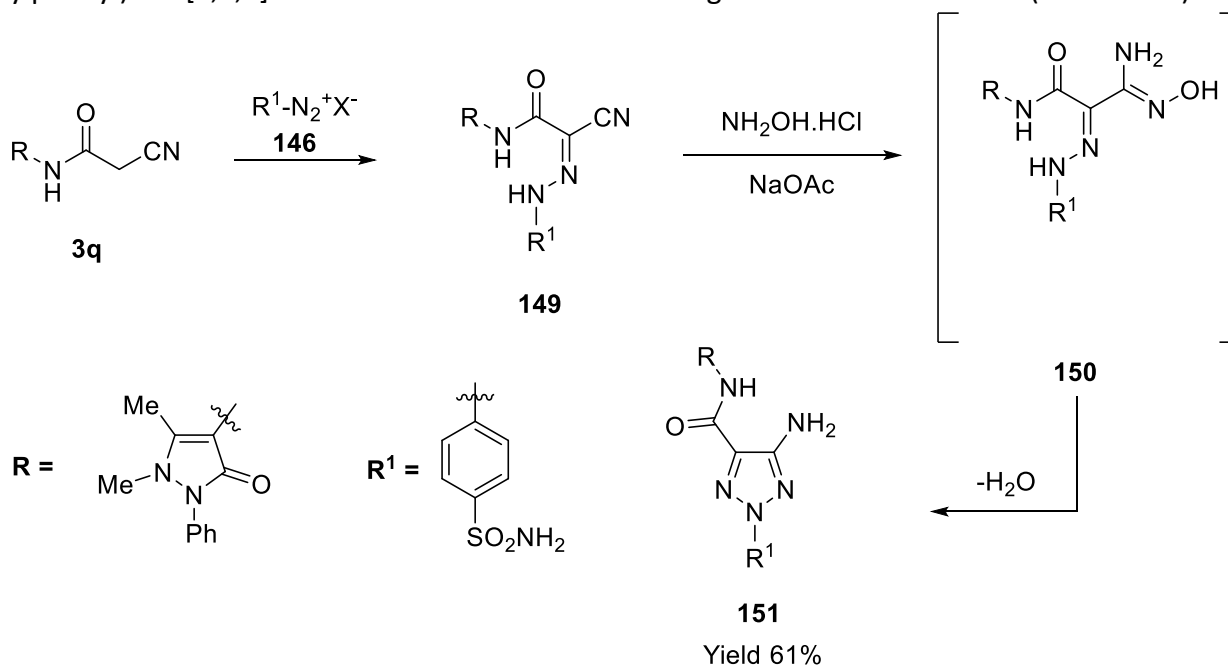
Scheme 62

3.1.3. Monocyclic five-membered rings with three hetero atoms

3.1.3.1. Triazole derivatives

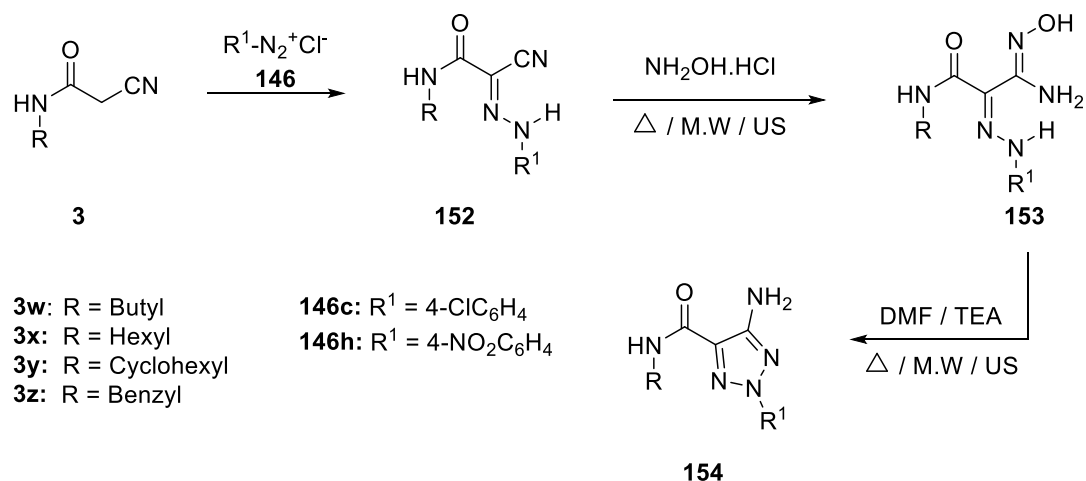
A. Synthesis *via* coupling reactions

Coupling of cyanoacetamide **3q** with diazonium salts **146** in pyridine gave the hydrazone **149**. Treatment of compound **149** with hydroxylamine hydrochloride in DMF in the presence of anhydrous sodium acetate furnished the corresponding 5-amino-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-(4-sulfamoylphenyl)-2*H*-[1,2,3]triazole-4-carboxamide **151** through the intermediate **150** (Scheme 63).¹⁰⁵



Scheme 63

Compounds **3w-z** were readily coupled with aromatic diazonium salts **146** to afford the corresponding arylhydrazononitriles **152**. The reaction of compounds **152** with hydroxylamine hydrochloride in the presence of sodium acetate affords the amidoximes **153**. Upon heating **153** in DMF in different reaction conditions afforded the solid product **154** (Scheme 64, Table 23).²⁹



Scheme 64

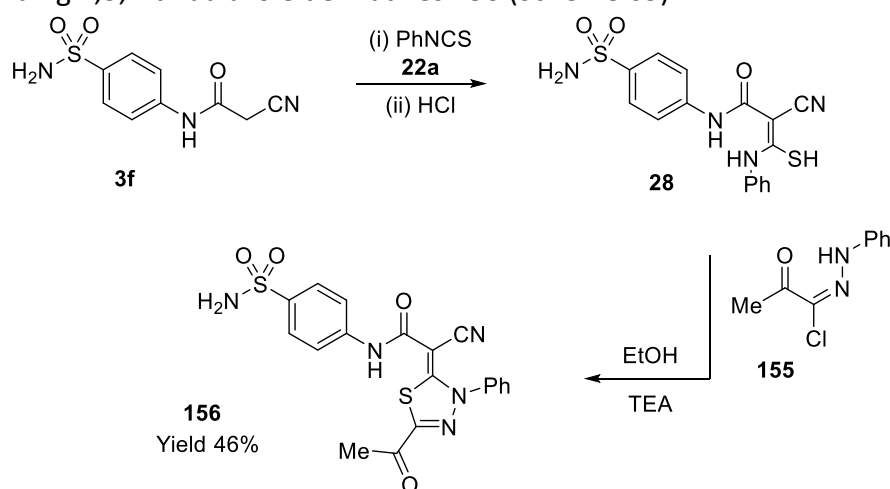
Table 23: Synthesis and % yields of **154a-e**

Product	R	R ¹	Yield (%)		
			Δ	M.W	US
154a	Butyl	4-ClC ₆ H ₄	60	77	73
154b	Benzyl	4-ClC ₆ H ₄	55	84	78
154c	Butyl	4-NO ₂ C ₆ H ₄	59	79	70
154d	Hexyl	4-NO ₂ C ₆ H ₄	58	89	84
154e	Cyclohexyl	4-NO ₂ C ₆ H ₄	54	80	78

3.1.3.2. 1,3,4-Thiadiazole derivatives

A. Synthesis *via* Michael addition reactions

The reaction of **3f** with phenyl isothiocyanate **22a** in DMF in the presence of KOH yielded the thioacetanilide **28**. Treatment of **28** with the hydrazonoyl chloride **155** in ethanol at reflux in the presence of triethylamine yielded the corresponding 1,3,4-thiadiazole derivatives **156** (Scheme 65).¹⁰⁶



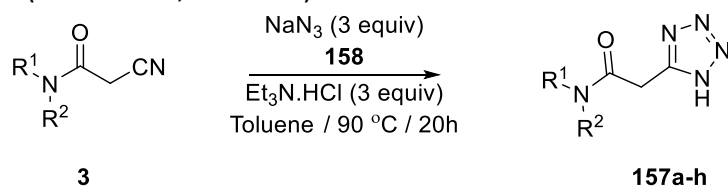
Scheme 65

3.1.4. Monocyclic five-membered rings with four hetero atoms

3.1.4.1. Tetrazole derivatives

A. Synthesis *via* cycloaddition reactions

Wang *et al*¹⁰⁷ reported the synthesis of 2-(1*H*-tetrazol-5-yl)acetamide **157a-h** through the cycloaddition of 2-cyanoacetamide derivatives **3cz-dg** with sodium azide **158** in the presence of triethylamine hydrochloride salt in toluene at 90°C for 20 hours (Scheme 66, Table 24).

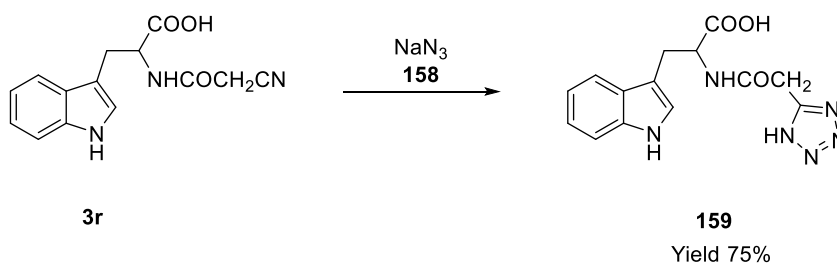


Scheme 66

Table 24. Synthesis and % yields of **157a-h**

Entry	Product	R ¹	R ²	Yield (%)
3cz	157a	Ph	Ph	56
3da	157b	Benzyl	Benzyl	67
3db	157c	PhCH ₂ CH ₂	PhCH ₂ CH ₂	74
3dc	157d	4-ClC ₆ H ₄	4-ClC ₆ H ₄	64
3dd	157e	2-furyl	2-furyl	21
3de	157f	Cyclopropanyl	Cyclopropanyl	55
3df	157g	Allyl	Allyl	25
3dg	157h	2-Naphthyl	2-Naphthyl	89

The reaction of compound **3r** with sodium azide **158** in DMF containing a catalytic amount of ammonium chloride has been carried out, and the indolyl tetrazolopropanoic acid **159** has been synthesized (Scheme 67).²⁴



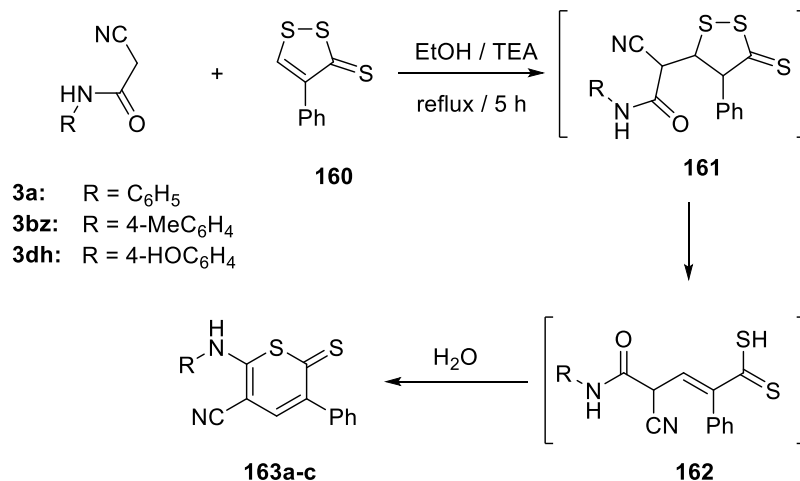
Scheme 67

3.1.5. Monocyclic six-membered rings with one hetero atom

3.1.5.1. Thiopyran (Thiine) derivatives

A. Synthesis *via* Michael addition reactions

The reaction of *N*-arylcianoacetamide compounds **3** with 4-phenyl-3*H*-1,2-dithiole-3-thione **160** in ethanol at reflux in the presence of triethylamine as a basic catalyst afforded the thiopyran derivatives **163a-c** *via* the intermediacy of **161** and **162** (Scheme 68, Table 25).¹⁰⁸



Scheme 68

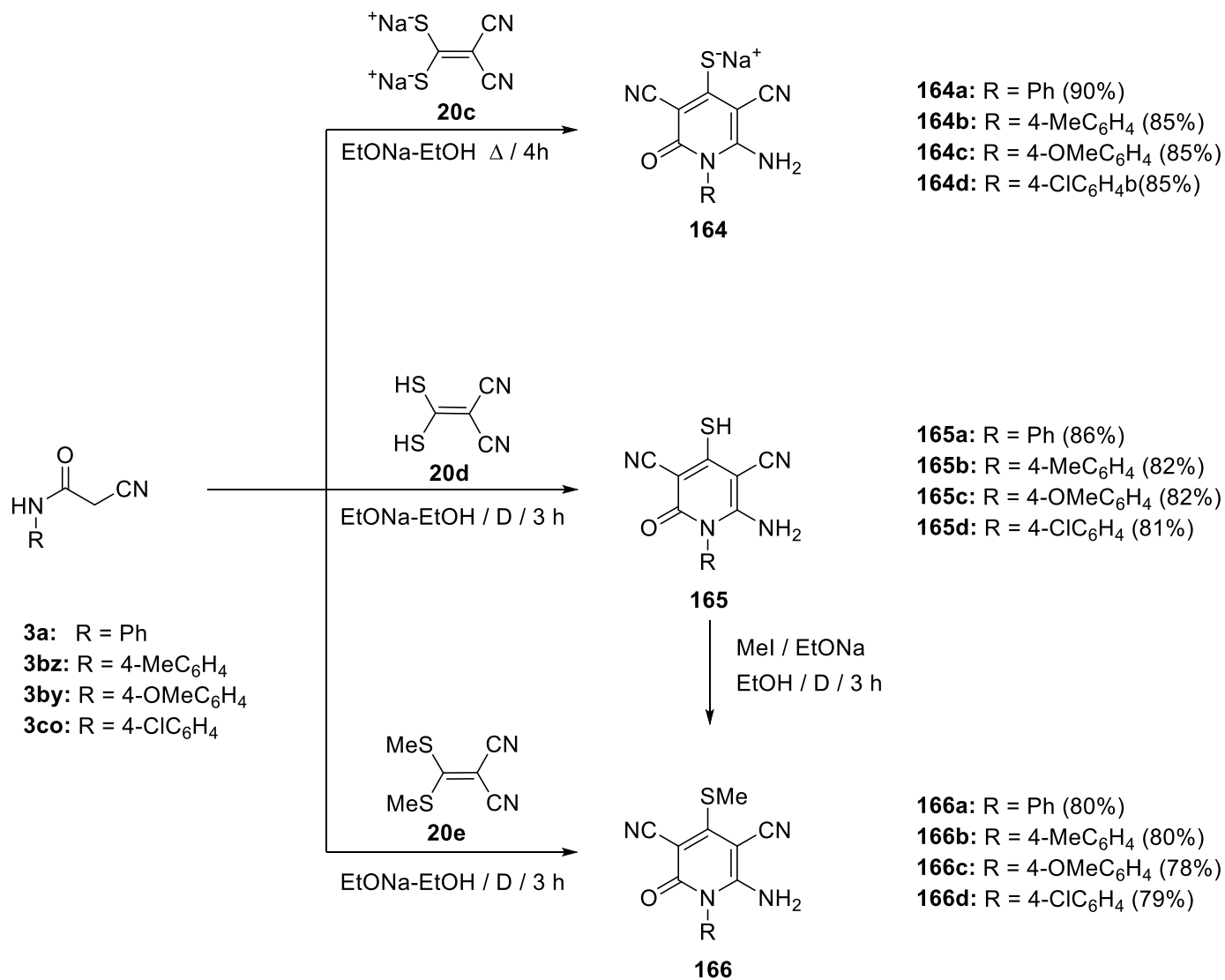
Table 25. Synthesis and % yields of **163a-c**

Product	Ar	Yield (%)
163a	C ₆ H ₅	83
163b	4-MeC ₆ H ₄	76
163c	4-HOC ₆ H ₄	77

3.1.5.2. Pyridine derivatives

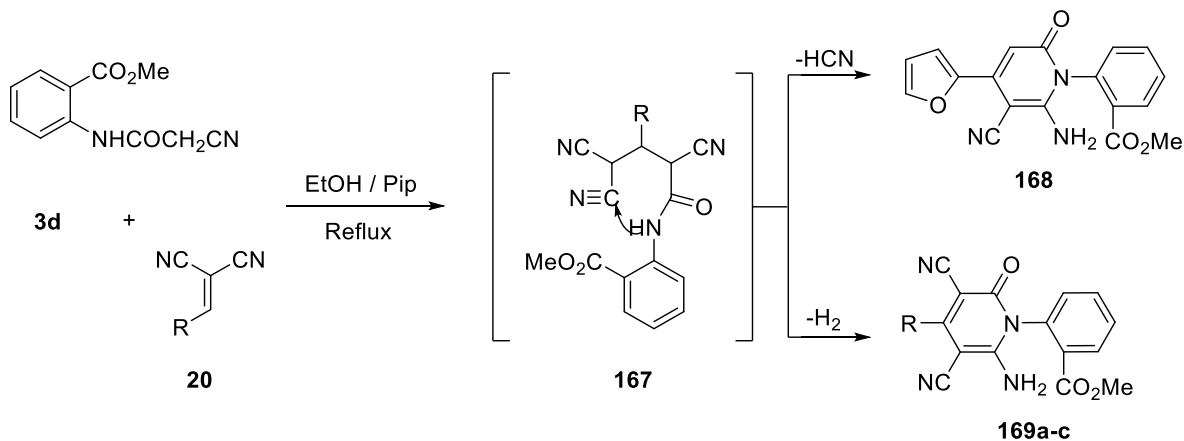
3.1.5.2.1. Synthesis *via* Michael addition reactions

Compound **20c** is readily reacted with a series of 2-cyano-*N*-arylacetylamine **3** in sodium ethoxide to yield the corresponding sodium thiolate derivatives **164** in good yields. Treatment of compounds **3** with **20d** in sodium ethoxide, followed by acidification furnished the corresponding 4-mercaptopyridines **165**. Methylation of compounds **165** with methyl iodide in sodium ethoxide afforded the 4-methylsulfanylpyridines **166**. Compounds **166** can also be prepared by reaction of **3** with [bis(methylthio)methylene]malononitrile **20e** in sodium ethoxide (Scheme 69).¹⁰⁹



Scheme 69

It was assumed that pyridones **168** and **169** were formed *via* the Michael addition of active methylene group of compound **3d** to the β-carbon of cinnamionitriles **20h-k** to afford the Michael adduct **167**. Intramolecular cyclization of **167** followed by HCN or H₂ elimination afforded pyridones **168** and **169a-c** respectively (Scheme 70, Table 26).¹⁶

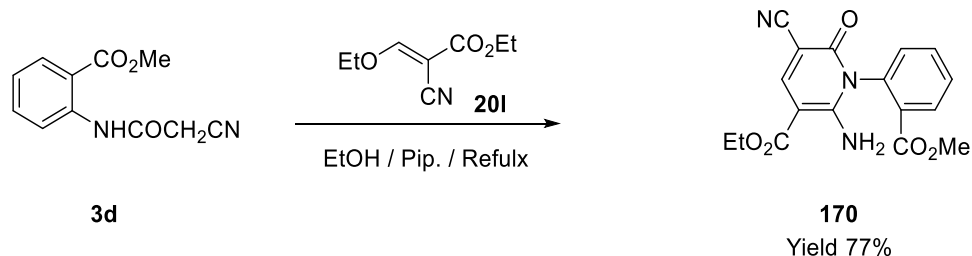


Scheme 70

Table 26. Synthesis and % yields of **168** and **169a-c**

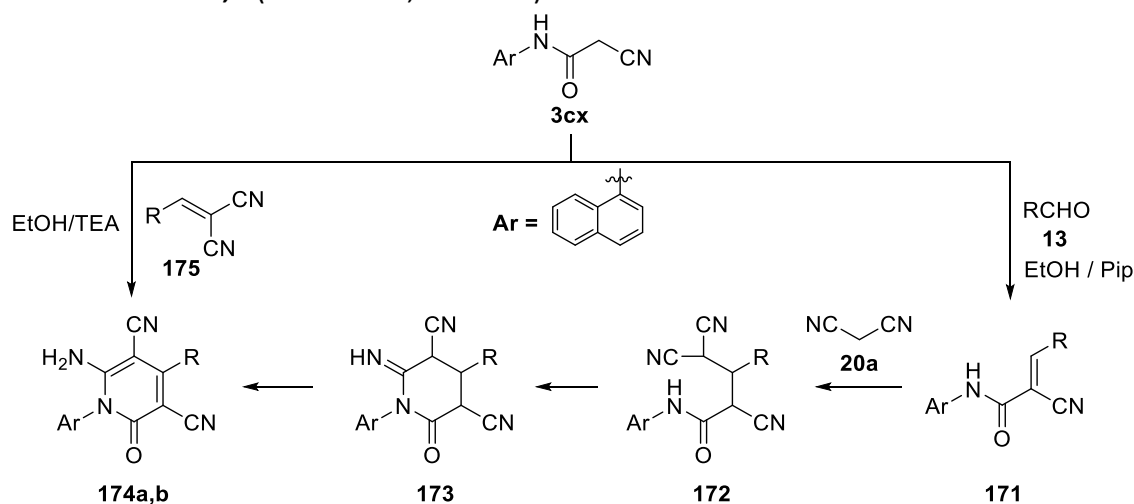
Entry	Product	R	Yield (%)
20h	168	2-Furyl	60
20i	169a	2-ClC ₆ H ₄	71
20j	169b	2,4-Cl ₂ C ₆ H ₄	74
20k	169c	4-N(Me) ₂ C ₆ H ₄	86

Also, reaction of **3d** with ethyl (*E*)-2-cyano-3-ethoxyacrylate **20i** furnished the pyridone **170** (Scheme 71).¹⁶



Scheme 71

Compound **3cx** reacted with aldehydes **13i** and **13j** to afford the corresponding cyanoacrylamide derivatives **171a,b**. The reaction of the latter compounds with malononitrile **20a** afforded the aminopyridone derivatives **174a,b** via Michael type addition followed by auto-oxidation of the intermediates **172** and **173**. Reaction of **3cx** with the benzylidenemalononitriles **175a,b** under the same reaction conditions affords products identical with **174a,b** (Scheme 72, Table 27).¹¹⁰

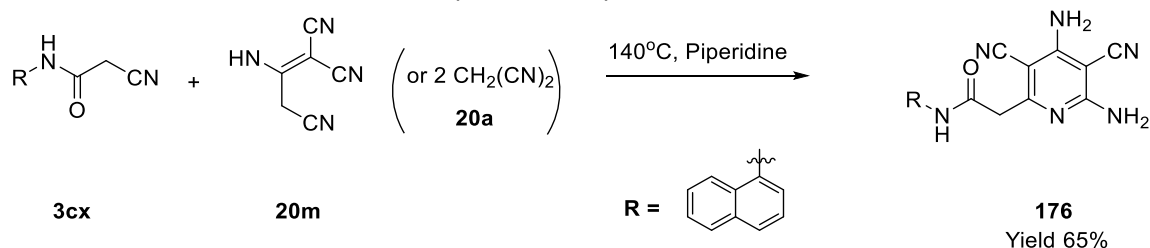


Scheme 72

Table 27. Synthesis and % yields of **174a,b**

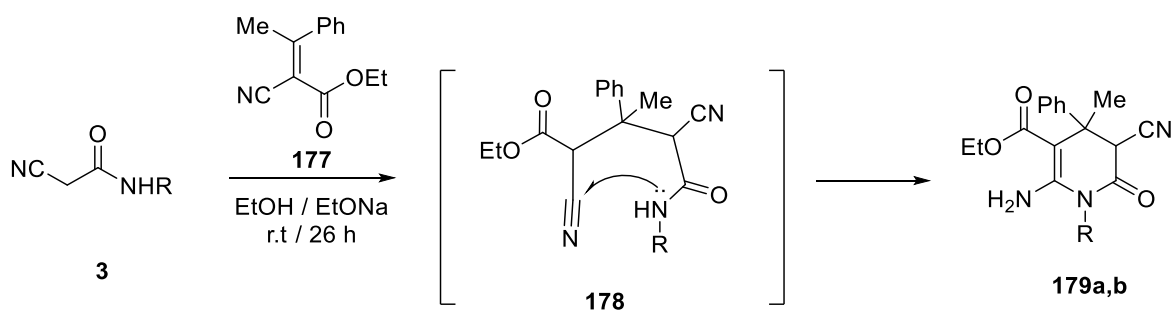
Entry	Product	R	Yield (%)
13i & 175a	174a	4-OHC ₆ H ₅	85
13j & 175b	174b	3,4-OCH ₂ OC ₆ H ₃	80

Reaction of **3cx** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **20m** or malononitrile **20a** in the molar ratio 1:2 give pyridine carboxamide derivative **176** (Scheme 73).¹¹⁰



Scheme 73

Cyanoacetanilides **3a** and **3di** reacted with ethyl 2-cyano-3-phenylbut-2-enoate **177** to give 6-aminopyridones **179a** and **179b** through the intermediacy of Michael adduct **178** when (Scheme 74, Table 28).¹¹¹

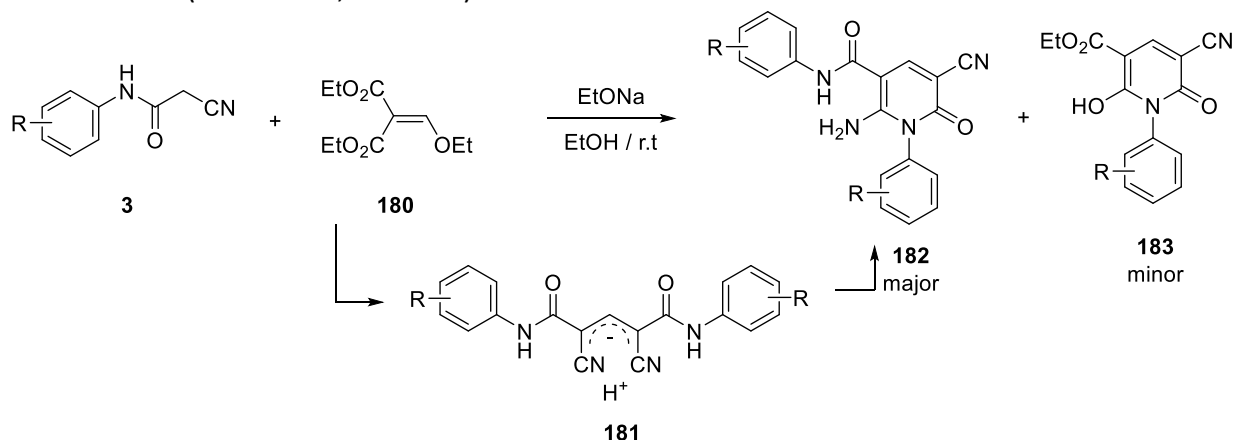


Scheme 74

Table 28: Synthesis and % yields of **179a,b**:

Entry	Product	R	Yield (%)
3a	179a	Ph	32
3di	179b	3-MeC ₆ H ₄	72

The reaction of diethyl ethoxymethylenemalonate (DEEMM) **180** with cyanoacetanilides **3** was found to give *N*,1-diaryl-substituted pyridone-3-carboxamides **182** instead of the expected ethyl 1-arylpyridone-3-carboxylates **183**, which also was formed in low % yields. Compound **182** was expected to be formed through the intermediate **181** (Scheme 75, Table 29).¹¹²



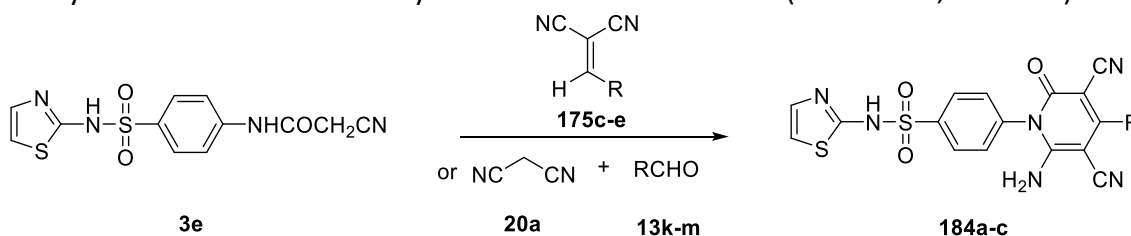
Scheme 75

Table 29. Synthesis of **182a-g**

Entry	Product	R
3a	182a	H
3bz	182b	4-Me
3co	182c	4-Cl
3di	182d	3-Me

Entry	Product	R
3dj	182e	2-MeO
3dk	182f	2-Et
3dl	182g	2-NO ₂

One-pot three component reactions of the cyanoacetanilide derivative **3e** with aldehydes **13k-m** and malononitrile **20a** (1:1:1 molar ratio) at reflux in the presence of piperidine afforded the 2-pyridone derivatives **184**. The 2-pyridone derivatives **184a-c** were also obtained under the same reaction conditions *via* the reaction of cyanoacetanilide **3e** with arylidenemalononitrile **175c-e** (Scheme 76, Table 30).¹⁷

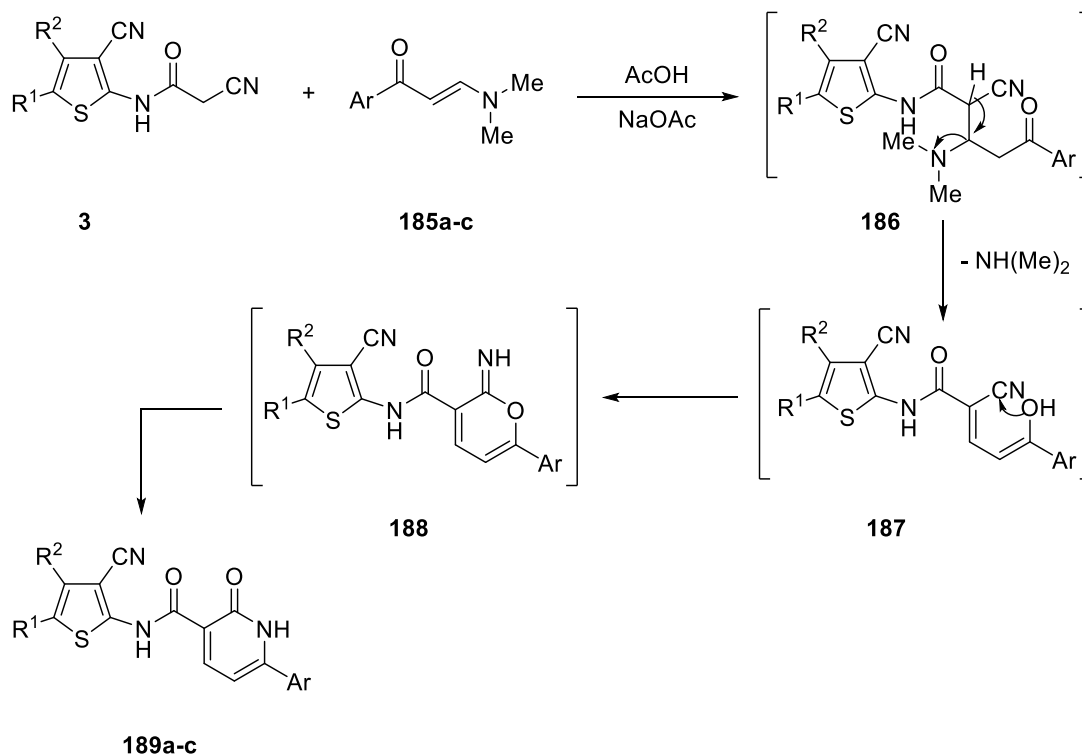


Scheme 76

Table 30. Synthesis and % yields of **184a-c**

Entry	Product	R	Yield (%)
13k, 175c	184a	Ph	61
13l, 175d	184b	4-MeOC ₆ H ₄	63
13m, 175e	184c	4-NO ₂ C ₆ H ₄	65

The addition of a variety of enaminones **185a-c** to cyanoacetamides **3** gave intermediate adduct **186**, that eliminates dimethylamine group to give **187** that cyclized to **188** which then rearranged to the final pyridine derivatives **189a-c** (Scheme 77, Table 31).⁴²

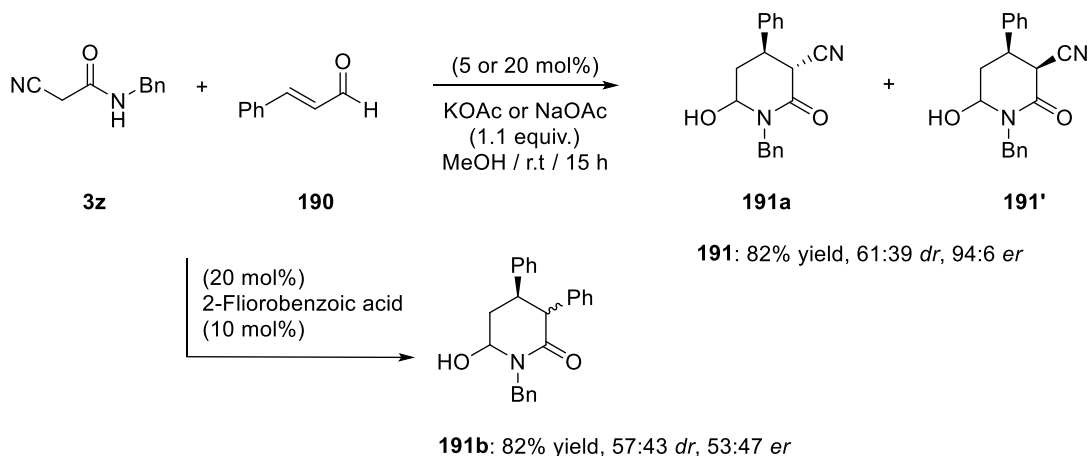


Scheme 77

Table 31. Synthesis and % yields of 189a-c

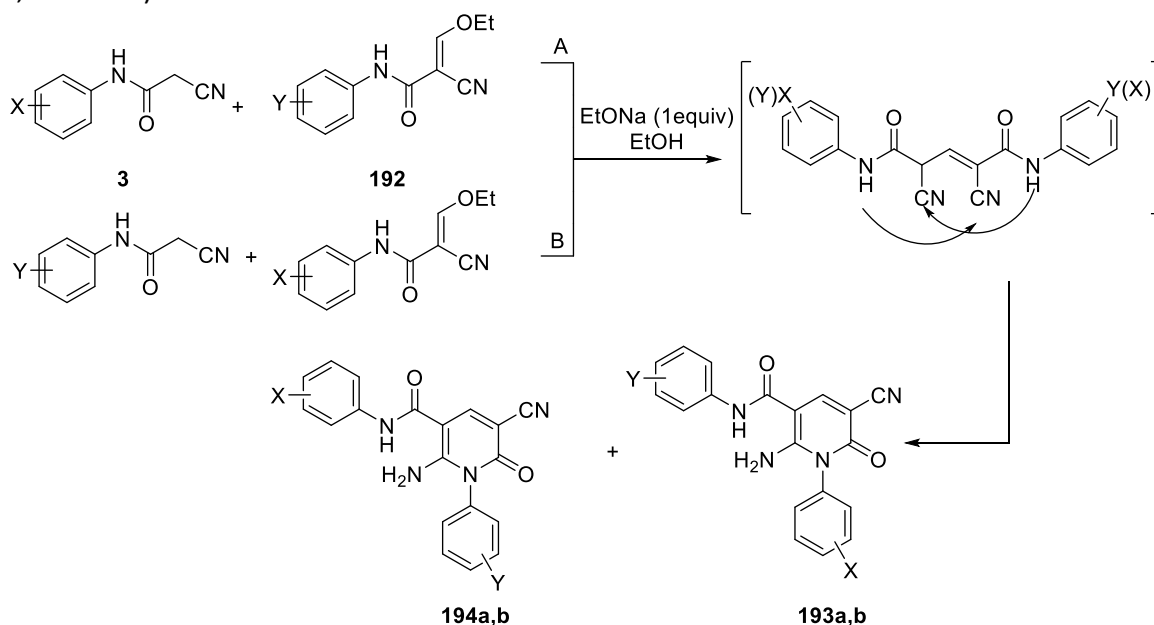
Entry	Product	R ¹	R ²	Ar	Yield (%)
3aw, 185a	189a	H	Ph	Ph	70
3ax, 185b	189b	H	4-ClC ₆ H ₄		68
3ay, 185c	189c	CO ₂ Et	Me		63

The catalytic asymmetric Michael / hemiaminal cascade reaction of α -cyanoacetate ester **3z** with enal **190** afforded the corresponding hemiaminal **191b** in high yield and very low *dr* and *er* under the acid additive condition. The use of a base additive instead gave the corresponding heminal **191a** with high *er* but low *dr* (Scheme 78).¹¹³



Scheme 78

A series of reactions with compounds **3co**, **3dj** and **192a,b** having different substituents in the benzene rings was performed. These reactions led to the formation of two regioisomers **193** and **194** at different ratios (Scheme 79, Table 32).¹¹⁴

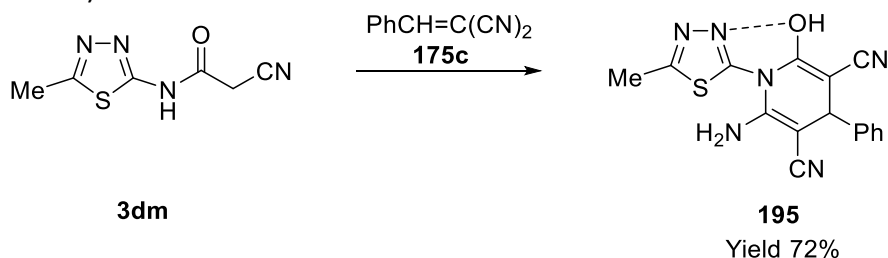


Scheme 79

Table 32 Synthesis and % yields of **193a-d** and **194a-d**

Path	X	Y	Products (ratio, %)
A	4-Cl	H	193a, 194a (71:29)
	4-Cl	2-MeO	193b, 194b (91:09)
B	4-Cl	H	193c, 194c (68:32)
	4-Cl	2-MeO	193d, 194d (83:17)

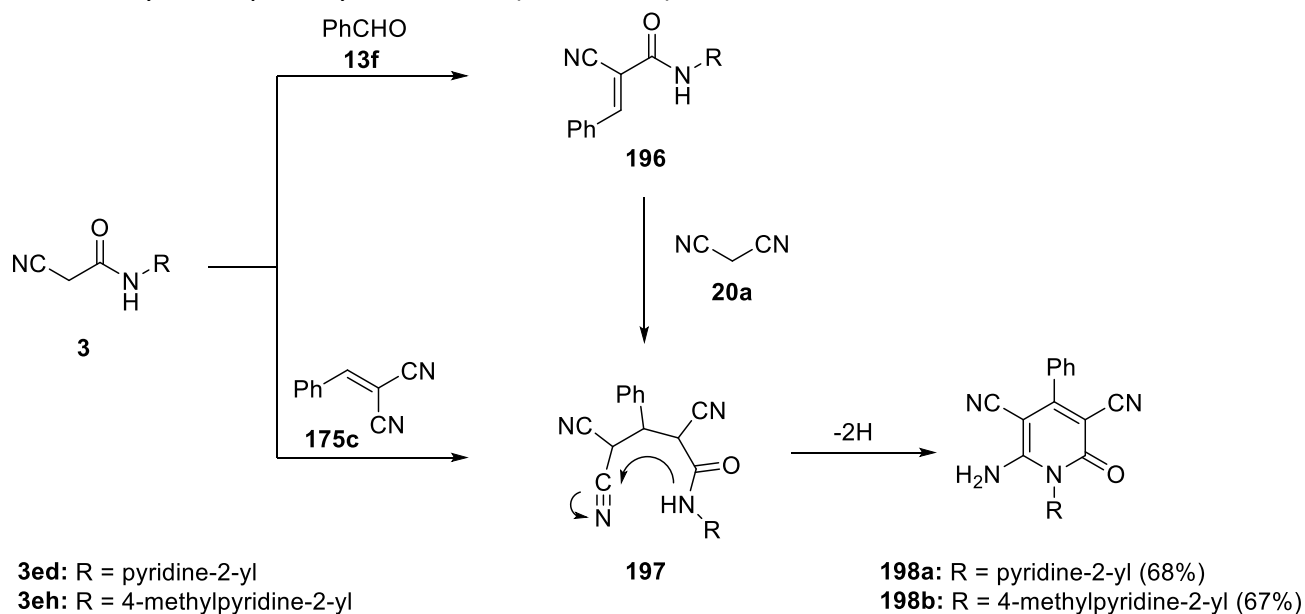
When compound **3dm** was reacted with benzylidenemalononitrile **175c** in a basic medium a pyridine derivative **195** was achieved. The resulting compound **195** exists in an enolic form, which is stabilized by the hydrogen bond (Scheme 80).¹¹⁵



Scheme 80

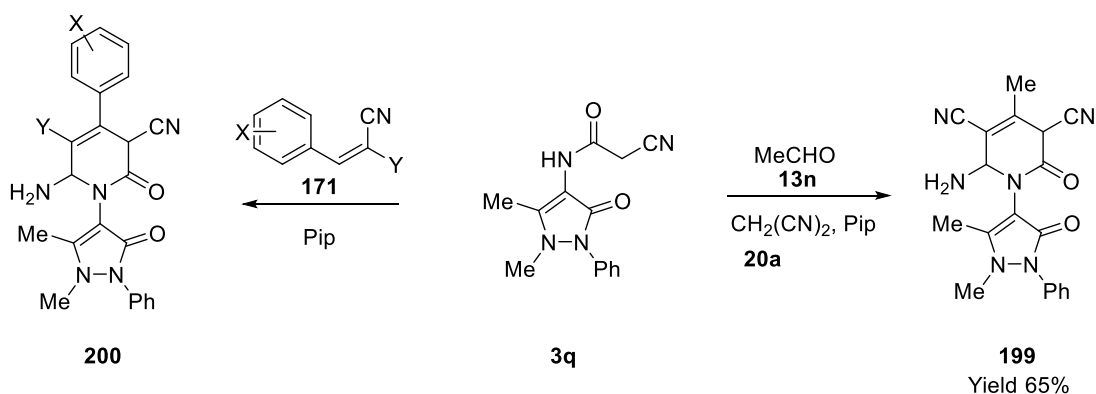
The Knoevenagel condensation of **3ed** and **3eh** with benzaldehyde **13f** in the presence of piperidine resulted in the formation of *N*-hetaryl-2-cyanoacrylamides **196**. The reaction of substituted acrylamide **196** as Michael acceptor with malononitrile **20a** afforded 6-amino-2-oxo-4-phenyl-1-aryl-1,2-dihydropyridine-3,5-dicarbonitrile **198a,b** through the intermediacy of the primary adduct **197** which undergoes chemoselective

heterocyclization with elimination of hydrogen. The substituted pyridin-2(1*H*)-one derivatives **198a,b** were also obtained *via* the reaction **3ed** and **3eh** with benzylidenemalononitrile **175c** according to Michael through the intermediacy of the primary adduct **197** (Scheme 81).¹¹⁶



Scheme 81

The 6-amino-1-(1*H*-pyrazol-4-yl)-4-methyl-2-oxotetrahydropyridine-3,5-dicarbonitrile **199** was obtained through a one-pot reaction of cyanoacetanilide **3q** with acetaldehyde **13n** and malononitrile **20a** in ethanol / piperidine. On the other hand, reaction of **3q** with arylidenes **171c-g** in presence of piperidine afforded substituted 6-amino-1-(1*H*-pyrazol-4-yl)-4-aryl-2-oxotetrahydropyridine-3,5-dicarbonitrile **200a-e** (Scheme 82, Table 33).¹¹⁷

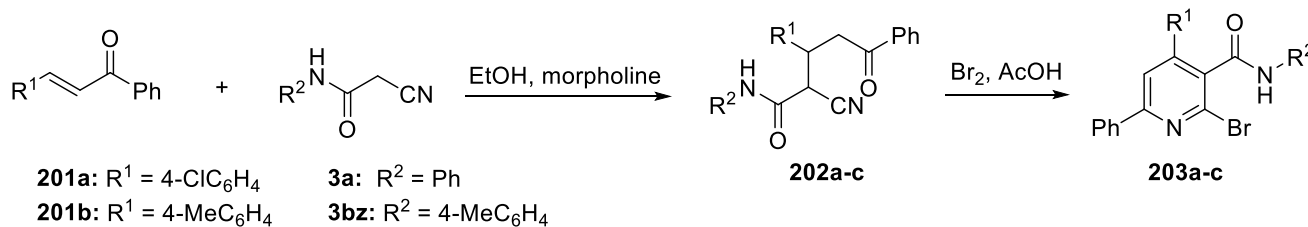


Scheme 82

Table 33. Synthesis and % yields of **200a-e**

Entry	Product	X	Y	Yield (%)
171c	200a	4-MeO	CN	55.5
171d	200b	3,4,5-(MeO) ₃	CN	82
171e	200c	4-Cl	CN	47
171f	200d	4-MeO	CO ₂ Et	40
171g	200e	4-Cl	CO ₂ Et	39

Reaction of chalcones **201a** and **201b** with cyanacetamides **3a** and **3bz** in ethanol at reflux in the presence of morpholine as a basic catalyst furnished the corresponding 2-cyanopentamides **202a-c**. Addition of bromine to pentamides **202a-c** in glacial acetic acid at 60–70°C afforded the 2-bromopyridine-3-carboxamides **203a-c** in 80–77% yield (Scheme 83, Table 34).¹¹⁸

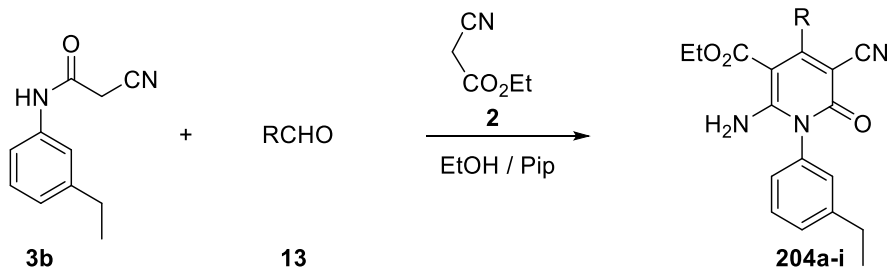


Scheme 83

Table 34. Synthesis and % yields of **203a-c**

Product	R ¹	R ²	Yield (%)
203a	4-ClC ₆ H ₄	Ph	82
203b	4-MeC ₆ H ₄	4-MeC ₆ H ₄	80
203c	4-MeC ₆ H ₄	Ph	77

A mixture of compound **3b**, aldehyde **13** and ethyl cyanoacetate **2** in ethanol containing a catalytic amount of piperidine was refluxed for 4 hours to give **204a-i** (Scheme 84, Table 35).¹⁵



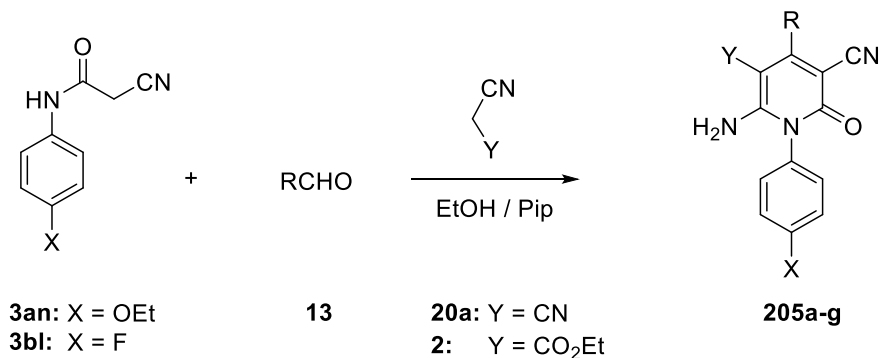
Scheme 84

Table 35. Synthesis and % yields of **204a-i**

Entry	Product	R	Yield (%)
13o	204a	4-MeC ₆ H ₄	71
13l	204b	4-MeOC ₆ H ₄	89
13p	204c	3-NO ₂ C ₆ H ₄	80
13m	204d	4-NO ₂ C ₆ H ₄	78
13j	204e	Pipronyl	81

Entry	Product	R	Yield (%)
13s	204f	2,3,4-(MeO) ₃ C ₆ H ₂	87
13t	204g	2-ClC ₆ H ₄	90
13u	204h	3-BrC ₆ H ₄	62
13v	204i	2-thienyl	91

6-Amino-2-oxo-1,2-dihydropyridine-3-carbonitriles **205a-g** were formed through the condensation and cycloaddition reaction of cyanoacetanilides **3an** and **3bl** with various aldehydes **13**, malononitrile **20a** /ethyl cyanoacetate **2** in ethanol/piperidine (Scheme 85, Table 36).¹¹⁹

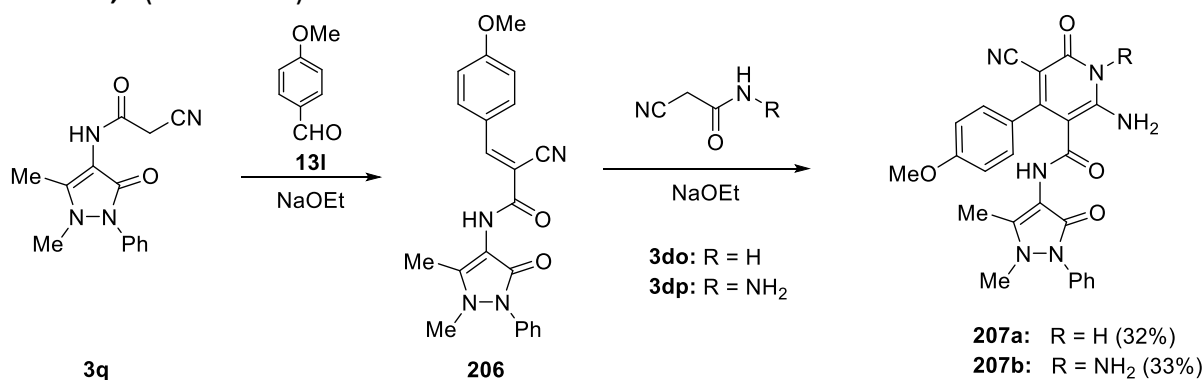


Scheme 85

Table 36. Synthesis and % yields of 205a-g

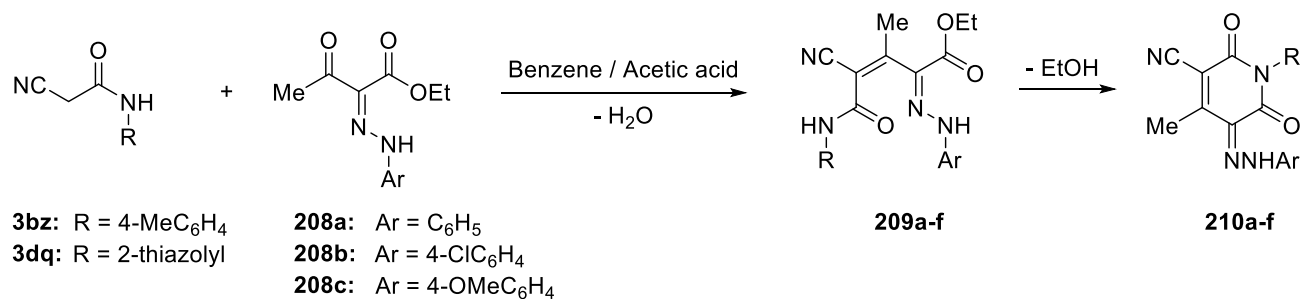
Entry	Product	X	Y	R	Yield (%)
13n	205a	F	CN	Me	80
13k	205b	F	CN	Ph	70
13k	205c	EtO	CN	Ph	76
13w	205d	F	CN	4-ClC ₆ H ₄	60
13w	205e	F	CO ₂ Et	4-ClC ₆ H ₄	65
13x	205f	F	CO ₂ Et	4-MeOC ₆ H ₄	70
13s	205g	F	CN	3,4,5-(MeO) ₃ C ₆ H ₂	75

Treatment of **3q** with 4-anisaldehyde **13l** resulted in the formation of the arylidene **206** which undergoes Michael addition reaction with cyanoacetamide **3do** or cyano-acetic acid hydrazide **3dp** to afford the desired compounds **207a,b** (Scheme 86).¹¹⁷



Scheme 86

The reaction of ethyl 2-arylhya-zono-3-butyrates **208a-c** with cyanoacetamide derivatives **3bz** and **dq** in a mixture of benzene/acetic acid solution afforded pyridine-2,6-dione derivatives **210a-f**. The key precursor for the products is the expected Knoevenagel condensation intermediate **209**. Elimination of ethanol yields the isolable pyridine-2,6-diones **210a-f** (Scheme 87, Table 37).¹²⁰

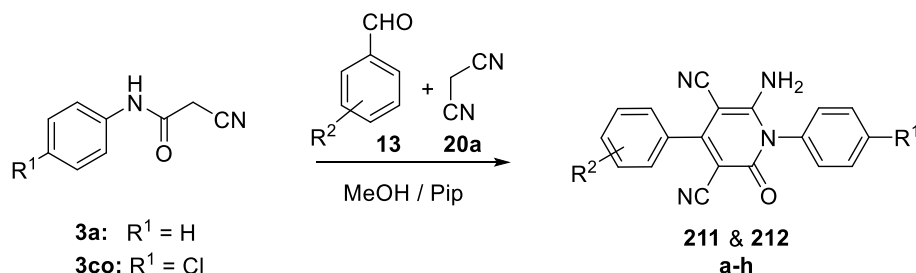


Scheme 87

Table 37. Synthesis and % yields of **210a-f**

Product	R	Ar	Yield (%)
210a	4-MeC ₆ H ₄	Ph	75
210b	4-MeC ₆ H ₄	4-ClC ₆ H ₄	70
210c	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	65
210d	2-thiazolyl	Ph	60
210e	2-thiazolyl	4-ClC ₆ H ₄	64
210f	2-thiazolyl	4-MeOC ₆ H ₄	60

The 6-amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **211a-h** and **212a-h** were prepared by reacting cyanoacetamides **3a** and **3co** with aldehydes **13** and malononitrile **20a** *via* Michael addition reaction (Scheme 88, Table 38).¹³



Scheme 88

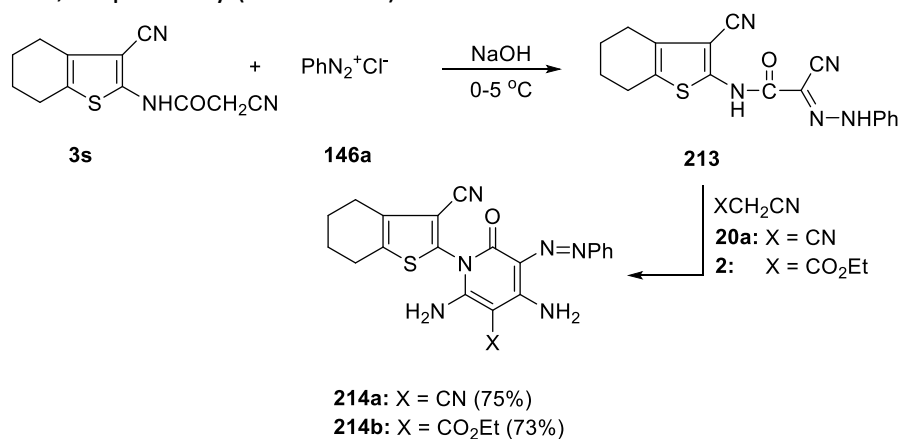
Table 38. Synthesis and % yields of **211a-h** and **212a-h**

Entry	Product	R ¹	R ²	Yield (%)
13m	211a	H	4-NO ₂	76
13o	211b	H	4-CH ₃	78
13p	211c	H	3-NO ₂	69
13t	211d	H	2-Cl	77
13w	211e	H	4-Cl	72
13x	211f	H	4-OCH ₃	73
13y	211g	H	3-Cl	69
13z	211h	H	4-Br	78

Entry	Product	R ¹	R ²	Yield (%)
13m	212a	Cl	4-NO ₂	76
13o	212b	Cl	4-CH ₃	70
13p	212c	Cl	3-NO ₂	79
13t	212d	Cl	2-Cl	77
13w	212e	Cl	4-Cl	70
13x	212f	Cl	4-OCH ₃	72
13y	212g	Cl	3-Cl	69
13z	212h	Cl	4-Br	71

3.1.5.2.2. Synthesis *via* coupling reactions

Compound **3s** reacted with benzenediazonium chloride **146a** to give the phenylhydrazo derivative **213**, which then reacted with either malononitrile **20a** or ethyl cyanoacetate **2** to give the 3-phenylazo-pyridone derivatives **214a** or **214b**, respectively (Scheme 89).²⁵

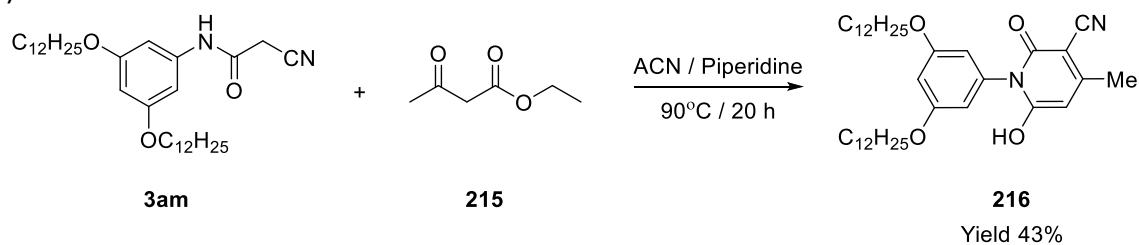


Scheme 89

C. Synthesis *via* Knoevenagel condensation reactions

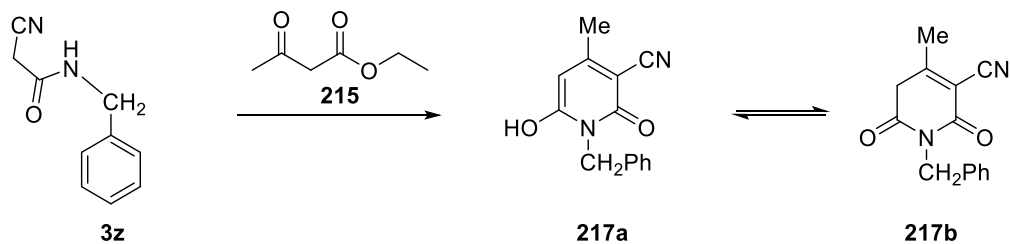
Knoevenagel condensation of cyanoacetamides with β -Ketoesters and 1,3-diketones

The bis(dodecyloxy)amide **3am** is condensed with ethyl acetoacetate **215** to give hydroxypyridone **216** (Scheme 90).³⁸



Scheme 90

The condensation of compound **3z** with ethyl acetoacetate **215** mediated by either microwave or US led to the formation of product **217a** in equilibrium with its tautomeric form **217b** (Scheme 91, Table 39).³¹

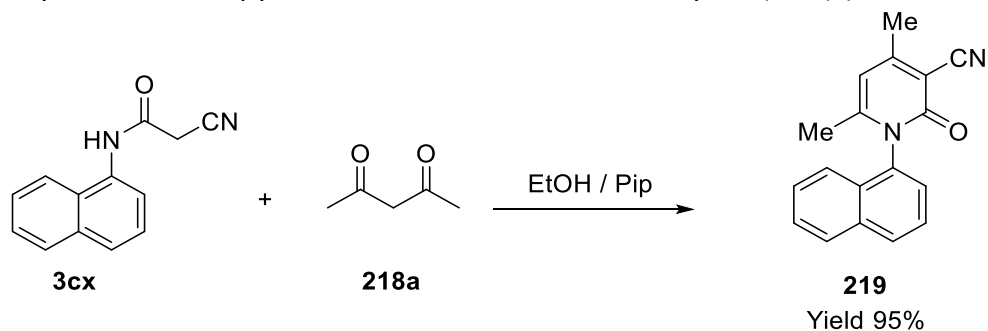


Scheme 91

Table 39. Synthesis and % yields of **217a,b**

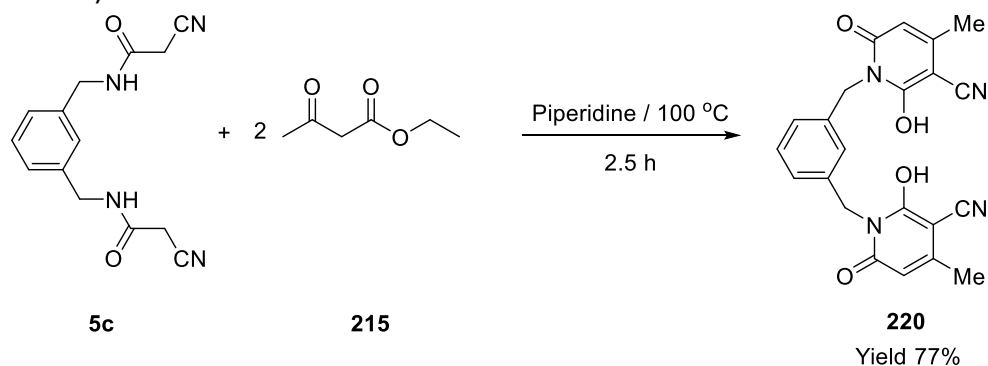
Compound	Yield (%)		
	Δ	M.W	US
217a,b	72	93	88

2-Cyano-*N*-(1-naphthyl)acetamide **3cx** was reacted with acetylacetone **218a** in ethanol in the presence of piperidine as a catalyst to form the pyridine-2-one **219** in an excellent yield (95%) (Scheme 92).¹¹⁰



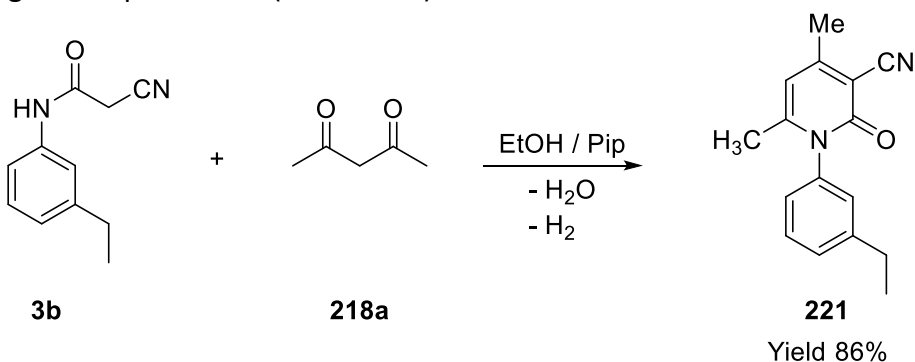
Scheme 92

The condensation of diamide **5c** with two moles of ethyl acetoacetate **215** afforded the bis(pyridone) **220** in 77% yield (Scheme 93).¹²¹



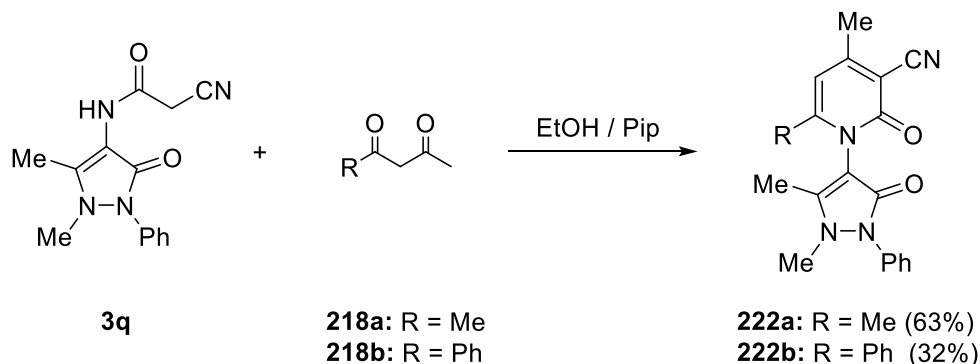
Scheme 93

Equimolar amounts of compound **3b** and acetylacetone **218a** were refluxed in ethanol containing piperidine for 5 h to give compound **221** (Scheme 94).¹⁵



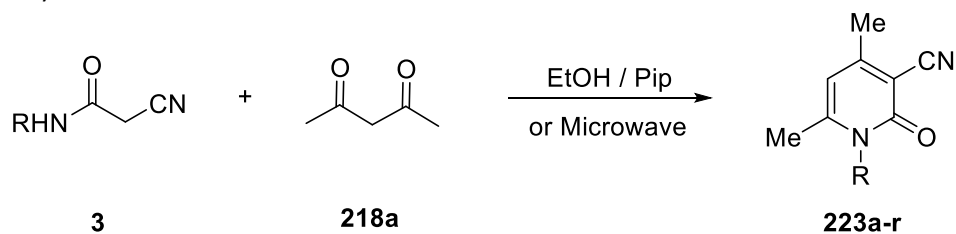
Scheme 94

Cyclocondensation of **3q** with acetylacetone **218a** or benzoylacetone **218b** in ethanol containing piperidine as a catalyst furnished the pyrazolyl-pyridine derivatives **222a,b** (Scheme 95).¹¹⁷



Scheme 95

N-Substituted-2-oxopyridine-3-carbonitrile derivatives **223a-r** were readily obtained through the reaction of acetylacetone **218a** and cyanoacetamides **3** under both conditions of microwave and thermal heating (Scheme 96, Table 40).⁹¹

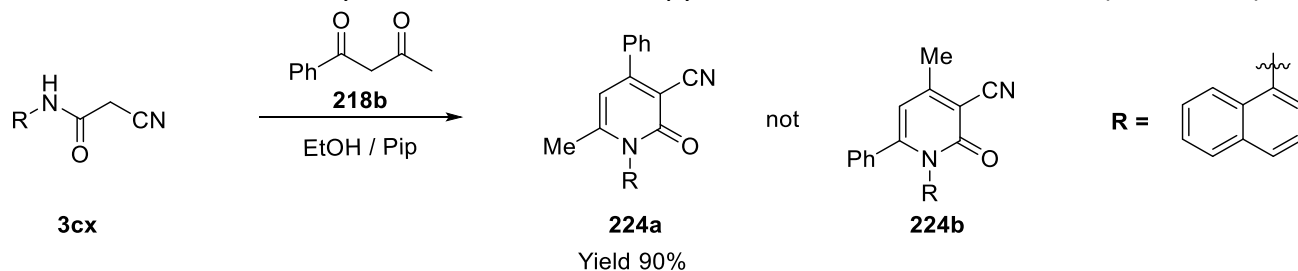


Scheme 96

Table 40: Synthesis and % yields of **223a-r**

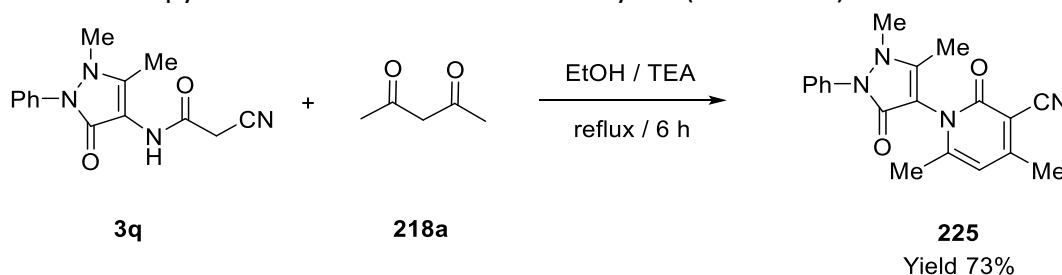
Entry	Product	R	Yield (%)	
			Microwave synthesis	Conventional synthesis
3do	223a	H	85	80
3ca	223b	Me	81	60
3ch	223c	Et	71	55
3bw	223d	Pr	72	46
3w	223e	Bu	66	30
3a	223f	Ph	96	75
3by	223g	4-MeOC ₆ H ₄	95	72
3co	223h	4-ClC ₆ H ₄	95	73
3bz	223i	4-MeC ₆ H ₄	97	75
3bl	223j	4-FC ₆ H ₄	99	72
3dr	223k	4-EtC ₆ H ₄	84	73
3ds	223l	4-NMe ₂ C ₆ H ₄	90	73
3bi	223m	4-BrC ₆ H ₄	86	76
3dt	223n	4-IC ₆ H ₄	86	73
3du	223o	4-AcC ₆ H ₄	91	80
3bj	223p	4-NO ₂ C ₆ H ₄	84	64
3cy	223q	4-CO ₂ HC ₆ H ₄	78	13
3dh	223r	4-OHC ₆ H ₄	34	91

Reaction of **3cx** with benzoylacetone **218b** afforded pyridones **224a** rather than **224b** (Scheme 97).¹¹⁰



Scheme 97

The nitrile derivative **3q** was treated with acetylacetone **218a** in the presence of triethylamine at reflux temperature to afford the pyridine-3-carbonitrile **225** in 73% yield (Scheme 98).²³

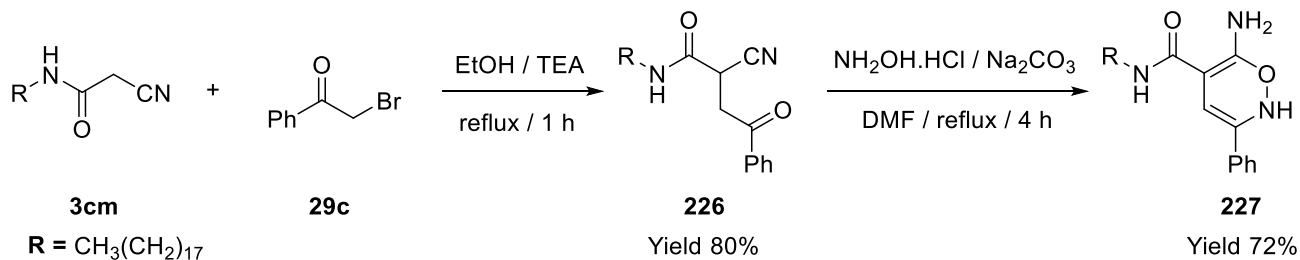


Scheme 98

3.1.6. Monocyclic six-membered rings with two hetero atoms

3.1.6.1. Oxazine derivatives

El-Sayed and Ahmed⁷⁹ reported the reaction of *N*-octadecyl-2-cyanoacetamide **3cm** with phenacyl bromide **29c** in ethanol in the presence of triethylamine under reflux affording the corresponding butanamide derivative **226** which was further cyclized with hydroxylamine hydrochloride in the presence of sodium carbonate in DMF under reflux to give the *2H*-1,2-oxazine-5-carboxamide derivative **227** (Scheme 99).

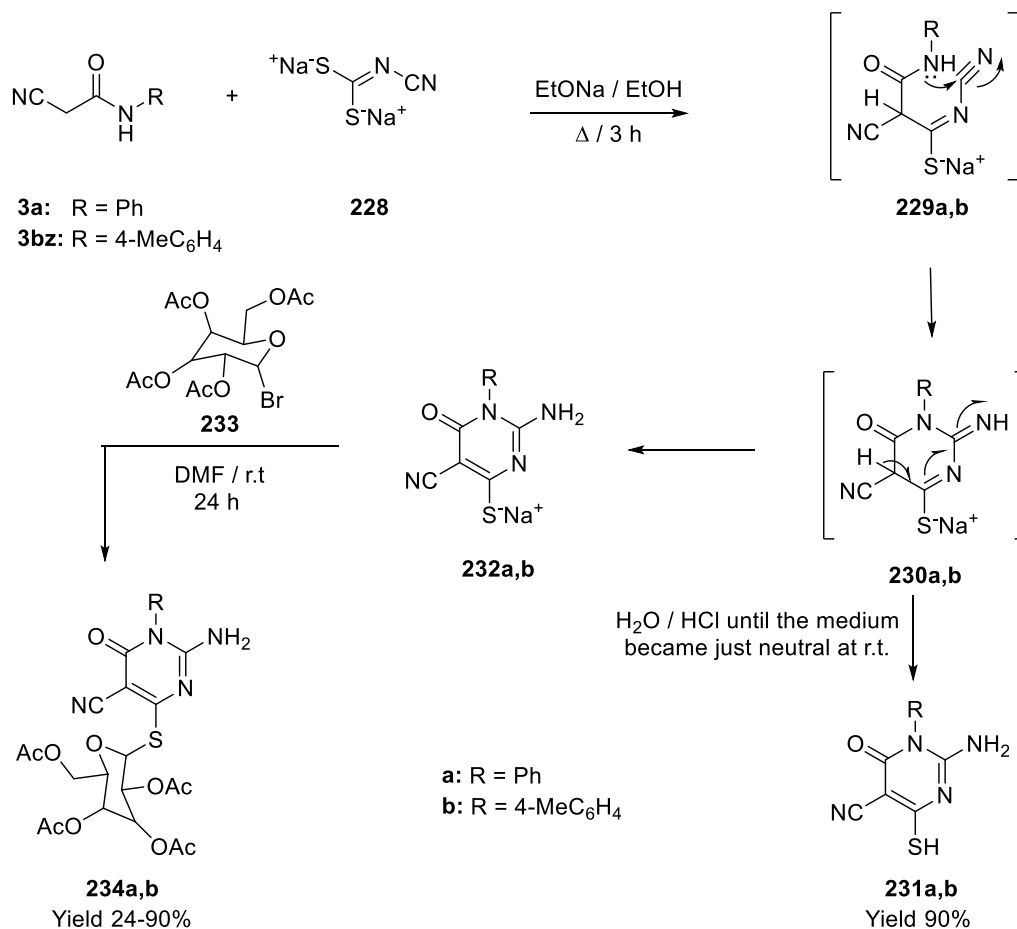


Scheme 99

3.1.6.2. Pyrimidine derivatives

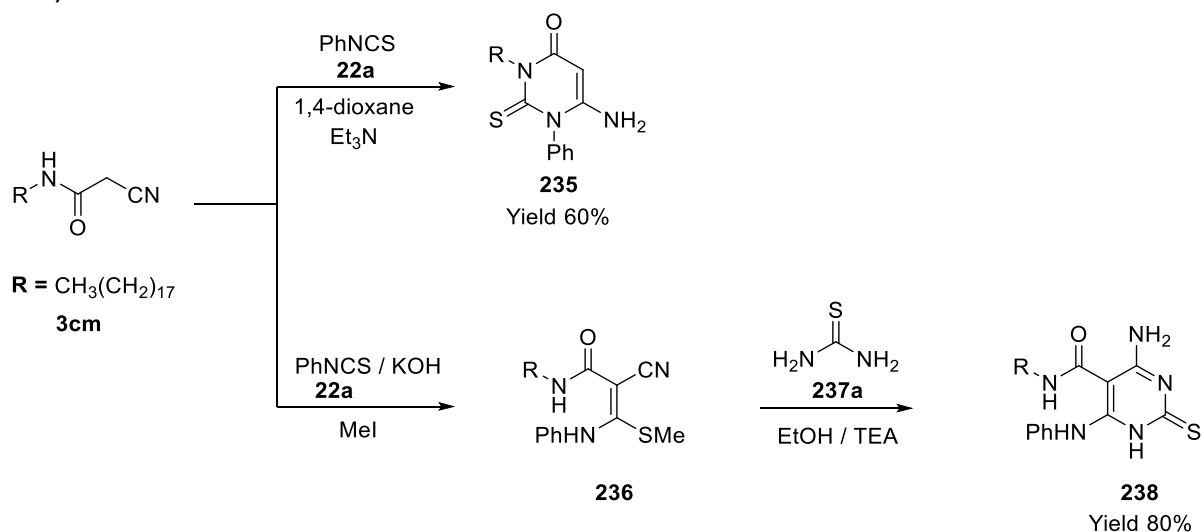
A. Synthesis *via* Michael addition reactions

The reaction of disodium cyanocarbonimidodithioate **228** and 2-cyano-*N*-arylacetamides **3a**, **3bz** in sodium ethoxide for 3 hours gave sodium pyrimidine-4-thiolate derivatives **230a,b**. A subsequent treatment with hydrochloric acid produced pyrimidine-4-thiol derivatives **231a,b**. The intermediates **230a,b** tautomerize into **232a,b** which reacted with bromosugar **233** in DMF in the presence of potassium hydroxide yielding S-glycosides **234a,b** (Scheme 100).¹²²



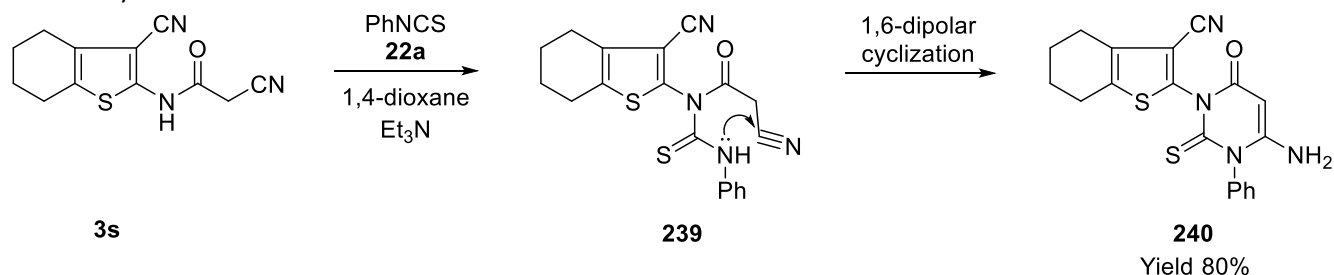
Scheme 100

When compound **3cm** was reacted with phenyl isothiocyanate **22a** in 1,4-dioxane containing triethylamine, 2-thioxo-6-pyrimidone derivative **235** was formed in moderate yield (60%). On the other hand, the reaction of **3cm** with phenyl isothiocyanate **22a** in DMF in the presence of potassium hydroxide followed by treatment with methyl iodide gave the 2-cyanoacrylamide derivative **236**. Heating a mixture of **236** and thiourea **237a** in ethanol containing triethylamine at reflux afforded pyrimidine-2-thione derivative **238** (Scheme 101).⁷⁹



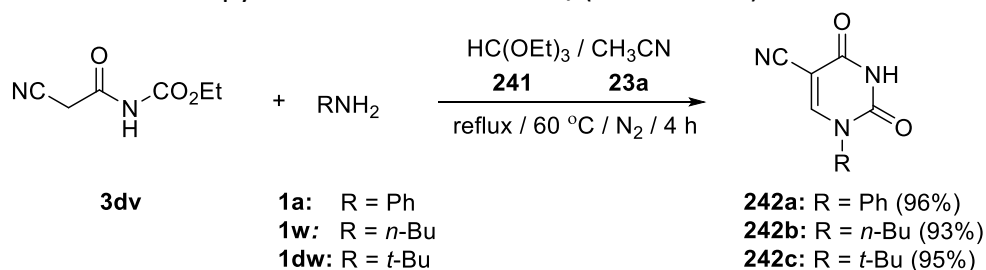
Scheme 101

The reaction of compound **3s** with phenyl isothiocyanate **22a** in 1,4-dioxane containing trimethylamine is assumed to involve a nucleophilic attack of the amidic NH in **3** on the C=S of the isocyanate to give the addition adduct **239** which undergoes 1,6-dipolar cyclization to form 2-thioxo-6-pyrimidone derivative **240** (Scheme 102).²⁵



Scheme 102

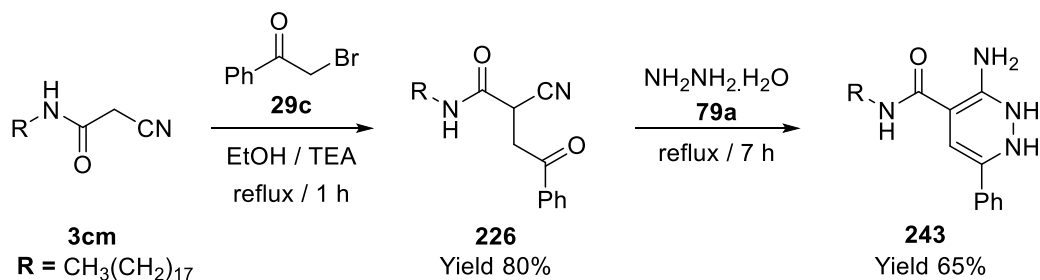
The reaction of ethyl (2-cyanoacetyl)carbamate **3dv** with amines **1** and triethyl orthoformate **241** in acetonitrile **23a** at reflux afforded pyridimine derivatives **242**, (Scheme 103).¹²³



Scheme 103

3.1.6.3. Pyridazine derivatives

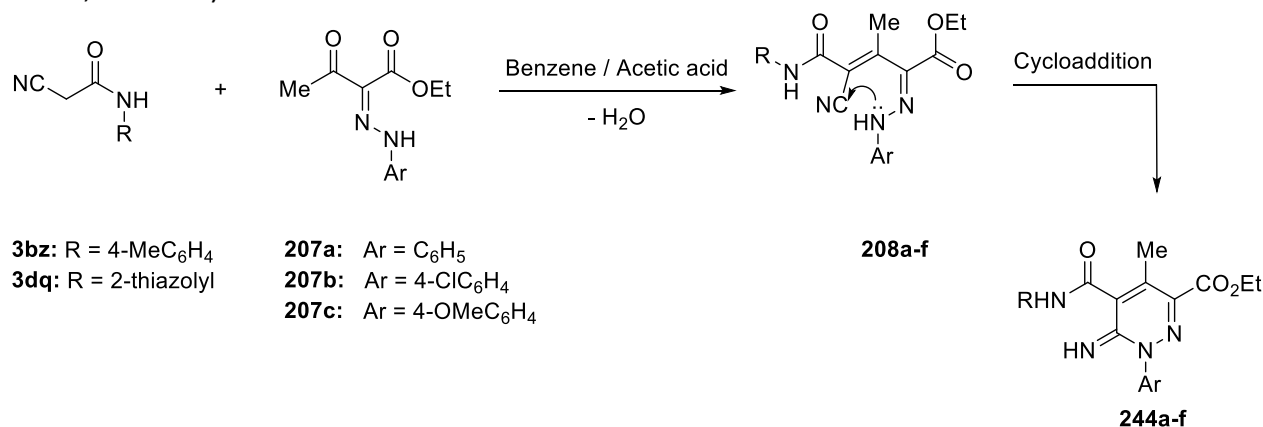
2-Cyano-4-phenylbutanamide **226** (prepared through the reaction of cyanoacetamide **3cm** with phenacyl bromide **29c** in ethanol containing triethylamine under reflux) underwent a cyclization affected by hydrazine hydrate **79a** in DMF containing triethylamine to give the 1,2-dihydropyridazine-4-carboxamide **243** (Scheme 104).⁷⁹



Scheme 104

Ethyl 2-arylhydrazono-3-oxobutyrates **207a-c** were reacted with cyanoacetamide derivatives **3bz** and **3dq** in benzene containing acetic acid to yield the pyridazine **244** derivatives. This reaction proceeds through the

formation of Knoevenagel adducts **208a-f** which undergo cyclization to form the pyridazine products **244a-f** (Scheme 105, Table 41).¹²⁰



Scheme 105

Table 41: Synthesis and % yields of **244a-f**

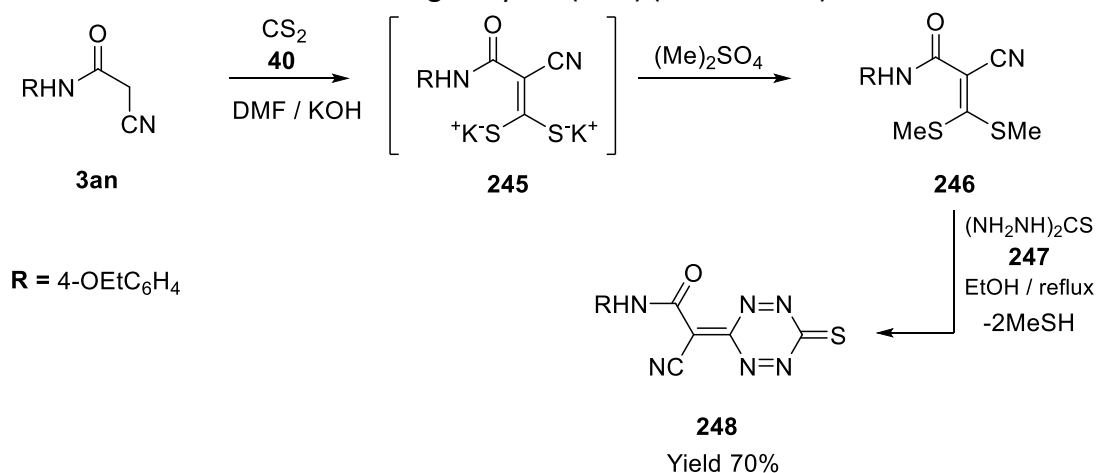
Product	R	Ar	Yield (%)
244a	4-MeC ₆ H ₄	Ph	25
244b	4-MeC ₆ H ₄	4-ClC ₆ H ₄	23
244c	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	21
244d	2-thiazolyl	Ph	18
244e	2-thiazolyl	4-ClC ₆ H ₄	18
244f	2-thiazolyl	4-MeOC ₆ H ₄	20

3.1.7. Monocyclic six-membered rings with four hetero atoms

3.1.7.1. Tetrazine derivatives

A. Synthesis *via* Michael addition reactions

Treatment of compound **3an** with carbon disulfide **40** in DMF containing potassium hydroxide led to the formation of the non-isolable adduct **245**, which was further treated with dimethyl sulfate at room temperature to give the cyanoacrylamide **246**. The reaction of compound **246** with thiocarbonylhydrazide **247** in boiling ethanol furnished the tetrazine **248** in good yield (70%) (Scheme 106).⁹³



Scheme 106

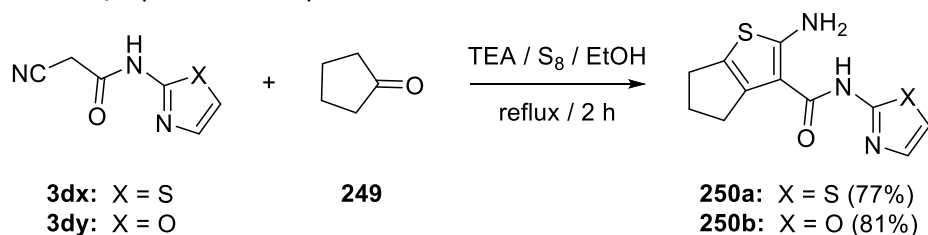
3.2. Fused Heterocycles

3.2.1. Carbocyclic fused heterocycles

3.2.1.1. Fused [5-5] systems

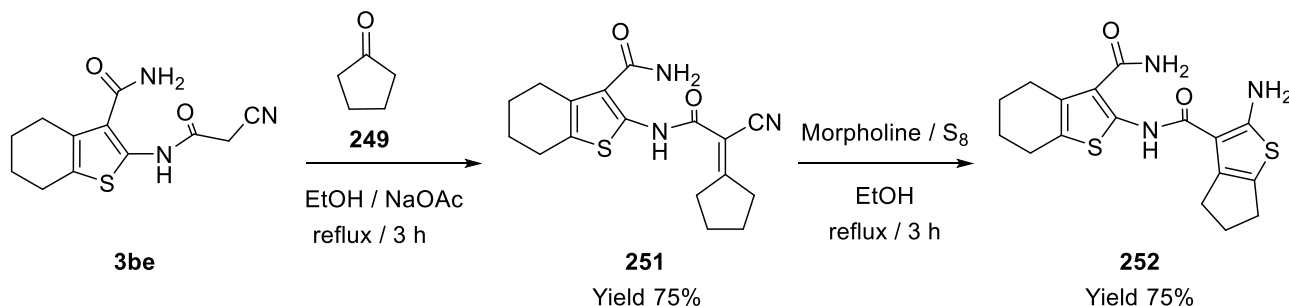
3.2.1.1.1. 5,6-Dihydro-4*H*-cyclopenta[*b*]thiophene

The Gewald reaction of cyanoacetamides **3dx** and **3dy** with cyclopentanone **249** and sulfur furnished the fused thiophene derivatives **250a,b** (Scheme 107).¹²⁴



Scheme 107

Khalil *et al*⁶⁷ reported that the reaction of cyanoacetamide **3be** with cyclopentanone **249** in ethanol containing sodium acetate at reflux for 3 h afforded the condensation product **251**. Heating **251** at reflux with elemental sulfur in absolute ethanol in the presence of a catalytic amount of morpholine furnished **252** in good yield (75%) (Scheme 108).



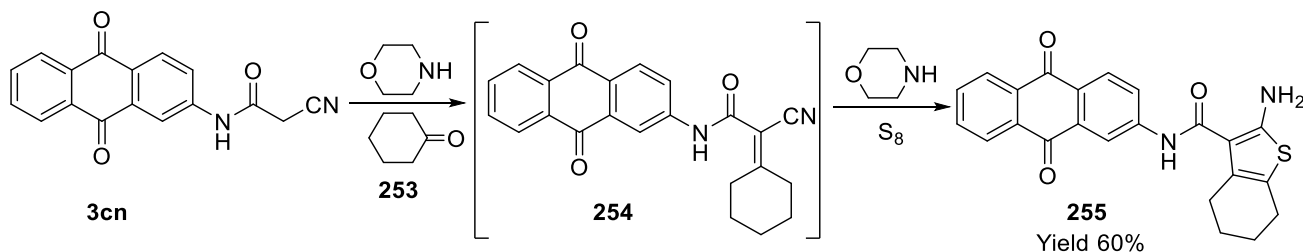
Scheme 108

3.2.1.2. Fused [6-5] systems

3.2.1.2.1. 4,5,6,7-Tetrahydrobenzo[*b*]thiophene

A. Synthesis *via* Gewald reactions

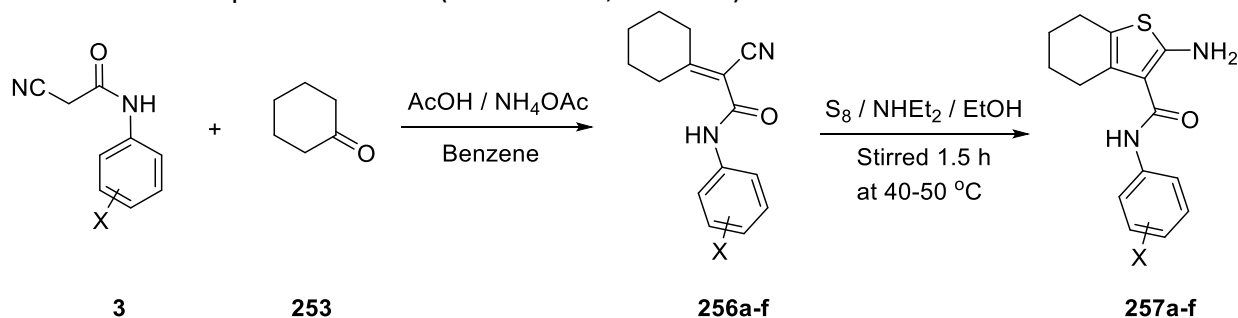
N-Anthracenyl-benzo[*b*]thiophene derivative **255** was synthesized from the reaction of **3cn** with cyclohexanone **253** and sulfur in a mixture of DMF/EtOH containing morpholine as a catalyst. Clearly, the reaction proceeded *via* the intermediacy of Knoevenagel adduct **254** (Scheme 109).⁸⁰



Scheme 109

Compounds **257a-f** were obtained when the appropriate *N*-phenyl cyanoacetamide **3**, cyclohexanone **253**, ammonium acetate and glacial acetic acid were refluxed in benzene for 16 hours in a Dean Stark apparatus.

The Knoevenagel product **256a-f** and sulfur were then dissolved in dry EtOH in presence of *N,N*-diethylamine and stirred at 40-50°C to produce **257a-f** (Scheme 110, Table 42).¹²⁵

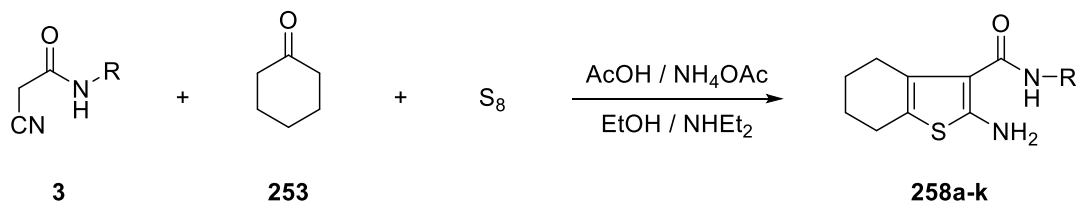


Scheme 110

Table 42. Synthesis and % yields of **257a-f**

Entry	Product	X	Yield (%)
3bm	257a	3-CF ₃ C ₆ H ₅	20
3by	257b	4-MeOC ₆ H ₅	28
3co	257c	4-ClC ₆ H ₅	29
3bi	257d	4-BrC ₆ H ₅	88
3dt	257e	4-IC ₆ H ₅	24
3dn	257f	4-CF ₃ C ₆ H ₅	29

Benzo[*b*]thiophene derivatives **258a-k** were synthesized through Gewald reaction of cyanoacetamides **3**, cyclohexanone **253** and sulfur in acetic acid containing ammonium acetate at reflux (Scheme 111, Table 43).¹²⁶

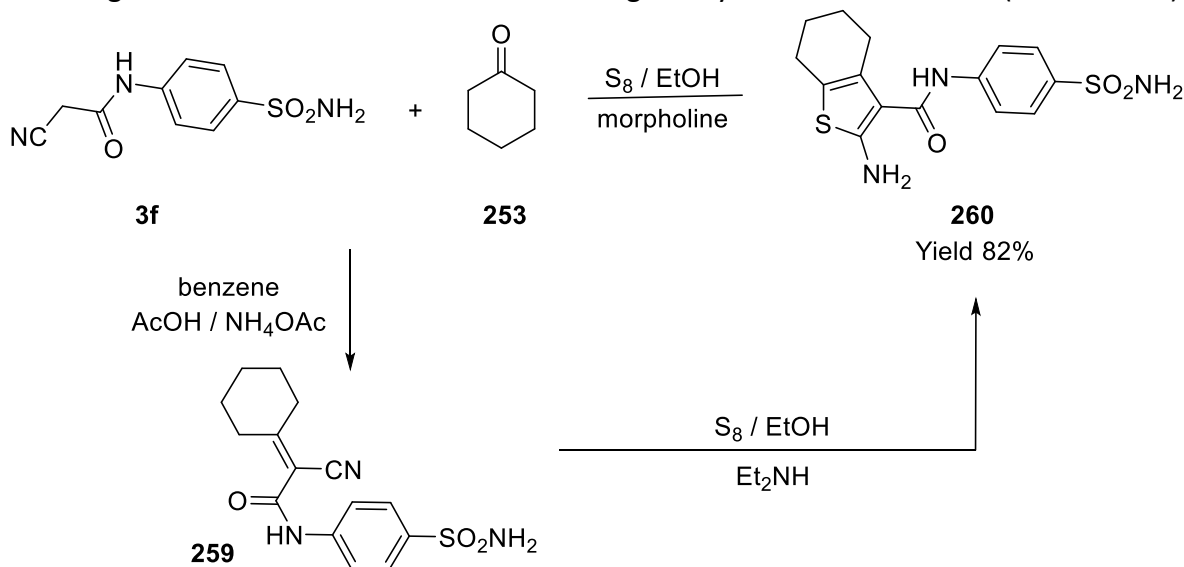


Scheme 111

Table 43: Synthesis and % yields of **258a-k**

Entry	Product	R	Yield (%)
3do	258a	H	52
3ca	258b	Me	46
3ch	258c	Et	49
3a	258d	Ph	47
3cu	258e	2-MeC ₆ H ₅	51
3bz	258f	4-MeC ₆ H ₅	71
3bl	258g	4-FC ₆ H ₅	67
3cp	258h	2-ClC ₆ H ₅	76
3dz	258i	3-ClC ₆ H ₅	71
3co	258j	4-ClC ₆ H ₅	62
3ea	258k	3-Cl-4-FC ₆ H ₅	79

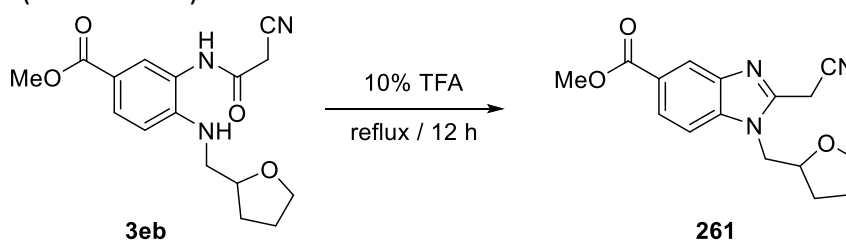
Aminothiophene-3-carboxamide **260** was successfully obtained in 80% yield *via* Gewald reaction of **3f** with sulfur and cyclohexanone **253** in ethanol containing morpholine.⁵⁸ Schellhase *et al*¹²⁷ similarly reported the synthesis of aminothiophene derivative **260** *via* a two step procedure, where **3f** was first condensed with cyclohexanone **253** in benzene containing AcOH and ammonium acetate to give the arylidene derivative **259**. A subsequent boiling of **259** with sulfur in ethanol containing diethylamine afforded **260** (Scheme 112).



Scheme 112

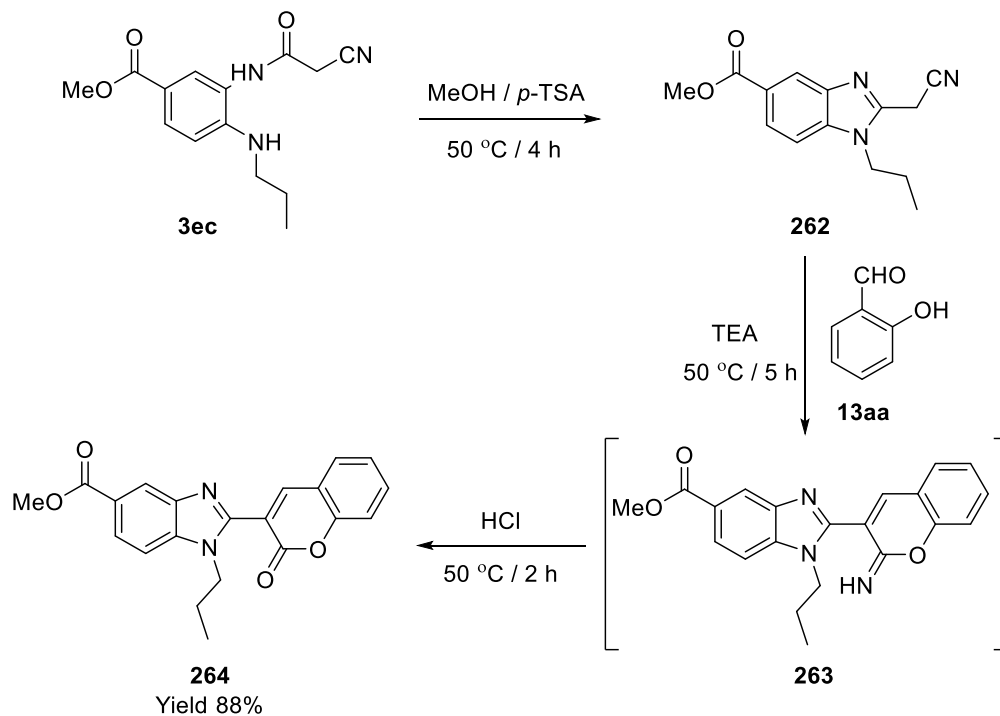
3.2.1.2.2. 1H-Benzo[d]imidazole

Methyl 1-alkyl-(2-cyanomethyl)benzimidazole-5-carboxylate **261** was synthesized *via* boiling of **3eb** in 10% trifluoroacetic acid TFA (Scheme 113).³⁵



Scheme 113

Heating **3ec** at 50 °C for 4 h in methanol containing *p*-toluenesulfonic acid (*p*-TSA) gave 2-cyanomethylbenzimidazoles **262**. Then, the condensation of **262** with salicylaldehyde **13aa** in the presence of triethylamine produced the intermediate **263** which was hydrolyzed by the addition of HCl to give the target product **264** in 88% yield (Scheme 114).³⁶

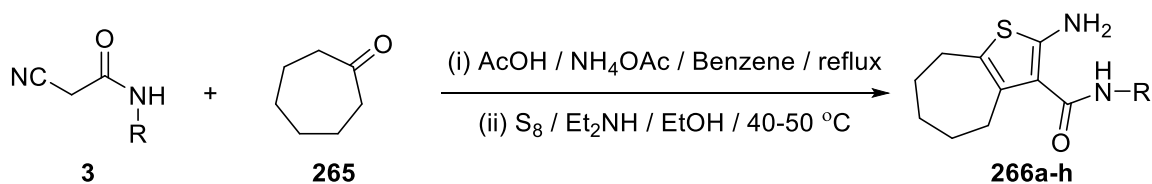


Scheme 114

3.2.1.3. Fused [7-5] system

3.2.1.3.1. 5,6,7,8-Tetrahydro-4*H*-cyclohepta[*b*]thiophene

Desantis *et al*¹²⁸ and Massari *et al*¹²⁹ conducted the reaction between cyanoacetamide compounds **3** with cycloheptanone **265** and elemental sulfur under reflux to give thiophene derivatives **266** (Scheme 115, Table 44).

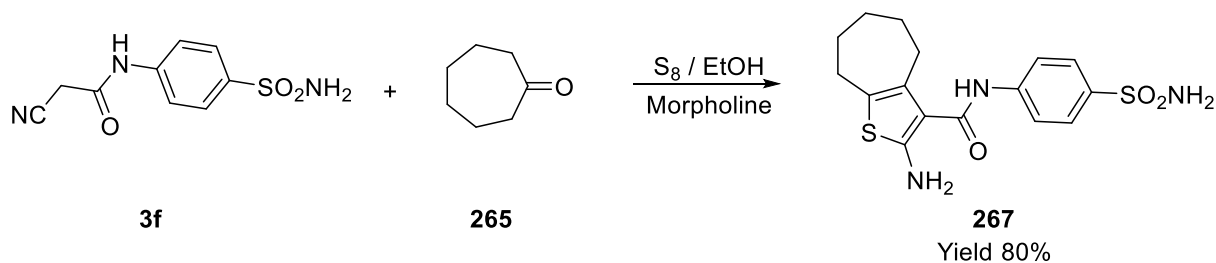


Scheme 115

Table 44. Synthesis and % yields of **266a-g**

Entry	Product	R	Yield (%)
3ed	266a	2-Pyridyl	not reported
3co	266b	4-ClC ₆ H ₄	61
3a	266c	Ph	64
3bl	266d	4-FC ₆ H ₄	41
3dq	266e	2-Thiazolyl	40
3y	266f	Cyclohexyl	55
3dj	266g	2-MeOC ₆ H ₄	not reported
3fy	266h	2-HOC ₆ H ₄	not reported

Aminothiophene-3-carboxamide **267** were synthesized by the reaction of **3f** with cycloheptanone **265** and sulfur in ethanol containing morpholine as a base (Scheme 116).⁵⁸

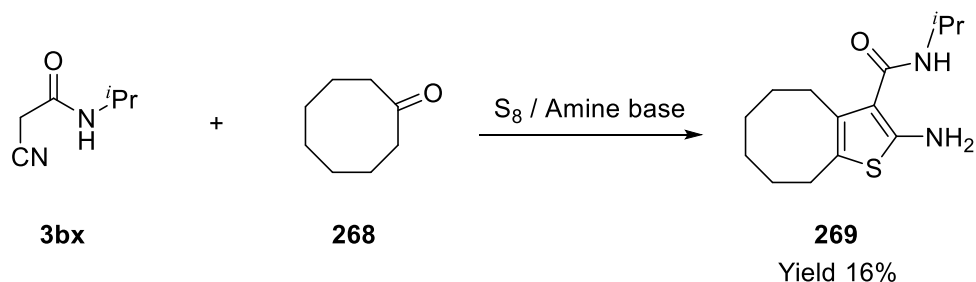


Scheme 116

3.2.1.4. Fused [8-5] bsystem

3.2.1.4.1. 4,5,6,7,8,9-Hexahydrocycloocta[b]thiophene

Treatment of cyclooctanone **268** with 2-cyano-*N*-isopropylacetamide **3bx** and sulfur in presence of amine base provides 2-amino-hexahydrocycloocta[b]thiophene **269** (Scheme 117).¹³⁰

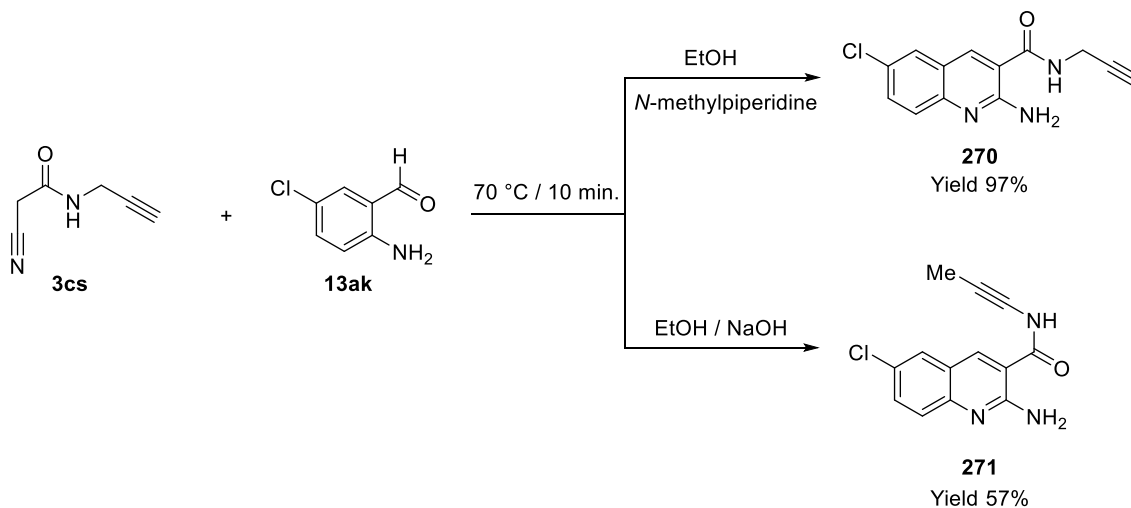


Scheme 117

3.2.1.5. Fused [6-6] system

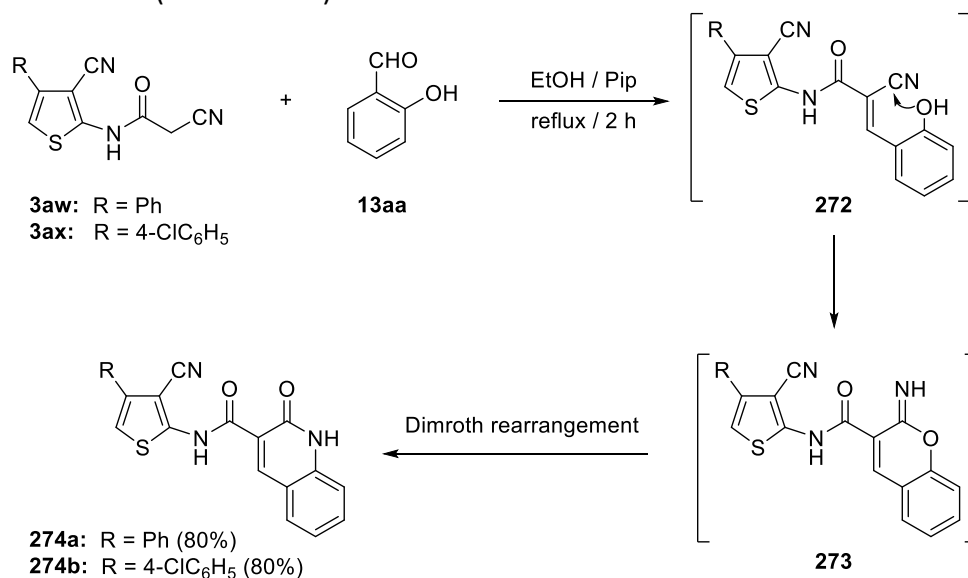
3.2.1.5.1. Quinoline derivatives

The condensation of 2-amino-5-chlorobenzaldehyde **13ak** with 2-cyano-*N*-(prop-2-yn-1-yl)acetamide **3cs** in ethanol containing sodium hydroxide as a base gave *N*-(prop-1-yn-1-yl)quinoline derivative **271** in which the position of triple bond was shifted, presumably due to the basic power of sodium hydroxide. In support with this thought, when the same reaction was carried out in the presence of a milder base (*N*-methylpiperidine) for a longer time, *N*-(prop-2-yn-1-yl)quinoline derivative **270** were produced without isomerization (Scheme 118).¹³¹



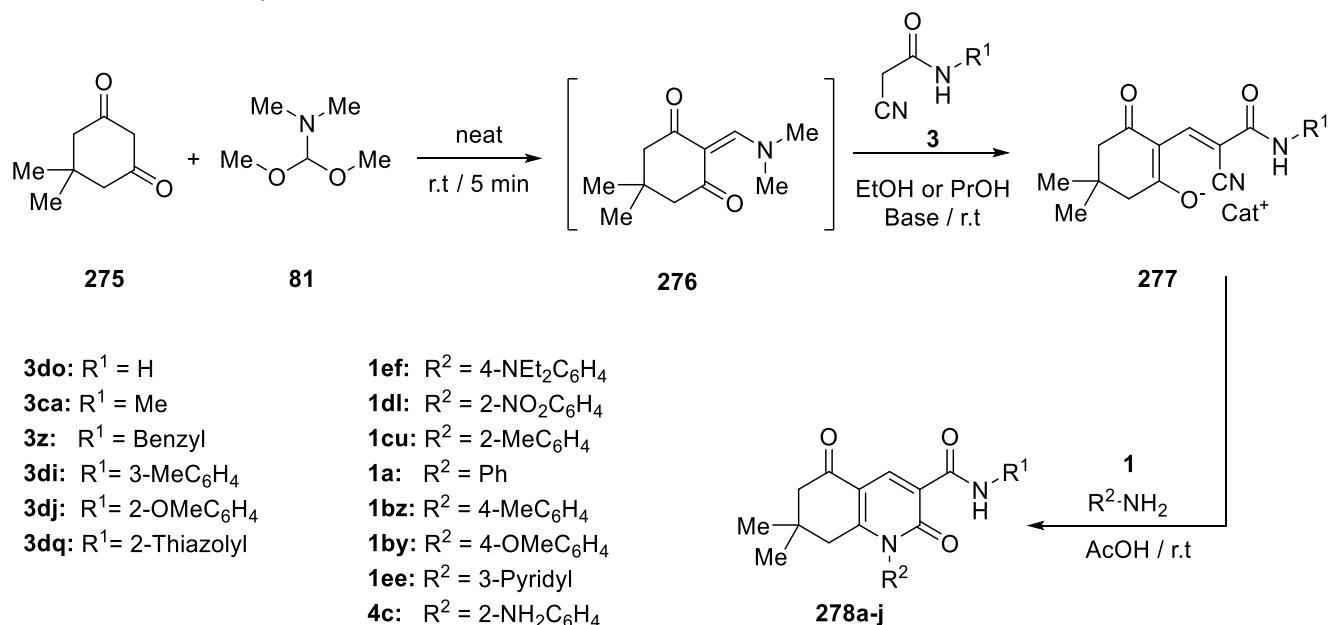
Scheme 118

Behbehani *et al*⁴² performed the reaction of 2-cyano-*N*-(3-cyano-4-arylthiophen-2-yl)acetamides **3aw** and **3ax** with salicylaldehyde **13aa** to form *N*-(4-arylthiophen-2-yl)quinoline derivatives **274a,b** via the intermediacy of **272** and **273** (Scheme 119).



Scheme 119

The reaction of enaminone **276** (*in situ* formed from mixing dimedone **275** with dimethylformamide dimethylacetal (DMF-DMA) **81**) with cyanacetamides **3** in the presence of a base at room temperature led to the formation of ylide salts **277**. These salts **277** were very reactive towards amines **1** and *o*-phenylenediamine **4c** in acetic acid at room temperature forming different *N*-substituted 2-quinolinones **278a-j** (Scheme 120, Table 45).¹³²



Scheme 120

Table 45. Synthesis and % yields of **278a-j**

Compound	R ¹	Cat ⁺	Compound	R ¹	R ²	Yield (%)
277a	H	Na ⁺	278a	H	4-NEt ₂ C ₆ H ₄	73

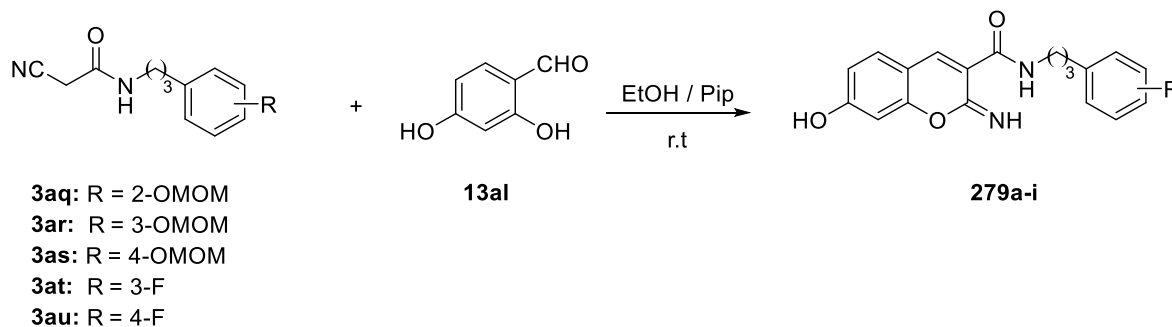
277b	H	(Me) ₂ NH ₂ ⁺	278b	H	2-NO ₂ C ₆ H ₄	60
277c	Me	(Me) ₂ NH ₂ ⁺	278c	H	2-MeC ₆ H ₄	78
277d	Me	Na ⁺	278d	2-Thiazolyl	Ph	82
277e	Me	(CH ₂) ₅ NH ₂ ⁺	278e	H	Ph	74
277f	CH ₂ C ₆ H ₅	(CH ₂) ₅ NH ₂ ⁺	278f	2-MeOC ₆ H ₄	4-MeC ₆ H ₄	74
277g	CH ₂ C ₆ H ₅	Na ⁺	278g	C ₆ H ₅ CH ₂	4-MeOC ₆ H ₄	89
277h	3-MeC ₆ H ₄	(CH ₂) ₅ NH ₂ ⁺	278h	Me	4-MeOC ₆ H ₄	77
277i	2-MeOC ₆ H ₄	(CH ₂) ₅ NH ₂ ⁺	278i	H	2-NH ₂ C ₆ H ₄	66
277j	2-Thiazolyl	(CH ₂) ₅ NH ₂ ⁺	278j	2-Thiazolyl	3-Pyridyl	75

Reaction Condition:
a- EtOH, Na (1 equiv.) **b-** *i*-PrOH, Piperidine (0.03 equiv.) **c-** *i*-PrOH, Piperidine (2 equiv.)

3.2.1.5.2. Chromene derivatives

3.2.1.5.2.1. Synthesis *via* Knoevenagel condensation reactions

Knoevenagel condensation of **3aq-au** with 2,4-dihydroxybenzaldehyde **13al** led to the formation of iminochromenes **279a-i** (Scheme 121, Table 46).⁴¹



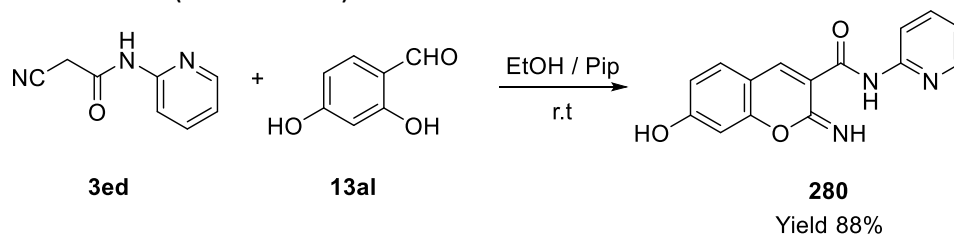
Scheme 121

Table 46. Synthesis and % yields of **279a-i**

Product	R	Yield (%)
279a	3-OMOM	67
279b	3-OH	65
279c	2-OMOM	63
279d	4-OMOM	76
279e	3-F	75

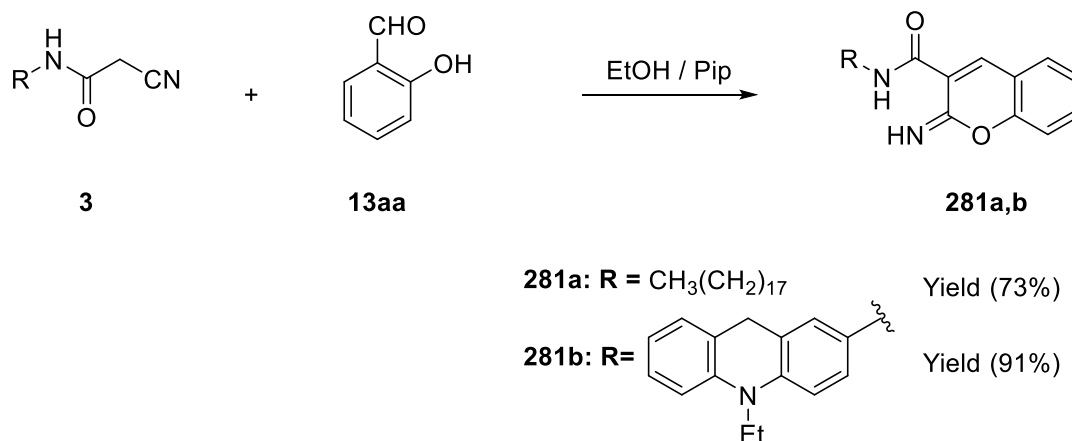
Product	R	Yield (%)
279f	4-F	68
279g	3,5-diF	85
279h	4-Me	82
279i	4-OMe	87

Similarly, the reaction of cyanoacetamide **3ed** with 2,4-dihydroxybenzaldehyde **13al** afforded the 2-iminochromene derivative **280** (Scheme 122).¹³³



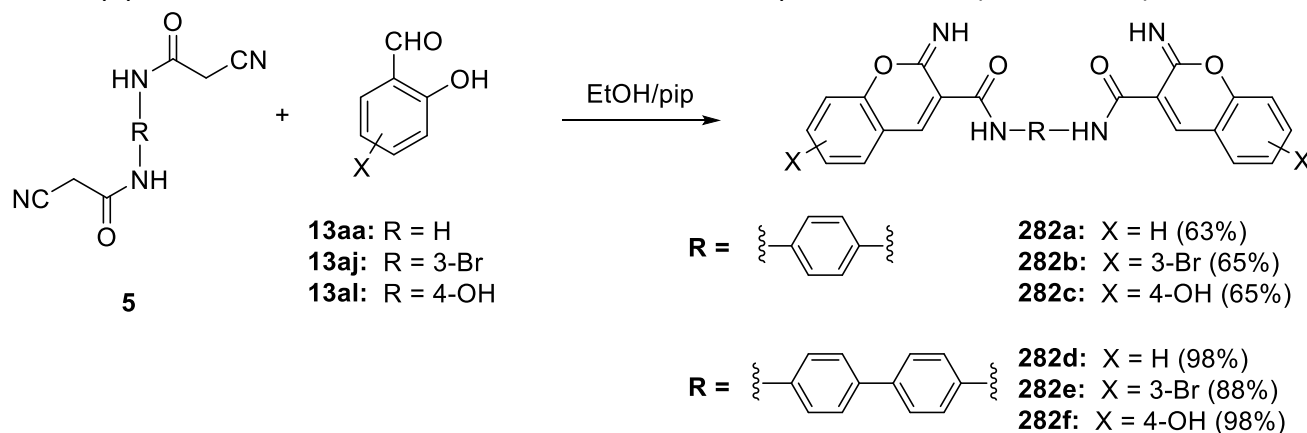
Scheme 122

The reaction of cyanoacetamide derivative **3** with salicylaldehyde **13aa** in ethanol containing piperidine as a catalyst at reflux furnished the coumarin product **281a,b** (Scheme 123).^{79,134}



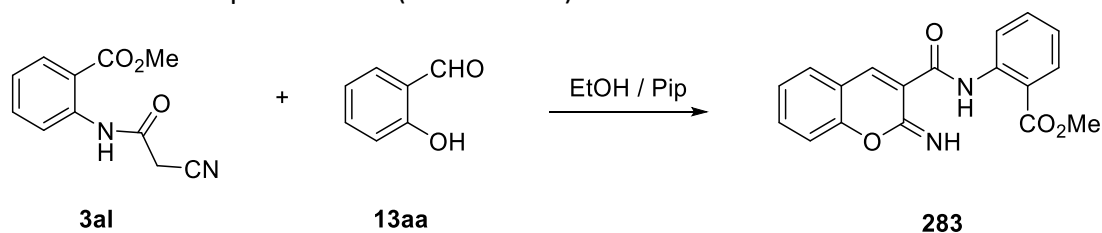
Scheme 123

Heating compound **5** with 2-hydroxybenzaldehyde derivatives **13** in absolute ethanol at reflux in the presence of piperidine led to the formation of bis-coumarin compounds **282a-f** (Scheme 124).^{33,135}



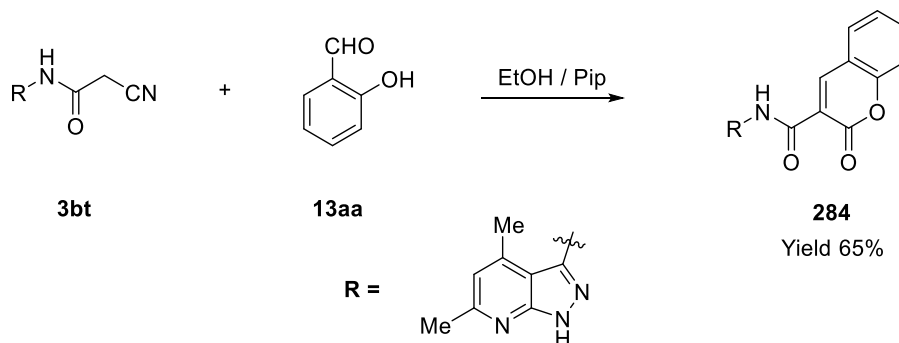
Scheme 124

The reaction of compound **3al** with 2-hydroxybenzaldehyde **13aa** in ethanol containing piperidine as a catalyst under reflux afforded product **283** (Scheme 125).¹¹



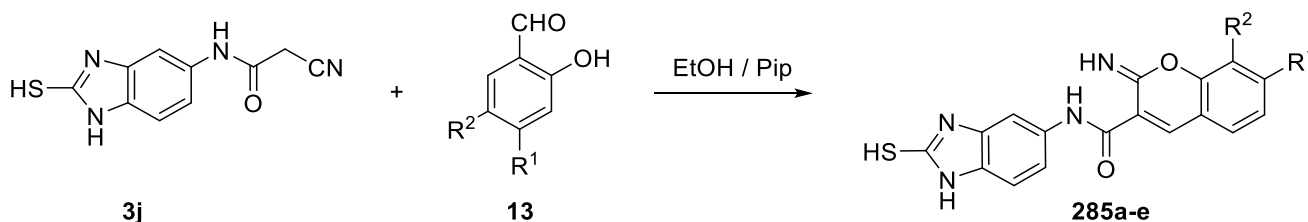
Scheme 125

The condensation reaction of cyanoacetamide **3bt** with salicylaldehyde **13aa** in ethanol catalyzed by piperidine led smoothly to the formation of the coumarine product **284** (Scheme 126).⁵⁹



Scheme 126

The condensation of compound **3j** with salicylaldehyde and its derivatives **13aa-ae** in absolute ethanol containing piperidine affords **285a-e** (Scheme 127, Table 47).²¹

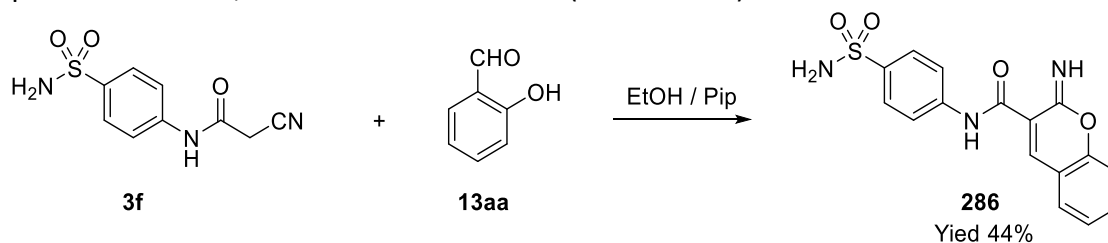


Scheme 127

Table 47. Synthesis and % yields of **285a-e**

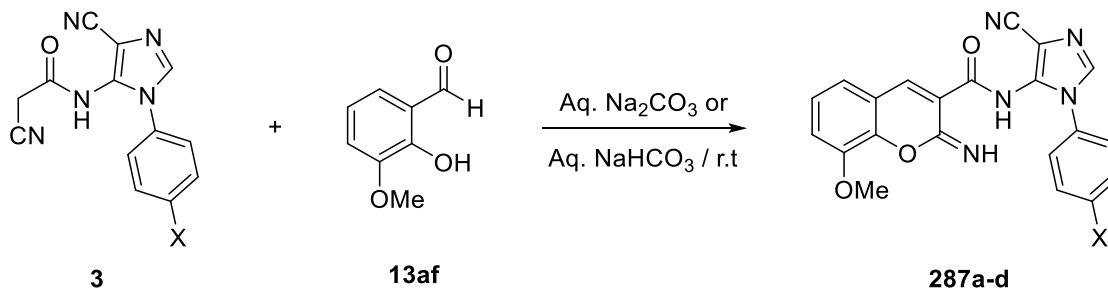
Entry	Product	R ¹	R ²	Yield (%)
13aa	285a	H	H	79
13ab	285b	OCH ₃	H	75
13ac	285c	Br	H	81
13ad	285d	Cl	H	84
13ae	285e	Br	Br	75

The cyanoacetamide **3f** was reacted with salicylaldehyde **13aa** in ethanol in the presence of a catalytic amount of piperidine at reflux, to afford chromene **286** (Scheme 128).¹⁰⁶



Scheme 128

The Knoevenagel condensation of 2-hydroxy-3-methoxybenzaldehyde **13af** with cyanoacetamides **3** in aqueous sodium carbonate or sodium hydrogen carbonate solution afforded chromene-3-carboxamide derivatives **287a-d** (Scheme 129, Table 48).¹³⁶

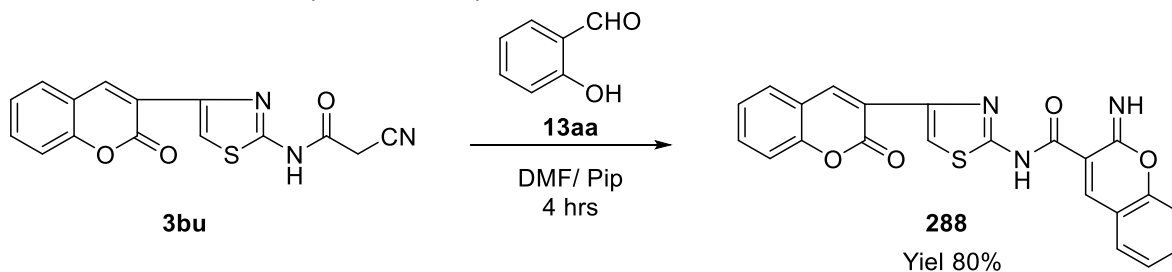


Scheme 129

Table 48. Synthesis and % yields of **287a-d**

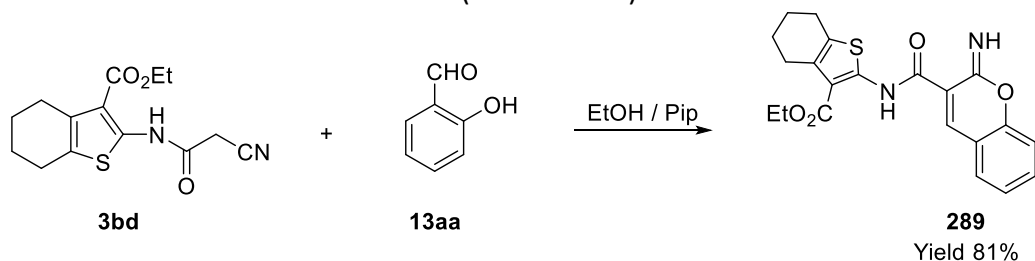
Entry	Product	X	Yield (%)
3em	287a	F	94
3en	287b	H	94
3eo	287c	OCH ₃	97
3ep	287d	CN	86

Knoevenagel condensation of compound **3bu** with salicylaldehyde **13aa** in DMF catalyzed by piperidine afforded the iminocoumarin **288** (Scheme 130).⁶⁴



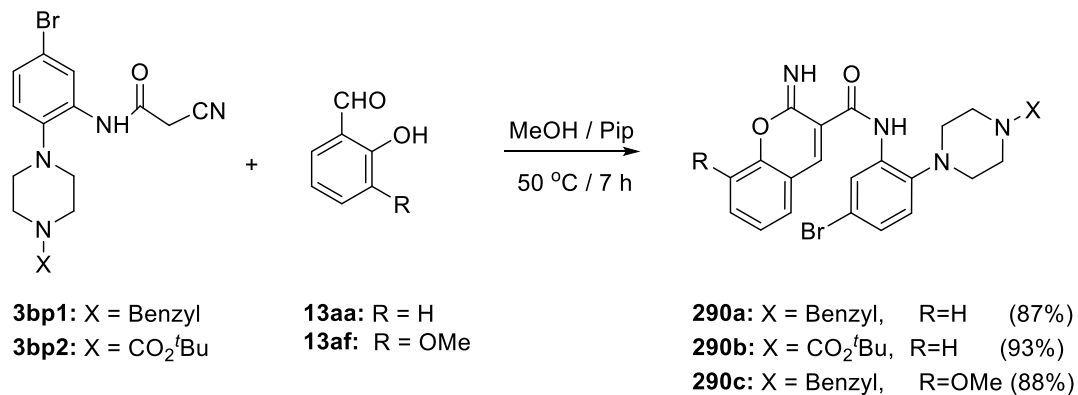
Scheme 130

Knoevenagel condensation of **3bd** with 2-hydroxybenzaldehyde **13aa** in ethanol containing piperidine afforded chromene-3-carboxamide derivative **289** (Scheme 131).⁴⁸



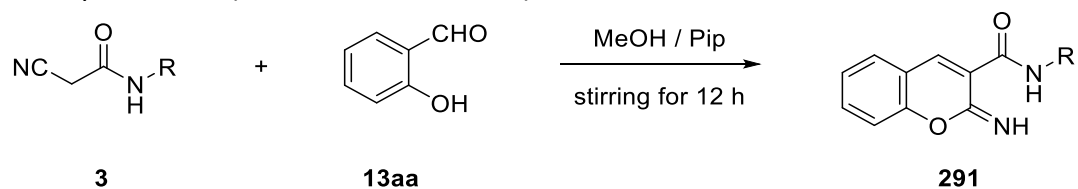
Scheme 131

Active methylene nitriles of type **3bp1** and **3bp2** were reacted with the salicylaldehyde derivatives **13aa** and **13af** in methanol containing piperidine in methanol to form 2-iminochromenes **290a-c** (Scheme 132).⁵⁶



Scheme 132

Different derivatives of **3** were reacted with 2-hydroxybenzaldehyde **13aa** in methanol and piperidine as catalyst to give compound **291** (Scheme 133, Table 49).⁵²

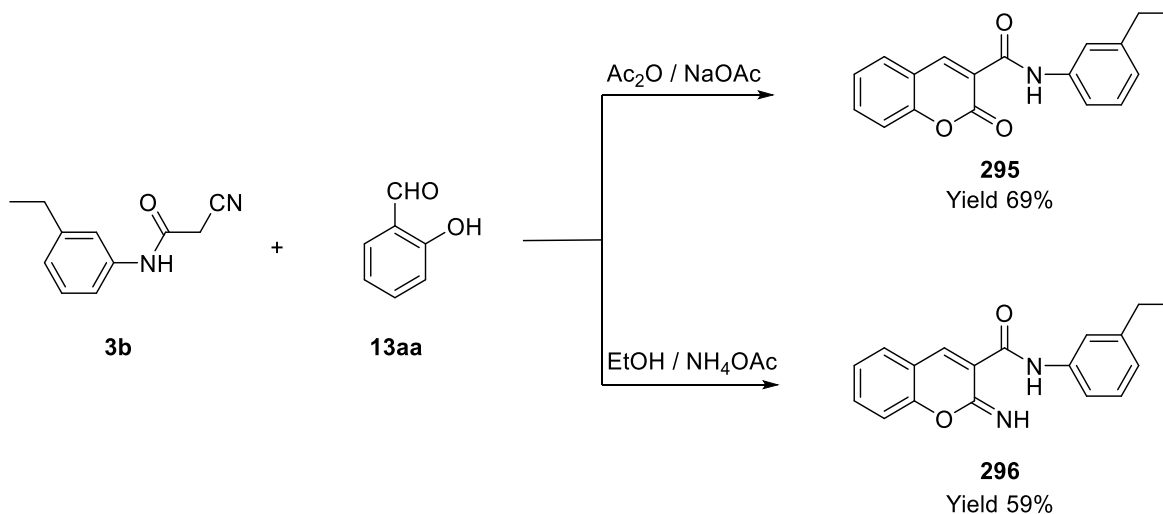


Scheme 133

Table 49. Synthesis and % yields of **291a-g**

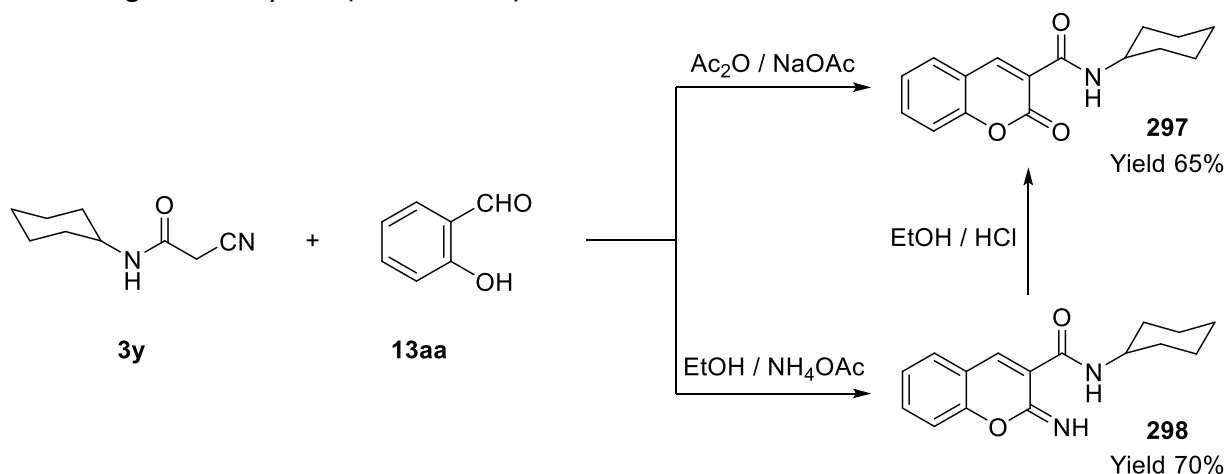
Entry	Product	R	Yield (%)
3bj	291a	4-NO ₂ C ₆ H ₅	81
3bi	291b	4-BrC ₆ H ₅	82
3bk	291c	3,4-Cl ₂ C ₆ H ₅	88
3bh	291d	3-NO ₂ C ₆ H ₅	85
3bl	291e	4-FC ₆ H ₅	76
3bm	291f	3-CF ₃ C ₆ H ₅	78
3bn	291g	3,4-MeO ₂ C ₆ H ₅	79

The reaction of **3b** with salicylaldehyde **13aa** in acetic anhydride containing fused sodium acetate gave compound **295**. On the other hand, when the mixture was refluxed in ethanol with anhydrous ammonium acetate for 2 hours it gave compound **296** (Scheme 134).¹⁵



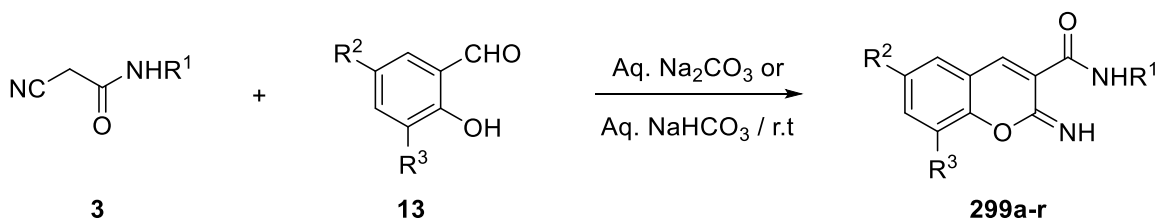
Scheme 134

Cyclocondensation of cyanoacetamide derivative **3y** with salicylaldehyde **13aa** in acetic anhydride containing fused sodium acetate at reflux furnished coumarin derivative **297**. While, heating the reaction mixture in ethanol containing ammonium acetate at reflux afforded 2-iminocoumarin derivative **298**. Acid hydrolysis of **298** gave readily **297** (Scheme 135).¹³⁷



Scheme 135

Synthesis of 2-imino-2*H*-chromene-3-carboxamides **299a-r** was achieved by the reaction of the cyanoacetamides **3** with salicylaldehydes **13aa** and **13ag-aj**, in aqueous sodium carbonate or hydrogen carbonate solution (Scheme 136, Table 50).¹³⁸

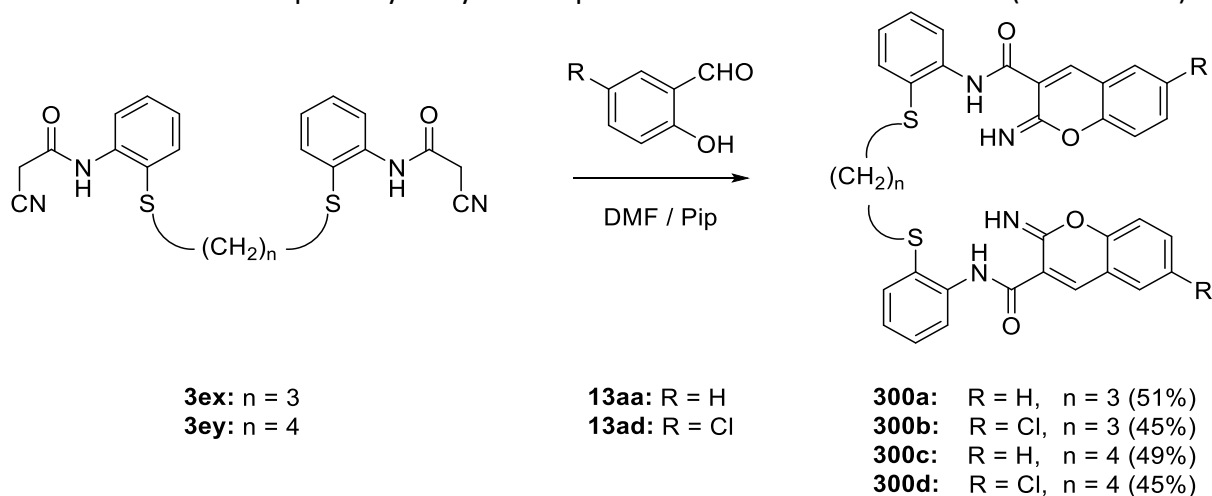


Scheme 136

Table 50. Synthesis and % yields of 299a-r

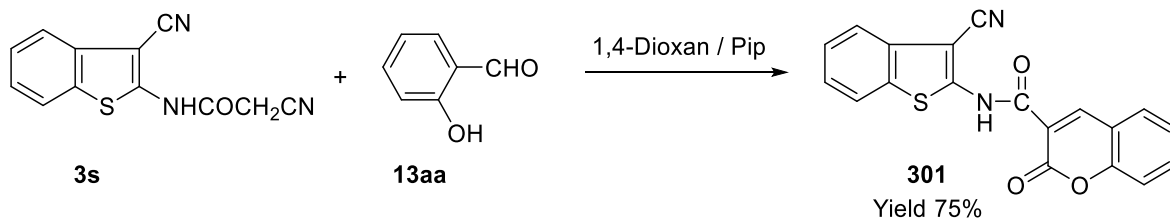
Entry	R ¹	Entry	R ³	R ²	Product	Yield (%)
3eq	—CH ₂ CH ₂ OCH ₃	13ag	H	MeO	299a	100
3er	—CH ₂ CH ₂ OH	13ag	H	MeO	299b	84
3es	—CH(CH ₂ CH ₃)CH ₂ OH	13ag	H	MeO	299c	87
3et	—CH ₂ CH(Ph)OH	13ag	H	MeO	299d	81
3eu	—CH ₂ CH(OCH ₂ CH ₃) ₂	13ag	H	MeO	299e	100
3ev	—(H ₂ C) ₃ —N _{1,4} —(CH ₂) ₃ NHCOCH ₂ CN	13ag	H	MeO	299f	100
3ew	—CH ₂ CH(OH)CH ₂ OH	13ah	H	OH	299g	not reported
3eq	—CH ₂ CH ₂ OCH ₃	13aa	H	H	299h	93
3es	—CH(CH ₂ CH ₃)CH ₂ OH	13aa	H	H	299i	91
3ew	—CH ₂ CH(OH)CH ₂ OH	13aa	H	H	299j	not reported
3ev	—(H ₂ C) ₃ —N _{1,4} —(CH ₂) ₃ NHCOCH ₂ CN	13aa	H	H	299k	not reported
3eq	—CH ₂ CH ₂ OCH ₃	13ai	Cl	H	299l	83
3ew	—CH ₂ CH(OH)CH ₂ OH	13ai	Cl	H	299m	not reported
3es	—CH(CH ₂ CH ₃)CH ₂ OH	13ai	Cl	H	299n	84
3eq	—CH ₂ CH ₂ OCH ₃	13aj	Br	H	299o	99
3ew	—CH ₂ CH(OH)CH ₂ OH	13aj	Br	H	299p	not reported
3et	—CH ₂ CH(Ph)OH	13aj	Br	H	299q	not reported
3eu	—CH ₂ CH(OCH ₂ CH ₃) ₂	13aj	Br	H	299r	99

The reaction of **3ex** and **3ey** with salicylaldehyde derivatives **13aa** and **13ad** gave bis[2-imino-2*H*-1-benzopyran-3-carboxamides] **300a-d**, presumably *via* initial aldehydic condensation reaction with the active methylene function and subsequent hydroxyl nucleophilic attack at the nitrile residue (Scheme 137).¹³⁹

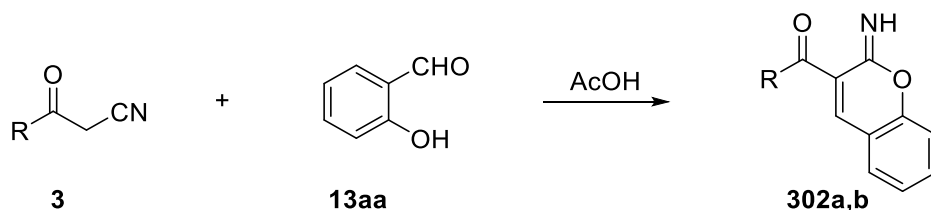


Scheme 137

Cyanoacetamide **3s** was reacted with salicylaldehyde **13aa** to yield the coumarin product **301** (Scheme 138).²⁵

**Scheme 138**

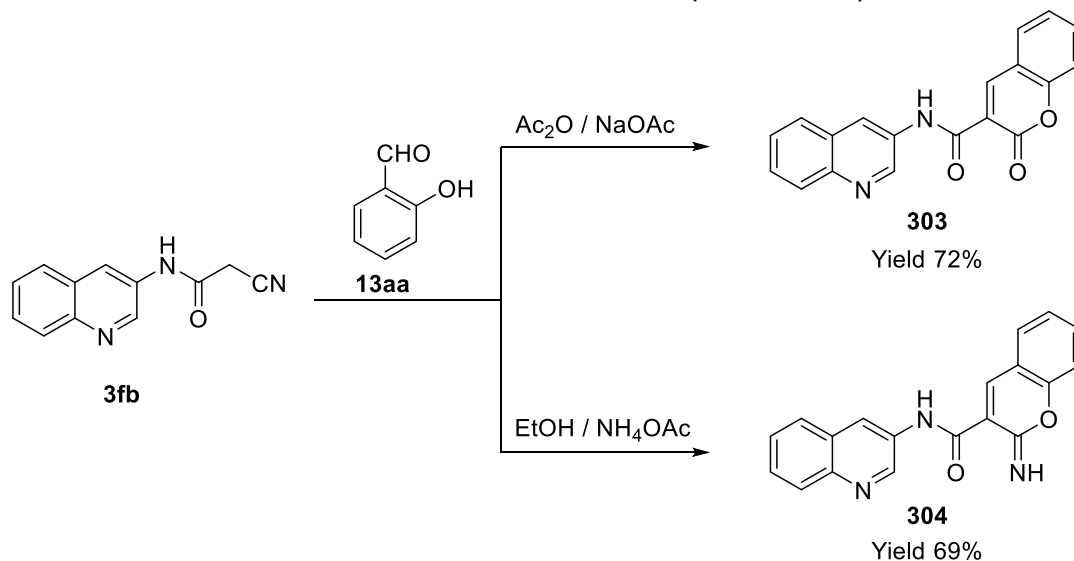
The reaction of compounds **3ez** and **3fa** with salicylaldehyde **13aa** in acetic acid at reflux led to the synthesis of the corresponding chromene derivatives **302a** and **302b** in moderate yields (Scheme 139, Table 51).¹¹⁵

**Scheme 139****Table 51.** Synthesis and % yields of **302a,b**

Entry	Product	R	Yield (%)
3ez	302a		55
3fa	302b		60

3.2.1.5.2.2. Synthesis via Perkin reaction

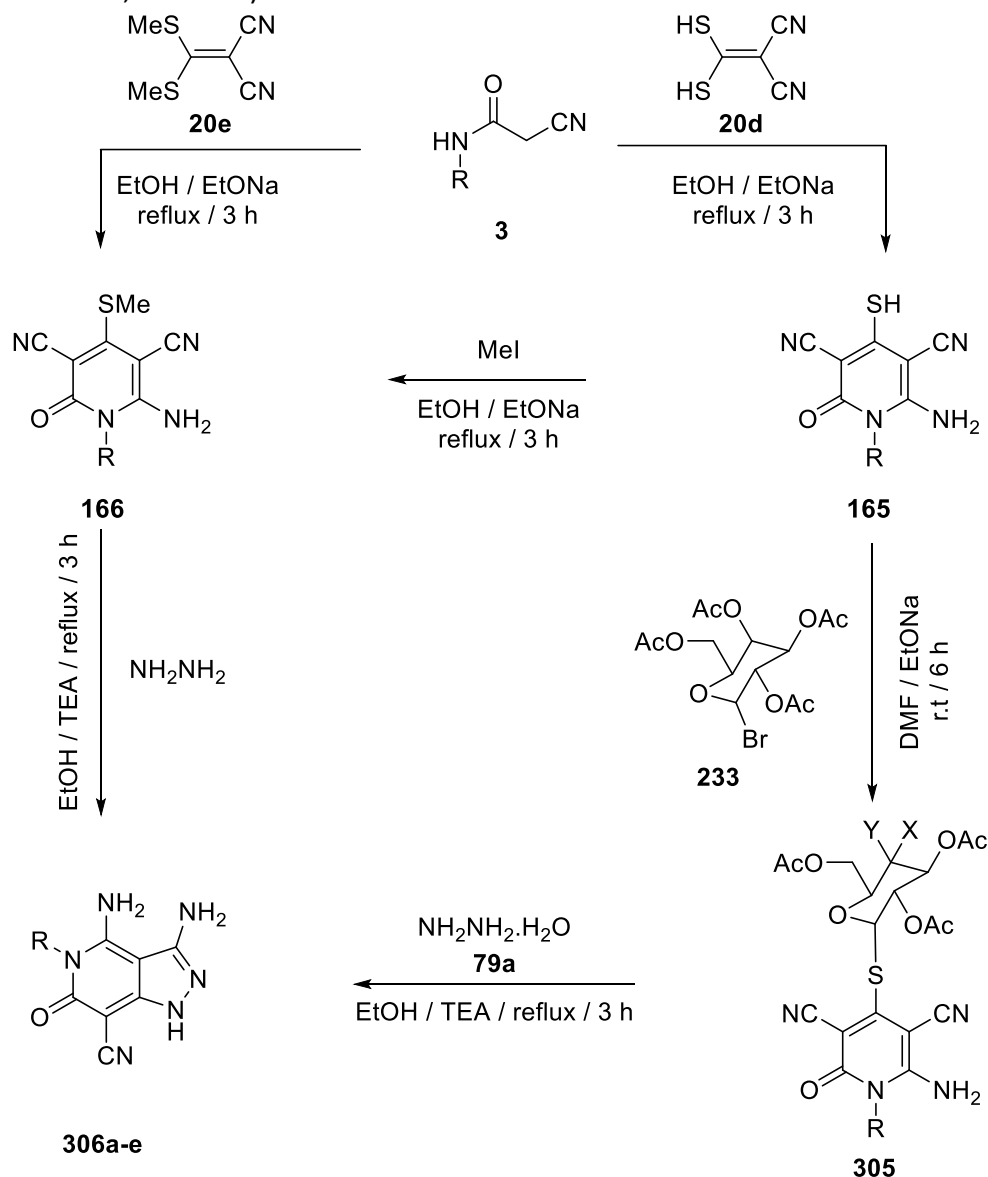
Perkin reaction was conducted through the reaction of salicylaldehyde **13aa** with cyanoacetamide **3fb** in acetic anhydride containing sodium acetate forming coumarin **303**. Carrying out this reaction in ethanol containing ammonium acetate led to the formation of 2-iminochromene **304** (Scheme 140).¹⁴⁰

**Scheme 140****3.2.2. Two fused heterocycles**

3.2.2.1. Fused [5-6] system

3.2.2.1.1. Pyrazolo[4,3-c]pyridine

The condensation of cyanoacetamides **3** with 2-(dimercaptomethylene)malononitrile **20d** or [bis(methylthio)methylene]malononitrile **20e** in ethanol containing sodium ethoxide afforded **165** or **166**, respectively. When compounds **166** were treated with hydrazine hydrate **79a**, the pyrazolo[4,3-c]pyridines **306** were produced, while when compounds **165** were reacted with bromosugar **233**, compounds **305** were formed. Further reaction of **305** with hydrazine hydrate **79a** afforded compounds **306a-e** via the elimination of sugar moiety (Scheme 141, Table 52).¹⁰⁹



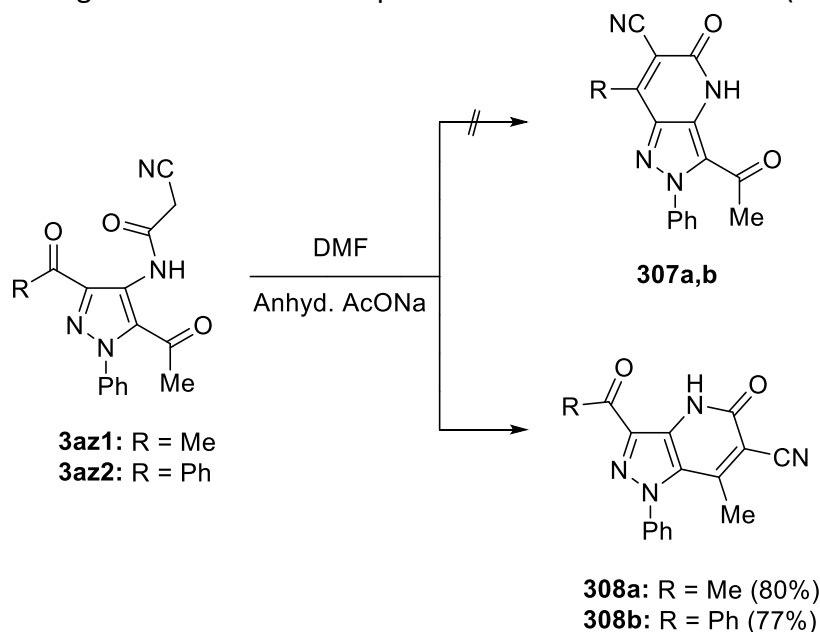
Scheme 141

Table 52. Synthesis and % yields of **306a-e**

Entry	Product	Ar	Yield (%)
3a	306a	Ph	30
3bz	306b	4-MeC ₆ H ₄	27
3by	306c	4-MeOC ₆ H ₄	31
3co	306d	4-ClC ₆ H ₄	30

3cx	306e	1-Naphthyl	29
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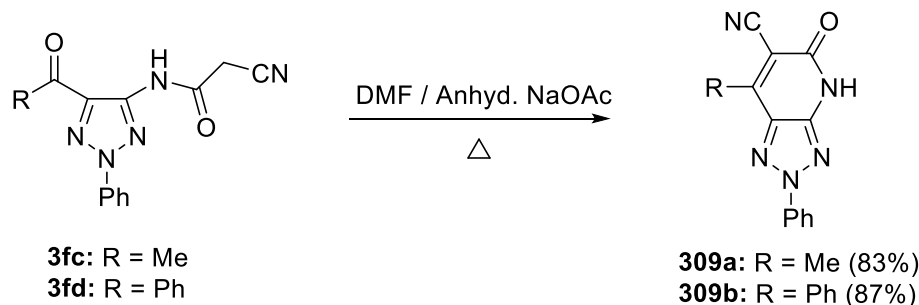
The 2-cyano-*N*-(pyrazol-4-yl)acetamide derivatives **3az1** and **3az2** underwent intramolecular cyclization under reflux in DMF containing anhydrous sodium acetate to give either **307a,b** or their isomers **308a,b**. Compounds **308a,b** were assigned to be the formed products based on its ¹³C-NMR (Scheme 142).⁴³



Scheme 142

3.2.2.1.2. 4,5-Dihydro-2*H*-[1,2,3]triazolo[4,5-*b*]pyridine

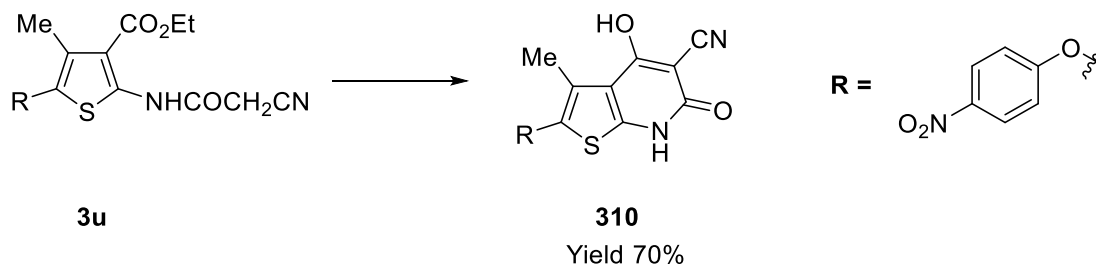
The cyanoacetamides **3fc** and **3fd** were cyclized into [1,2,3]triazolo[4,5-*b*]pyridines **309a,b** upon heating at reflux in DMF using anhydrous sodium acetate as a base (Scheme 143).⁴³



Scheme 143

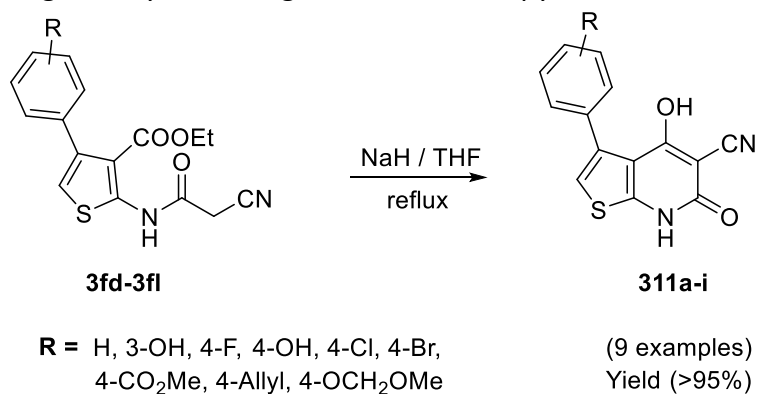
3.2.2.1.3. 6,7-Dihydrothieno[2,3-*b*]pyridine

The cyanoacetamide derivative **3u** is cyclized by heating in ethanolic solution of sodium ethoxide at reflux to give thieno[2,3-*b*]pyridine-5-carbonitrile derivative **310** (Scheme 144).²⁷



Scheme 144

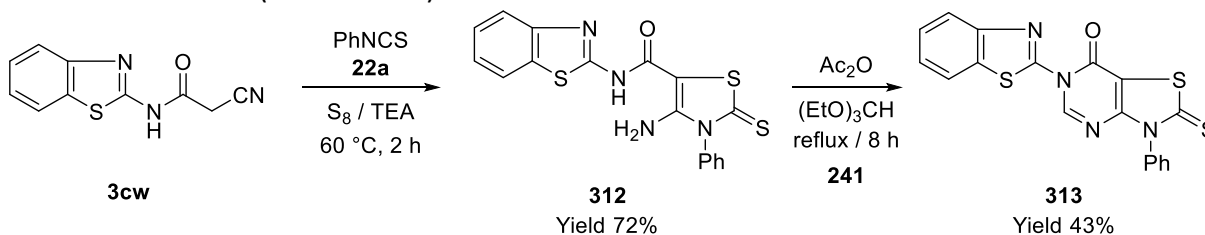
Zhao *et al.*¹⁴¹ reported that the treatment of ethyl 2-(2-cyanoacetamido)-4-arylthiophene-3-carboxylate **3fd-3fl** with sodium hydride in boiling tetrahydrofuran gave thieno[2,3-*b*]pyridine derivatives **311a-i** (Scheme 145).



Scheme 145

3.2.2.1.4. 2,3-Dihydrothiazolo[4,5-*d*]pyrimidine

Cyanoacetamide **3cw** was reacted with phenyl isothiocyanate **22a**, sulfur and triethylamine to form compound **312** which then treated with triethyl orthoformate **241** in acetic anhydride at reflux to give thiazolo[4,5-*d*]pyrimidine derivative **313** (Scheme 146).⁹⁹

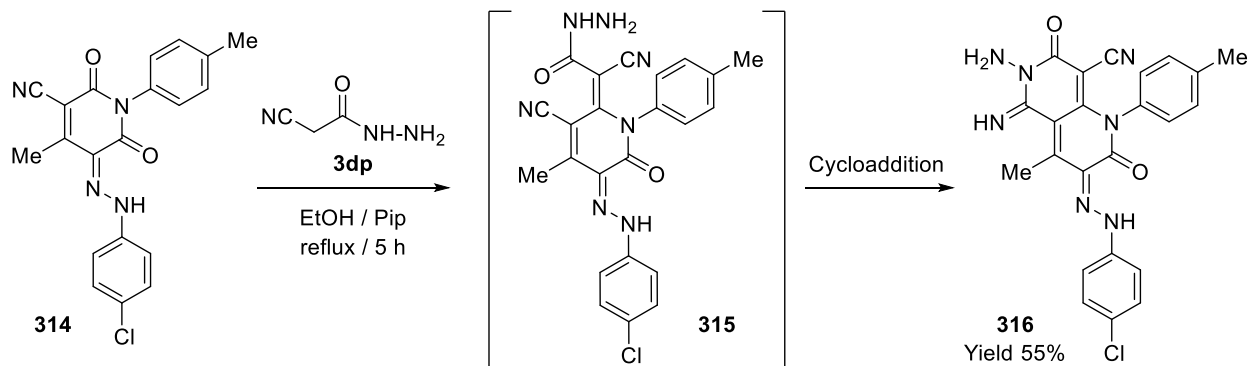


Scheme 146

3.2.2.2. Fused [6-6] system

3.2.2.2.1. 1,6-Naphthyridine

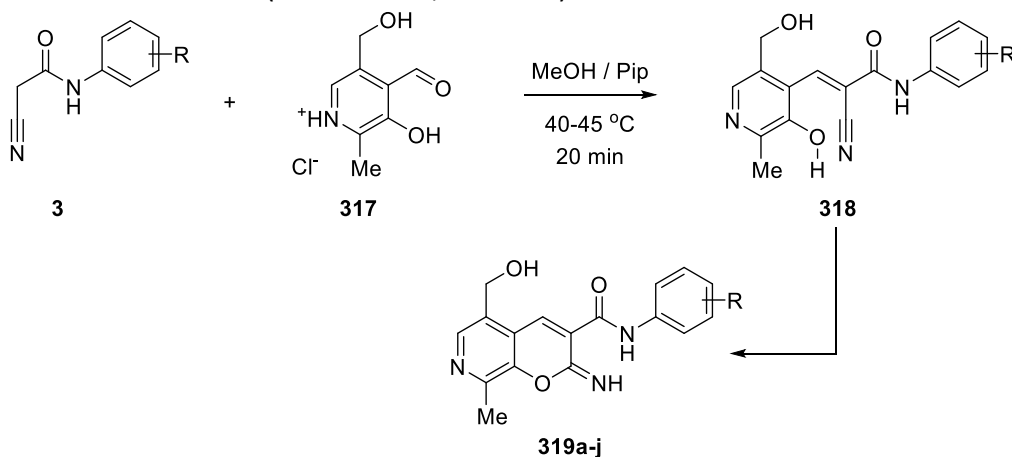
Cyanoacetylhydrazide **3dp** was reacted with compound **314** in ethanol containing piperidine furnishing 1,6-naphthyridine derivative **316** *via* the intermediacy of **315** (Scheme 147).¹⁴²



Scheme 147

3.2.2.2.2. Pyrano[2,3-c]pyridine

The condensation of pyridoxal hydrochloride **317** with different 2-cyano-*N*-arylacetyl amides **3** in methanol containing piperidine afforded 2*H*-pyrano[2,3-*c*]pyridine derivatives **319** through the formation of 2-cyanoacrylamide intermediates **318** (Scheme 148, Table 53).¹⁴³



Scheme 148

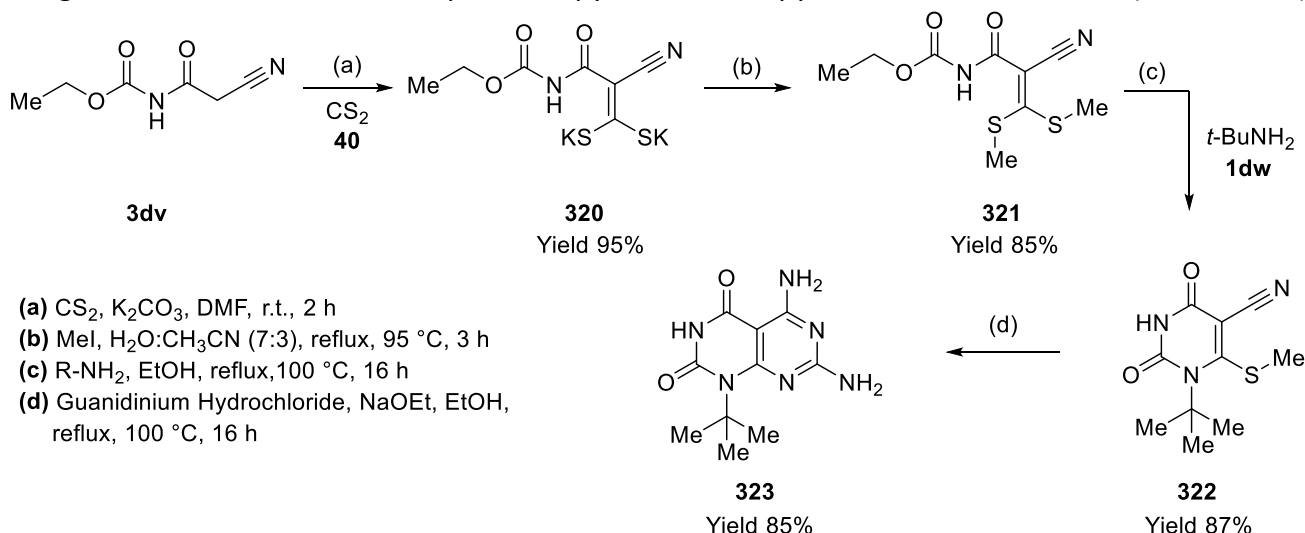
Table 53. Synthesis and % yields of **319a-j**

Entry	Product	R	Yield (%)
3a	319a	H	56-88%
3cu	319b	2-Me	
3di	319c	3-Me	
3bz	319d	4-Me	
3dk	319e	2-Et	
3dr	319f	4-Et	
3by	319g	4-OMe	
3ek	319h	2,4-di-OMe	
3el	319i	3,5-di-OMe	
3cq	319j	2-F	

3.2.2.2.3. Pyrimido[4,5-*d*]pyrimidine

The condensation of *N*-cyanoacetylurethane **3dv** with carbon disulfide **40** in DMF containing potassium carbonate, with a subsequent treatment with methyl iodide in water-acetonitrile mixture produced ketene

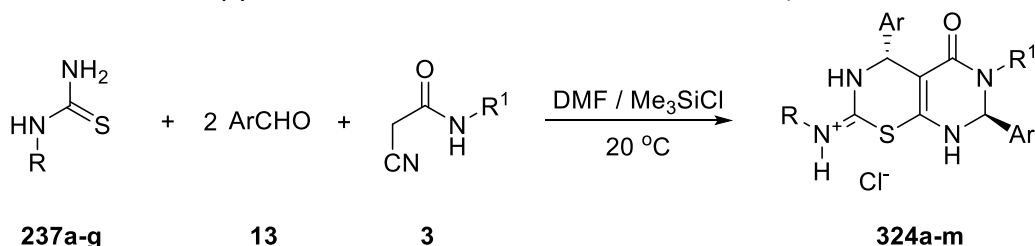
dithioacetal **321** which was heated at reflux with amine **1dw** in ethanol to give **322**. Subsequent reaction of **322** with guanidine in ethanol at reflux produces pyrimido[4,5-*d*]pyrimidine derivatives **323** (Scheme 149).¹⁴⁴



Scheme 149

3.2.2.2.4. Pyrimido[4,5-*e*][1,3]thiazine

The reaction of cyanoacetamides **3** with thioureas **237a-g** and aldehydes **13** in DMF containing trimethylsilyl chloride led to the formation of pyrimido[5,4-*e*][1,3]thiazin-5-ones **324a-m** (Scheme 150, Table 54).¹⁴⁵



Scheme 150

Table 54: Synthesis and % yields of **324a-m**

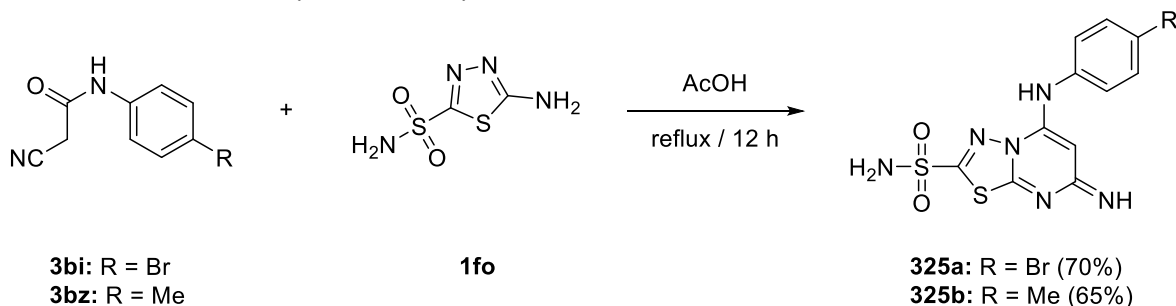
Entry	R	Entry	R ¹	Entry	Ar	Product	Yield (%)
237a	H	3do	H	13k	Ph	324a	85
237b	Me	3do	H	13k	Ph	324b	73
237a	H	3ca	Me	13k	Ph	324c	88
237c	Et	3ca	Me	13k	Ph	324d	61
237d	Ph	3ca	Me	13k	Ph	324e	75
237a	H	3z	Bn	13k	Ph	324f	68
237a	H	3co	4-ClC ₆ H ₄	13w	4-ClC ₆ H ₄	324g	92
237d	Ph	3co	4-ClC ₆ H ₄	13x	4-MeOC ₆ H ₄	324h	86
237e	(CH ₂) ₂ MeO	3fm	(CH ₂) ₂ MeO	13k	Ph	324i	72
237f	CH ₂ THF	3fm	(CH ₂) ₂ MeO	13k	Ph	324j	59
237g	(CH ₂) ₂ OEt	3fn	(CH ₂) ₂ OEt	13k	Ph	324k	64
237g	(CH ₂) ₂ OEt	3fn	(CH ₂) ₂ OEt	13k	Ph	324l	59
237f	CH ₂ THF	3fn	(CH ₂) ₂ OEt	13k	Ph	324m	56

3.2.3. Two heterocycles with one hetero atom as bridgehead

3.2.3.1. Fused [5-6] system

3.2.3.1.1. Thiadiazolo[3,2-*a*]pyrimidine

The condensation of 5-amino-1,3,4-thiadiazole-2-sulfonamide **1fo** with cyanoacetanilide derivatives **3bi** and **3bz** under reflux in glacial acetic acid was reported by El-Ghory and Shaaban¹⁴⁶ to give [1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives **325a,b** (Scheme 151).

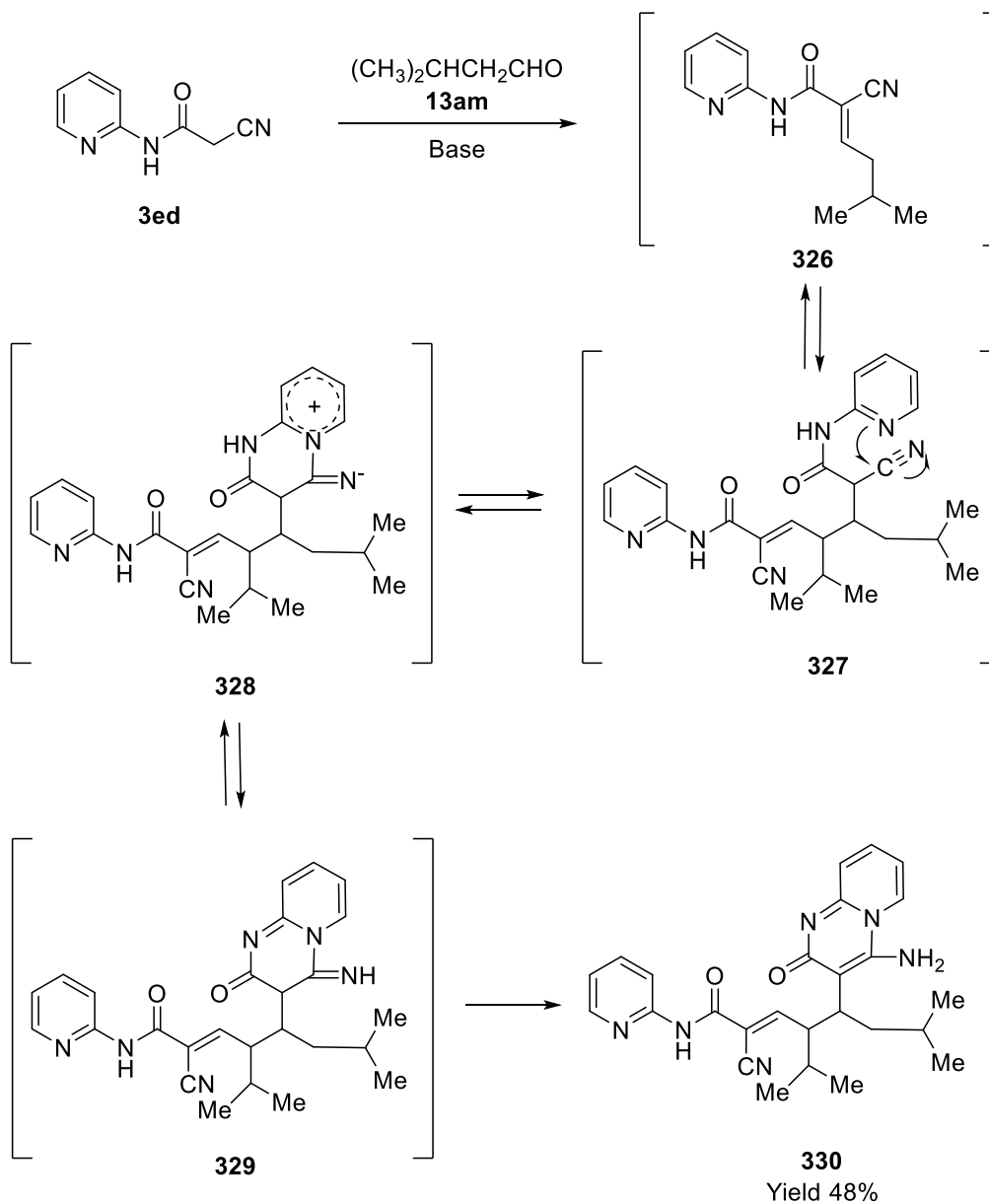


Scheme 151

3.2.3.2. Fused [6-6] system

3.2.3.2.1. Pyrido[1,2-*a*]pyrimidine

The reaction of *N*-(pyridin-2-yl)-2-cyanoacetamide **3ed** with 3-methylbutanal **13am** in ethanol containing piperidine at 20 °C furnished the (pyrido[1,2-*a*]pyrimidin-3-yl)oct-2-enamide derivative **330**. The process is likely to include a set of consecutive reactions (Knoevenagel condensation, Michael addition, and intramolecular heterocyclization). Intermediate Knoevenagel condensation product, alkene **326**, undergoes dimerization according to Michael to form adduct **327**. Intramolecular heterocyclization of that adduct gives zwitterionic system **328** which is transformed into imine **329**. Then, the latter is stabilized as enamine tautomer **330** (Scheme 152).¹¹⁶



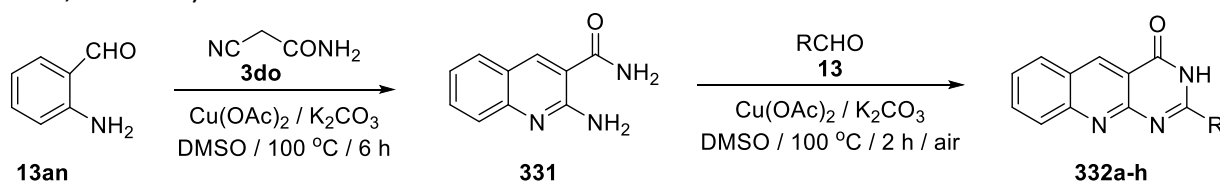
Scheme 152

3.2.4. Three fused heterocycles

3.2.4.1. Fused [6-6-6] system

3.2.4.1.1. Pyrimido[4,5-*b*]quinolone

2-aminoquinoline-3-carboamides **331** is obtained from the reaction of **3do** with **13an** in dimethylsulfoxide containing $\text{Cu}(\text{OAc})_2$ and K_2CO_3 at 100°C for 6 hours. The subsequent addition of aldehyde **13** to the reaction mixture and heating at 100°C for further 2 hours yielded pyrimido[4,5-*b*]quinolin-4-one compounds **332a-h** (Scheme 153, Table 55).¹⁴⁷



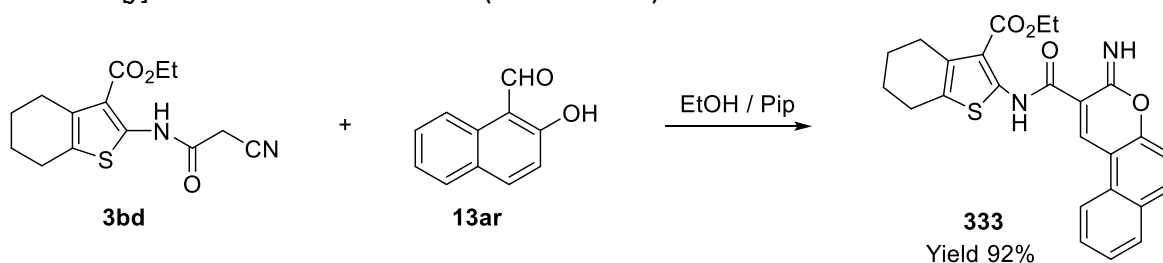
Scheme 153

Table 55: Synthesis and % yields of **332a-h**

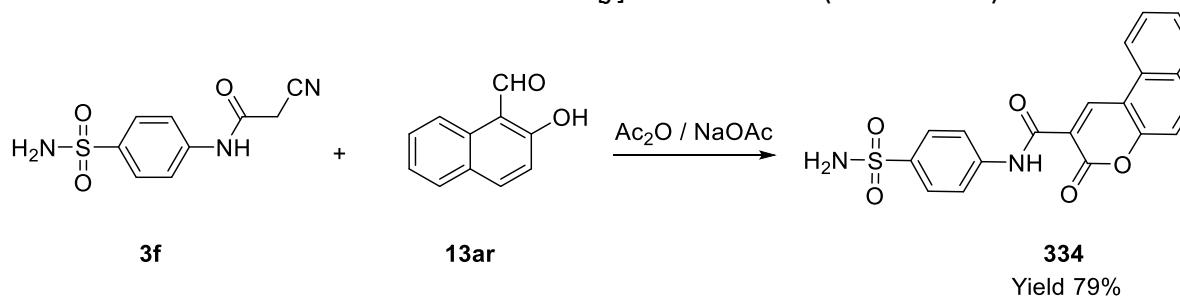
Entry	Product	R	Yield (%)
13ao	332a	C ₃ H ₇	44
13k	332b	Ph	46
13ap	332c	2-MeC ₆ H ₅	55
13o	332d	4-MeC ₆ H ₅	46
13l	332e	4-MeOC ₆ H ₅	54
13w	332f	4-ClC ₆ H ₅	45
13y	332g	3-ClC ₆ H ₅	44
13aq	332h	2-FC ₆ H ₅	60

3.2.4.1.2. Benzo[f]chromene**3.2.4.1.2.1. Synthesis *via* Knoevenagel condensation reactions**

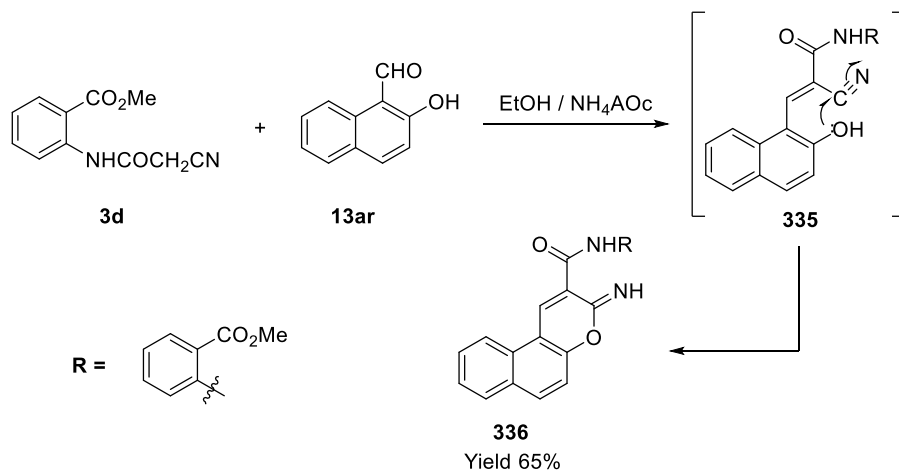
Knoevenagel condensation of **3bd** with 2-hydroxy-1-naphthaldehyde **13ar** in ethanol/piperidine mixture afforded the benzo[f]chromene derivative **333** (Scheme 154).⁴⁸

**Scheme 154**

Furthermore, compound **3f** was reacted with 2-hydroxy-1-naphthaldehyde **13ar** in acetic anhydride using anhydrous sodium acetate as a base to form the benzo[f]chromene **334** (Scheme 155).¹⁴⁸

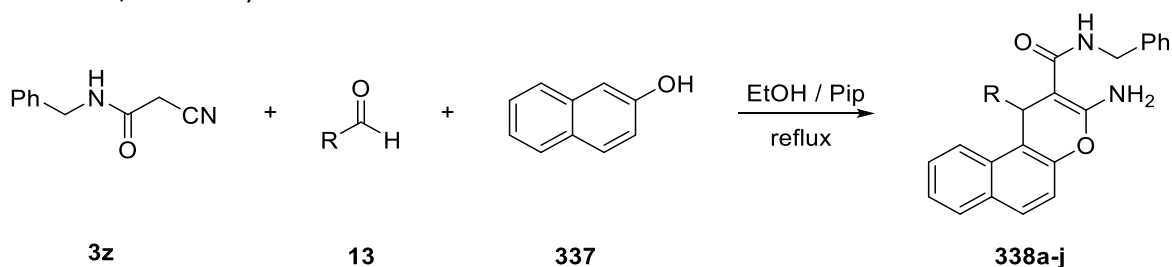
**Scheme 155**

The reaction of **3d** with 2-hydroxy-1-naphthaldehyde **13ar** in ethanol containing ammonium acetate as a catalyst afforded compound **336**, through the intermediate **335** (Scheme 156).¹¹



Scheme 156

Benzo[*f*]chromene-2-carboxamide derivatives **338a-j** were synthesized *via* the reaction of *N*-benzyl-2-cyanoacetamide **3z**, aromatic aldehydes **13**, 2-naphthol **337** and piperidine in absolute ethanol at reflux for 3 hours (Scheme 157, Table 56).¹⁴⁹



Scheme 157

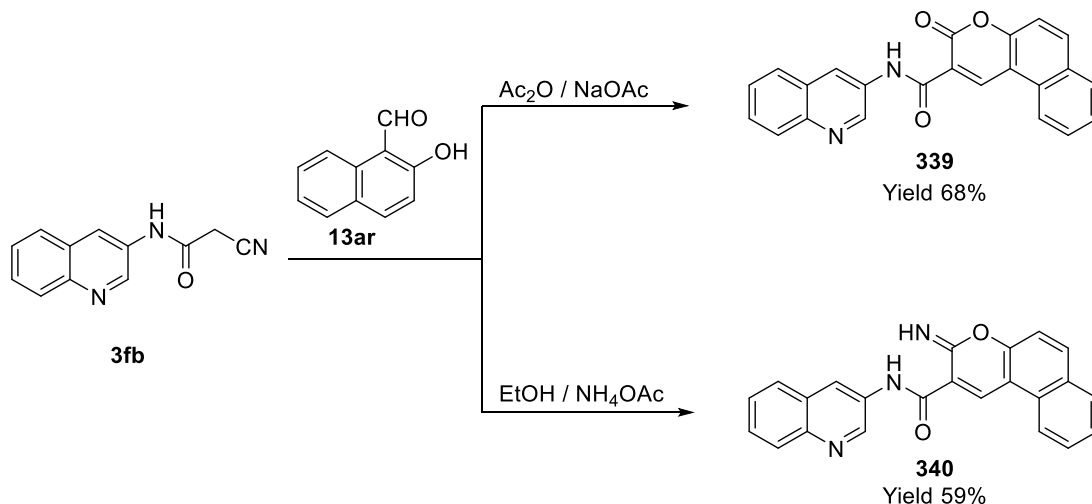
Table 56: Synthesis and % yields of **338a-j**

Entry	Product	R	Yield (%)
13k	338a	Ph	75
13w	338b	4-ClC ₆ H ₄	70
13z	338c	4-BrC ₆ H ₄	70
13m	338d	4-NO ₂ C ₆ H ₄	80
13p	338e	3-NO ₂ C ₆ H ₄	75

Entry	Product	R	Yield (%)
13o	338f	4-MeC ₆ H ₄	60
13x	338g	4-MeOC ₆ H ₄	68
13as	338h	2,4-Cl ₂ C ₆ H ₄	78
13r	338i	3-MeOC ₆ H ₄	65
13i	338j	4-OHC ₆ H ₄	70

3.2.4.1.2.2. Synthesis *via* Perkin reaction

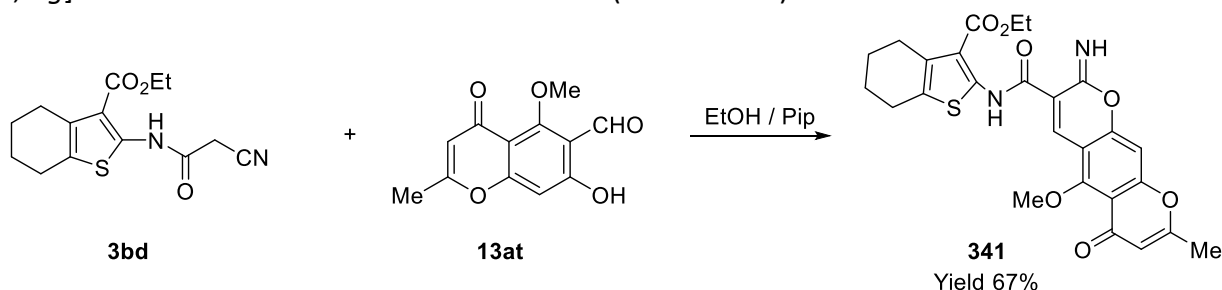
The reaction of 2-hydroxy-1-naphthaldehyde **13ar** with cyanoacetamide **3fb** in acetic anhydride containing sodium acetate gave the benzochromene-2-one **339**. However, performing the same reaction in ethanol containing ammonium acetate afforded 2-iminobenzochromene **340** (Scheme 158).¹⁴⁰



Scheme 158

3.2.4.1.3. Pyrano[3,2-*g*]chromene

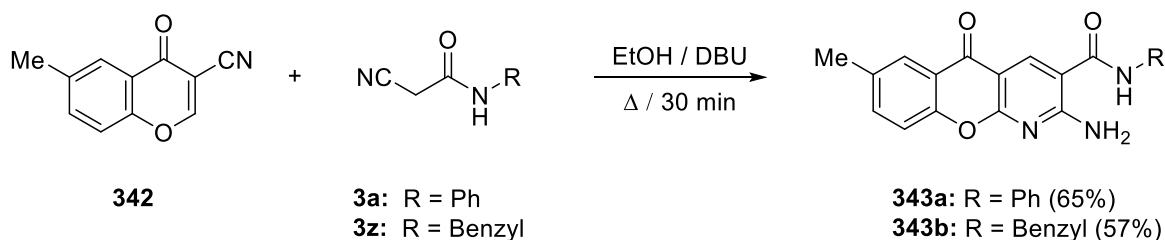
The reaction of **3bd** with chromene-6-carbaldehyde derivative **13at** in ethanol containing piperidine afforded pyrano[3,2-*g*]chromene-3-carboxamide derivative **341** (Scheme 159).⁴⁸



Scheme 159

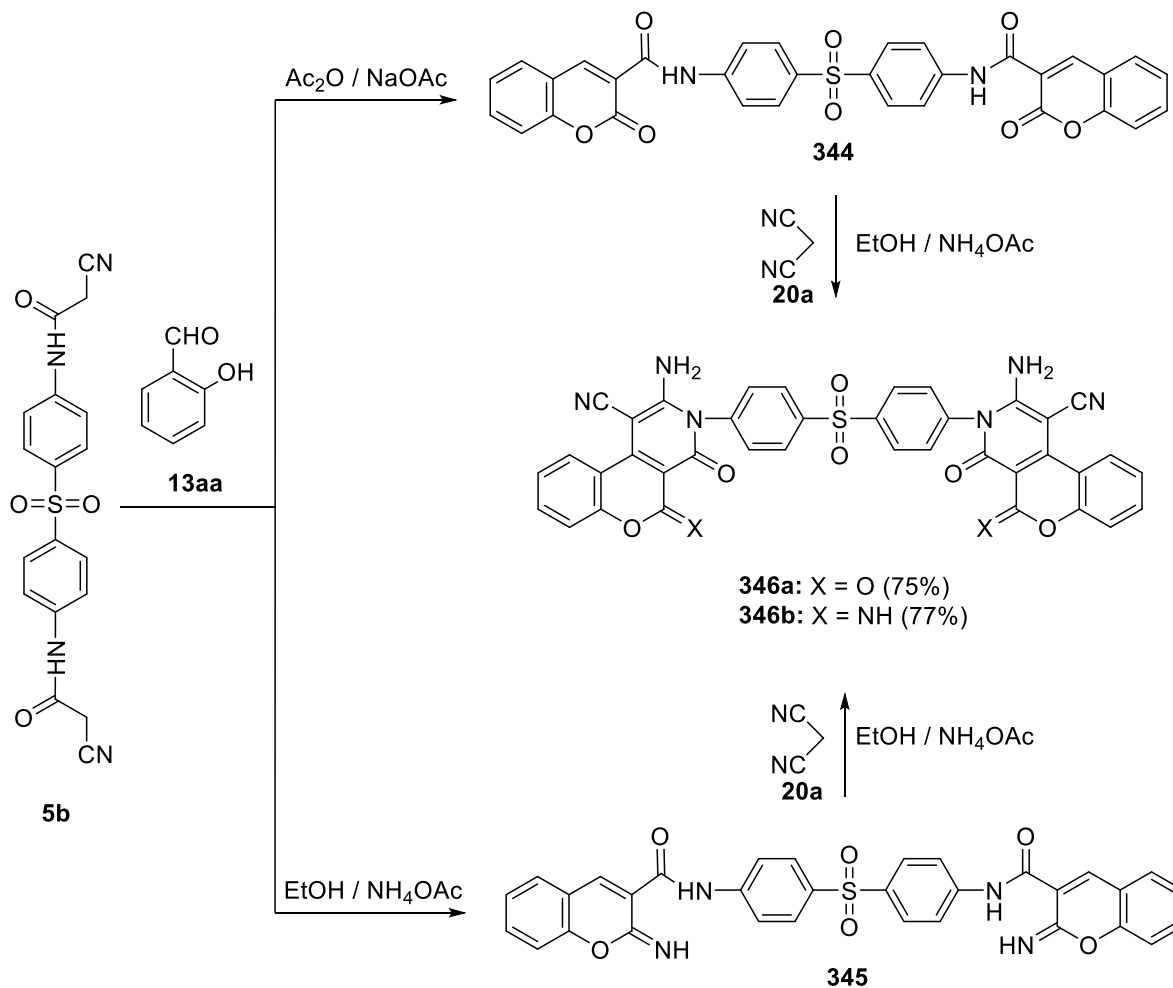
3.2.4.1.4. Chromeno[2,3-*b*]pyridine

The reaction of nitrile **342** with cyanoacetamide derivatives **3a** and **3z** furnished 2-aminochromeno[2,3-*b*]pyridine-3-carboxamide derivatives **343** in moderate yields (Scheme 160).¹⁵⁰



Scheme 160

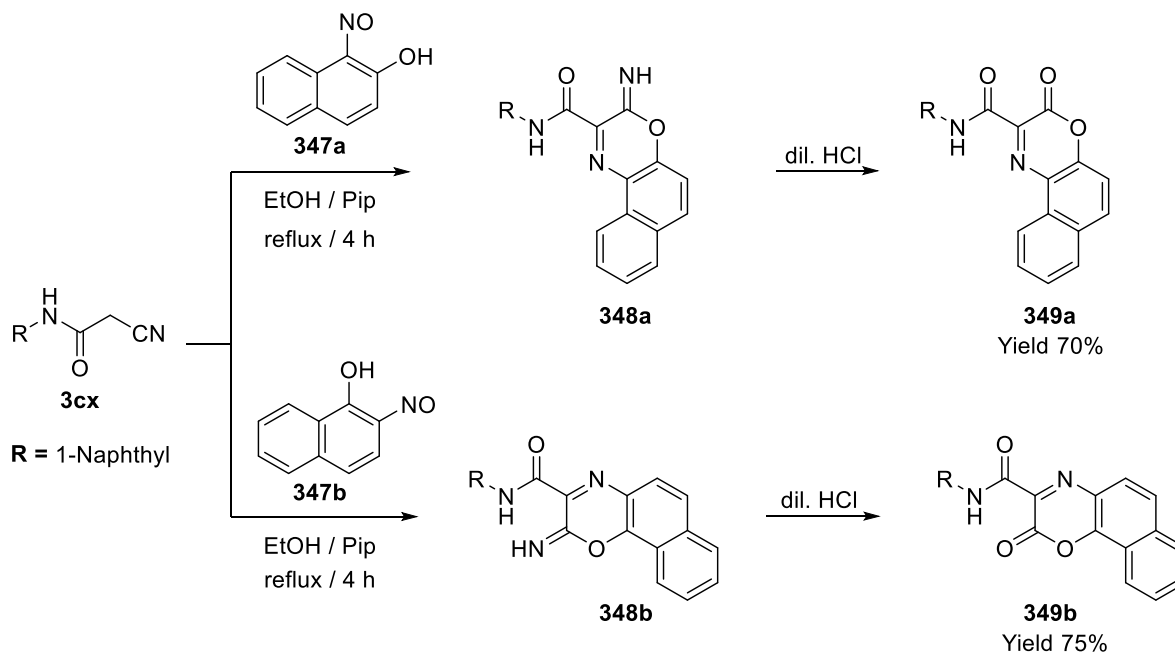
The condensation of compound **5b** with salicylaldehyde **13aa** in acetic anhydride containing anhydrous sodium acetate gave the chromene derivative **344**, while reaction of **5b** with salicylaldehyde **13aa** in the presence of ammonium acetate afforded 2-iminochromene derivative **345**. Reacting either of **344** or **345** with malononitrile in ethanol containing ammonium acetate gave the corresponding bis(4*H*-chromeno[3,4-*c*]pyridines), **346a,b** (Scheme 161).³⁴



Scheme 161

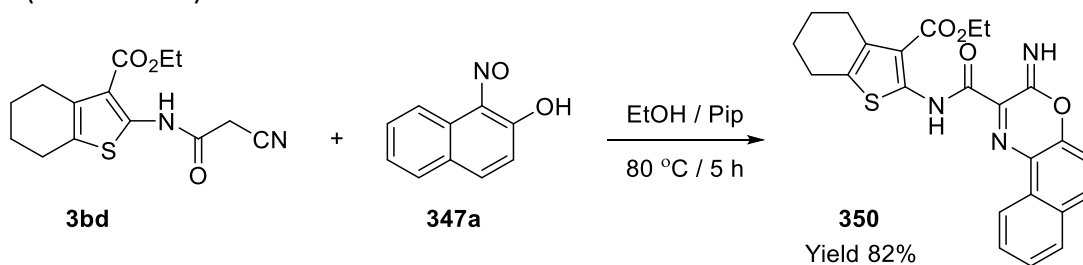
3.2.4.1.5. Naphthoxazine

The reaction of 2-cyano-*N*-(naphtha-1-yl)acetamide **3cx** with either 1-nitroso-2-naphthol **347a** or 2-nitroso-1-naphthol **347b** in boiling ethanol containing piperidine afforded naphthoxazine **349a** or **349b**, respectively (Scheme 162).¹¹⁰



Scheme 162

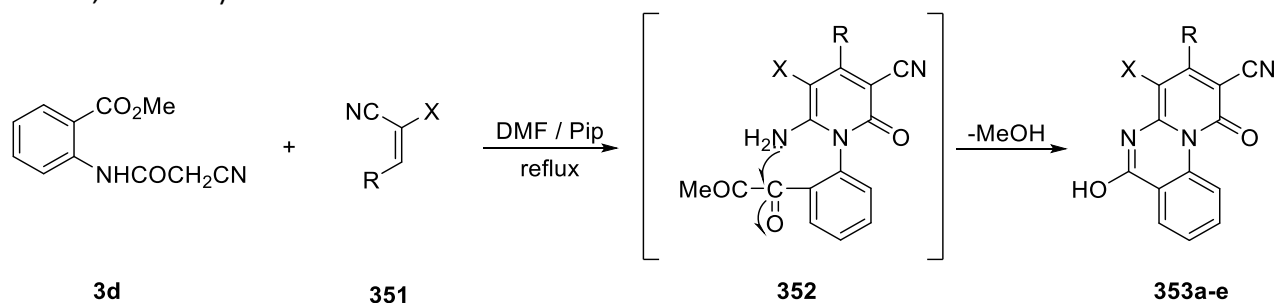
The treatment of cyanoacetamide **3bd** with 1-nitroso-2-naphthol **347a** produced naphtho[2,1-*b*]oxazine derivative **350** (Scheme 163).⁴⁸



Scheme 163

3.2.4.1.6. Pyrido[1,2-*a*]quinazoline

The synthesis of pyrido[1,2-*a*]quinazolines **353a-e** was carried out *via* the reaction of **3d** with cinnamionitriles **351a-e** in DMF at reflux in the presence of a catalytic amount of piperidine. The isolated product **353a-e** was thought to be formed *via* the formation of pyridine intermediate **352a-e** followed by methanol removal (Scheme 164, Table 57).¹⁶



Scheme 164

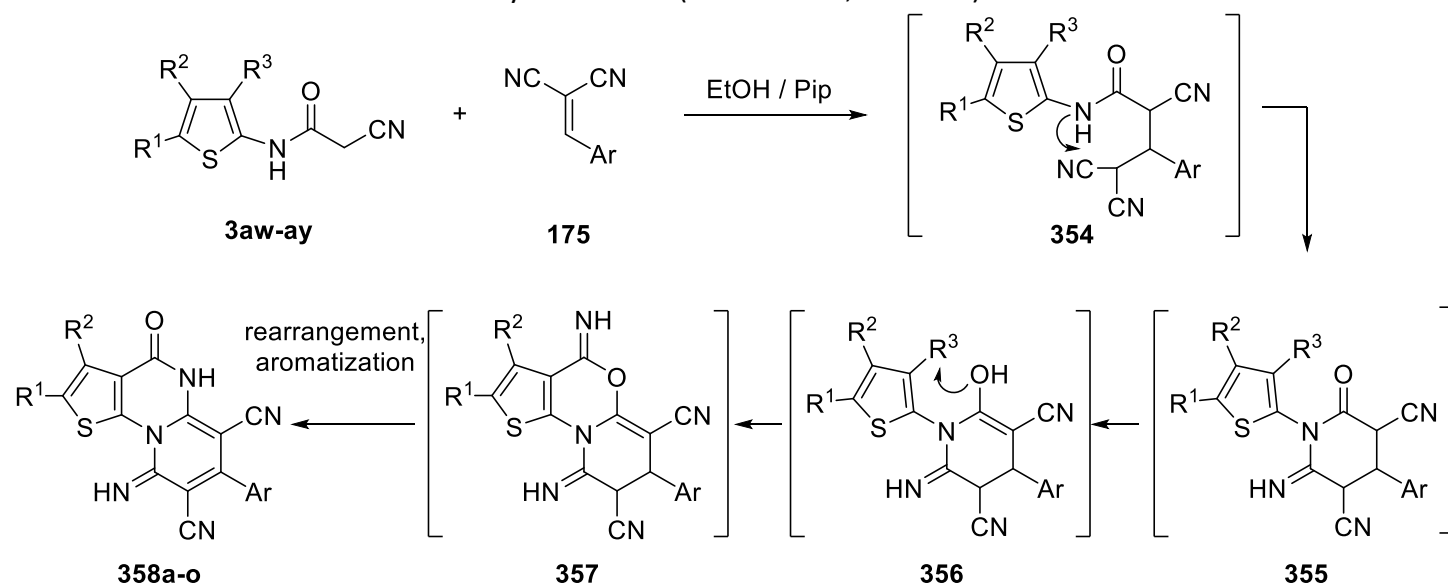
Table 57. Synthesis and % yields of **353a-e**

Entry	Product	R	X	Yield (%)
351a	353a	2,4-Cl ₂ C ₆ H ₃	CONH ₂	71
351b	353b	2-ClC ₆ H ₃	CONH ₂	63
351c	353c	4-N(Me) ₂ C ₆ H ₄	CONH ₂	65
351d	353d	2-ClC ₆ H ₃	CO ₂ Et	51
351e	353e	4-N(Me) ₂ C ₆ H ₄	CO ₂ Et	59

3.2.4.2. Fused [5-6-6] system

3.2.4.2.1. Pyrido[1,2-*a*]thieno[3,2-*e*]pyrimidine

Michael addition of activated methylene in the cyanoacetamides **3aw-fv** to several arylidenmalononitrile **175** in ethanol⁴² or pyridine⁴ containing piperidine at reflux yielded pyrido[1,2-*a*]thieno[3,2-*e*]pyrimidine derivatives **358a-v** via the intermediacy of **354-357** (Scheme 165, Table 58).



Scheme 165

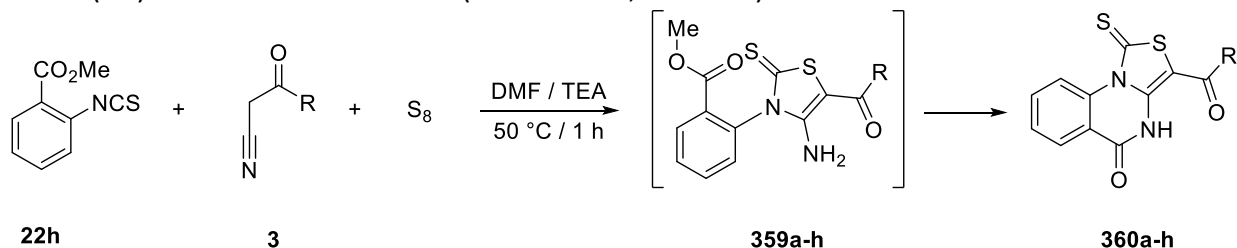
Table 58. Synthesis and % yields of **358a-o**

Entry	R ¹	R ²	R ³	Entry	Ar	Product	Yield (%)
3aw	H	Ph	CN	175c	Ph	358a	94
3aw	H	Ph	CN	175f	4-MeC ₆ H ₄	358b	91
3aw	H	Ph	CN	175d	4-MeOC ₆ H ₄	358c	88
3aw	H	Ph	CN	175e	4-NO ₂ C ₆ H ₄	358d	84
3aw	H	Ph	CN	175g	4-ClC ₆ H ₄	358e	90
3aw	H	Ph	CN	175h	C ₄ H ₃ S	358f	81
3ax	H	4-ClC ₆ H ₄	CN	175c	Ph	358g	89
3ax	H	4-ClC ₆ H ₄	CN	175f	4-MeC ₆ H ₄	358h	85
3ax	H	4-ClC ₆ H ₄	CN	175d	4-MeOC ₆ H ₄	358i	89
3ax	H	4-ClC ₆ H ₄	CN	175e	4-NO ₂ C ₆ H ₄	358j	86

3ax	H	4-ClC ₆ H ₄	CN	175g	4-ClC ₆ H ₄	358k	88
3ax	H	4-ClC ₆ H ₄	CN	175h	C ₄ H ₃ S	358l	85
3ay	Me	CO ₂ Et	CN	175c	Ph	358m	90
3ay	Me	CO ₂ Et	CN	175f	4-MeC ₆ H ₄	358n	81
3ay	Me	CO ₂ Et	CN	175g	4-ClC ₆ H ₄	358o	85
3fp	CO ₂ Et	Me	CO ₂ Et	175c	Ph	358p	81
3fq	CO ₂ Et	Me	CO ₂ Et	175f	4-MeC ₆ H ₄	358q	76
3fr	CO ₂ Et	Me	CO ₂ Et	175d	4-MeOC ₆ H ₄	358r	77
3fs	CO ₂ Et	Me	CO ₂ Et	175e	4-NO ₂ C ₆ H ₄	358s	72
3ft	CO ₂ Et	Me	CO ₂ Et	175g	4-ClC ₆ H ₄	358t	85
3fu	CO ₂ Et	Me	CO ₂ Et	175k	4-CH(CH ₃) ₂ C ₆ H ₄	358u	87
3fv	CO ₂ Et	Me	CO ₂ Et	175l	3,4-OCH ₂ OC ₆ H ₄	358v	79

3.2.4.2.2. Thiazolo[3,4-*a*]quinazoline

The reaction of methyl-2-isothiocyanatobenzoates **22h** with cyanoacetamide derivatives **3** and sulfur afforded 2(3*H*)-thioxo-1,3-thiazoles **359a-h** which underwent a further cyclization into 1-thioxo[1,3]thiazolo[3,4-*a*]quinazolin-5(4*H*)-one derivatives **360a-h** (Scheme 166, Table 59).¹⁵¹



Scheme 166

Table 59. Synthesis and % yields of **360a-h**

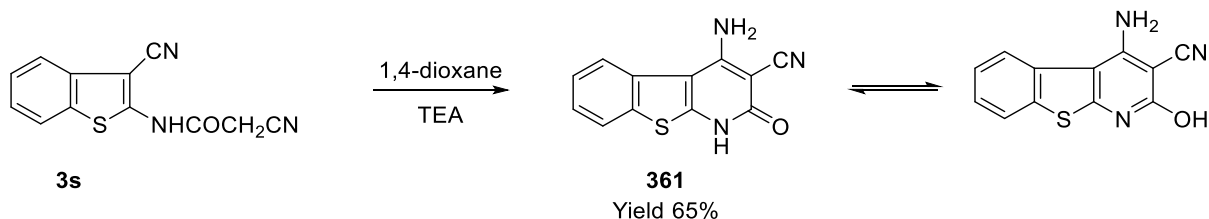
Entry	Product	R	Yield (%)
3a	360a	NHPh	70
3aa	360b	NH-Tetrahydrofuryl	69
3bl	360c	NH(4-F)C ₆ H ₄	67
3cd	360d	NH-n-C ₅ H ₁₁	77
3cq	360e	NH(2-F)C ₆ H ₄	63
3cv	360f	NH-CH(Me)Ph	69
3fw	360g	N(CH ₂) ₅	74
3fx	360h	NHCH ₂ (2-thienyl)	69

3.2.4.3. Fused [6-5-6] system

3.2.4.3.1. Benzo[4,5]thieno[2,3-*b*]pyridine

A. Synthesis *via* Michael addition reactions

Heating compound **3s** in 1,4-dioxane containing triethylamine affected cyclization into the tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine derivative **361** (Scheme 167).²⁵

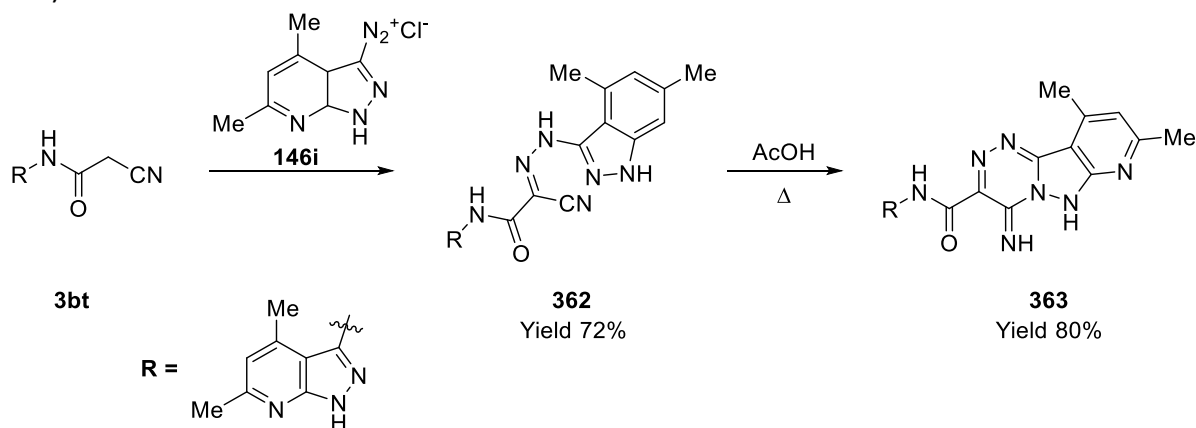


Scheme 167

3.2.4.3.2. Pyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine

A. Synthesis *via* coupling reactions

Coupling of **3bt** with 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-diazonium chloride **146i** in pyridine at 0-5 °C furnished the hydrazono compound **362**. When compound **362** is boiled in acetic acid, it was cyclized into **363**. (Scheme 168).⁵⁹

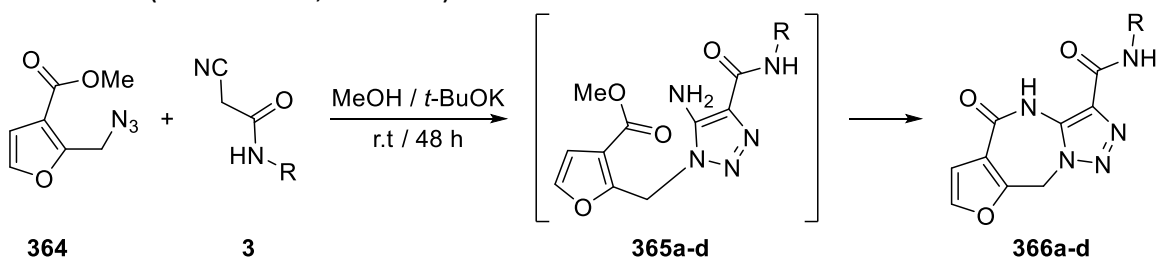


Scheme 168

3.2.4.3. Fused [5-7-5] system

3.2.4.3.1. Furo[3,2-*e*][1,2,3]triazolo[1,5-*a*][1,3]diazepine

Furo[3,2-*e*][1,2,3]triazolo[1,5-*a*][1,3]diazepines **366a-d** were produced by Yagodkina *et al*¹⁵² through the reaction of methyl 2-(azidomethyl)furan-3-carboxylate **364** with cyanoacetamides **3** in methanol containing potassium *t*-butoxide (Scheme 169, Table 60).



Scheme 169

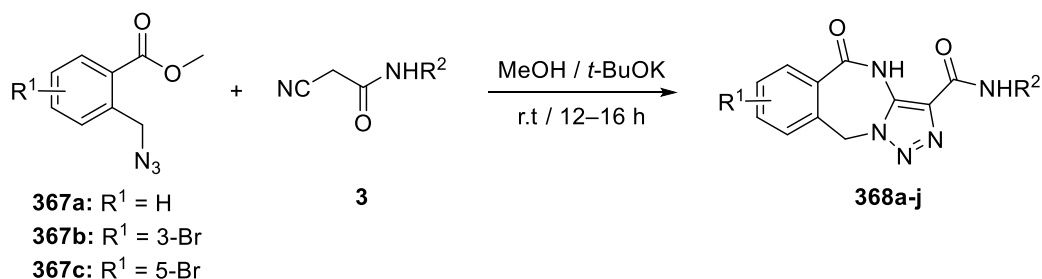
Table 60. Synthesis and % yields of **366a-d**

Entry	Product	R	Yield (%)
3do	366a	H	65
3ca	366b	Me	63
3z	366c	Benzyl	54
3by	366d	4-MeOC ₆ H ₄	79

3.2.4.4. Fused [5-7-6] system

3.2.4.4.1. Benzo[e][1,2,3]triazolo[1,5-*a*][1,3]diazepine

The reaction of methyl *o*-(azidomethyl)benzoates **367a-c** with 2-cyanoacetamides **3** to produce triazolo[1,5-*b*][2,4]benzodiazepines **368a-j** was achieved by the action of either MeONa, *t*-BuOK, EtONa, or KOH (Scheme 170, Table 61).¹⁵³



Scheme 170

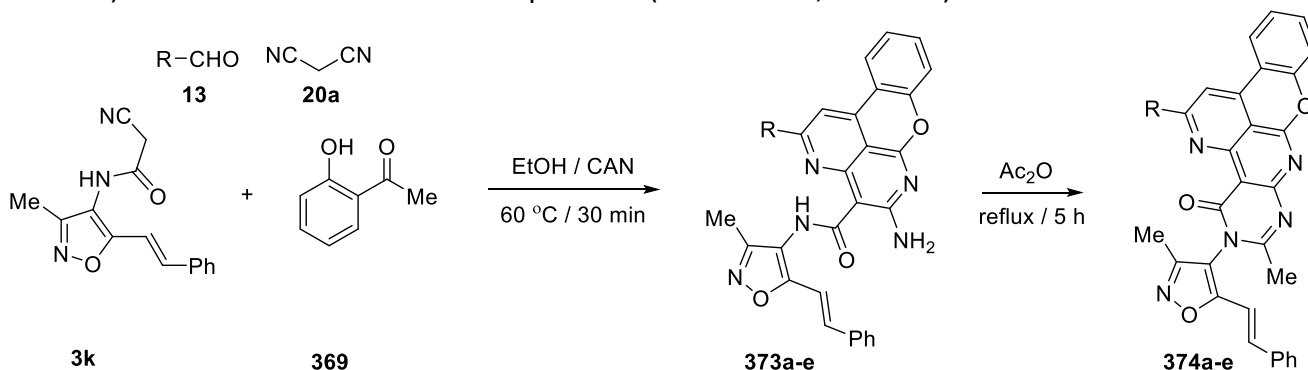
Table 61. Synthesis and % yields of **368a-j**

Entry	R ¹	Entry	R ²	Product	Yield (%)
367a	H	3do	H	368a	36
367a	H	3ca	Me	368b	36
367a	H	3z	Benzyl	368c	40
367a	H	3a	Ph	368d	44
367a	H	3co	4-ClC ₆ H ₄	368e	48
367a	H	3by	4-MeOC ₆ H ₄	368f	45
367b	3-Br	3do	H	368g	40
367c	5-Br	3ca	Me	368h	40
367c	5-Br	3z	Benzyl	368i	42
367c	5-Br	3by	4-MeOC ₆ H ₄	368j	48

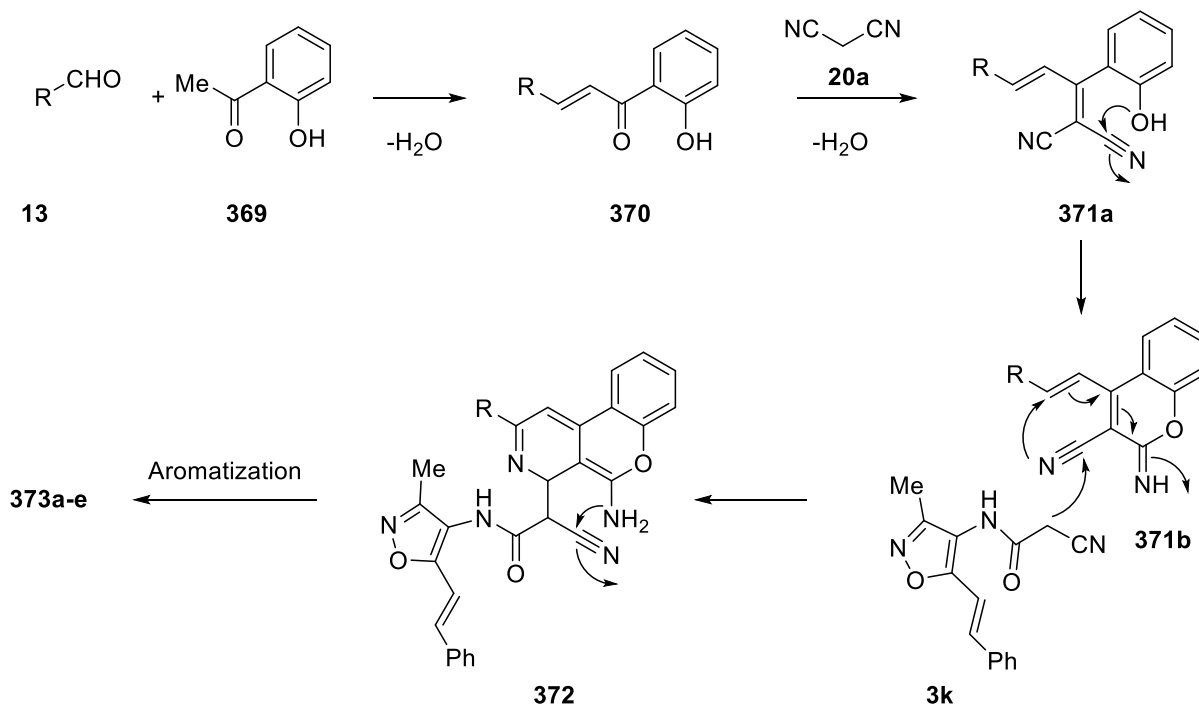
3.2.5. Four and Five fused heterocycles

3.2.5.1. Chromeno[4,3,2-*de*][1,6]naphthyridine and Chromeno[4,3,2-*de*]pyrimido[4,5-*h*][1,6]naphthyridine

Rajanarendar *et al*¹⁵⁴ showed that the reaction of aromatic aldehydes **13** with cyanoacetamide **3k**, malononitrile **20a** and *o*-hydroxyacetophenone **369** in ethanol containing ceric ammonium nitrate CAN under reflux produced chromeno[4,3,2-*de*][1,6]naphthyridines **373a-e**. Treating **373a-e** with acetic acid at reflux led to a further cyclization furnishing chromeno[4,3,2-*de*]pyrimido[4,5-*h*][1,6]naphthyridine derivatives **374a-e**, (Scheme 171). A reasonable mechanism is depicted in (Scheme 172, Table 62).



Scheme 171



Scheme 172

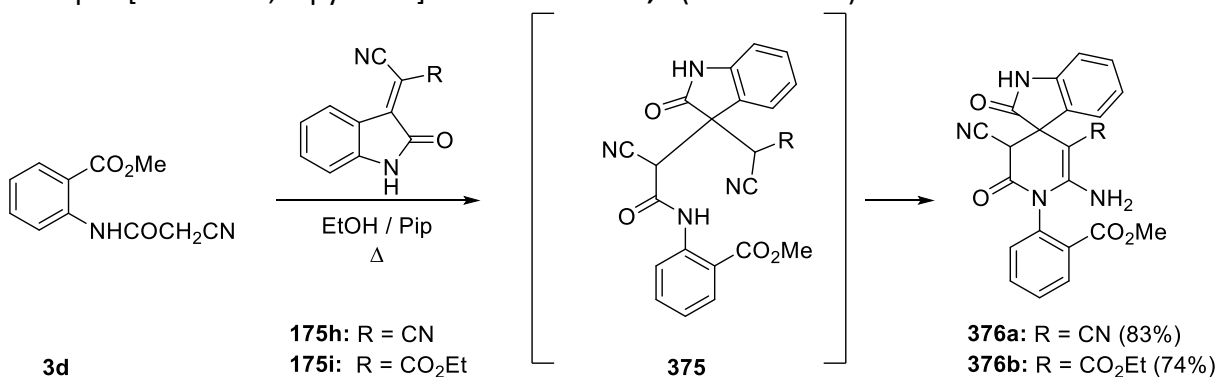
Table 62. Synthesis and % yields of **373a-e** and **374a-e**

Entry	R	Product	Yield (%)	Product	Yield (%)
13k	Ph	373a	60	374a	61
13t	2-ClC ₆ H ₄	373b	66	374b	65
13au	2-BrC ₆ H ₄	373c	67	374c	68
13o	4-MeC ₆ H ₄	373d	61	374d	61
13av	2-MeOC ₆ H ₄	373e	59	374e	63

3.2.6. Spiro compounds

3.2.6.1. Spiro[indoline-3,4'-pyridine]

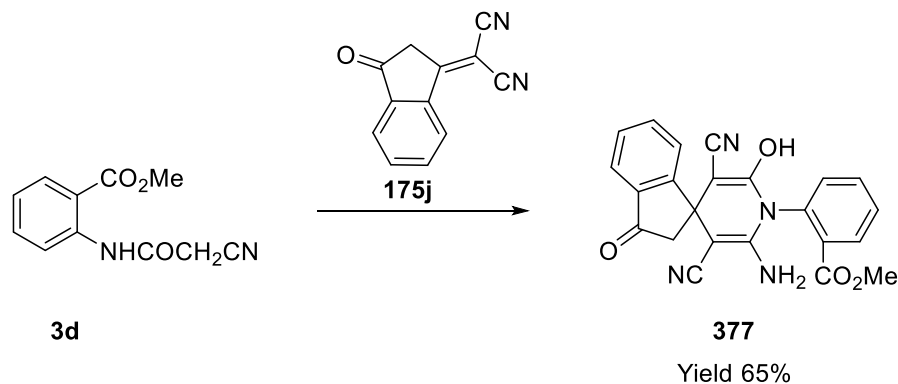
The reaction of **3d** with 2-oxoindolin-3-ylidene derivatives **175h,i** in ethanol containing piperidine under reflux afforded the spiro[indoline-3,4'-pyridine] derivatives **376a,b** (Scheme 173)¹¹



Scheme 173

3.2.6.2. Spiro[indene-1,4'-pyridine]

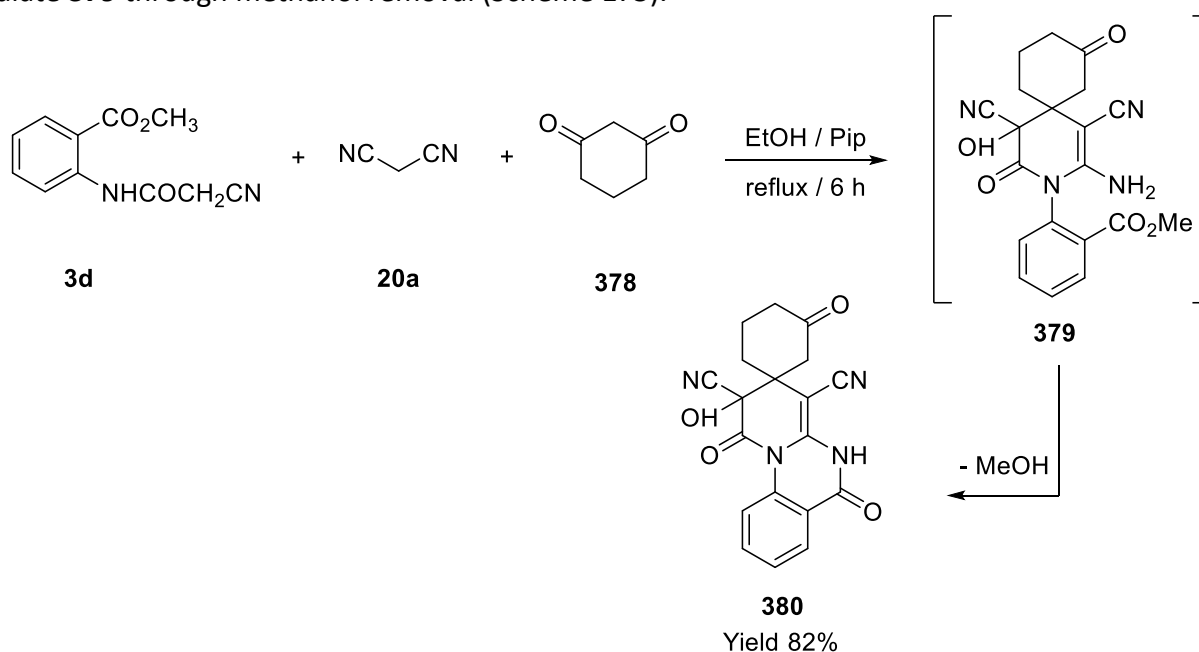
In a similar manner, reaction of **3d** with 2-(3-oxoindan-1-ylidene)malononitrile **175j** gave the spiro[indane-1,4'-pyridine] derivative **377** (Scheme 174).¹⁶



Scheme 174

3.2.6.3. Spiro[cyclohexane-1,3'-pyrido[1,2-*a*]quinazoline]

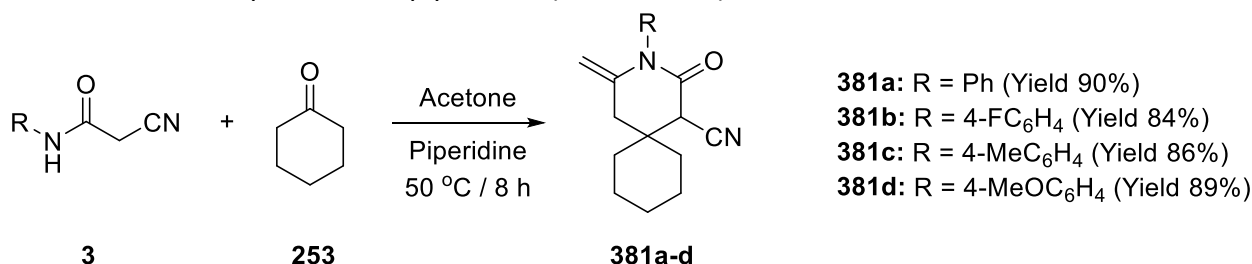
The reaction of methyl 2-(2-cyanoacetamido)benzoate **3d** with malononitrile **20a** and cyclohexane-1,3-dione **378** under reflux in ethanol containing piperidine produced pyrido[1,2-*a*]quinazoline compounds **380** via the intermediate **379** through methanol removal (Scheme 175).¹⁵⁵



Scheme 175

3.2.6.4. 3-Azaspiro[5.5]undecane-1-carbonitrile:

Compounds **381a-d** were synthesized in excellent yields when reacting cyanoacetamides **3** with cyclohexanone **253** in the presence of piperidine (Scheme 176).¹⁵⁶



4. Conclusions

In this review article, we clearly demonstrate the different methods for the synthesis of cyanoacetamide derivatives. Also, we report, the utility of these compounds as valuable building blocks for the synthesis of varieties of heterocycles that include monocyclic five- and six-membered heterocycles. Moreover, we report, the usefulness of cyanoacetamides for the synthesis of different types of fused heterocycles and their spiro cyclic analogues.

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6. Authors' Biographies



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