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Synthesis and synthetic applications of cyanoacetamides

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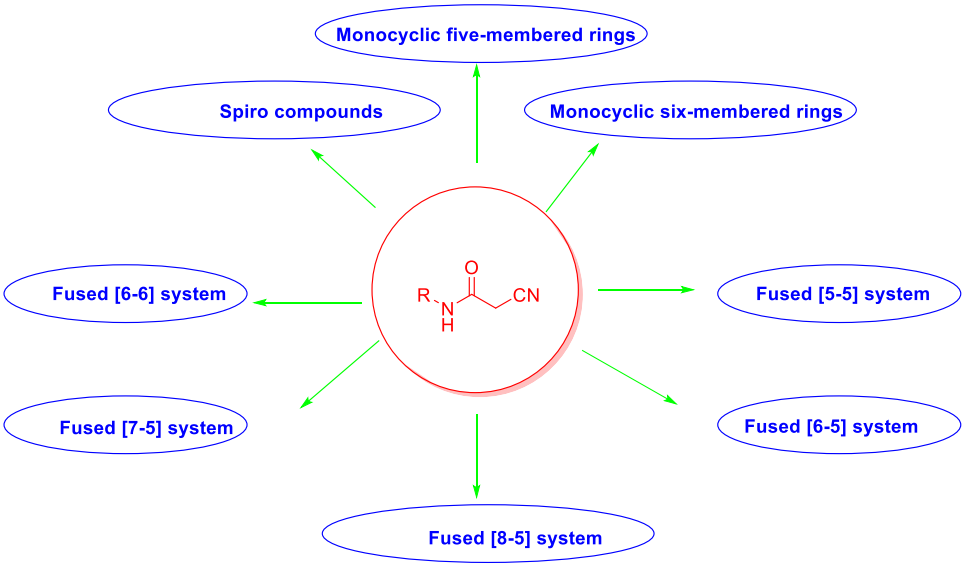
Abstract

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]

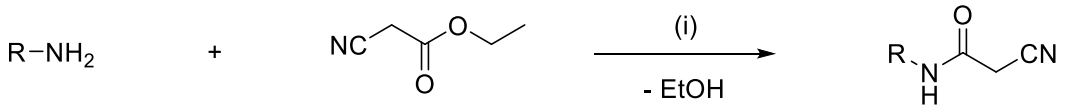
The present review of literature is expected to provide a comprehensive survey of the synthetic utility of cyanoacetamides as precursors for a variety of monocyclic five-membered, six-membered and fused heterocycles and to supplement the information available in two earlier reviews that have appeared in 1999 by Litvinov[9] 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]



1 **2** **3**

Scheme 1

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

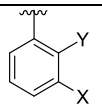
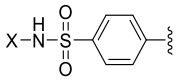
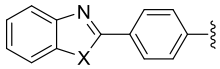
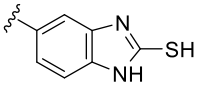
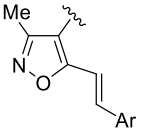
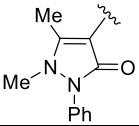
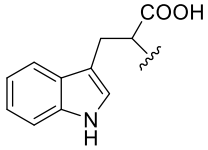
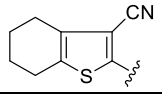
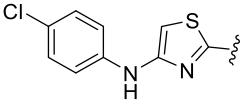
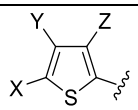
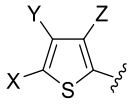
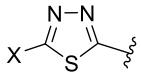
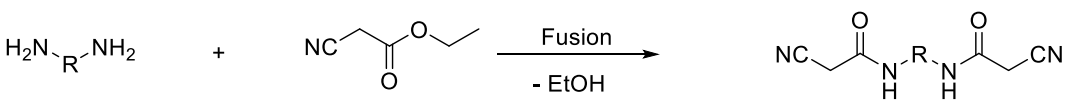
Product		R		Reaction condition (i)	Yield (%)	Ref.
3a		X = H	Y = H	Fusion or Solvent free	91-93	12,13
3b		X = Et	Y = H	Fusion	88	14,15
3c		X = Cl	Y = H	Solvent free	69	13
3d		X = H	Y = CO_2Me	Fusion, xylene	80	11,16
3e		X =		Fusion	80	17
3f		X =	H	m-Xylene, reflux	92	18
3g		X = NH		EtOH	80	19
3h		X = 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_6H_4			80	
3m		Ar = 2-MeC_6H_4			84	
3n		Ar = 4-$MeOC_6H_4$			74	
3o		Ar = 4-ClC_6H_4			78	
3p		Ar = 2-ClC_6H_4			80	
3q				EtOH, reflux	70	23
3r				DMF, reflux	75	24
3s				DMF, reflux, 5 h	73	25
3t				Ac_2O, 60-70 °C, 1 h	60	26
3u		X = 4-Nitrophenoxy Y = Me Z = CO_2Et		Dioxane, reflux, 3 h	69	27

Table 1. Continued

Product		R	Reaction condition (i)	Yield (%)	Ref.
3v		X = Ph-NH=N Y = Ph Z = CO_2Et	EtONa, EtOH, reflux, 6 h	31	28
3w	*n*-Butyl *n*-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-$MeOC_6H_4$ X = 2-ClC_6H_4 X = 2-$MeOC_6H_4$ X = 4-$MeOC_6H_4CH_2$ X =1-methylnaphthyl X = Benzyl X = 4-$FC_6H_4CH_2$ X = 3-$FC_6H_4CH_2$ X = 4-$ClC_6H_4CH_2$ X = 4-$MeC_6H_4CH_2$	MeONa, MeOH, reflux, 5 h	not reported	3
3y	Cyclohexyl		heat US (40 °C) or M.W EtONa, EtOH or Al_2O_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_2O_3, KF, r.t, 1 h DMF, Reflux, 8 h	72 89 37	29–32
3aa	Tetrahydrofurfuryl		EtONa, EtOH or Al_2O_3, KF, r.t	90	30

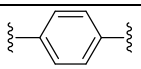
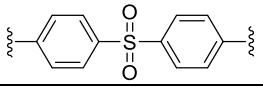
Similarly, *N,N*-(1,4-phenylene)bis(2-cyanoacetamide) **5a** [33] and *N,N'*-(4,4'-sulfonylbis(4,1-phenylene))bis(2-cyanoacetamid) **5b** [10,34] were also obtained *via* condensation of phenylene-1,4-diamine **4a** and Dapson **4b** with ethyl cyanoacetate **2** respectively (Scheme 2, Table 2).



4 **2** **5a,b**

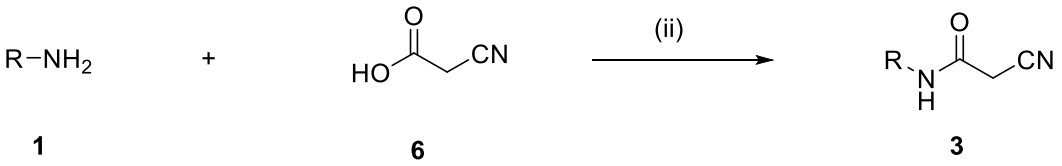
Scheme 2

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]



1 **6** **3**

Scheme 3

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

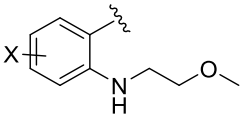
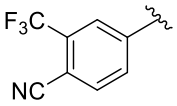
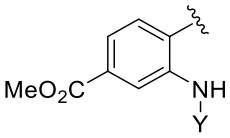
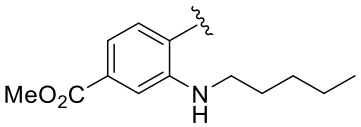
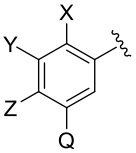
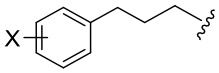
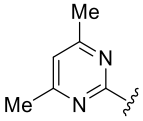
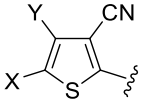
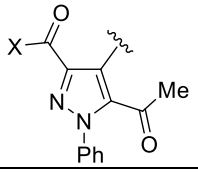
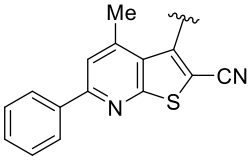
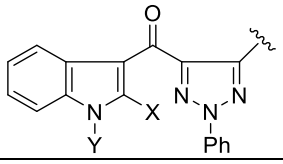
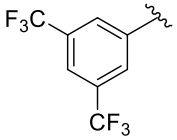
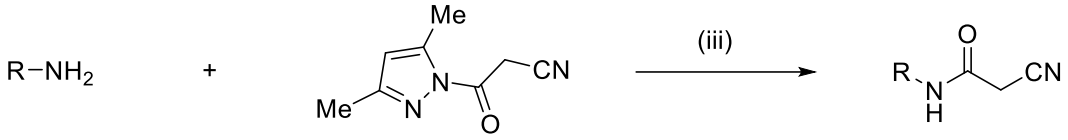
Product		R	Reaction condition (ii)	Yield (%)	Ref
3ab1		X = H	EDCI, HOBt, CH_2Cl_2, 0 °C, 30 min, r.t, 12 h	65-70	36
3ab2		X = 5-Cl			
3ac			PCl_5, CH_2Cl_2, 40 °C, 2 h	80	37
3ad		Y = Benzyl	EDCI, HOBt, CH_2Cl_2, 0 °C, 30 min, r.t, 12 h	65-70	36
3ae		Y = Cyclohexyl			
3af		Y = Cyclopentyl			
3ag		Y = Furan-2-ylmethyl			
3ah		Y = *n*-Propyl			
3ai		Y = CH_2CH_2OH			
3aj		Y = CH_2CH_2OAc			
3ak		Y = $CH(CH3)_2$			
3al			DCC, DMAP, MeCN, r.t, 16 h	not reported	35
3am		X = H	DCC, THF, 60 °C, 1 h	75	38
		Y = $OC_{12}H_{25}$			
		Z = H			
		Q = $OC_{12}H_{25}$			

Table 3. Continued

Product		R	Reaction condition (ii)	Yield (%)	Ref
3an		X = H Y = H Z = EtO Q = H	Ac_2O, 85 °C, 25 min	78	39
3ao-ap		X = Cl / F Y = H Z = H Q = NO_2	Ac_2O 80 °C	93 / 89	40
3aq		X = 2-OCH_2OMe	EDC, DMAP, CH_2Cl_2,	70	41
3ar		X = 3-OCH_2OMe	stirring 2 h, r.t	54	
3as		X = 4-OCH_2OMe		49	
3at		X = 3-F		58	
3au		X = 4-F		42	
3av			Ac_2O, 80 °C	85	40
3aw		X = H, Y = Ph	Ac_2O, M.W, 250W	72	42
3ax		X = H, Y = 4-ClC_6H_4		75	
3ay		X = CO_2Et, Y = Me		68	
3az1		X = Me	Ac_2O, M. W	95	43
3az2		X = Ph		98	
3ba			Ac_2O, Water bath, 1 h	73	44
3bb1		X = H, Y = Me	Ac_2O, 85°C, or M.W	58	45
3bb2		X = Me, Y = H		61	
3bc			EDC·HCl, DCM, RT 1 h	80	46

2.3 Cyanoacetylation of amine with 3-oxopropanenitriles in different conditions

The cyanoacetamides **3bd-bv** were obtained in high yields and purity *via* cyanoacetylation of **1bd-bv** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **7** (Scheme 4, Table 4). [47]



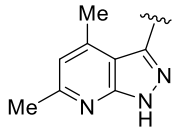
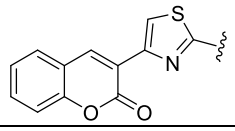
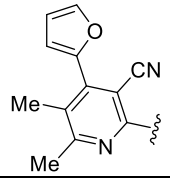
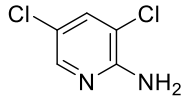
1 **7** **3**

Scheme 4

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

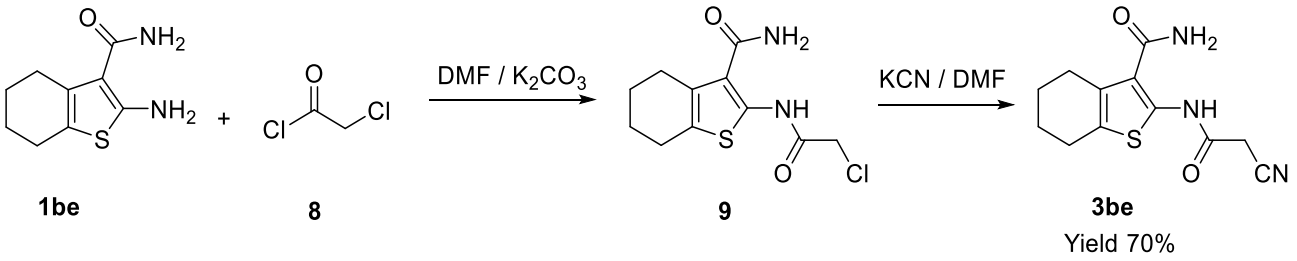
Product	R		Reaction condition (iii)	Yield (%)	Ref.
3bd	X = CO_2Et		Benzene, reflux, 5 h	90	47–
3be	X = $CONH_2$			90	49
3bf			Toluene, reflux, 3 h	80	50, 4
3bg	Y = COMe,	Z = H	Toluene, r.t, overnight	65-93	51–
3a	Y = H,	Z = H	or reflux, 10-15 min		55
3bh	Y = H,	Z = NO_2	Toluene or DMF, 80 °C,		
3bi	Y = Br,	Z = H	6–12 h		
3bj	Y = NO_2	Z = H	Toluene, reflux, 10-15		
3bk	Y = Cl,	Z = Cl	min		
3bl	Y = F,	Z = H			
3bm	Y = H,	Z = CF_3			
3bn	Y = MeO,	Z = MeO			
3bo	Y = H,	Z = NH_2			
3bp1	X = Benzyl piperazine		Toluene, r.t, overnight	75	56
3bp2	X = *N*-Boc-piperazine		or reflux, 10-15 min	81	
3bq			Toluene, reflux, 5 h	71	57
3f	X = H		Dioxane, reflux, 5 h or Toluene, reflux, 2 h	70	58, 59
3br1	X =		Dioxane, reflux, 3 h	80	
3br2	X =		Toluene, reflux, 2h	90	60
			dioxane, reflux	82	5 61
3bs			Toluene, reflux, 3 h	88	62

Table 4. Continued

Product	R	Reaction condition (iii)	Yield (%)	Ref.
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

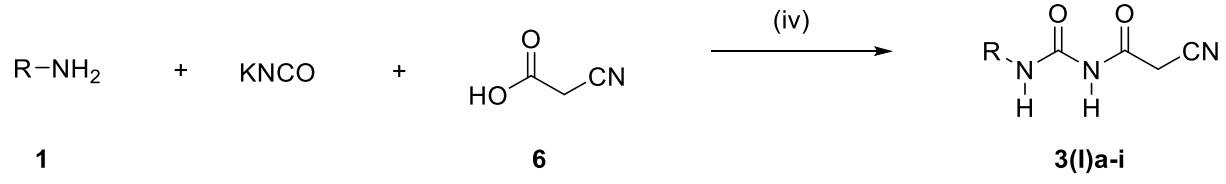
The compound 2-(2-cyano-acetylamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **3be** was obtained by treatment of **1be** with chloroacetyl chloride **8** and subsequent treatment with potassium cyanide in dimethylformamide (DMF) (Scheme 5).[67]



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]



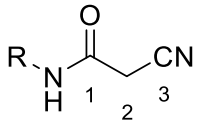
Scheme 6

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

Product	R	Reaction condition (iv)	Yield (%)	Ref.
3(I)a	Ph		83	68
3(I)b	*n*-Butyl		91	
3(I)c	Cyclohexyl		78	
3(I)d	Benzyl		88	
3(I)e	4-$NO_2C_6H_4$	AcOH, Ac_2O, 60°C	76	
3(I)f	*n*-Propyl,		90	
3(I)g	*i*-Propyl		91	
3(I)h	4-$MeOC_6H_4CH_2$		90	
3(I)i	4-MeC_6H_4		85	
3(I)d	Benzyl	[TMG][Ac], Ac_2O, 60°C, 5 h	89	69

3. Reactivity of Cyanoacetamide Derivatives

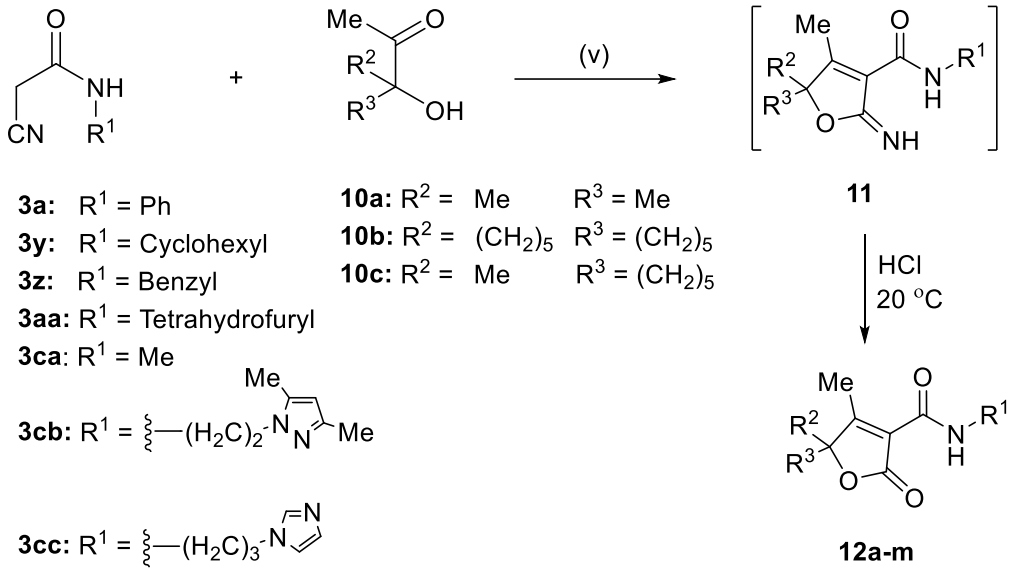
Cyanoacetamides have both electrophilic and nucleophilic characteristics. The nucleophilic positions are NH and C-2 with the nucleophilicity order: C-2 > NH. These chemical characteristics have been used to design a variety of heterocyclic compounds with various ring sizes such as triazine, pyrimidine, 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.

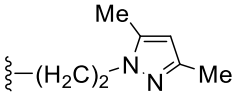
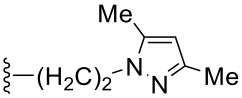
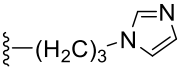
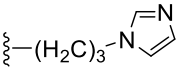
3.1 Monocyclic compounds

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 mthanol[70] or sodium ethoxide in ethanol[30] 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]

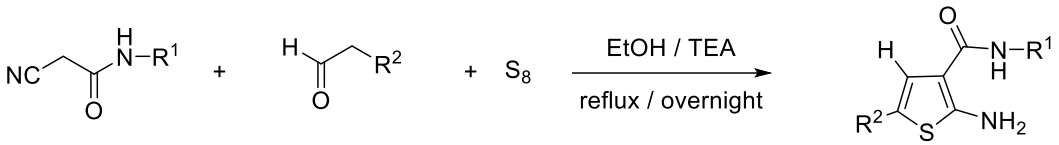


Scheme 7

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	99	[30]
				MeOH / MeONa / 40 °C	92	[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]



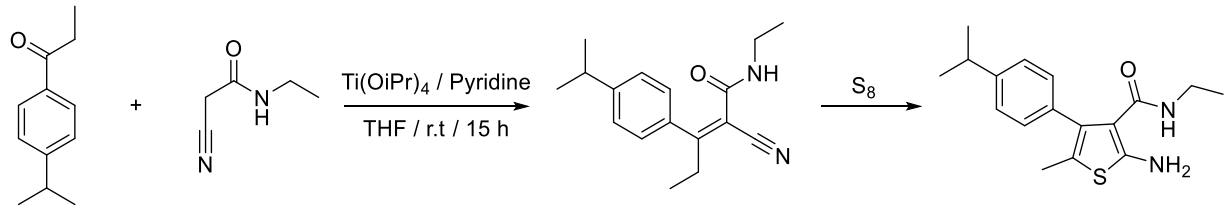
3 **13** **14a-l**

Scheme 8

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

Product	R^1	Product	R^2	Product	Yield (%)
3w	*n*-Butyl	**13f**	Ph	**14a**	73
3cd	*n*-Pentyl	**13f**	Ph	**14b**	40
3ce	*n*-Octyl	**13f**	Ph	**14c**	20
3cf	*n*-Dodecyl	**13f**	Ph	**14d**	30
3cg	$Ph(CH_2)_4$	**13f**	Ph	**14e**	29
3w	*n*-Butyl	**13a**	Me	**14f**	20
3w	*n*-Butyl	**13b**	Et	**14g**	30
3w	*n*-Butyl	**13c**	*n*-Propyl	**14h**	29
3w	*n*-Butyl	**13e**	*n*-Pentyl	**14i**	30
3w	*n*-Butyl	**13g**	$4\text{-}ClC_6H_4$	**14j**	23
3w	*n*-Butyl	**13h**	$4\text{-}BrC_6H_4$	**14k**	74
3w	*n*-Butyl	**13d**	*n*-Butyl	**14l**	56

Condensation of **15** with **3ch** in the presence of $Ti(OiPr)_4$ 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]

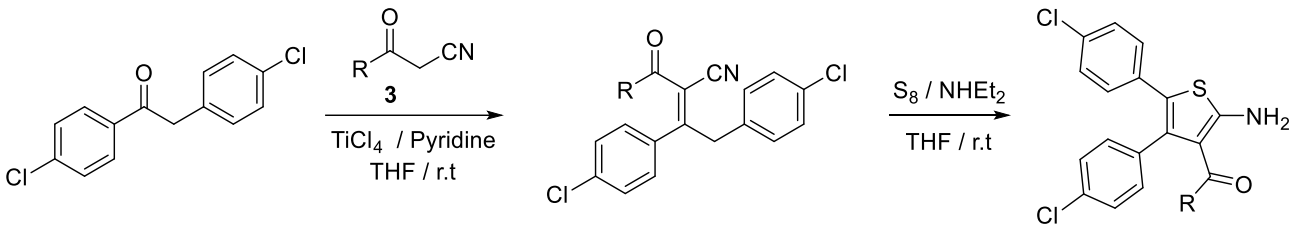


15 **3ch** **16** **14m**
Yield 83%

Scheme 9

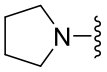
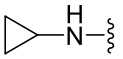
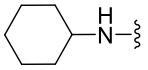
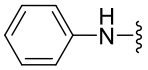
The condensation of compound **17** with 2-cyanoacetamide derivatives **3** in the presence of $TiCl_4$ afforded the olefin intermediates **18**. Treatment of olefin intermediates **18** with elemental sulfur and diethyl amine furnished the cyclized thiophene ring leading to the target compounds **19a-d**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

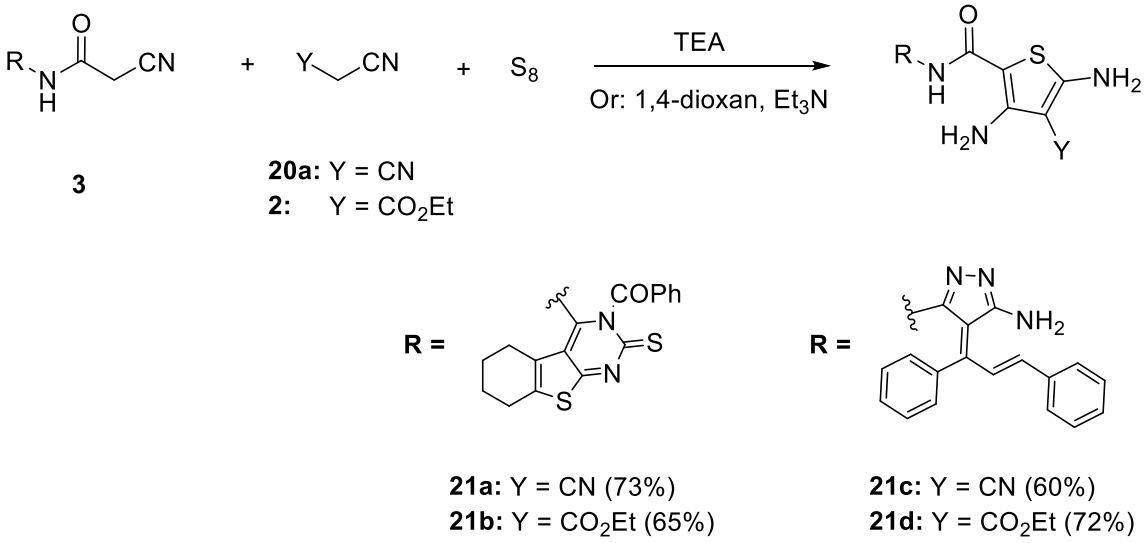
The reaction of compound **3** with sulfur and malononitrile **20a** or ethyl cyanoacetate **2** gave different thiophene derivatives **21a-f** (Scheme 11). [76,77]



Scheme 10

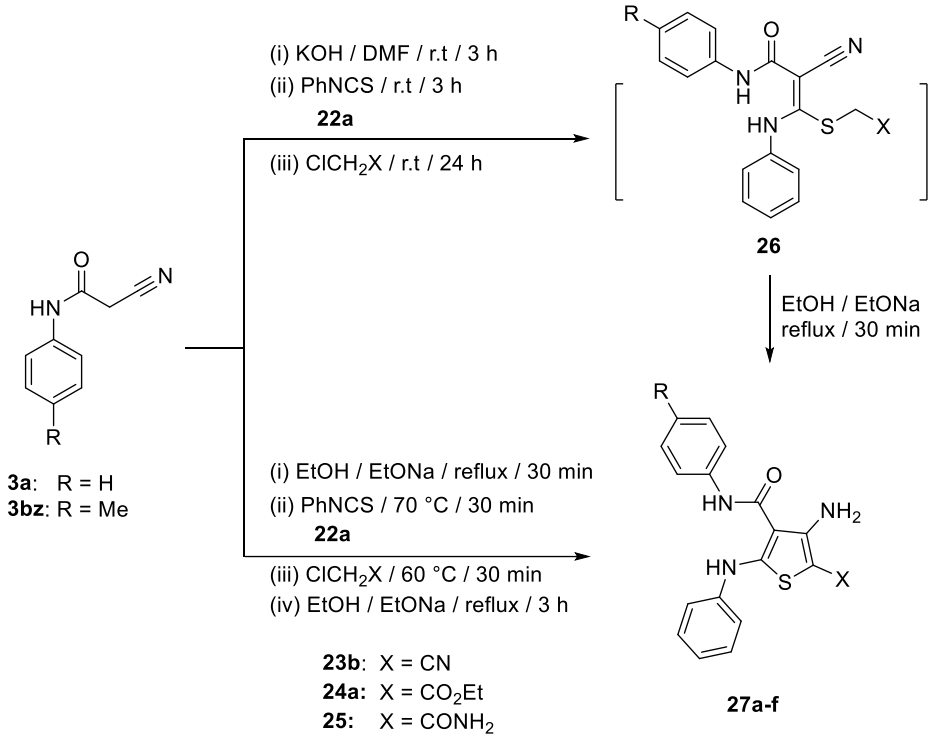
Table 8. Synthesis and % yields of **19a-d**

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



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]

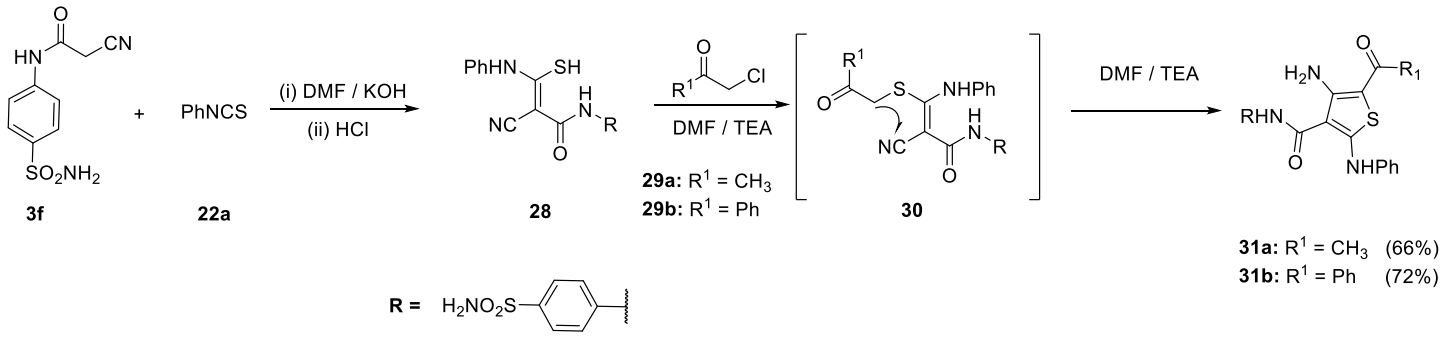


Scheme 12

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

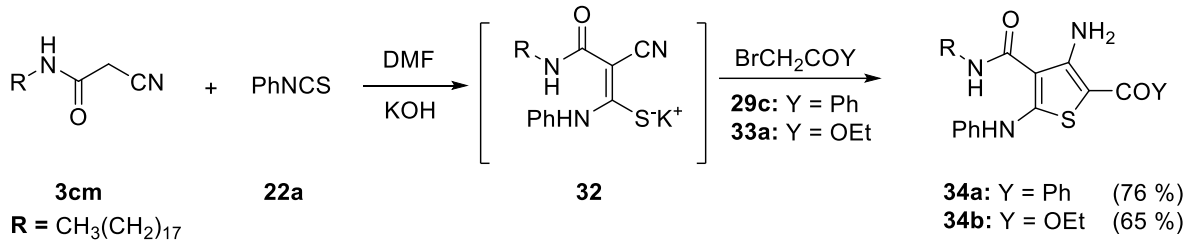
Product	R	X	Yield (%)
27a	H	CN	84
27b	H	CO_2Et	63
27c	H	$CONH_2$	71
27d	Me	CN	92
27e	Me	CO_2Et	61
27f	Me	$CONH_2$	75

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]



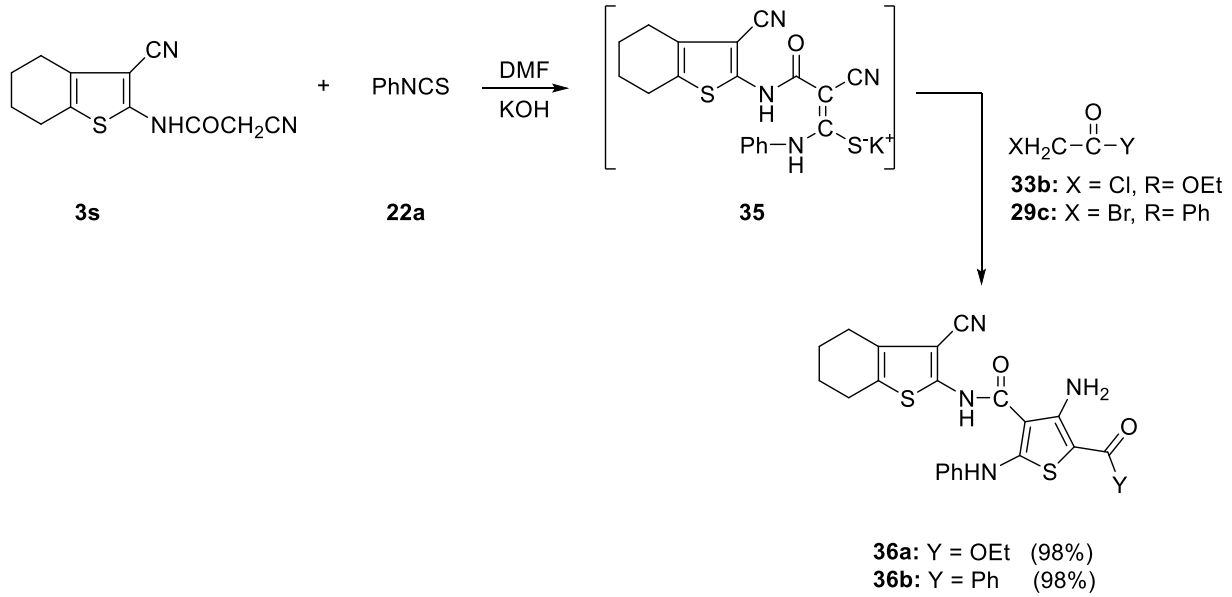
Scheme 13

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]

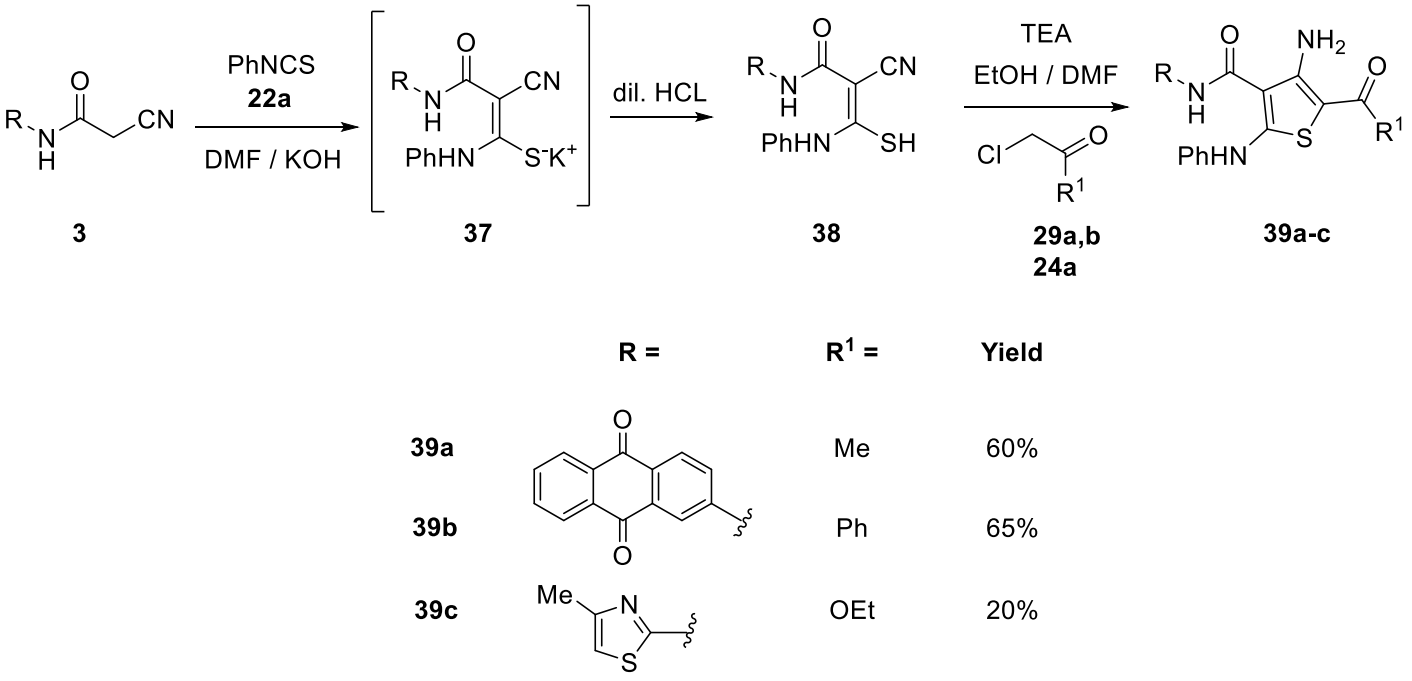


Scheme 15

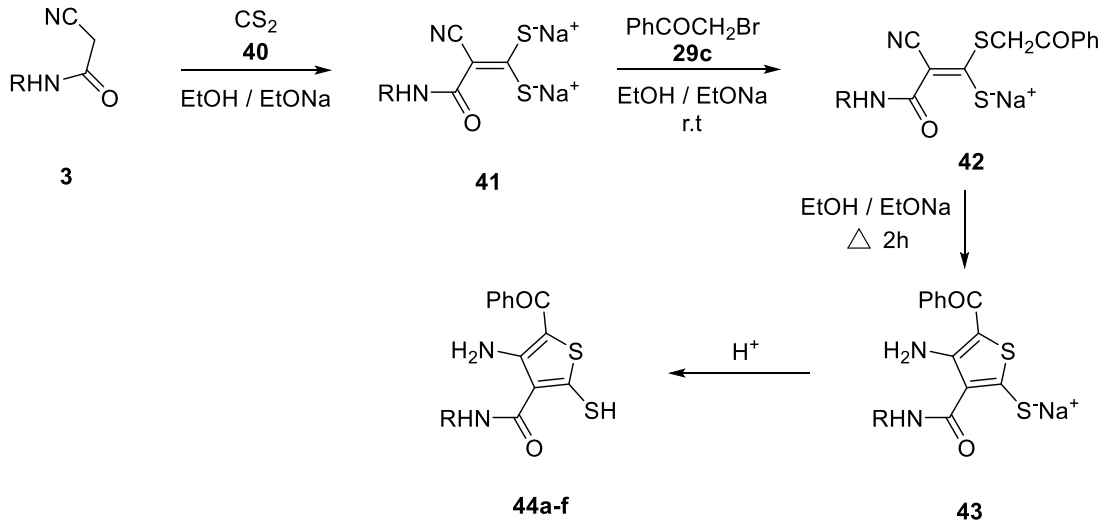
Treatment of cyanoacetamide **3** with phenyl isothiocyanate **22a**, in dry DMF in the presence of potassium hydroxide, afforded the potassium thiolate **37**. Acidification of the potassium salt **37** librated the *β*-sulfonylacetamide **38**. Heating of compound **38** with **29a,b** or **24a** in 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]

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 16

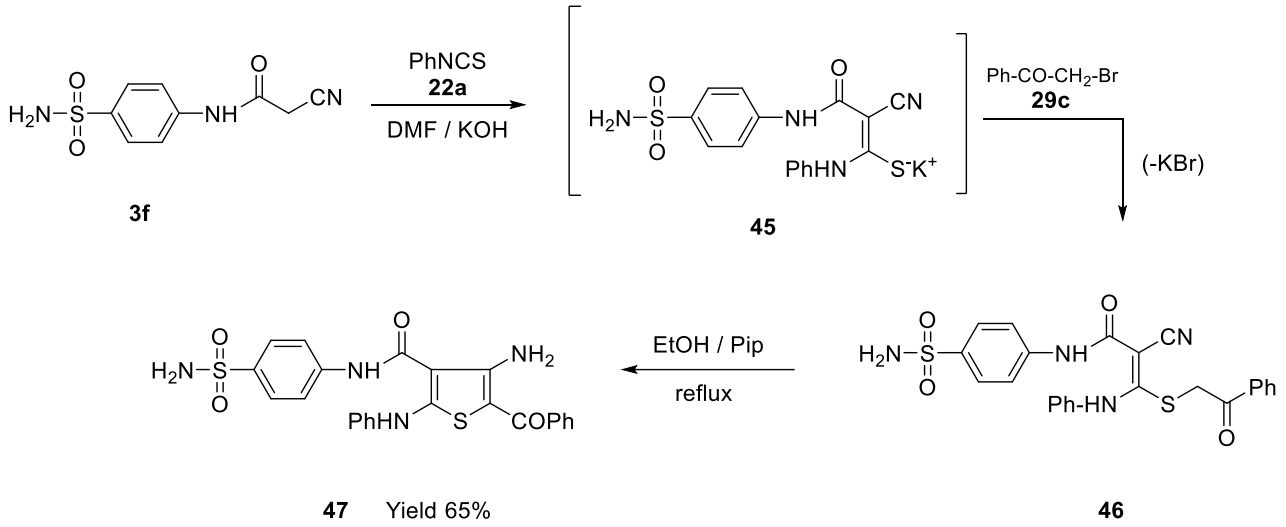


Scheme 17

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

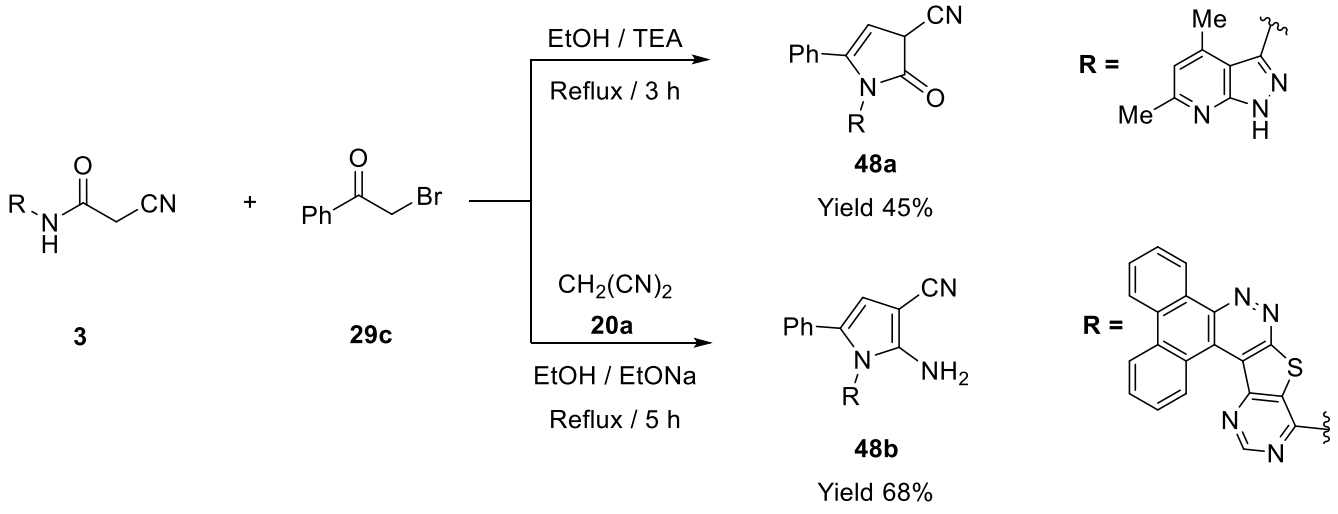
Entry	Product	R	Yield (%)
3a	**44a**	Ph	70
3cn	**44b**	4-ClC_6H_4	80
3co	**44c**	2-ClC_6H_4	81
3bz	**44d**	4-MeC_6H_4	78
3bi	**44e**	4-BrC_6H_4	80
3by	**44f**	4-$MeOC_6H_5$	75

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]



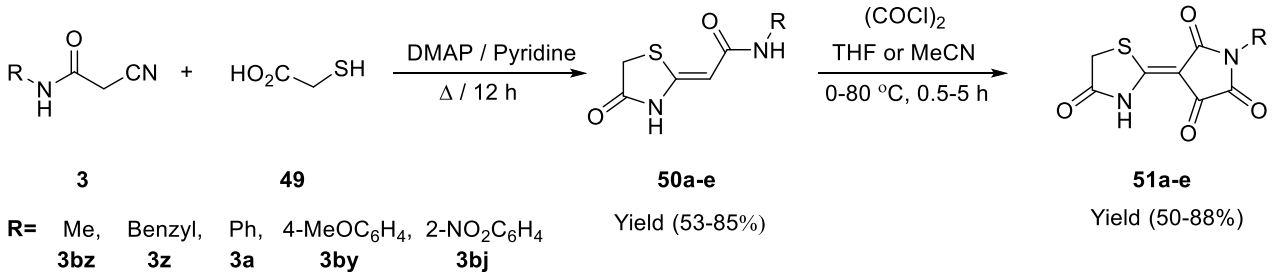
Scheme 18

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

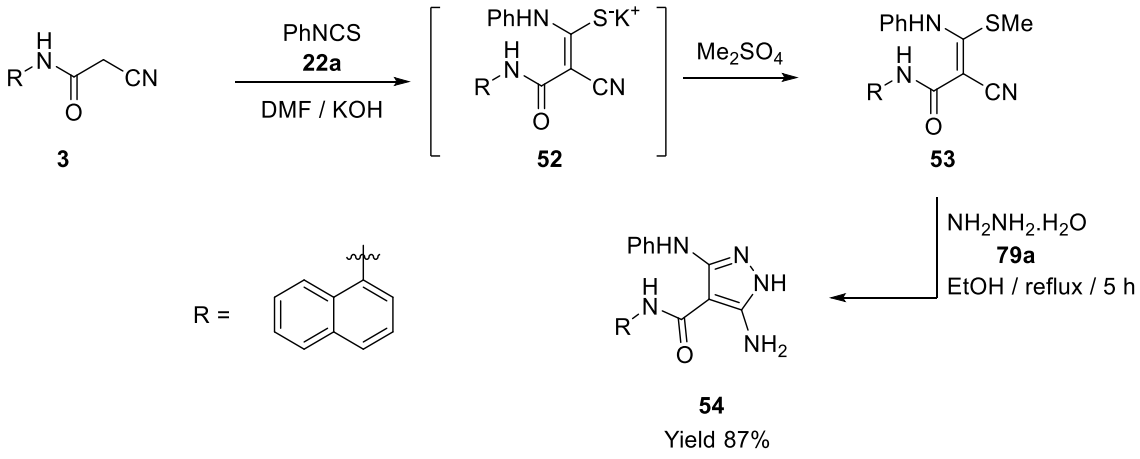
Cyanoacetamides **3** react with 2-mercaptoacetic acid **49** to produce 2-(1,3-thiazolidin-2-ylidene)acetamides **50** that undergo cyclocondensation reactions with oxalyl chloride to form 4-(4-oxo-1,3-thiazolidin-2-ylidene)pyrrolidine-2,3,5-triones **51a-e** (Scheme 20).[85]



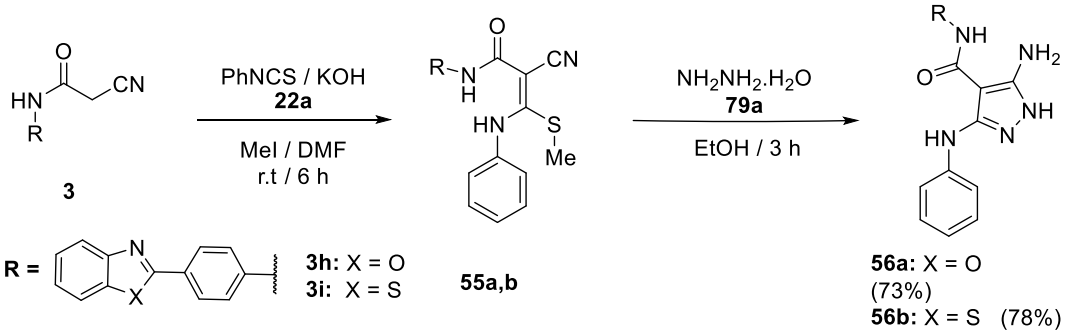
Scheme 20

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]

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]

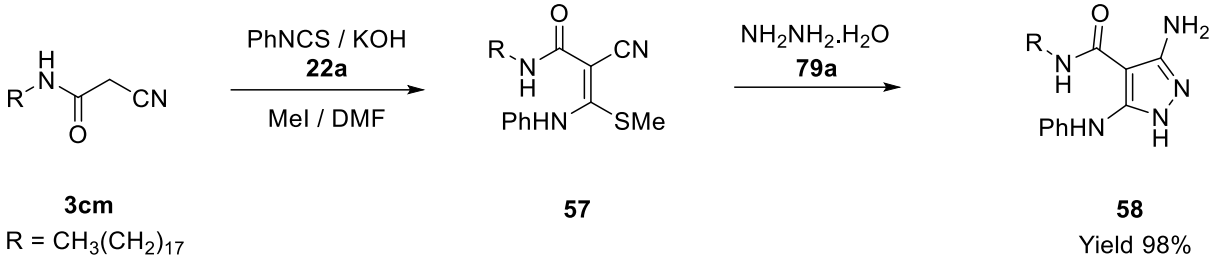


Scheme 21



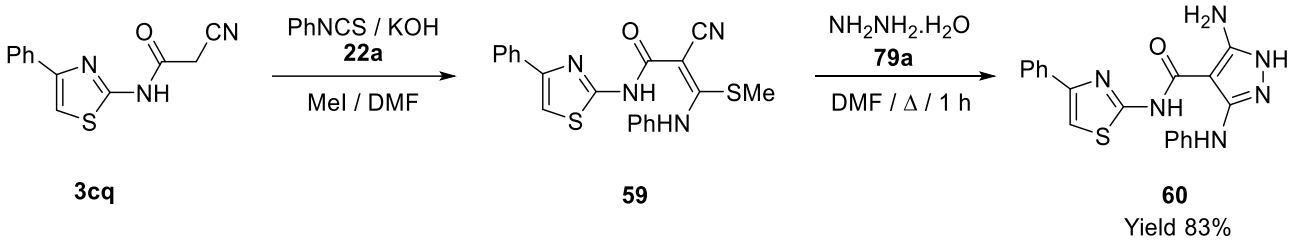
Scheme 22

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]



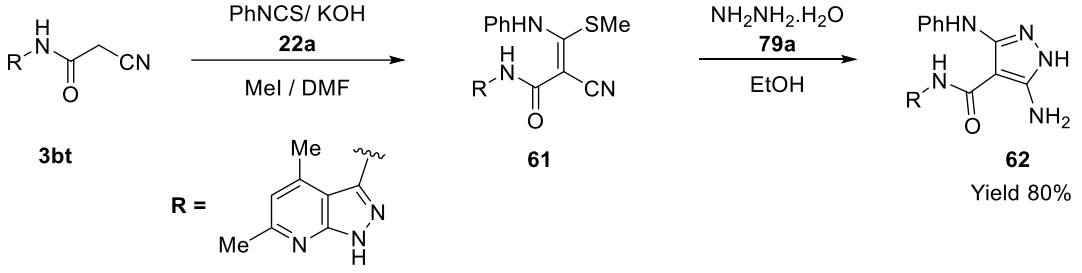
Scheme 23

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

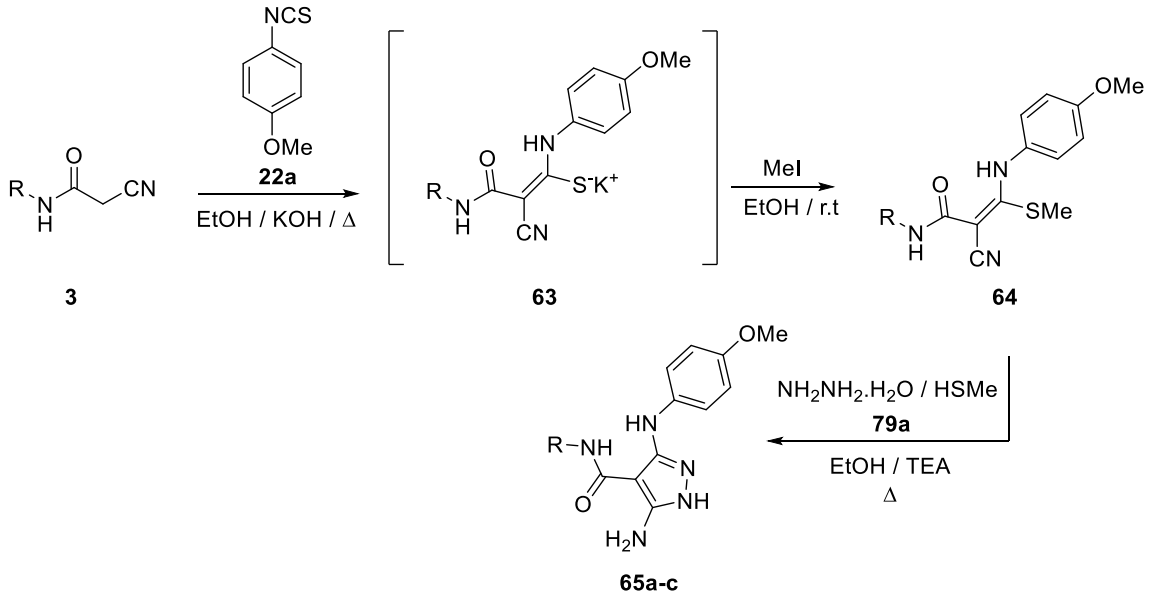
Treatment of compound **3bt** with phenyl isothiocyanate **22a** in DMF, and in the presence of KOH at room temperature, followed by addition of methyl iodide afforded the ketene *N,S*-acetal **61**. Reaction of **61** with hydrazine hydrate **79a** in ethanol at reflux gave the corresponding pyrazole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

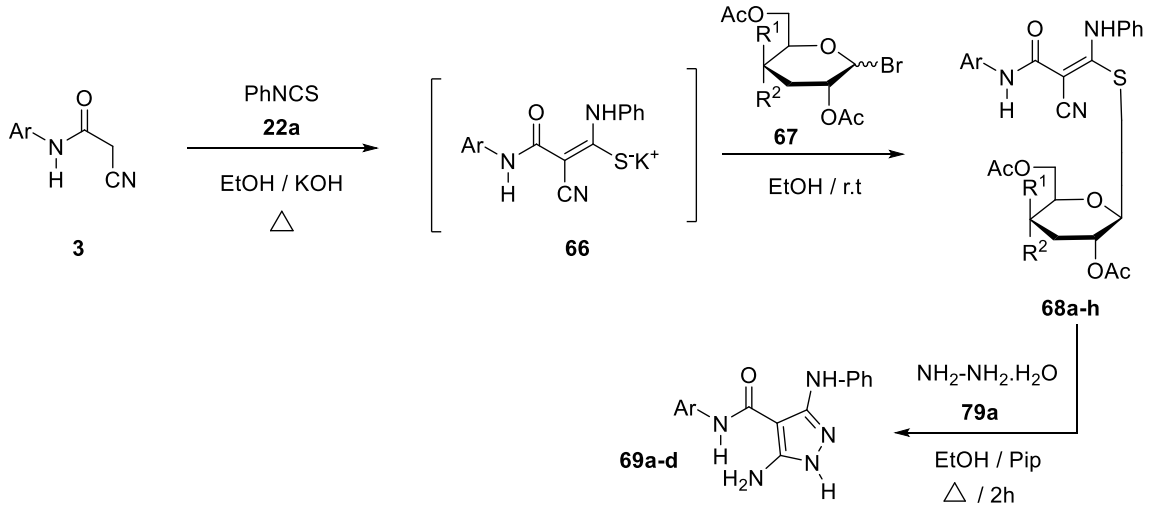
alkylated with methyl iodide in ethanol, it afforded the ketene *N,S*-acetals **64** which react with hydrazine **79a** to give amino pyrazole **65a-c** (Scheme 26, Table 11).[89]



Scheme 26

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

Entry	Product	R	Yield (%)
3a	**65a**	Ph	79
3bz	**65b**	4-MeC_6H_4	82
3co	**65c**	4-ClC_6H_4	80



Scheme 27

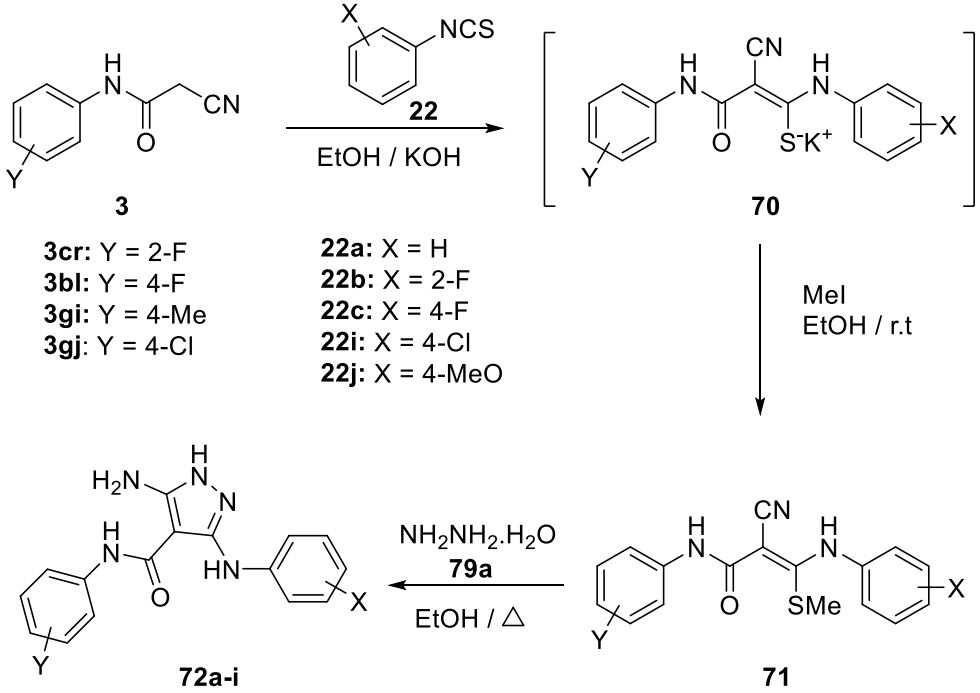
Heating the acetanilide derivatives **3** with phenyl isothiocyanate **22a** in EtOH-KOH affords the stable 2-cyano-ethylene-1-thiolate potassium salts **66**. The latter compounds react with *α*-D-gluco- and galacto-

pyranosyl 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]

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_6H_4	H	OAc	86
3by	**68c**	4-$MeOC_6H_4$	H	OAc	77
3co	**68d**	4-ClC_6H_4	H	OAc	77
3a	**68e**	Ph	OAc	H	85
3bz	**68f**	4-MeC_6H_4	OAc	H	86
3by	**68g**	4-$MeOC_6H_4$	OAc	H	76
3co	**68h**	4-ClC_6H_4	OAc	H	87
3a	**69a**	Ph	-	-	not reported
3bz	**69b**	4-MeC_6H_4	-	-	not reported
3by	**69c**	4-$MeOC_6H_4$	-	-	not reported
3co	**69d**	4-ClC_6H_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]

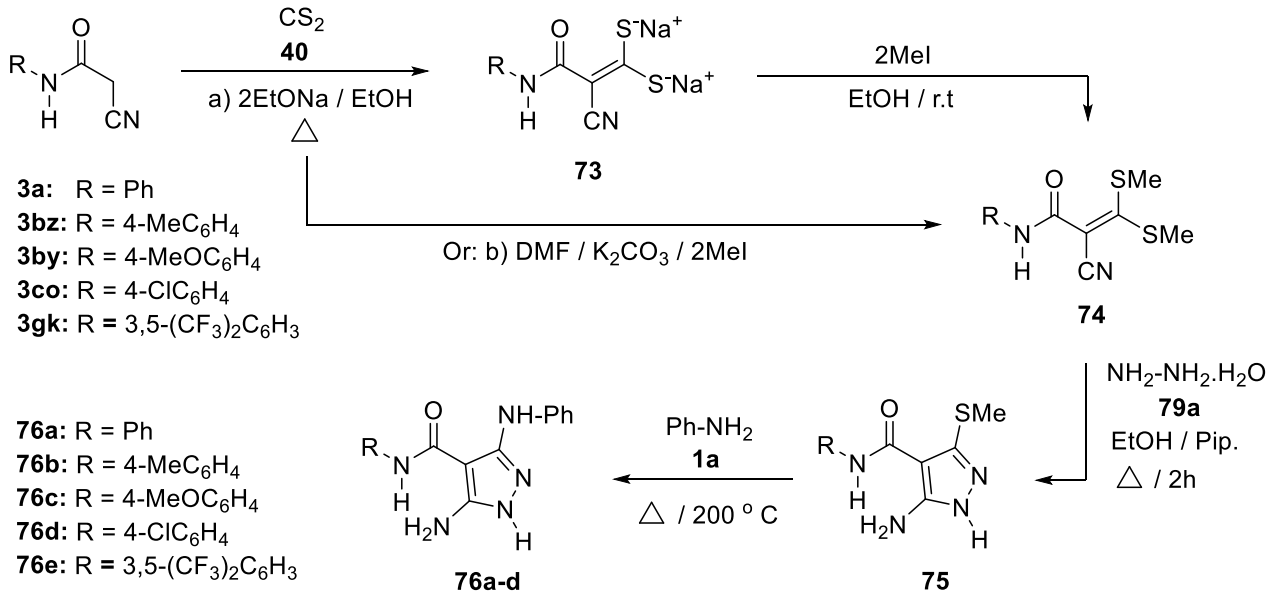


Scheme 28

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

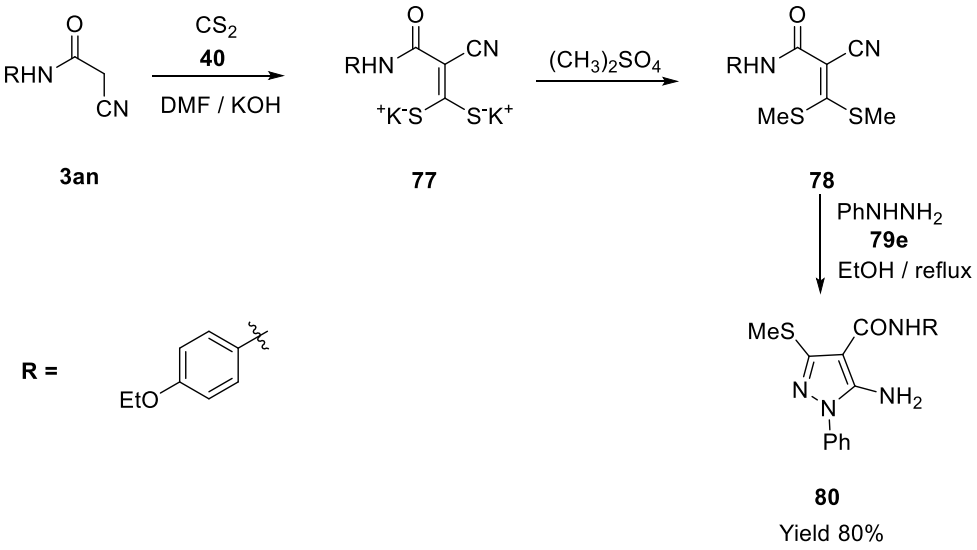
Product	Y	X	Yield (%)	Ref.
72a	2-F	H	78	91
72b	4-F	H	85	
72c	4-F	2-F	80	
72d	2-F	4-F	85	
72e	4-F	4-F	84	
72f	2-F	4-Cl	79	
72g	4-F	4-Cl	81	
72h	4-Me	4-MeO	not	92
72i	4-Cl	4-MeO	reported	

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/EtONa[90] or DMF/K_2CO_3[46] 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).



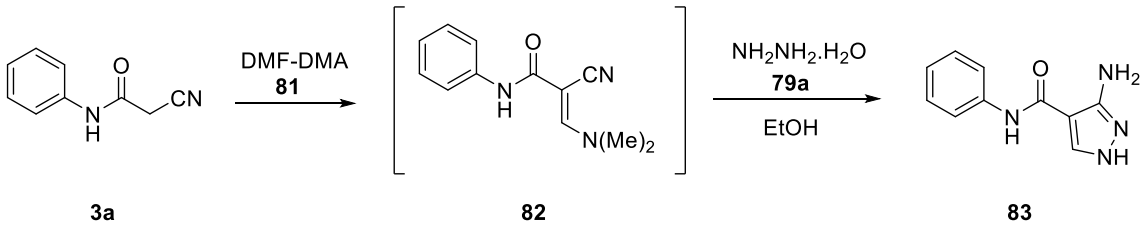
Scheme 29

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]



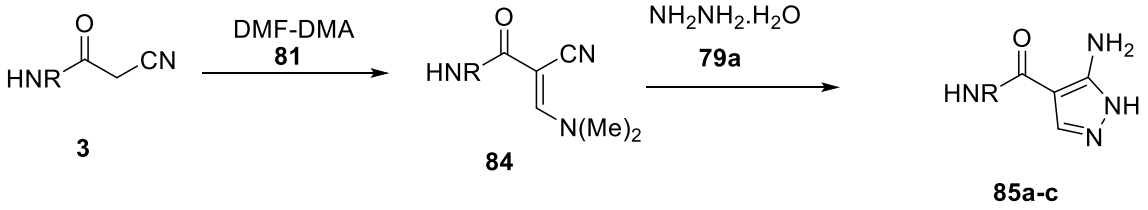
Scheme 30

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]



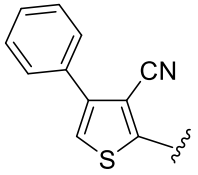
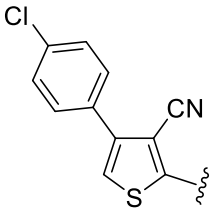
Scheme 31

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]

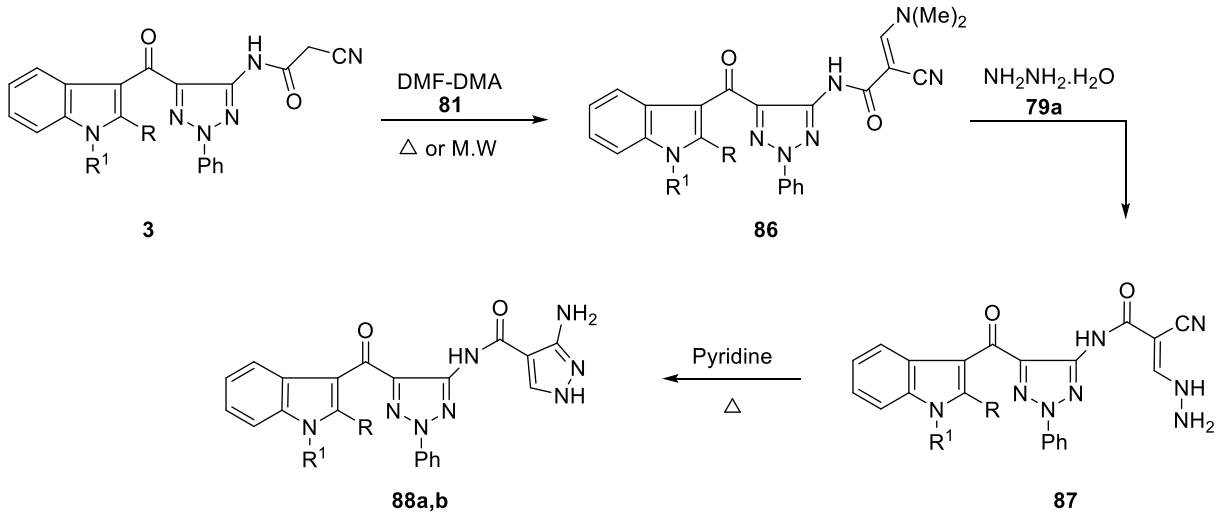


Scheme 32

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]

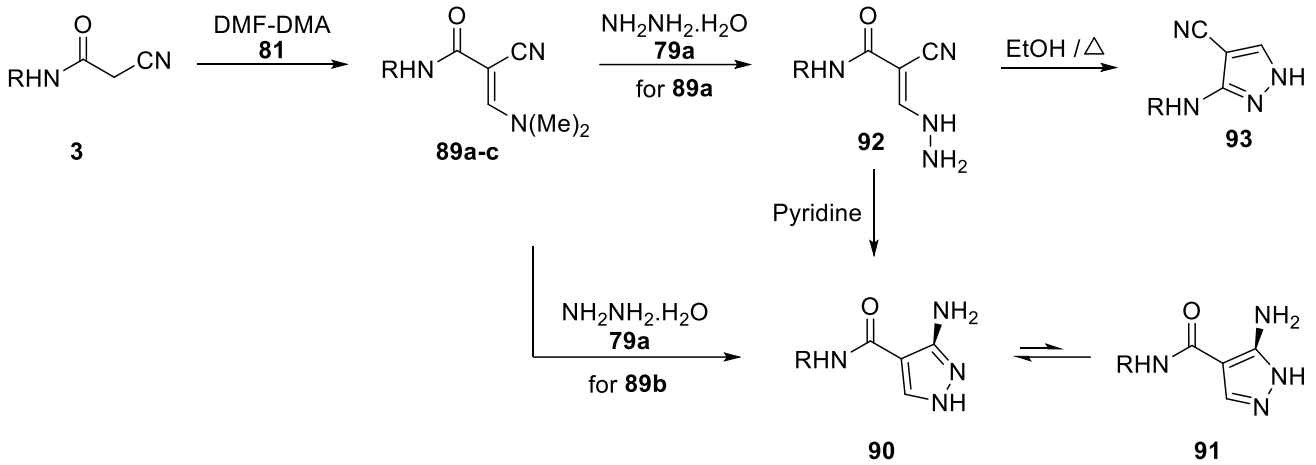


Scheme 33

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

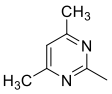
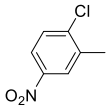
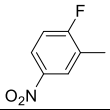
Entry	Product	R	R^1	Yield (%)
3bb1	**88a**	H	Me	73
3bb2	**88b**	Me	H	68

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]

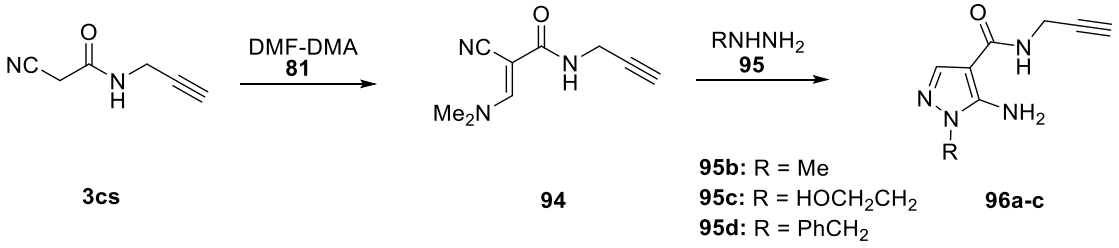


Scheme 34

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

Compound	Entry	Products	Ar	Yield (%)
R	**3av**	**89a**		76
		93		73
	3ao	**89b**		83
		91		74
	3ap	**89c**		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 alkylhydrazines **95b-d** (Scheme 35, Table 17).[95]

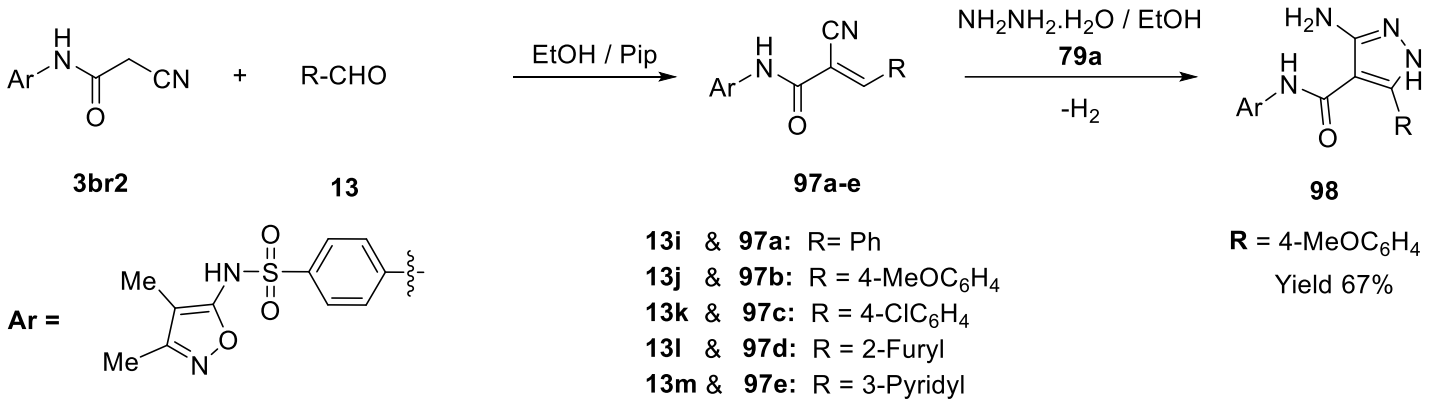


Scheme 35

Table 17. Synthesis and % yields of **96a-c**

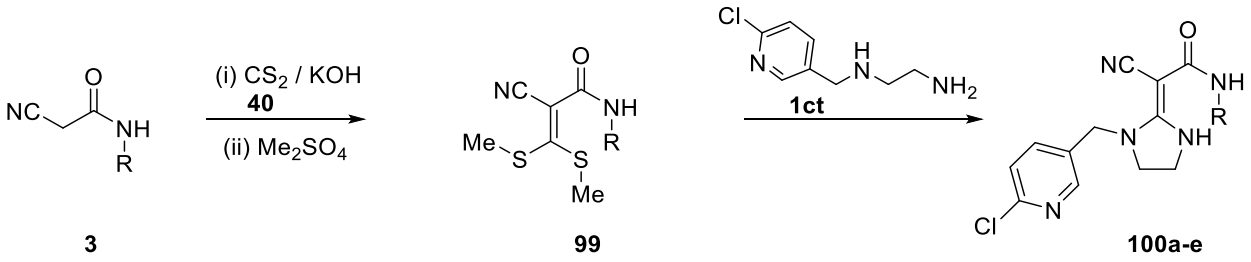
Product	R	Yield (%)
96a	Me	72
96b	$HOCH_2CH_2$	69
96c	$PhCH_2$	71

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. 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]

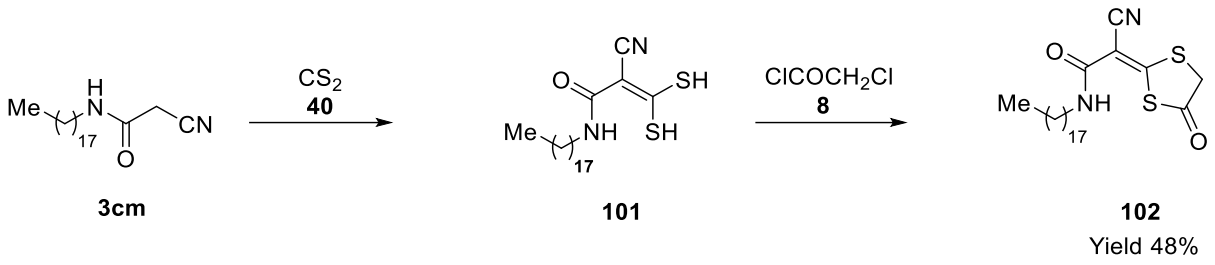


Scheme 37

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

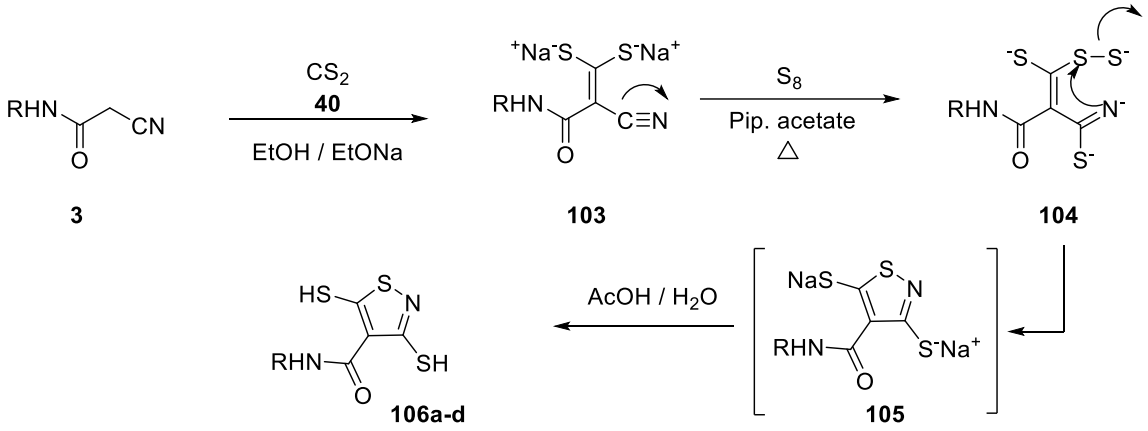
Entry	Product	R	Yield (%)
3z	**100a**	Benzyl	80
3a	**100b**	Ph	75
3co	**100c**	4-ClC_6H_4	72
3cu	**100d**	2-MeC_6H_4	70
3cv	**100e**	$CH_3(Ph)CH$	72

3.1.2.3 1,3-Dithiolan derivatives. 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. 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]

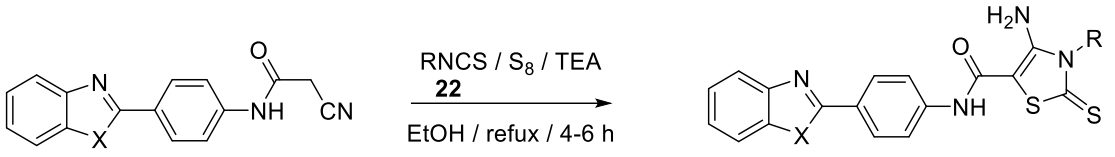


Scheme 39

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

Entry	Product	Ar	Yield (%)
3a	**106a**	Ph	70
3by	**106b**	4–$MeOC_6H_4$	90
3bz	**106c**	4–MeC_6H_4	90
3co	**106d**	4–ClC_6H_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]



3g: X = NH
3h: X = O
3i: X = S

22a: R = Ph
22c: R = Et

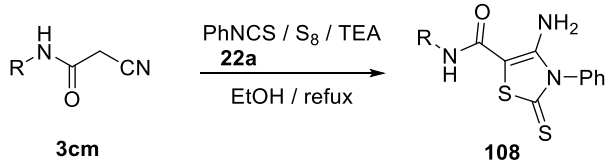
107a-f

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]

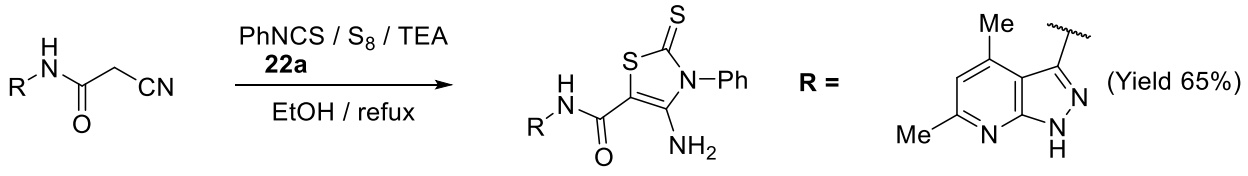


3cm
R = $CH_3(CH_2)_{17}$

108
Yield 60%

Scheme 41

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

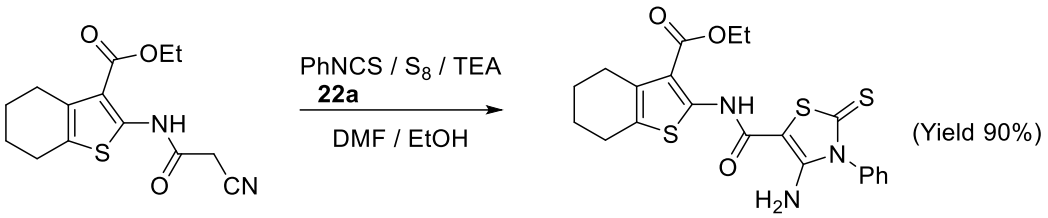


3bt

109

Scheme 42

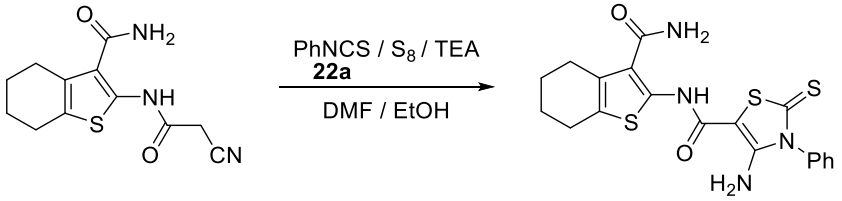
Ethyl 2-(4-amino-2,3-dihydrothiazole-5-carboxamido)-tetrahydrobenzo[*b*]thiophene-3-carboxylate **110** was formed by the reaction of **3bd** with phenyl isothiocyanate **22a** and sulfur (Scheme 43).[47]



3bd **110**

Scheme 43

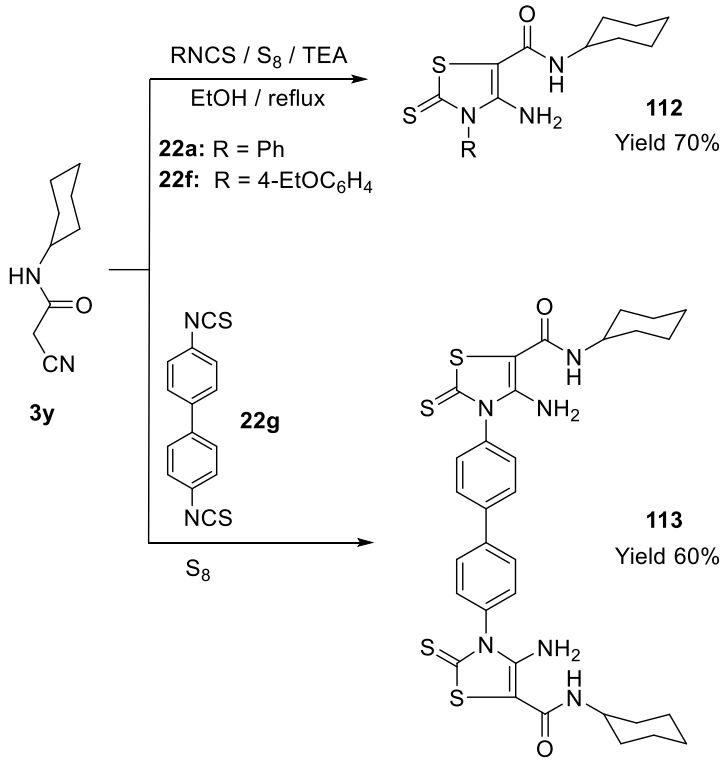
Stirring **3be** with sulfur and phenyl isothiocyanate **22a** in DMF containing triethylamine at 60 °C afforded **111** (Scheme 44).[67]



3be **111**
Yield 75%

Scheme 44

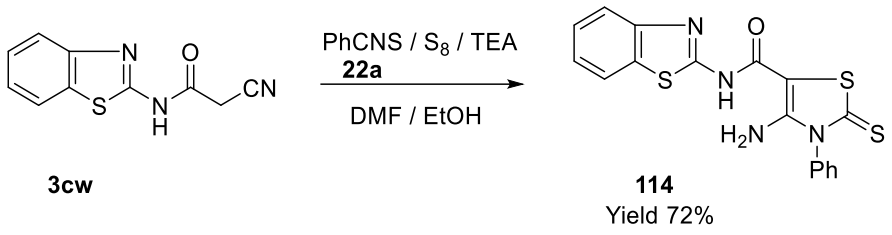
The reaction of *N*-cyclohexyl-2-cyano-acetamide **3y** with isothiocyanate derivatives **22a,f** and/or biphenyl isothiocyanate **22g** and sulfur in ethanol catalysed with triethylamine gave thiazolidine **112** and bisthiazolidine **113** derivatives (Scheme 45).[98]



3y **112**
Yield 70%
113
Yield 60%

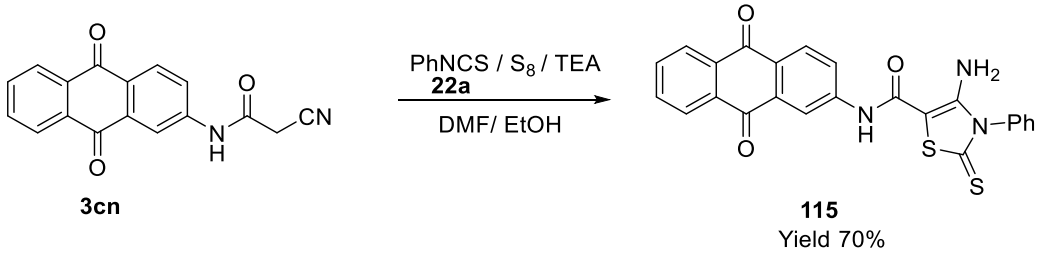
Scheme 45

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]



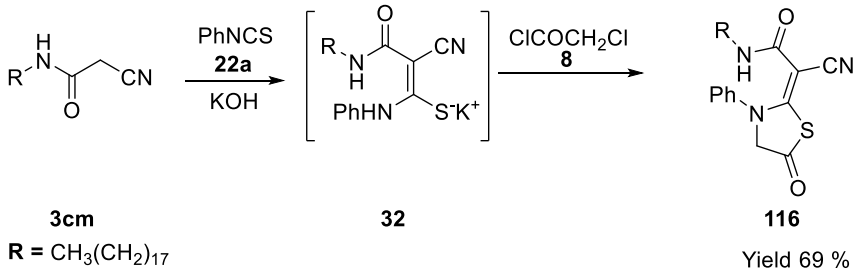
Scheme 46

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



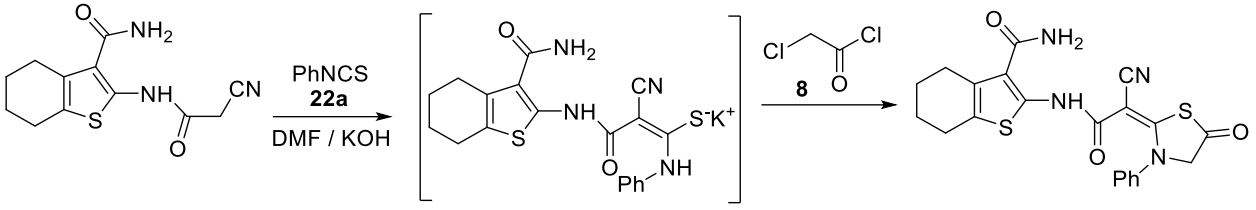
Scheme 47

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

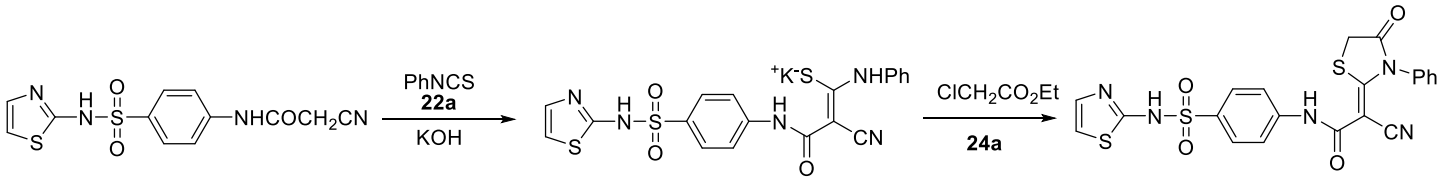
The reaction of **3be** with phenyl isothiocyanate **22a** in DMF in presence of potassium hydroxide afforded **117**. When the intermediate **117** is reacted with 2-chloroacetyl chloride **8**, *N*-phenylthiazolone **118** is afforded (Scheme 49).[49]



3be **117** **118**

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]

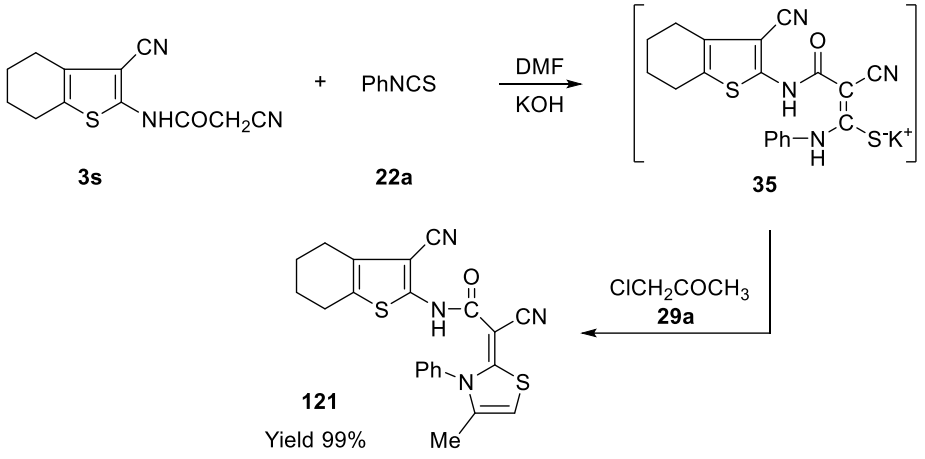


3e **119** **120**

Yield 68%

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]



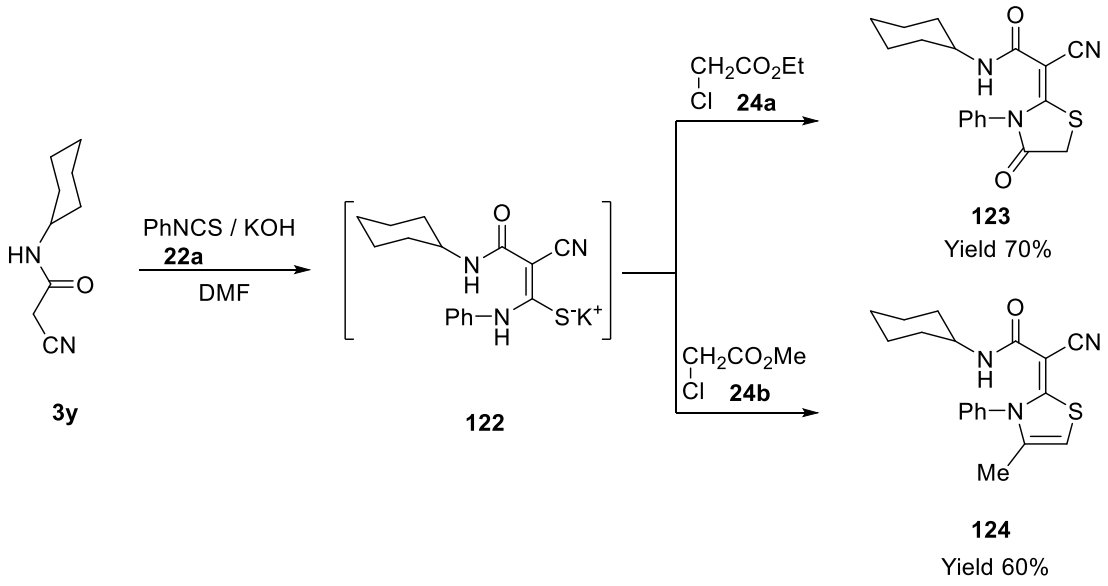
3s **22a** **35**

121

Yield 99%

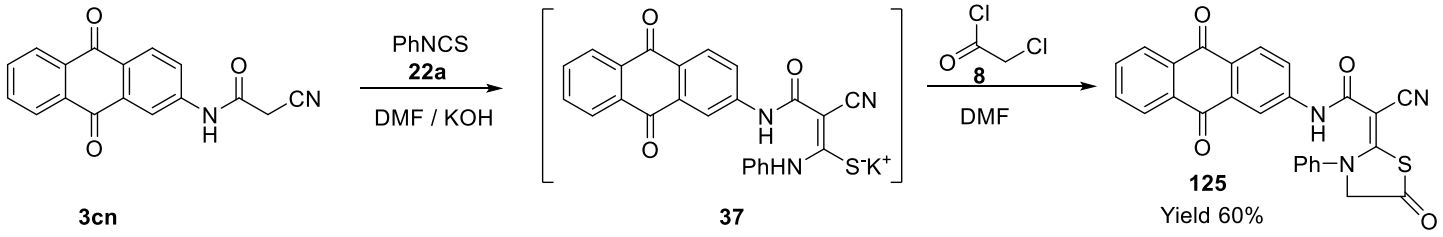
Scheme 51

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-thiaozlidinone 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]

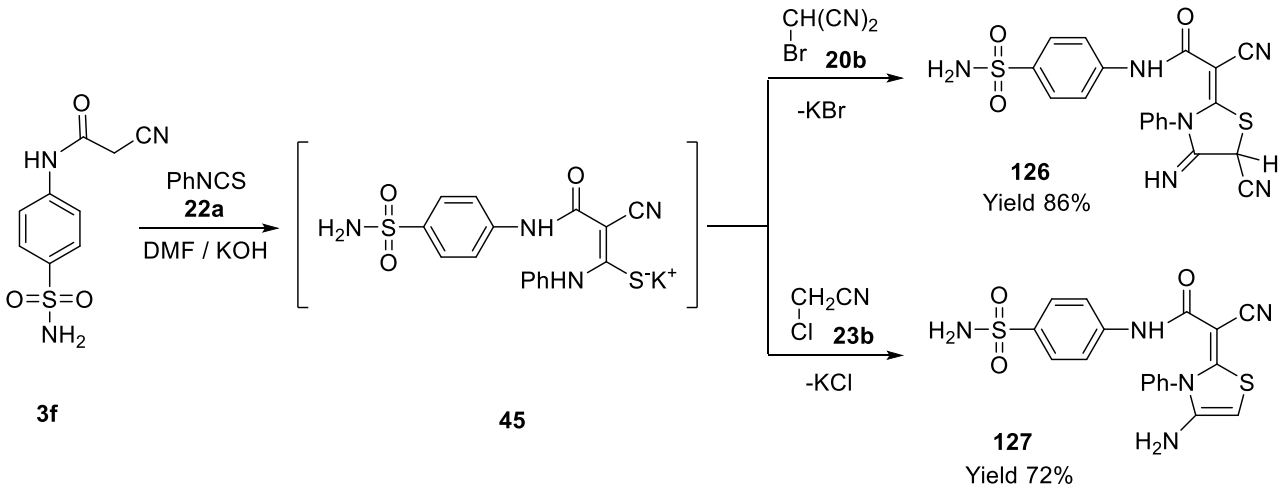


Scheme 52

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]



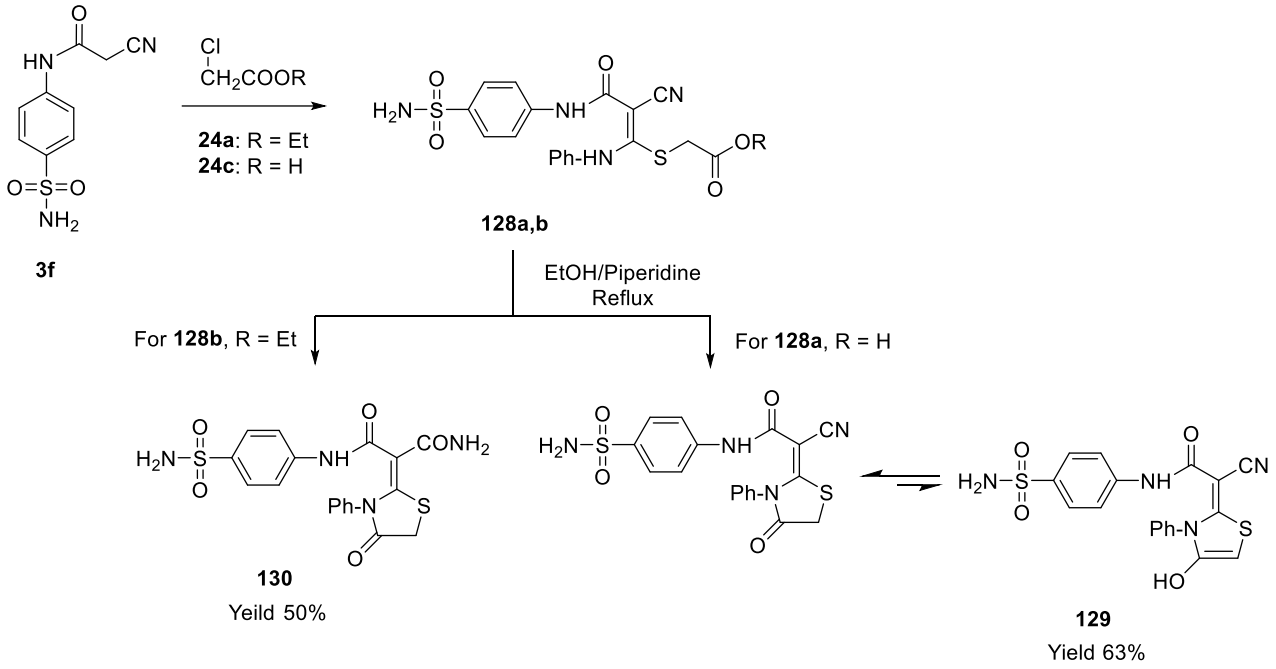
Scheme 53



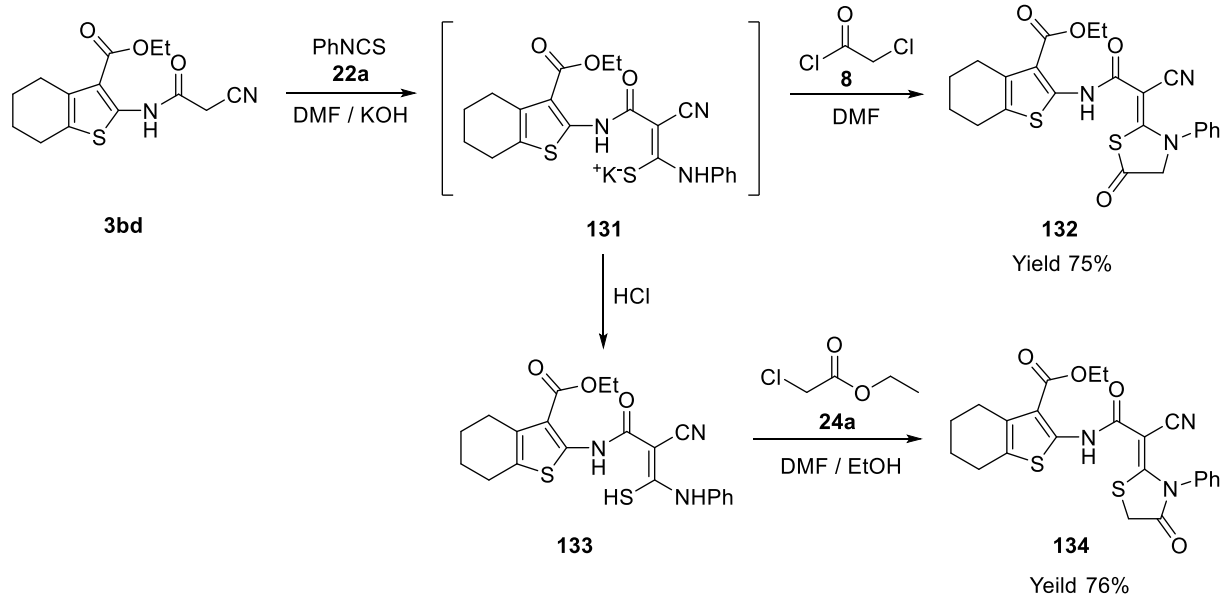
Scheme 54

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]

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]

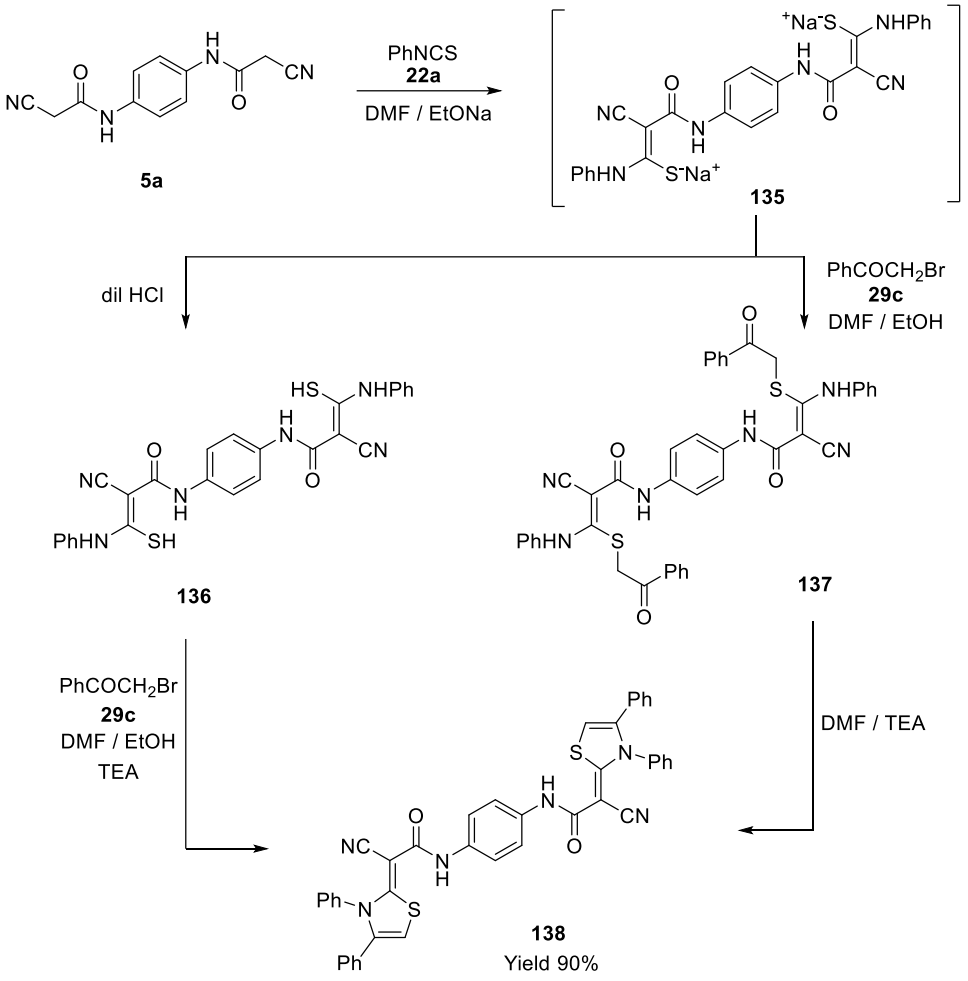


Scheme 55



Scheme 56

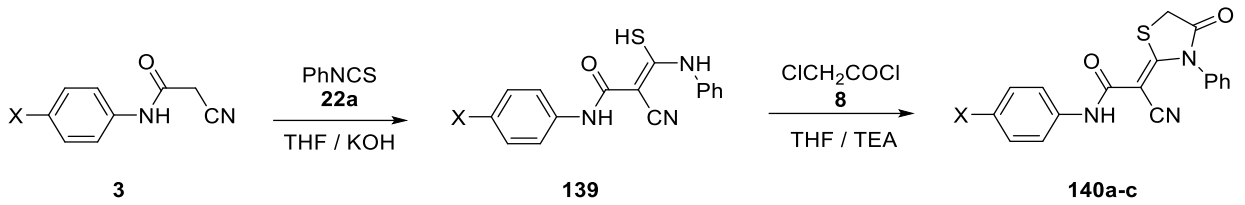
Compound **3bd** reacted with phenyl isothiocyanate **22a** in dry DMF in the presence of KOH followed by addition of chloroacetyl chloride **8** to give 2-(5-oxothiazolidin-2-ylidene)cyanoacetamido derivative **132** *via* the intermediate **131**. Acidification of the potassium salt **131** gave the 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 57

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]

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]

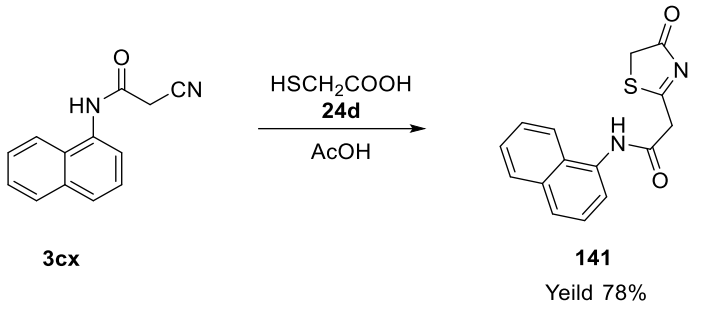


Scheme 58

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

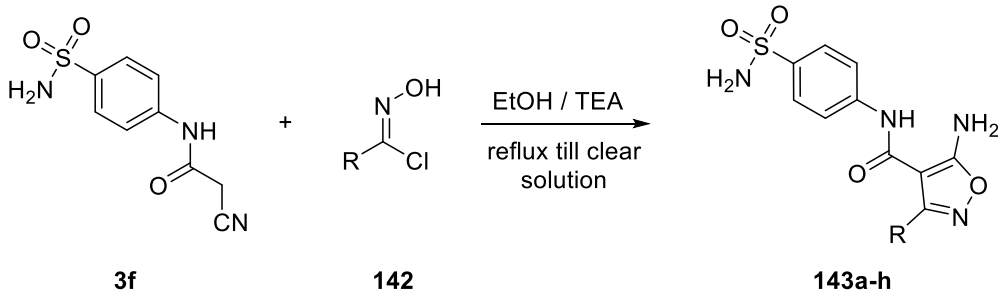
Entry	Product	X	Yield (%)
3a	**140a**	H	73
3bz	**140b**	Me	67
3co	**140c**	Cl	65

3.1.2.5.3 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. 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]

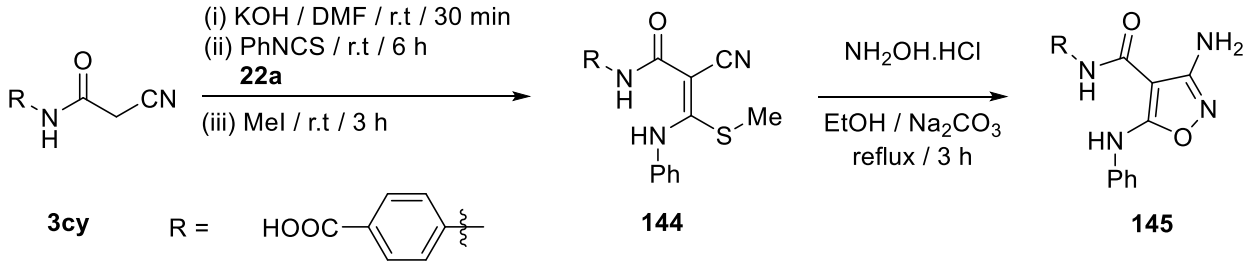


Scheme 60

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

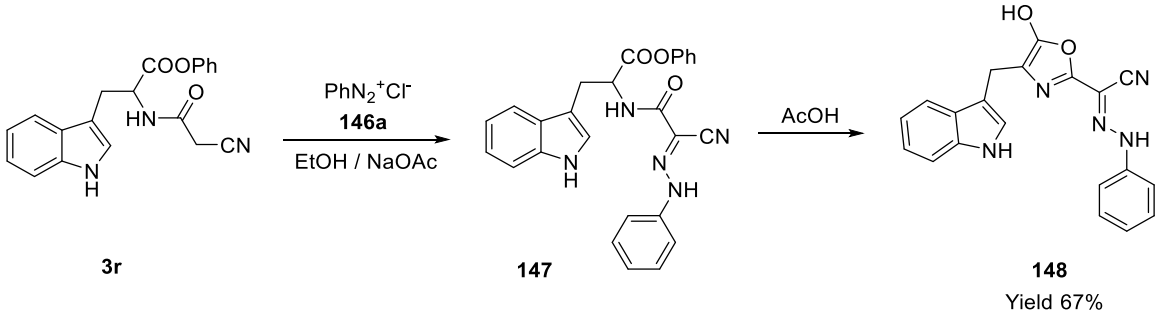
Entry	Product	R	Yield (%)	Entry	Product	R	Yield (%)
142a	**143a**	2,6-$Cl_2C_6H_3$	52	**142e**	**143e**	Ph	35
142b	**143b**	2,4-$Cl_2C_6H_3$	27	**142f**	**143f**	2-$NO_2C_6H_4$	64
142c	**143c**	4-ClC_6H_4	24	**142g**	**143g**	5-Cl-2-furyl	53
142d	**143d**	4-BrC_6H_4	26	**142h**	**143h**	5-Cl-2-thienyl	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

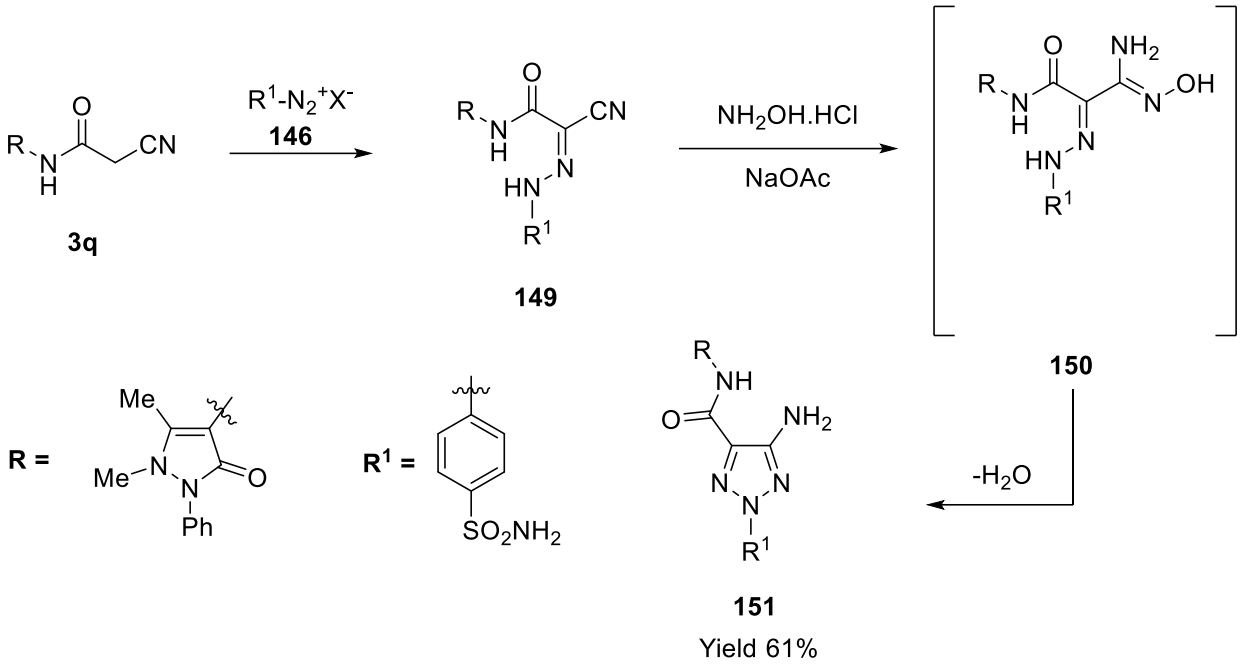
3.1.2.7 Oxazole derivatives. Synthesis *via* coupling reactions. The reaction of **3r** with benzenediazonium chloride **146a** afforded the hydrazone **147**. Heating of compound **147** in acetic acid furnished the phenylhydrazonoindol-3-ylhydroxyoxazol-2-yl acetonitrile derivative **148** (Scheme 62).[104]



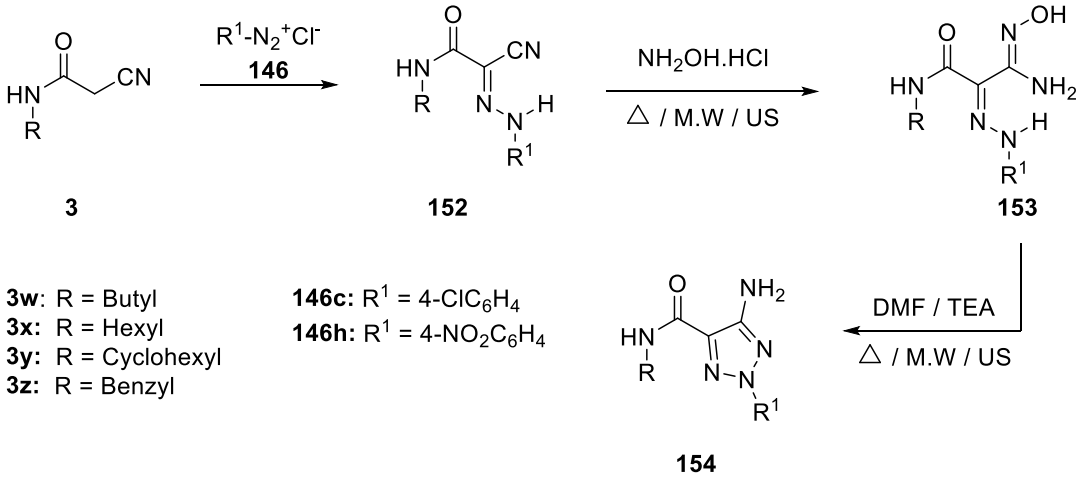
Scheme 62

3.1.3 Monocyclic five-membered rings with three hetero atoms. 3.1.3.1 Triazole derivatives. 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]

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 63

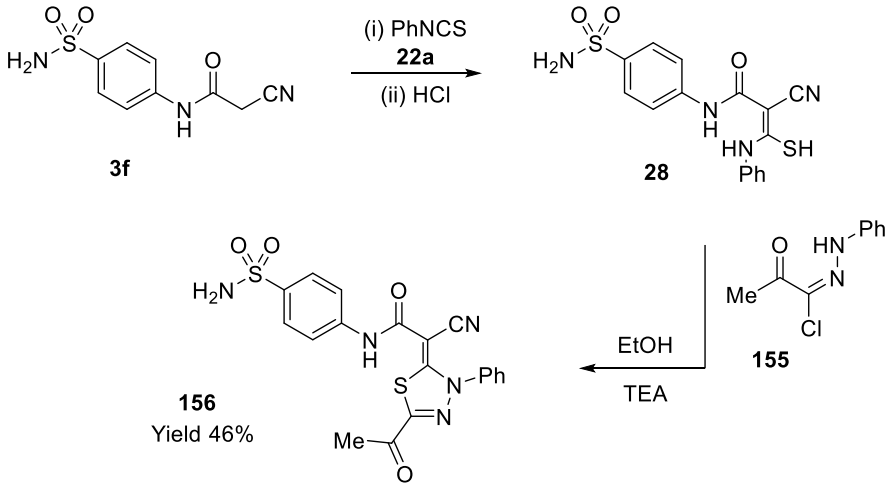


Scheme 64

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

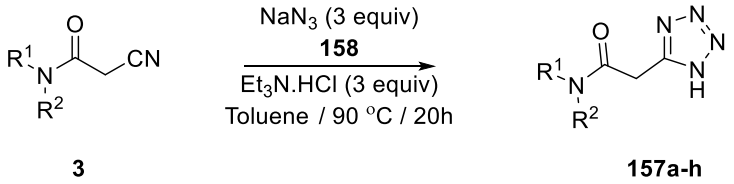
Product	R	R^1	Yield (%)		
			Δ	M.W	US
154a	Butyl	4-ClC_6H_4	60	77	73
154b	Benzyl	4-ClC_6H_4	55	84	78
154c	Butyl	4-$NO_2C_6H_4$	59	79	70
154d	Hexyl	4-$NO_2C_6H_4$	58	89	84
154e	Cyclohexyl	4-$NO_2C_6H_4$	54	80	78

3.1.3.2 1,3,4-Thiadiazole derivatives. 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. Tetrazole derivatives. 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-cyanoactamide 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).

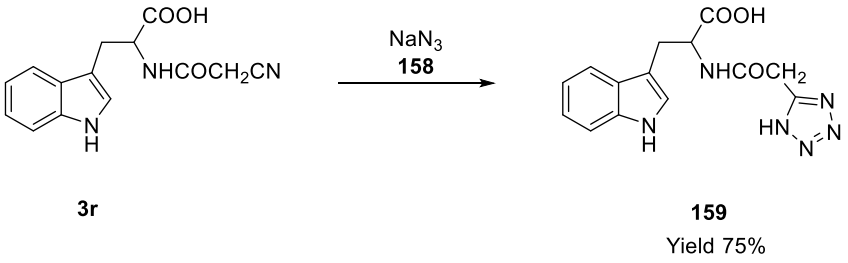


Scheme 66

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

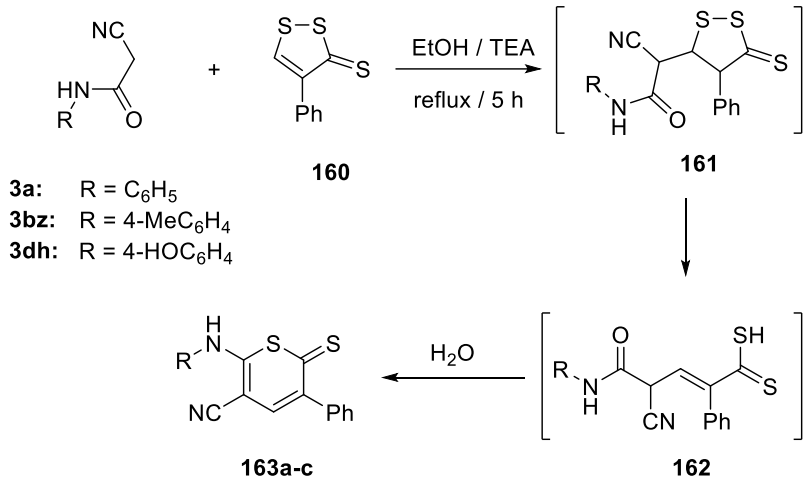
Entry	Product	R^1	R^2	Yield (%)
3cz	**157a**	Ph	Ph	56
3da	**157b**	Benzyl	Benzyl	67
3db	**157c**	$PhCH_2CH_2$	$PhCH_2CH_2$	74
3dc	**157d**	4-ClC_6H_4	4-ClC_6H_4	64
3dd	**157e**	2-furyl	2-furyl	21
3de	**157f**	Cyclopropanyl	Cyclopropanyl	55
3df	**157g**	Allyl	Allyl	25
3dg	**157h**	2-Naphthyl	2-Naphthyl	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. Synthesis *via* Michael addition reactions. The reaction of *N*-arylcyanoacetamide 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]



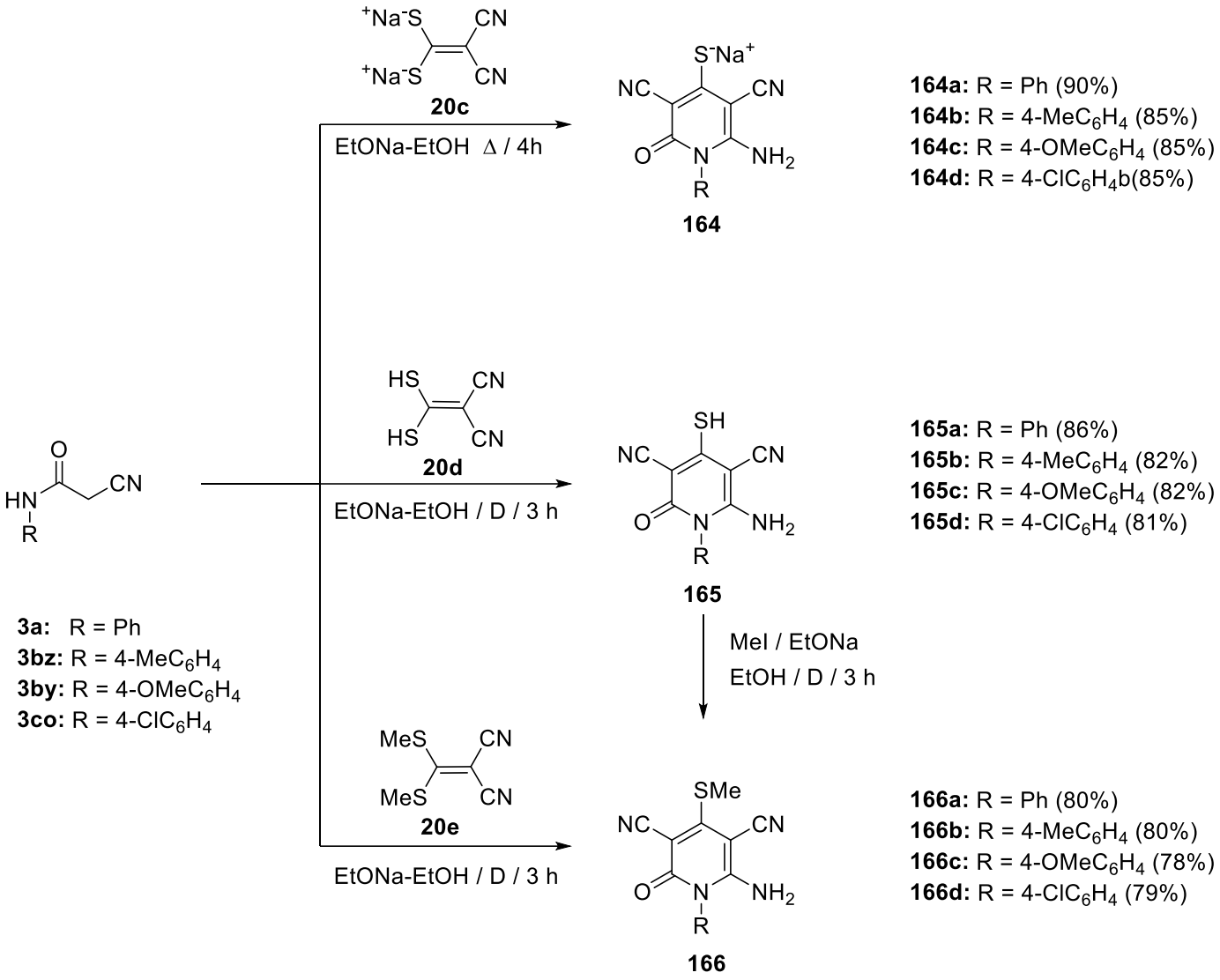
Scheme 68

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

Product	Ar	Yield (%)
163a	C_6H_5	83
163b	4-MeC_6H_4	76
163c	4-HOC_6H_4	77

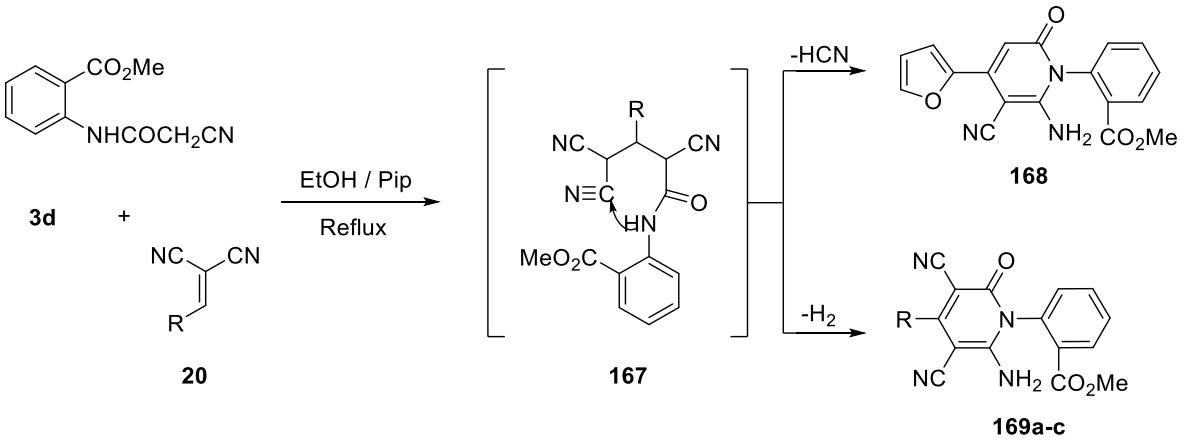
3.1.5.2 Pyridine derivatives. 3.1.5.2.1 Synthesis *via* Michael addition reactions. Compound **20c** is readily reacted with a series of 2-cyano-*N*-arylacetamides **3** in sodium ethoxide to yield the corresponding sodium thiolate derivatives **164** in good yields. Treatment of compounds **3** with **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 cinnamonitriles **20h-k** to afford the Michael adduct **167**. Intramolecular cyclization of **167** followed by HCN or H_2 elimination afforded pyridones **168** and **169a-c** respectively (Scheme 70, Table 26).[16]

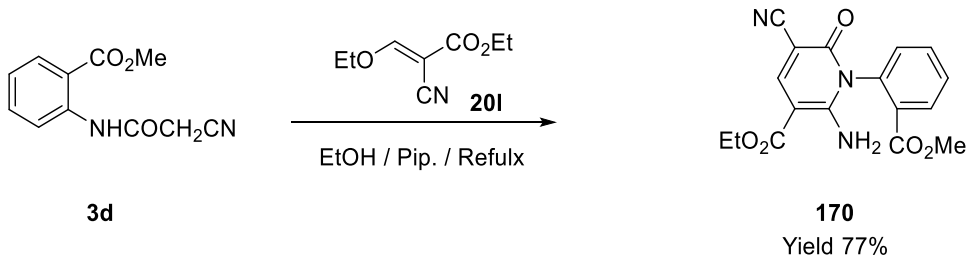


Scheme 70

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

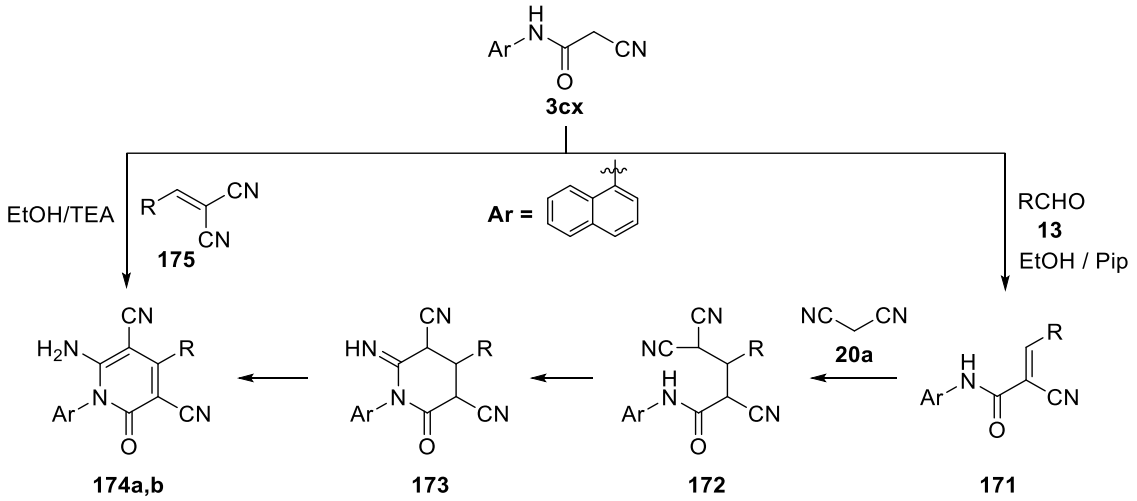
Entry	Product	R	Yield (%)
20h	**168**	2-Furyl	60
20i	**169a**	2-ClC_6H_4	71
20j	**169b**	2,4-$Cl_2C_6H_4$	74
20k	**169c**	4-$N(Me)_2C_6H_4$	86

Also, reaction of **3d** with ethyl (*E*)-2-cyano-3-ethoxyacrylate **20l** 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]

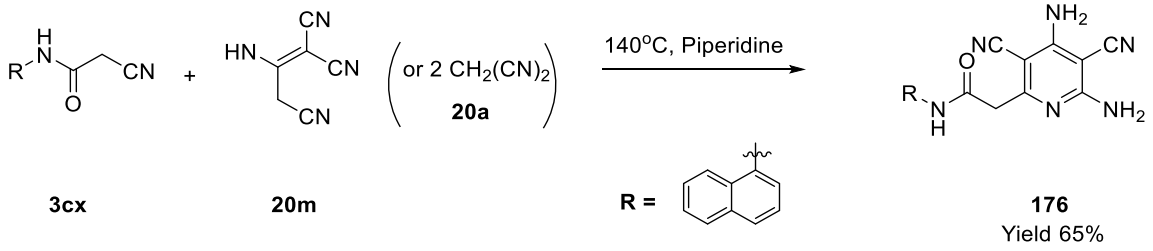


Scheme 72

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

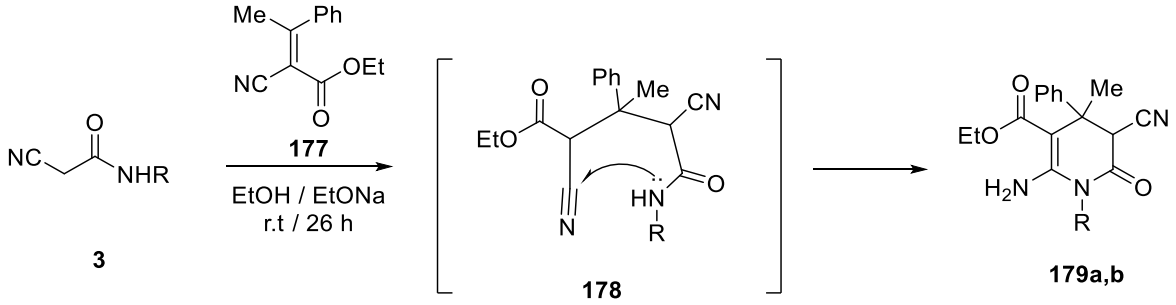
Entry	Product	R	Yield (%)
13i & 175a	**174a**	4-OHC_6H_5	85
13j & 175b	**174b**	3,4-$OCH_2OC_6H_3$	80

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]

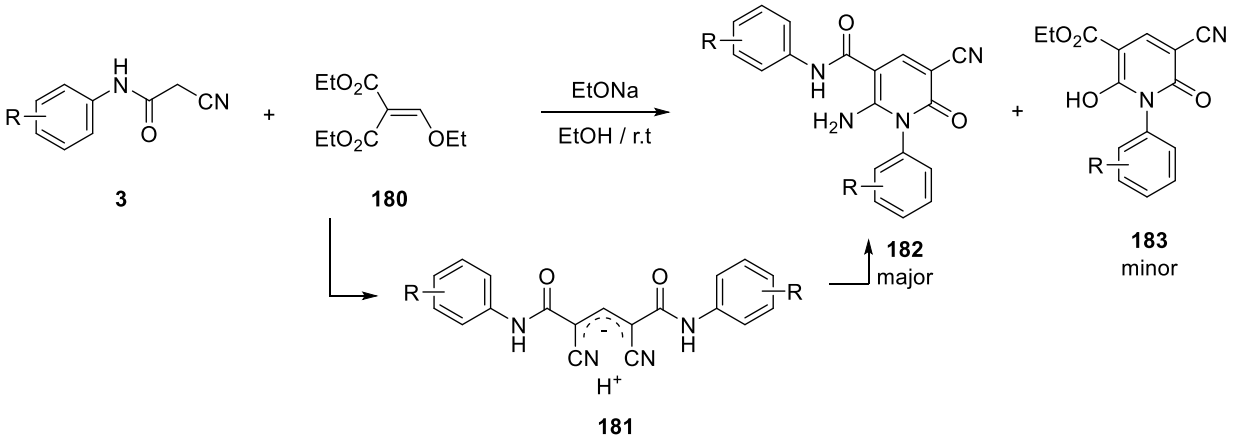


Scheme 74

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

Entry	Product	R	Yield (%)
3a	**179a**	Ph	32
3di	**179b**	3-MeC_6H_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]

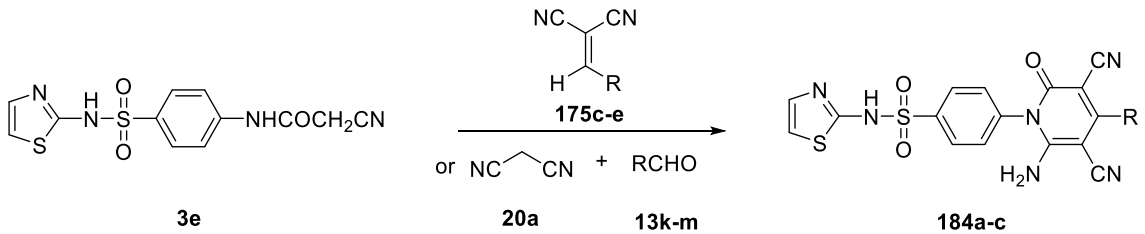


Scheme 75

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

Entry	Product	R	Entry	Product	R
3a	**182a**	H	**3dj**	**182e**	2-MeO
3bz	**182b**	4-Me	**3dk**	**182f**	2-Et
3co	**182c**	4-Cl	**3dl**	**182g**	2-NO_2
3di	**182d**	3-Me			

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]

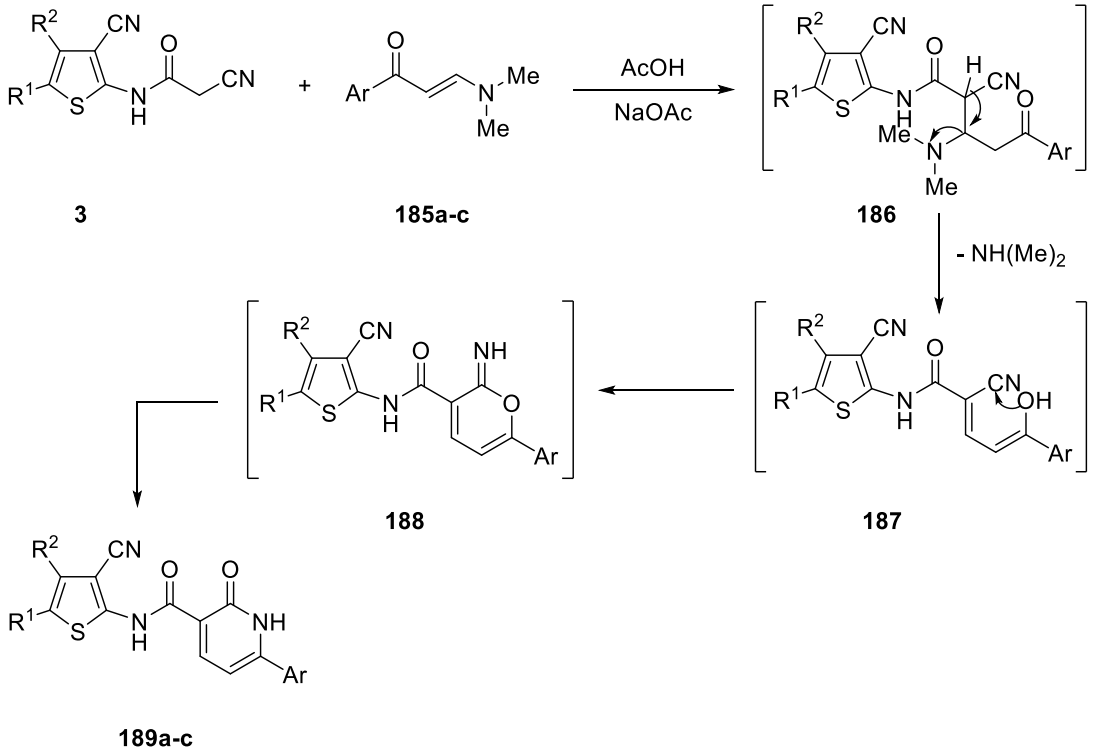


Scheme 76

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

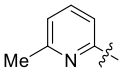
Entry	Product	R	Yield (%)
13k, 175c	184a	Ph	61
13l, 175d	184b	4-$MeOC_6H_4$	63
13m, 175e	184c	4-$NO_2C_6H_4$	65

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]

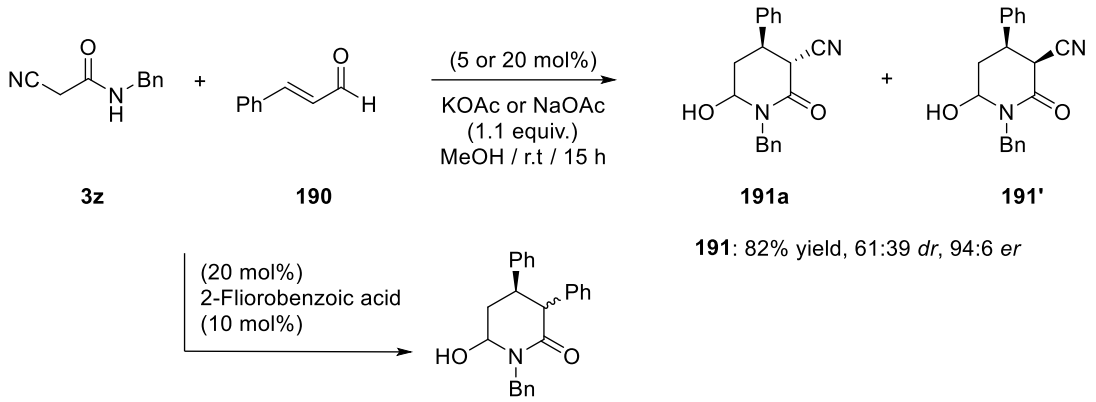


Scheme 77

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

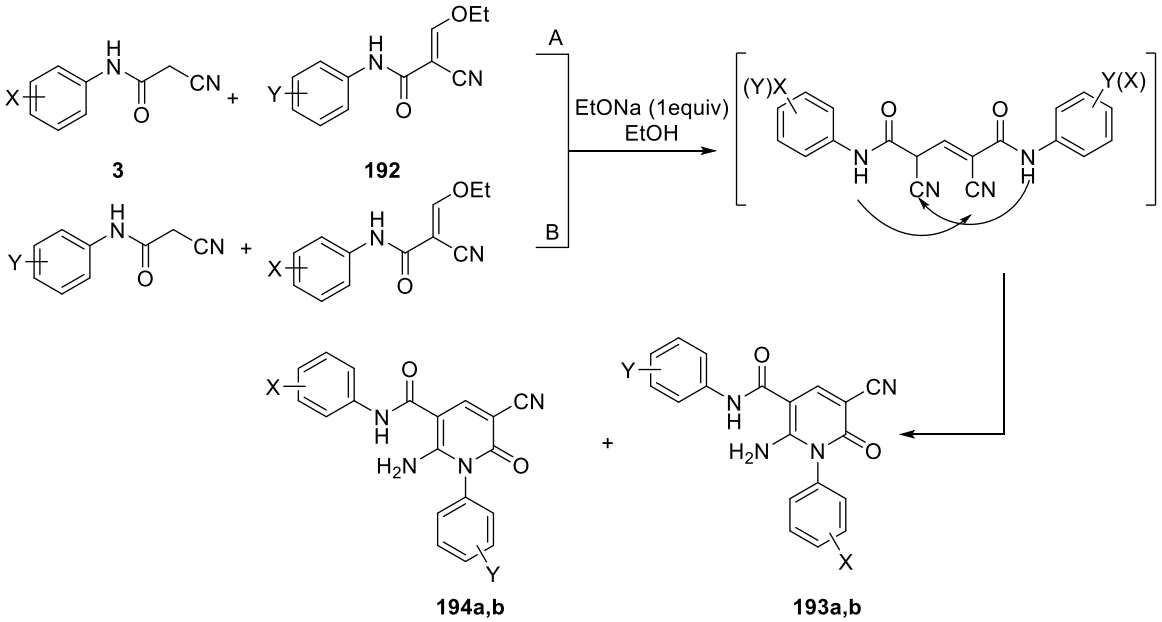
Entry	Product	R^1	R^2	Ar	Yield (%)
3aw, 185a	**189a**	H	Ph	Ph	70
3ax, 185b	**189b**	H	4-ClC_6H_4		68
3ay, 185c	**189c**	CO_2Et	Me		63

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]

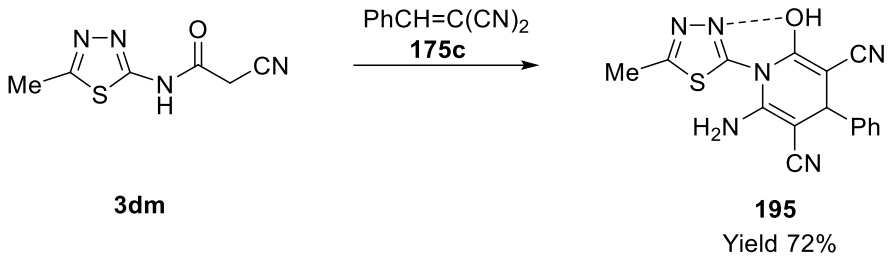


Scheme 79

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)

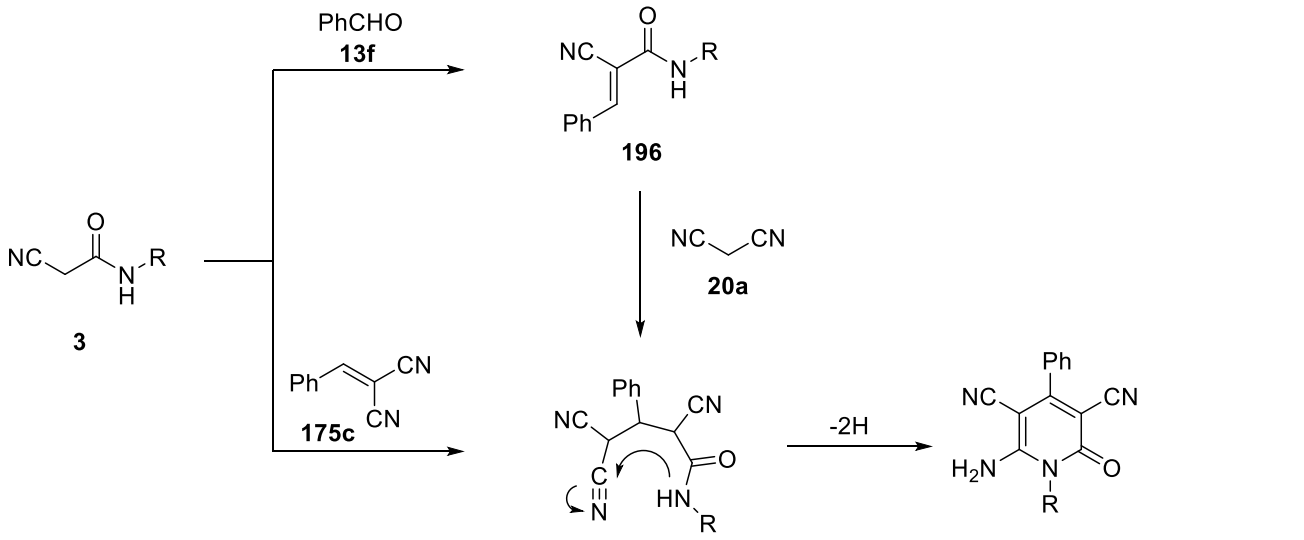
When compound **3dm** was reacted with benzylidenemalononitrile **175c** in a basic medium a pyridine derivative **195** was achieved. The resulting compound **195** exists in an enolic form, which is stabilized by the hydrogen bond (Scheme 80). [115]



3dm **195**
Yield 72%

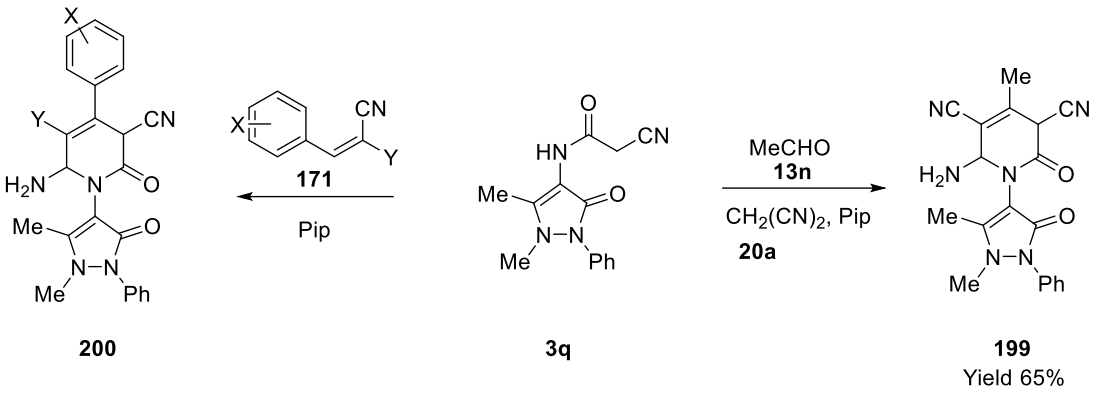
Scheme 80

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]

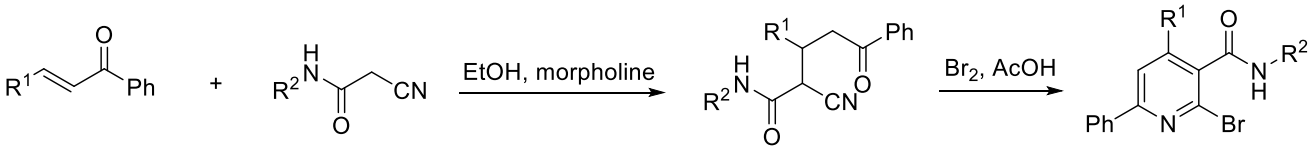


Scheme 82

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_2Et	40
171g	**200e**	4-Cl	CO_2Et	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]

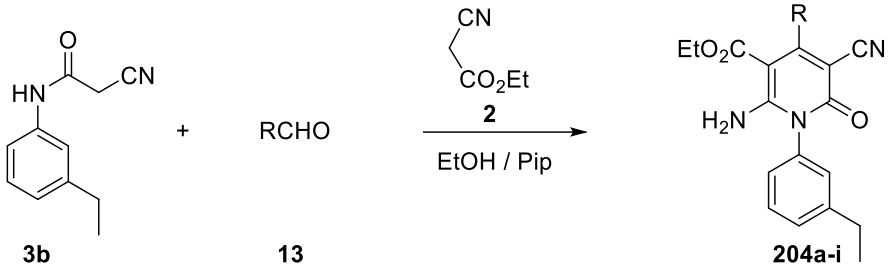


Scheme 83

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

Product	R^1	R^2	Yield (%)
203a	4-ClC_6H_4	Ph	82
203b	4-MeC_6H_4	4-MeC_6H_4	80
203c	4-MeC_6H_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]

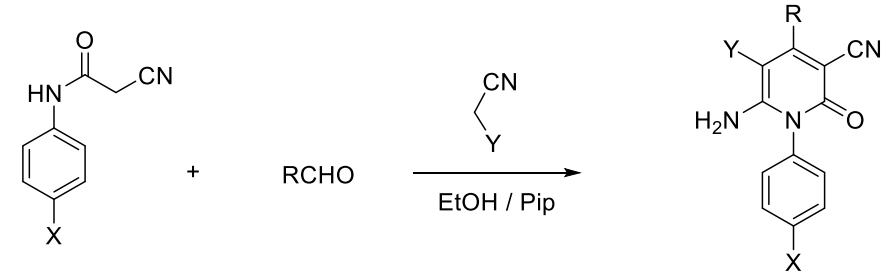


Scheme 84

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

Entry	Product	R	Yield (%)	Entry	Product	R	Yield (%)
13o	**204a**	4-MeC_6H_4	71	**13s**	**204f**	2,3,4-$(MeO)_3C_6H_2$	87
13l	**204b**	4-$MeOC_6H_4$	89	**13t**	**204g**	2-ClC_6H_4	90
13p	**204c**	3-$NO_2C_6H_4$	80	**13u**	**204h**	3-BrC_6H_4	62
13m	**204d**	4-$NO_2C_6H_4$	78	**13v**	**204i**	2-thienyl	91
13j	**204e**	Pipronyl	81				

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]

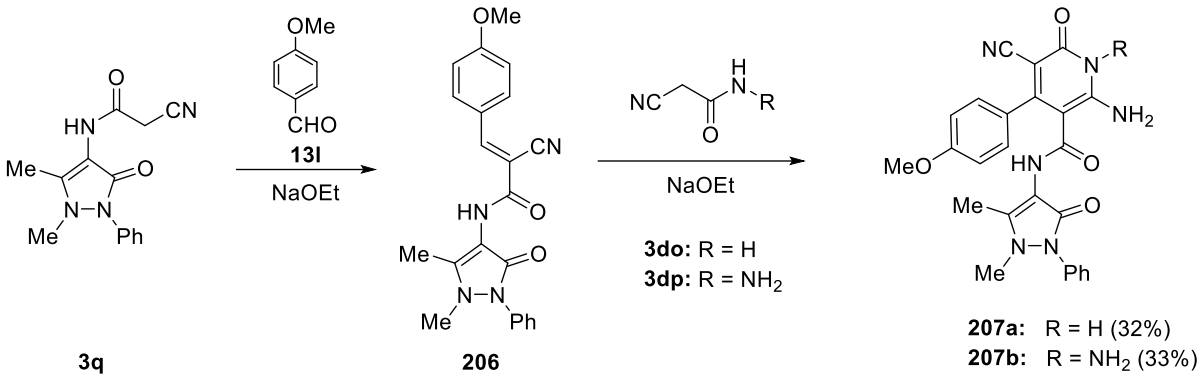


Scheme 85

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

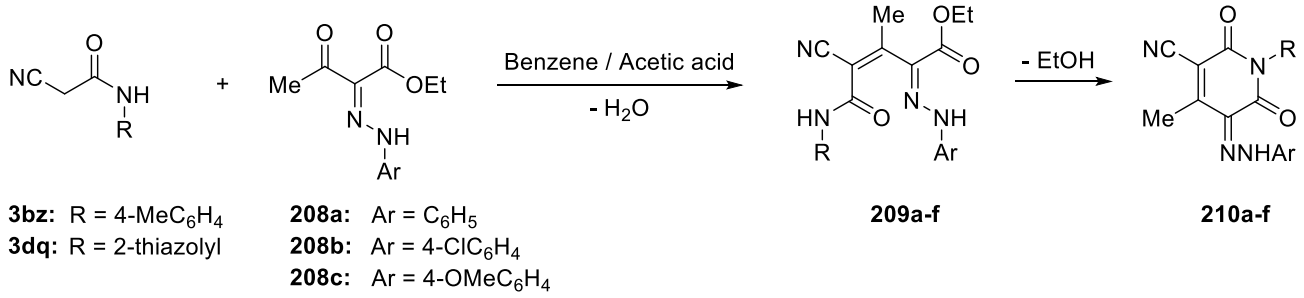
Entry	Product	X	Y	R	Yield (%)
13n	**205a**	F	CN	Me	80
13k	**205b**	F	CN	Ph	70
13k	**205c**	EtO	CN	Ph	76
13w	**205d**	F	CN	4-ClC_6H_4	60
13w	**205e**	F	CO_2Et	4-ClC_6H_4	65
13x	**205f**	F	CO_2Et	4-$MeOC_6H_4$	70
13s	**205g**	F	CN	3,4,5-$(MeO)_3C_6H_2$	75

Treatment of **3q** with 4-anisaldehyde **13l** resulted in the formation of the arylidine **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-arylhydrazono-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]

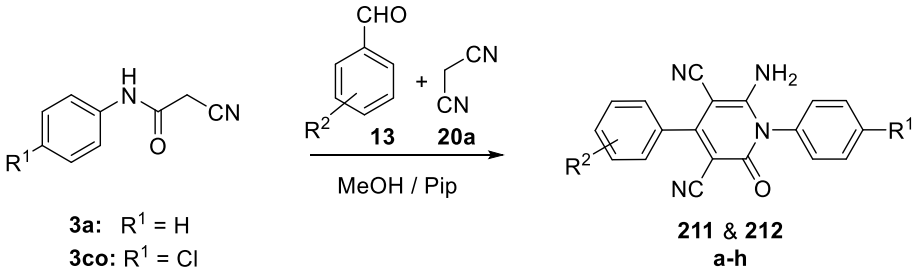


Scheme 87

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

Product	R	Ar	Yield (%)
210a	4-MeC_6H_4	Ph	75
210b	4-MeC_6H_4	4-ClC_6H_4	70
210c	4-MeC_6H_4	4-$MeOC_6H_4$	65
210d	2-thiazolyl	Ph	60
210e	2-thiazolyl	4-ClC_6H_4	64
210f	2-thiazolyl	4-$MeOC_6H_4$	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]

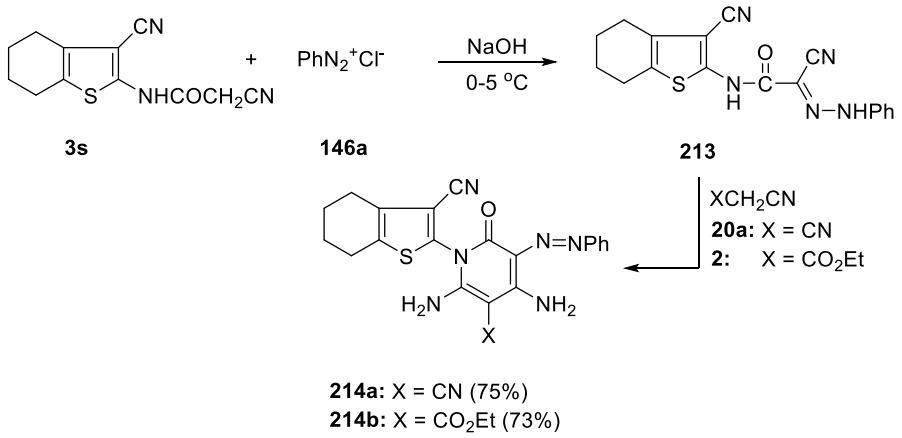


Scheme 88

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

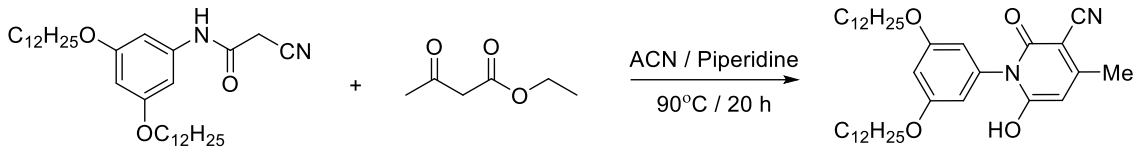
Entry	Product	R^1	R^2	Yield (%)	Entry	Product	R^1	R^2	Yield (%)
13m	**211a**	H	4-NO_2	76	**13m**	**212a**	Cl	4-NO_2	76
13o	**211b**	H	4-CH_3	78	**13o**	**212b**	Cl	4-CH_3	70
13p	**211c**	H	3-NO_2	69	**13p**	**212c**	Cl	3-NO_2	79
13t	**211d**	H	2-Cl	77	**13t**	**212d**	Cl	2-Cl	77
13w	**211e**	H	4-Cl	72	**13w**	**212e**	Cl	4-Cl	70
13x	**211f**	H	4-OCH_3	73	**13x**	**212f**	Cl	4-OCH_3	72
13y	**211g**	H	3-Cl	69	**13y**	**212g**	Cl	3-Cl	69
13z	**211h**	H	4-Br	78	**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

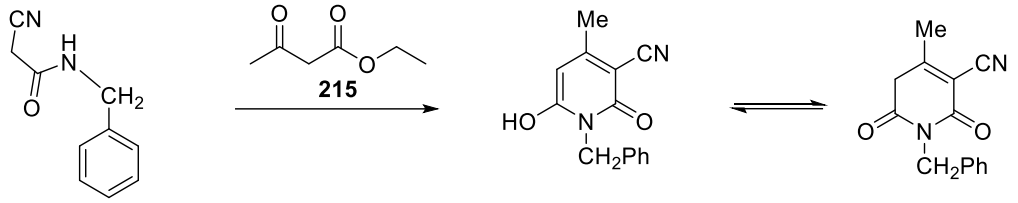
3.1.5.2.2 Synthesis *via* Knoevenagel condensation reactions. Knoevenagel condensation of cyanoacetamides with *β*-Ketoesters and 1,3-diketones. The bis(dodecyloxy)amide **3am** is condensed with ethyl acetoacetate **215** to give hydroxypyridone **216** (Scheme 90).[38]



3am **215** **216**
Yield 43%

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]



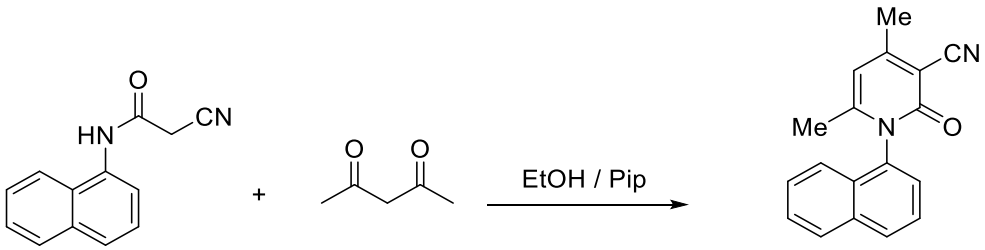
3z **217a** **217b**

Scheme 91

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

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

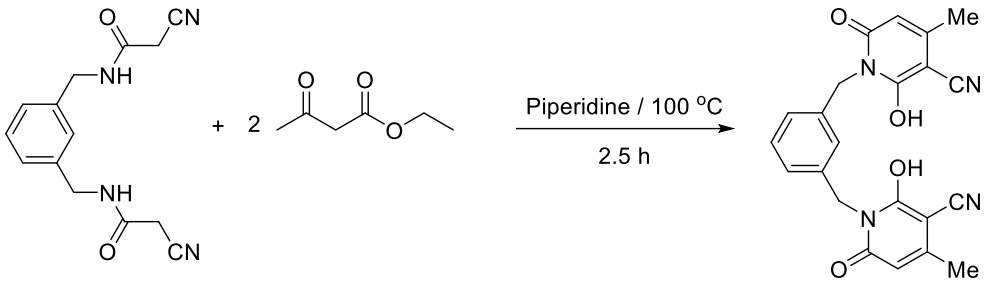
2-Cyano-*N*-(1-naphthyl)acetamide **3cx** was reacted with acetylacetone **218a** in ethanol in the presence of piperidine as a catalyst to form the pyridine-2-one **219** in an excellent yield (95%) (Scheme 92).[110]



3cx **218a** **219**
Yield 95%

Scheme 92

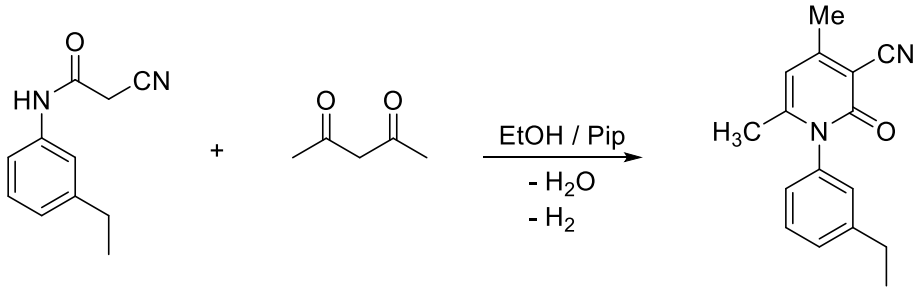
The condensation of diamide **5c** with two moles of ethyl acetoacetate **215** afforded the bis(pyridone) **220** in 77% yield (Scheme 93).[121]



5c **215** **220**
Yield 77%

Scheme 93

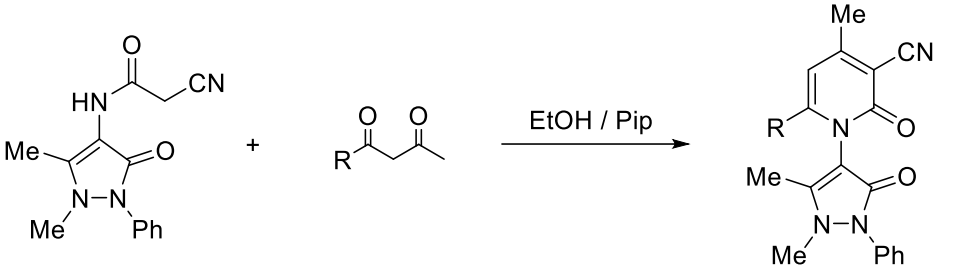
Equimolar amounts of compound **3b** and acetylacetone **218a** were refluxed in ethanol containing piperidine for 5 h to give compound **221** (Scheme 94).[15]



3b **218a** **221**
Yield 86%

Scheme 94

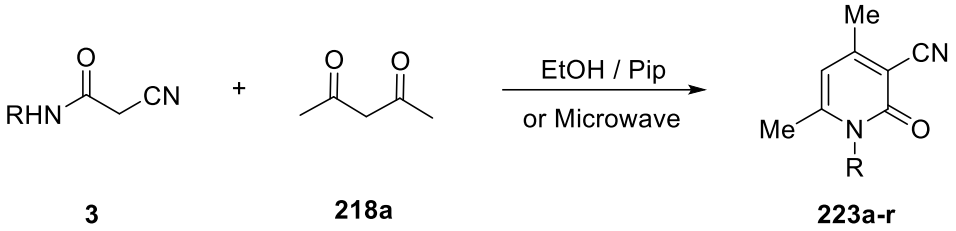
Cyclocondensation of **3q** with acetylacetone **218a** or benzoylacetone **218b** in ethanol containig piperidine as a catalyst furnished the pyrazolyl-pyridine derivatives **222a,b** (Scheme 95).[117]



3q **218a:** R = Me
218b: R = Ph
222a: R = Me (63%)
222b: R = Ph (32%)

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]



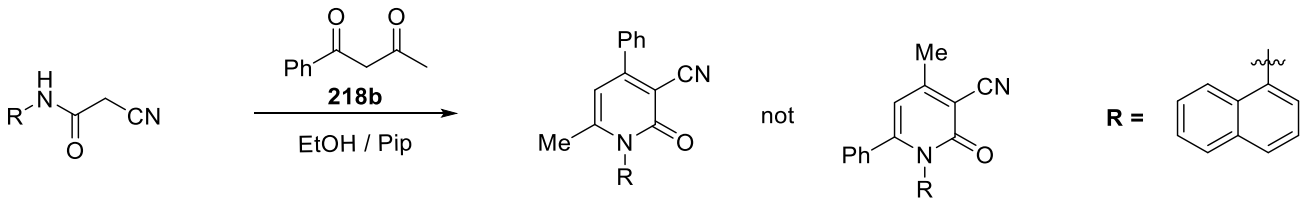
3 **218a** **223a-r**

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-$MeOC_6H_4$	95	72
3co	**223h**	4-ClC_6H_4	95	73
3bz	**223i**	4-MeC_6H_4	97	75
3bl	**223j**	4-FC_6H_4	99	72
3dr	**223k**	4-EtC_6H_4	84	73
3ds	**223l**	4-$NMe_2C_6H_4$	90	73
3bi	**223m**	4-BrC_6H_4	86	76
3dt	**223n**	4-IC_6H_4	86	73
3du	**223o**	4-AcC_6H_4	91	80
3bj	**223p**	4-$NO_2C_6H_4$	84	64
3cy	**223q**	4-$CO_2HC_6H_4$	78	13
3dh	**223r**	4-OHC_6H_4	34	91

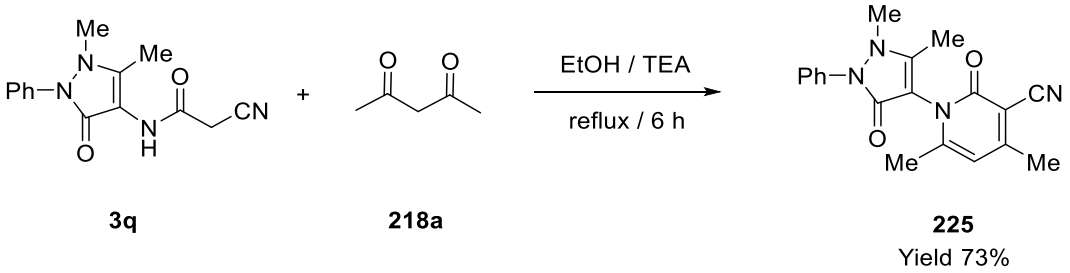
Reaction of **3cx** with benzoylacetone **218b** afforded pyridones **224a** rather than **224b** (Scheme 97).[110]



3cx **224a** Yield 90% **224b**

Scheme 97

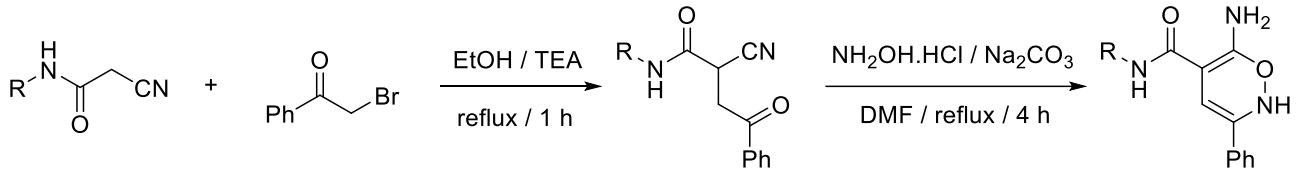
The nitrile derivative **3q** was treated with acetylacetone **218a** in the presence of triethylamine at reflux temperature to afford the pyridine-3-carbonitrile **225** in 73% yield (Scheme 98).[23]



3q **218a** **225**
Yield 73%

Scheme 98

3.1.6 Monocyclic six-membered rings with two hetero atoms. 3.1.6.1 Oxazine derivatives. El-Sayed and Ahmed[79] 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 2*H*-1,2-oxazine-5-carboxamide derivative **227** (Scheme 99).

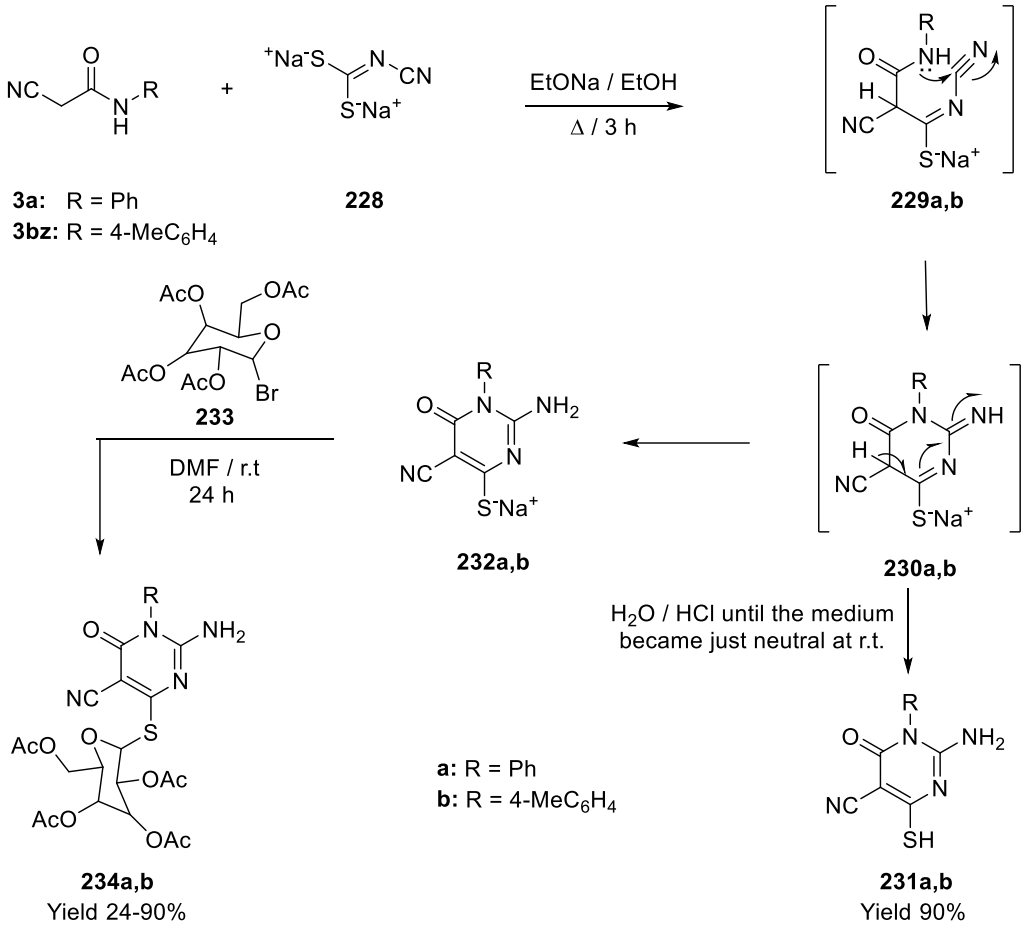


3cm **29c** **226** **227**
R = $CH_3(CH_2)_{17}$
Yield 80% Yield 72%

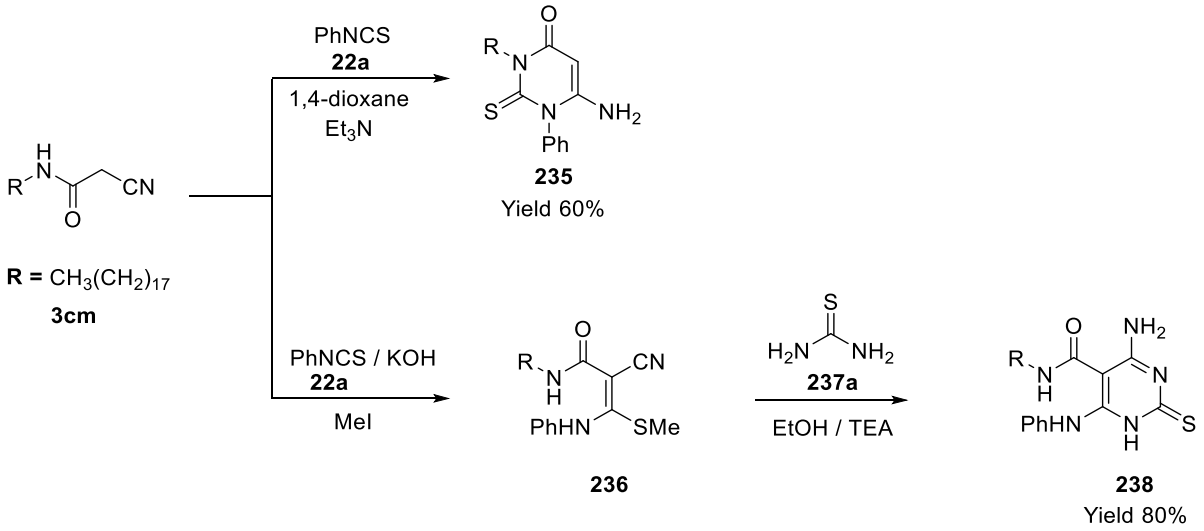
Scheme 99

3.1.6.2 Pyrimidine derivatives. 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]

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]

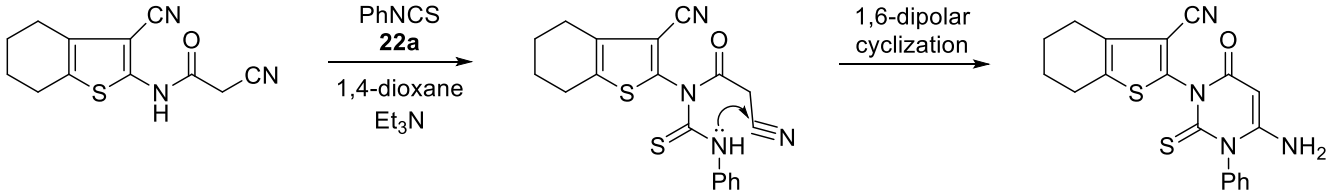


Scheme 100



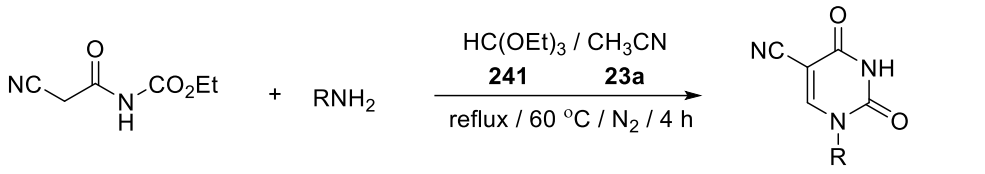
Scheme 101

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]



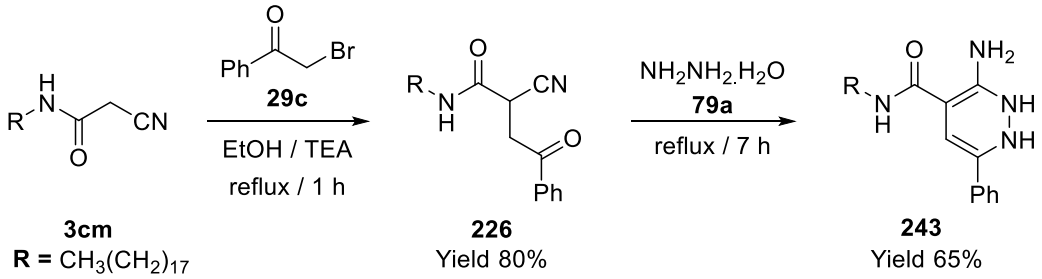
Scheme 102

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]



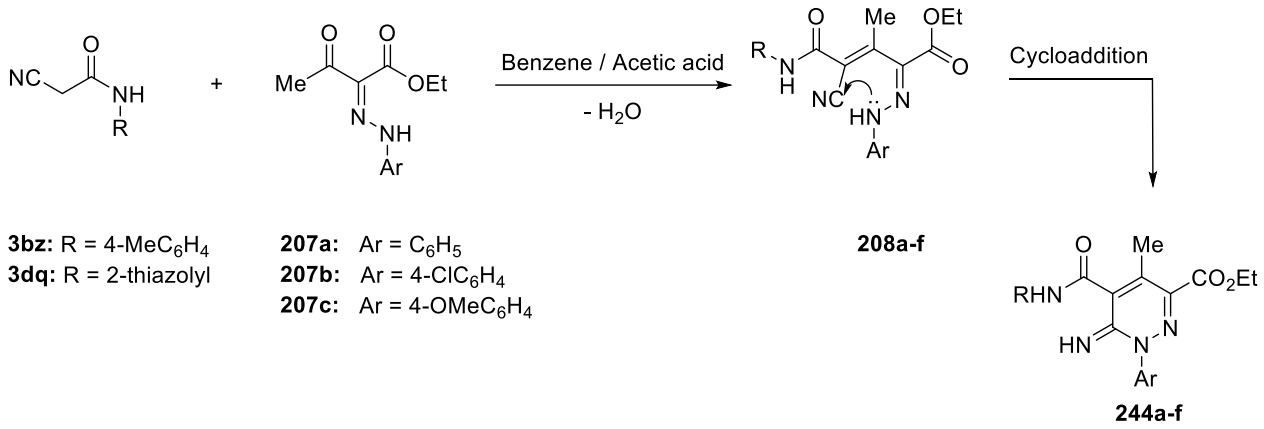
Scheme 103

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]

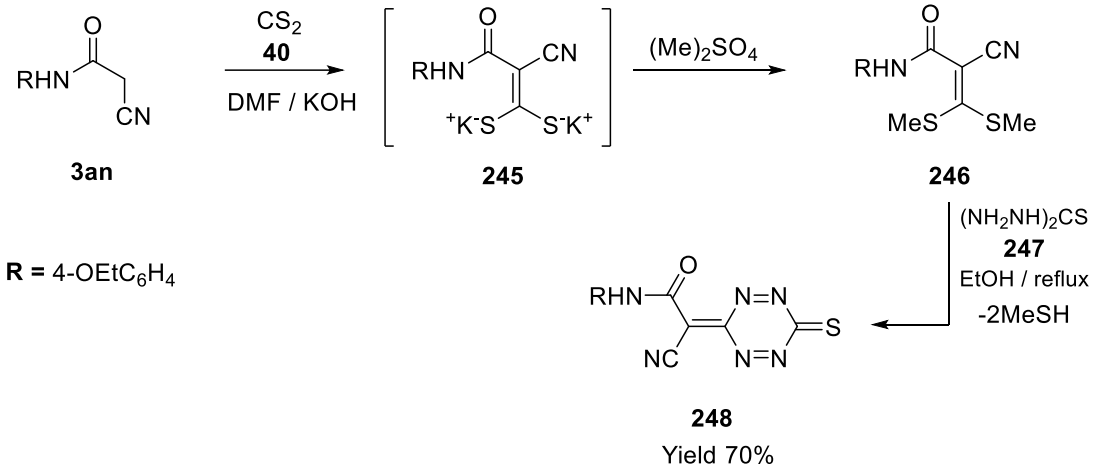


Scheme 105

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

Product	R	Ar	Yield (%)
244a	4-MeC_6H_4	Ph	25
244b	4-MeC_6H_4	4-ClC_6H_4	23
244c	4-MeC_6H_4	4-$MeOC_6H_4$	21
244d	2-thiazolyl	Ph	18
244e	2-thiazolyl	4-ClC_6H_4	18
244f	2-thiazolyl	4-$MeOC_6H_4$	20

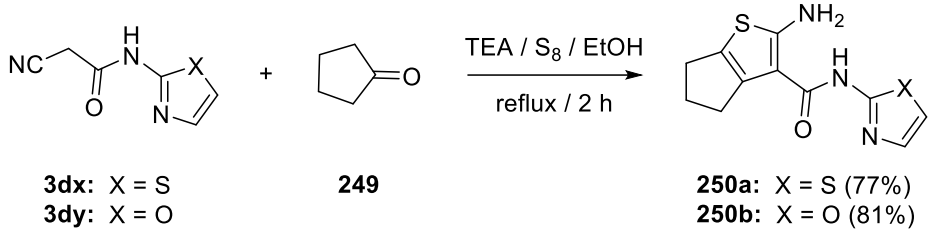
3.1.7 Monocyclic six-membered rings with four hetero atoms. 3.1.7.1 Tetrazine derivatives. Synthesis *via* Michael addition reactions. Treatment of compound **3an** with carbon disulfide **40** in DMF containing potassium hydroxide led to the formation of the non-isolable adduct **245**, which was further treated with dimethyl sulfate at room temperature to give the cyanoacrylamide **246**. The reaction of compound **246** with thiocarbohydrazide **247** in boiling ethanol furnished the tetrazine **248** in good yield (70%) (Scheme 106).[93]



Scheme 106

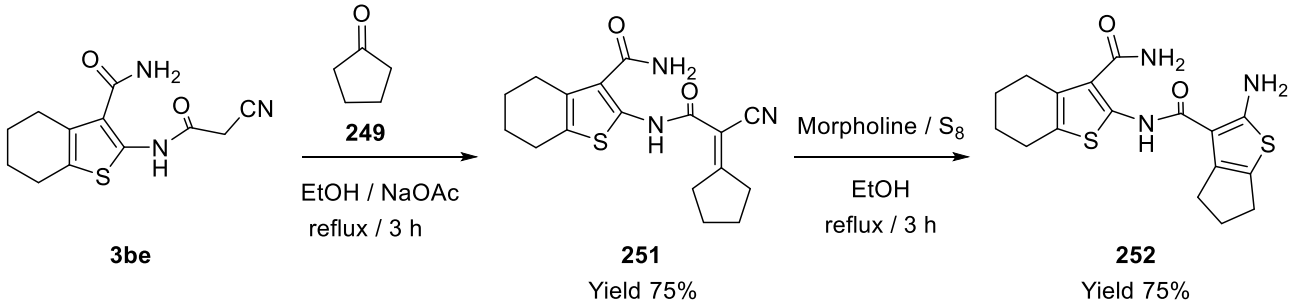
3.2.Fused heterocycles

3.2.1 Carbocyclic fused heterocycles. 3.2.1.1 Fused [5-5] systems. 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]



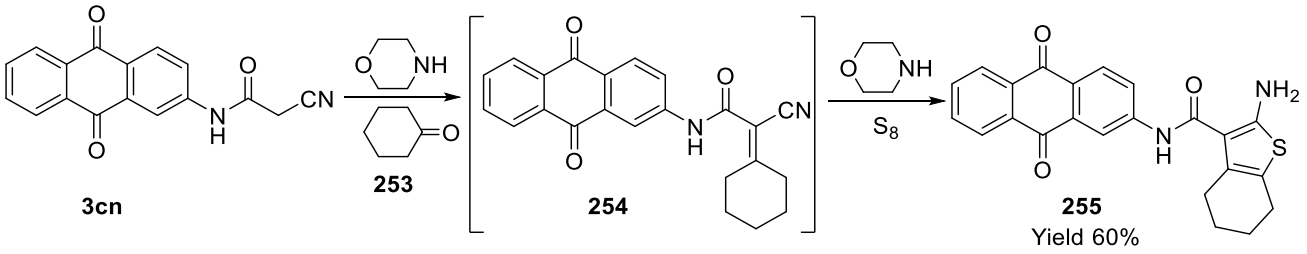
Scheme 107

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).



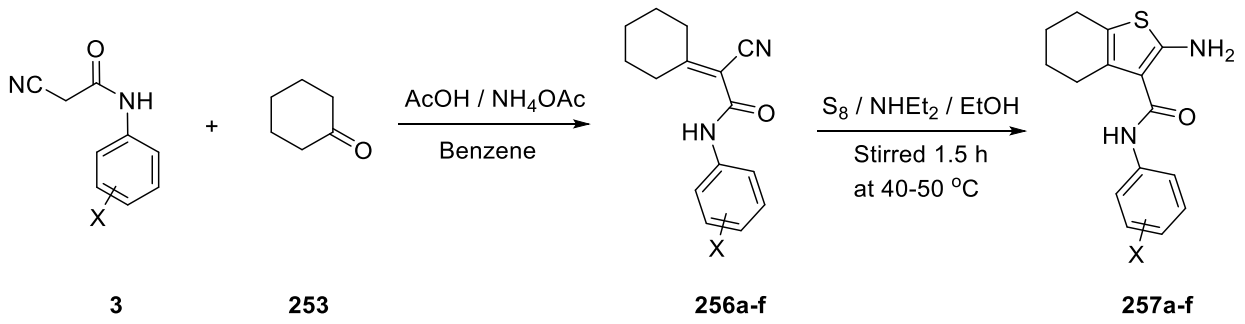
Scheme 108

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



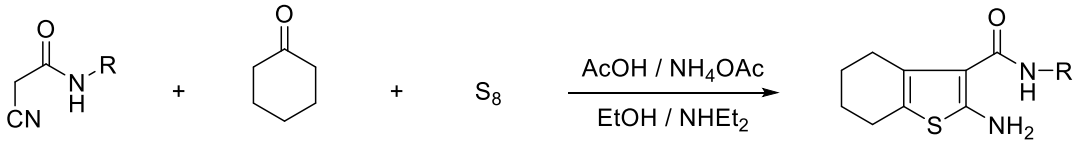
3 **253** **256a-f** **257a-f**

Scheme 110

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

Entry	Product	X	Yield (%)
3bm	**257a**	3-$CF_3C_6H_5$	20
3by	**257b**	4-$MeOC_6H_5$	28
3co	**257c**	4-ClC_6H_5	29
3bi	**257d**	4-BrC_6H_5	88
3dt	**257e**	4-IC_6H_5	24
3dn	**257f**	4-$CF_3C_6H_5$	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]



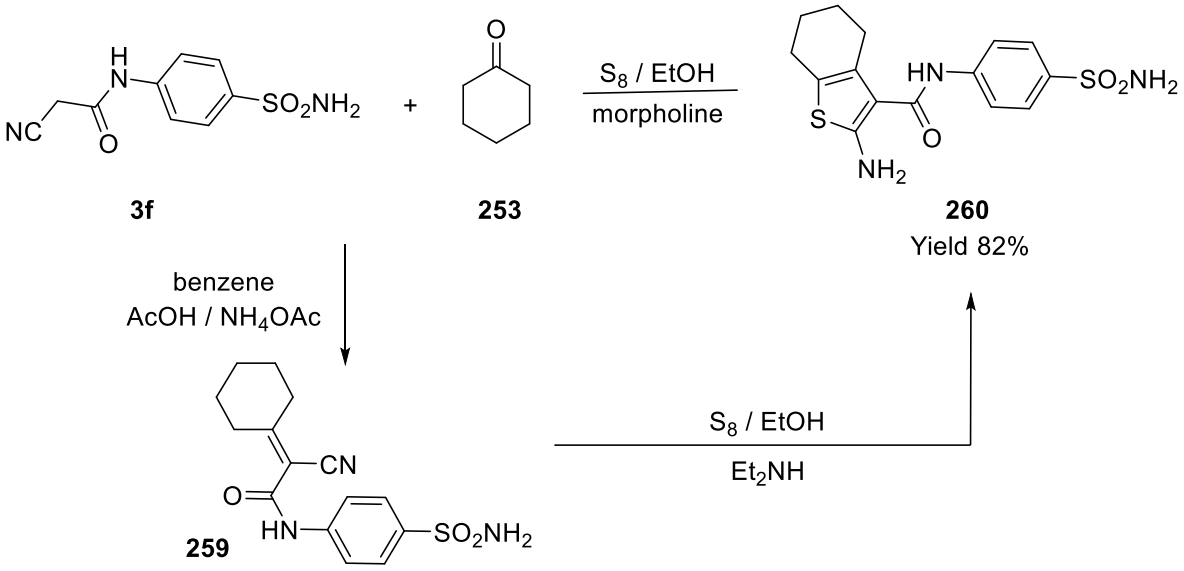
3 **253** **258a-k**

Scheme 111

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 containg 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).

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

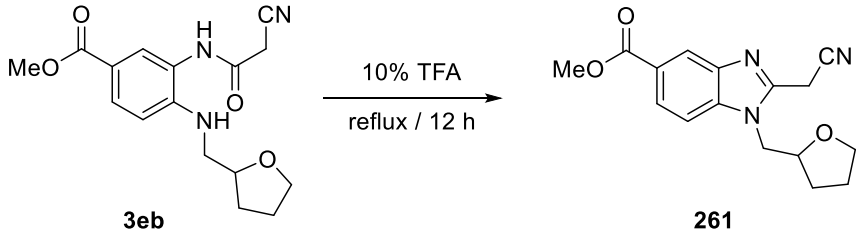
Entry	Product	R	Yield (%)
3do	**258a**	H	52
3ca	**258b**	Me	46
3ch	**258c**	Et	49
3a	**258d**	Ph	47
3cu	**258e**	2-MeC_6H_5	51
3bz	**258f**	4-MeC_6H_5	71
3bl	**258g**	4-FC_6H_5	67
3cp	**258h**	2-ClC_6H_5	76
3dz	**258i**	3-ClC_6H_5	71
3co	**258j**	4-ClC_6H_5	62
3ea	**258k**	3-Cl-4-FC_6H_5	79



3f **253** **260** **259**

Scheme 112

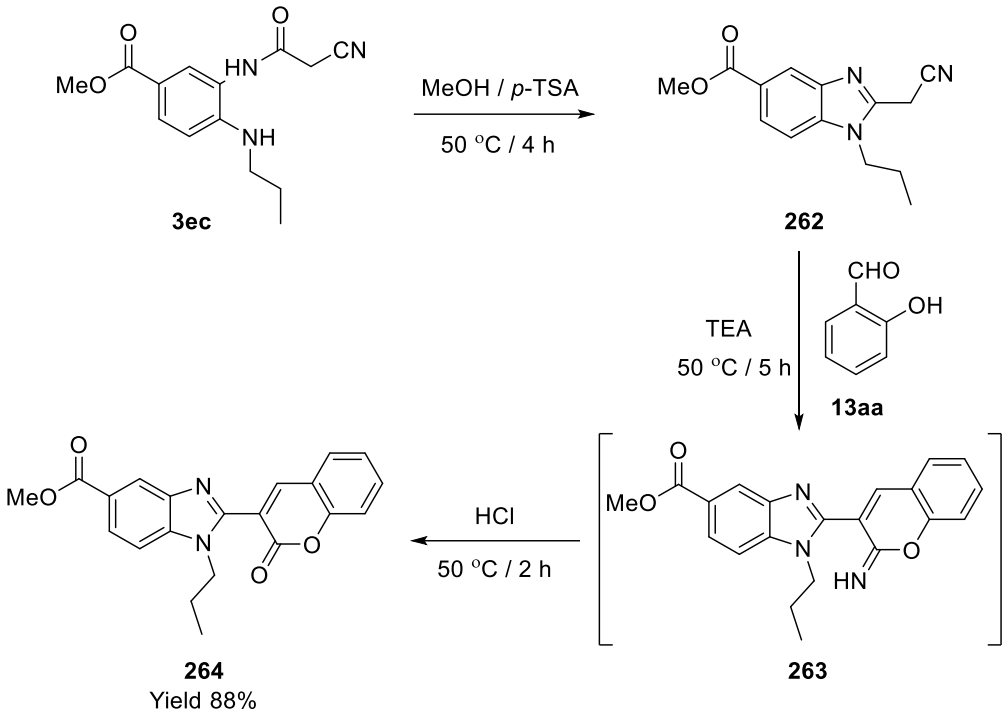
3.2.1.2.2 1*H*-Benzo[*d*]imidazole. Methyl 1-alkyl-(2-cyanometyl)benzimidazole-5-carboxylate **261** was synthesized *via* boiling of **3eb** in 10% trifluoroacetic acid TFA (Scheme 113).[35]



3eb **261**

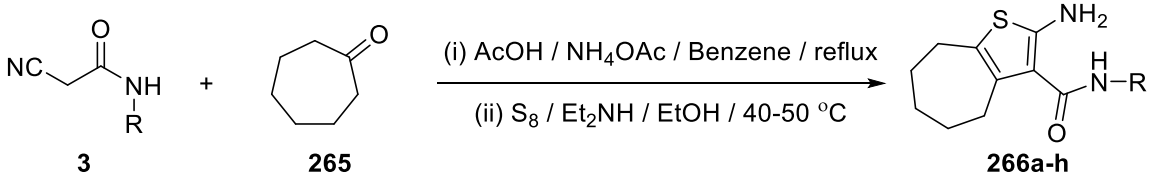
Scheme 113

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. 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).

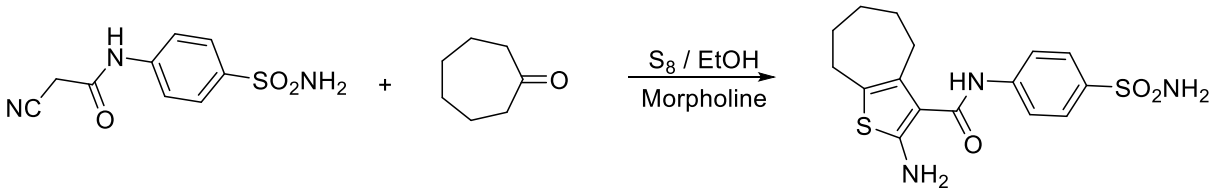


Scheme 115

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]

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

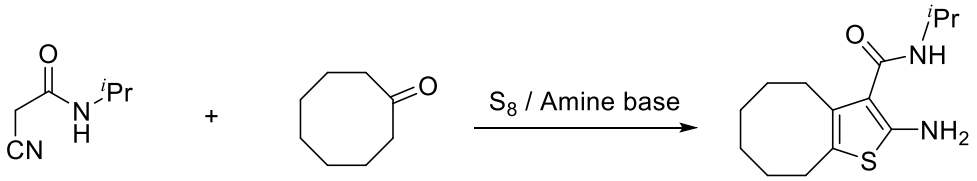
Entry	Product	R	Yield (%)
3ed	**266a**	2-Pyridyl	not reported
3co	**266b**	4-ClC_6H_4	61
3a	**266c**	Ph	64
3bl	**266d**	4-FC_6H_4	41
3dq	**266e**	2-Thiazolyl	40
3y	**266f**	Cyclohexyl	55
3dj	**266g**	2-$MeOC_6H_4$	not reported
3fy	**266h**	2-HOC_6H_4	not reported



3f **265** **267**
Yield 80%

Scheme 116

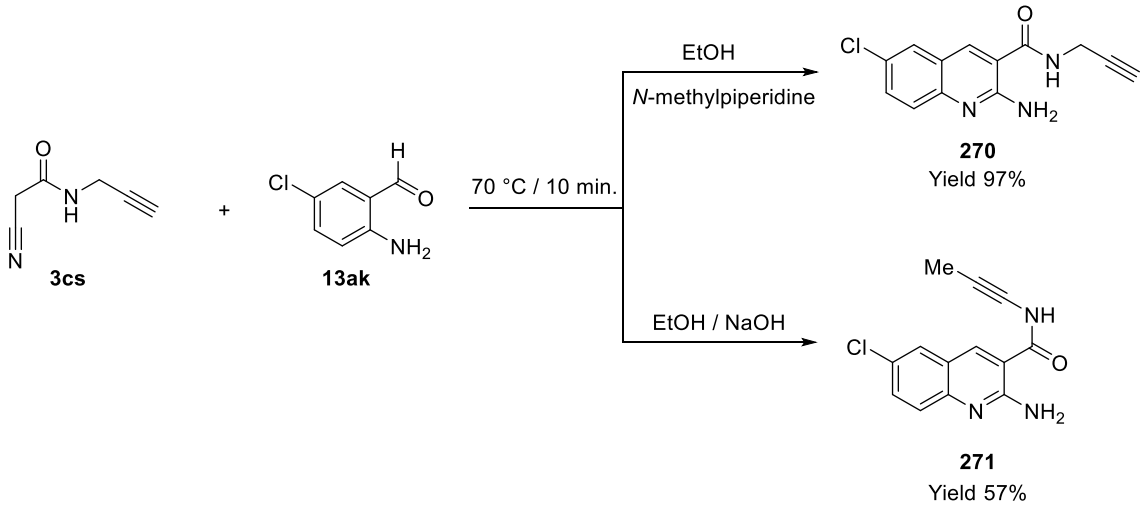
3.2.1.4 Fused [8-5] bsystem. 4,5,6,7,8,9-Hexahydrocycloocta[*b*]thiophene. Treatment of cyclooctanone **268** with 2-cyano-*N*-isopropylacetamide **3bx** and sulfur in presence of amine base provides 2-amino-hexahydrocycloocta[*b*]thiophene **269** (Scheme 117).[130]



3bx **268** **269**
Yield 16%

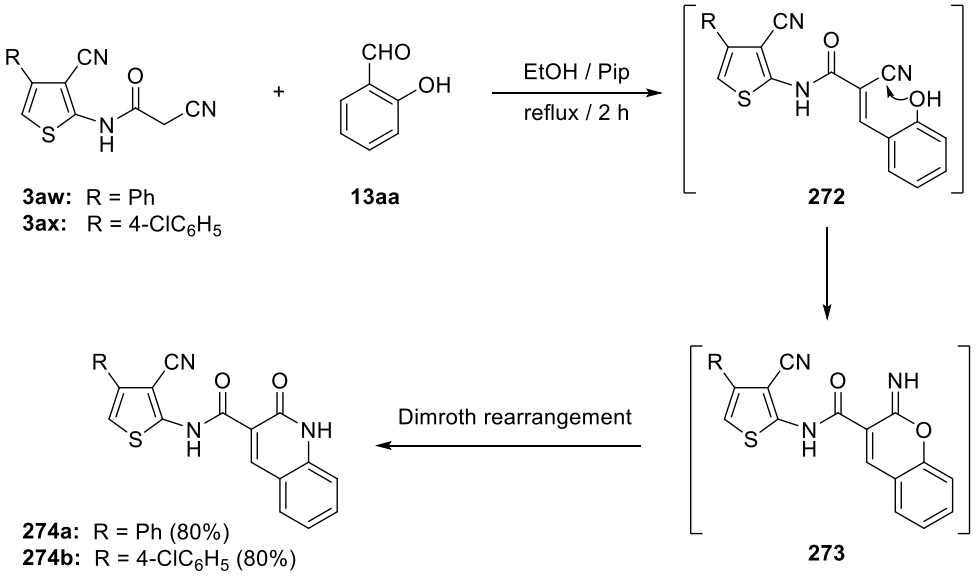
Scheme 117

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]



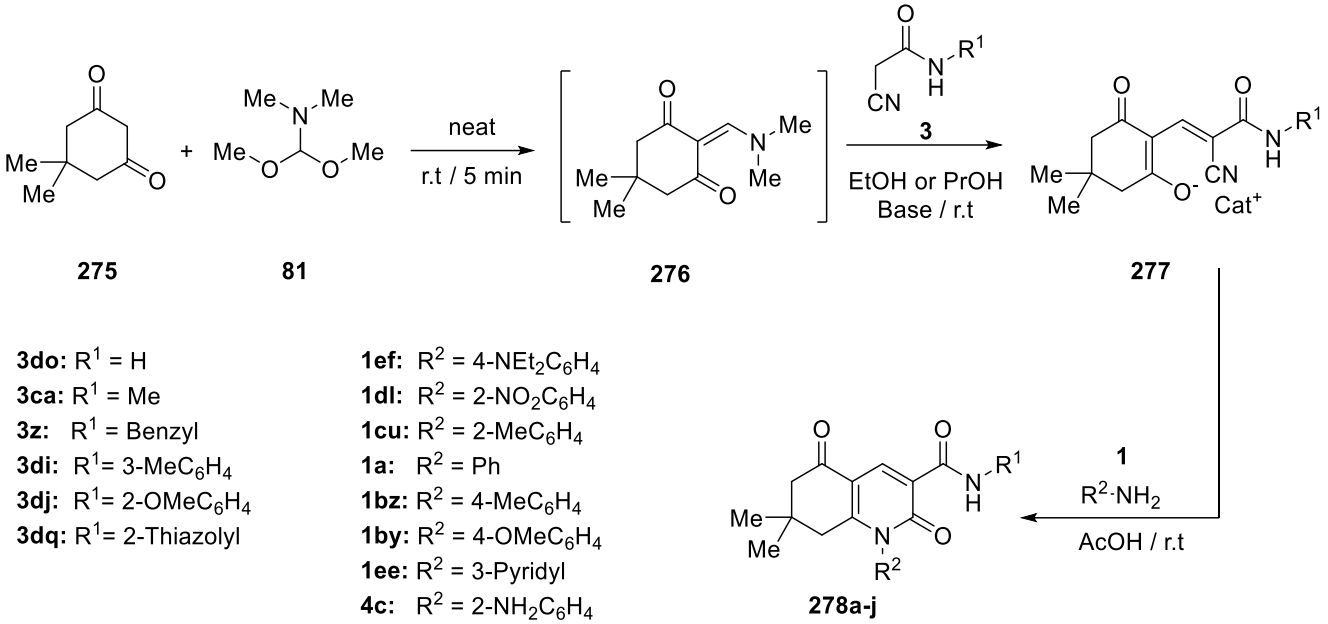
Scheme 118

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 ylidene 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]



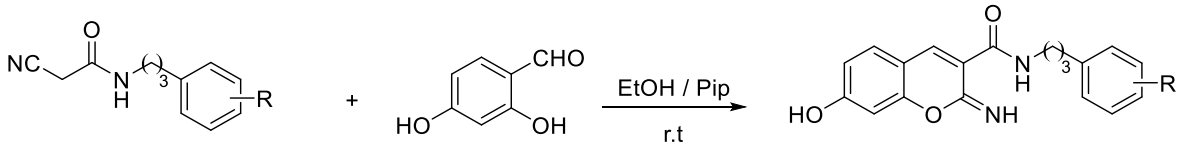
Scheme 120

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

Compound	R^1	Cat^+	Compound	R^1	R^2	Yield (%)
277a	H	Na^+	**278a**	H	4-$NEt_2C_6H_4$	73
277b	H	$(Me)_2NH_2^+$	**278b**	H	2-$NO_2C_6H_4$	60
277c	Me	$(Me)_2NH_2^+$	**278c**	H	2-MeC_6H_4	78
277d	Me	Na^+	**278d**	2-Thiazolyl	Ph	82
277e	Me	$(CH_2)_5NH_2^+$	**278e**	H	Ph	74
277f	$CH_2C_6H_5$	$(CH_2)_5NH_2^+$	**278f**	2-$MeOC_6H_4$	4-MeC_6H_4	74
277g	$CH_2C_6H_5$	Na^+	**278g**	$C_6H_5CH_2$	4-$MeOC_6H_4$	89
277h	3-MeC_6H_4	$(CH_2)_5NH_2^+$	**278h**	Me	4-$MeOC_6H_4$	77
277i	2-$MeOC_6H_4$	$(CH_2)_5NH_2^+$	**278i**	H	2-$NH_2C_6H_4$	66
277j	2-Thiazolyl	$(CH_2)_5NH_2^+$	**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]

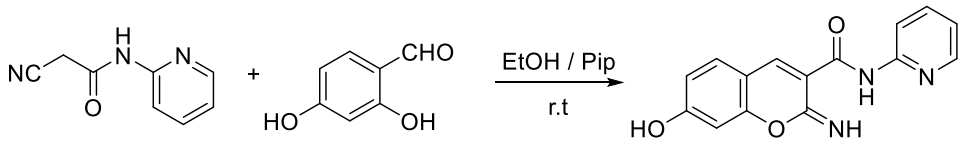


Scheme 121

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

Product	R	Yield (%)	Product	R	Yield (%)
279a	3-OMOM	67	**279f**	4-F	68
279b	3-OH	65	**279g**	3,5-diF	85
279c	2-OMOM	63	**279h**	4-Me	82
279d	4-OMOM	76	**279i**	4-OMe	87
279e	3-F	75			

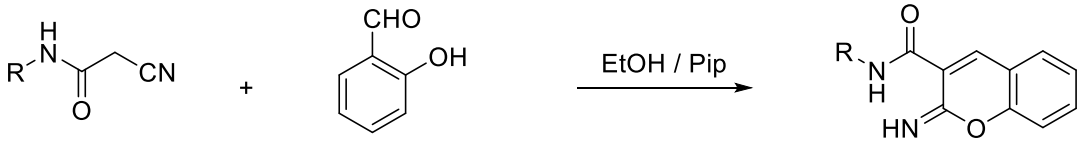
Similarly, the reaction of cyanoacetamide **3ed** with 2,4-dihydroxybenzaldehyde **13al** afforded the 2-iminochromene derivative **280** (Scheme 122).[133]



3ed **13al** **280**
Yield 88%

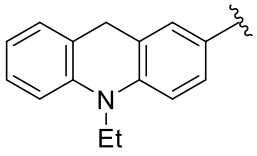
Scheme 122

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]



3 **13aa** **281a,b**

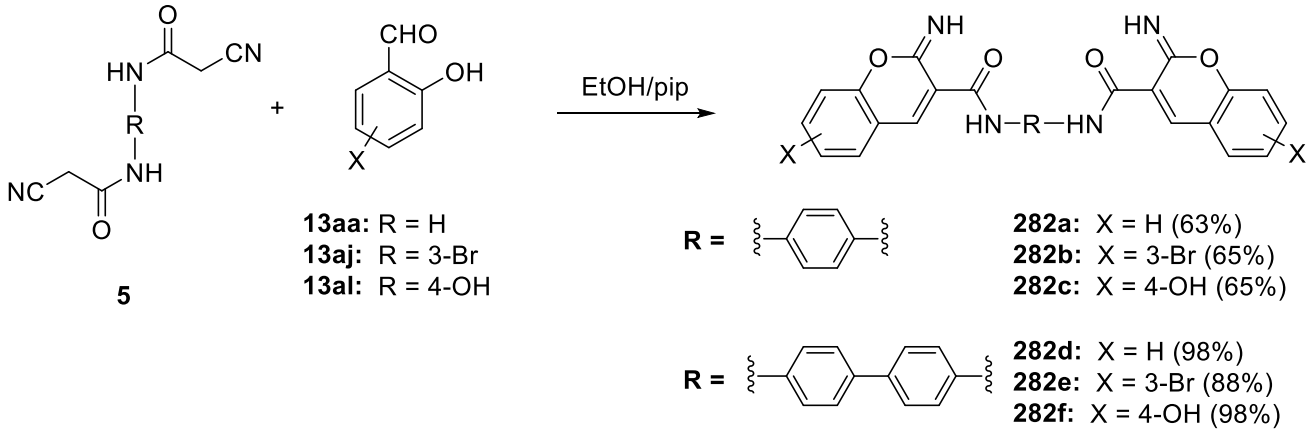
281a: R = $CH_3(CH_2)_{17}$ Yield (73%)

281b: R= 

Yield (91%)

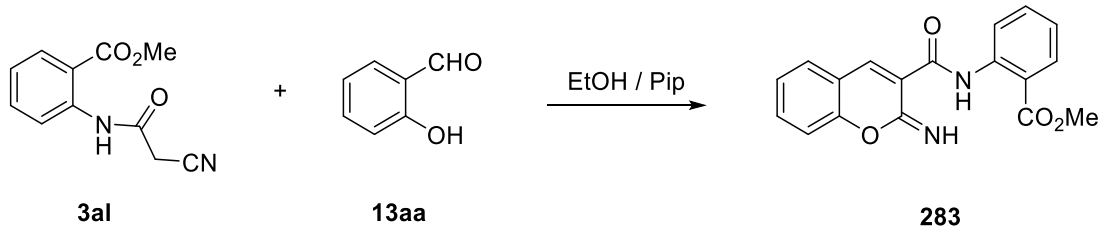
Scheme 123

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]



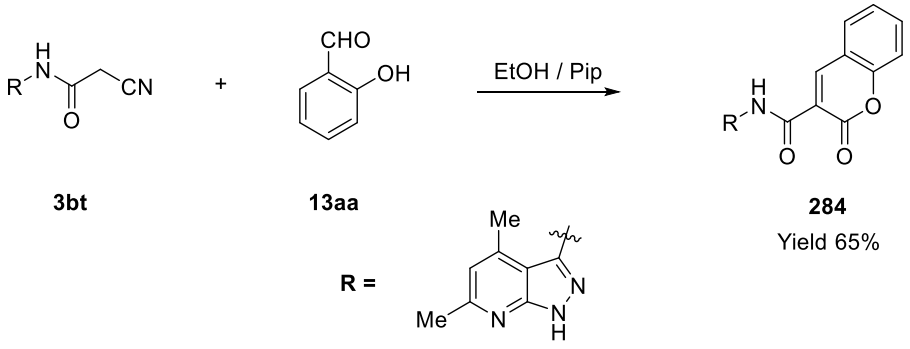
Scheme 124

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



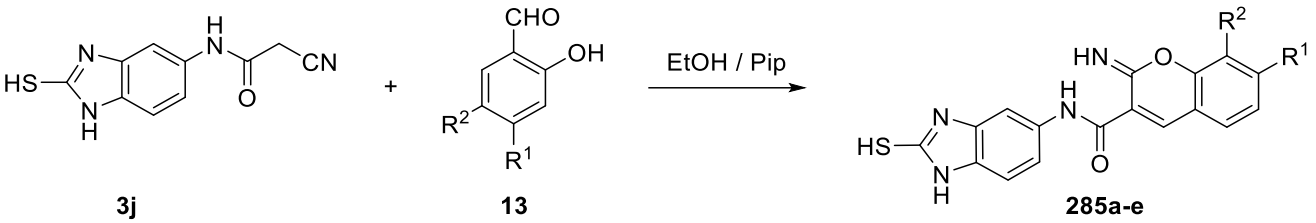
Scheme 125

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]

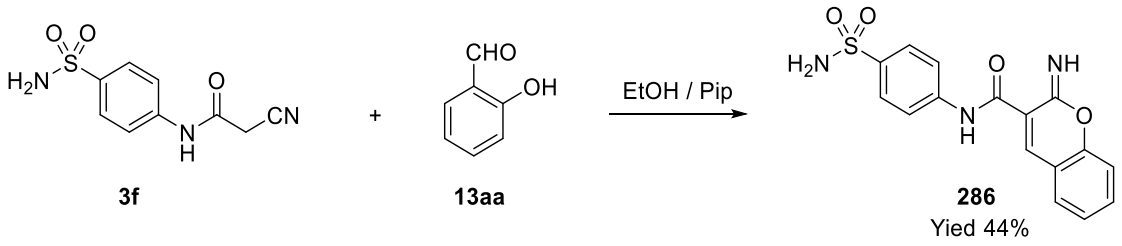


Scheme 127

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

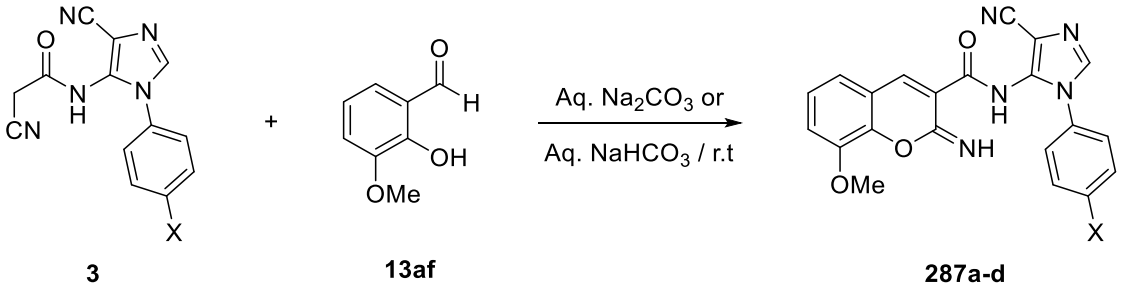
Entry	Product	R^1	R^2	Yield (%)
13aa	**285a**	H	H	79
13ab	**285b**	OCH_3	H	75
13ac	**285c**	Br	H	81
13ad	**285d**	Cl	H	84
13ae	**285e**	Br	Br	75

The cyanoacetamide **3f** was reacted with salicyaldehyde **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]

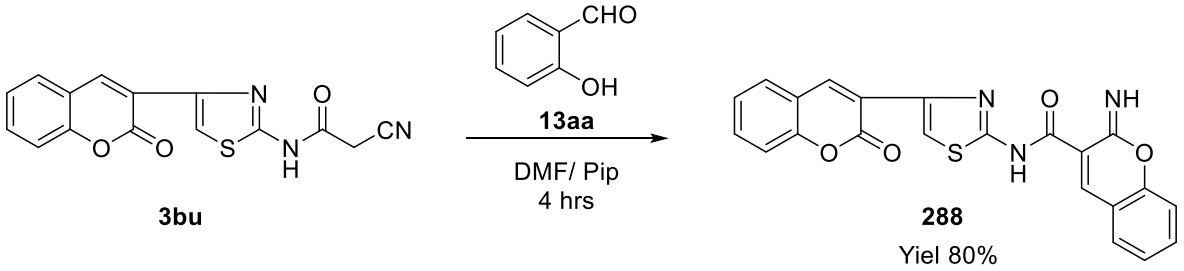


Scheme 129

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

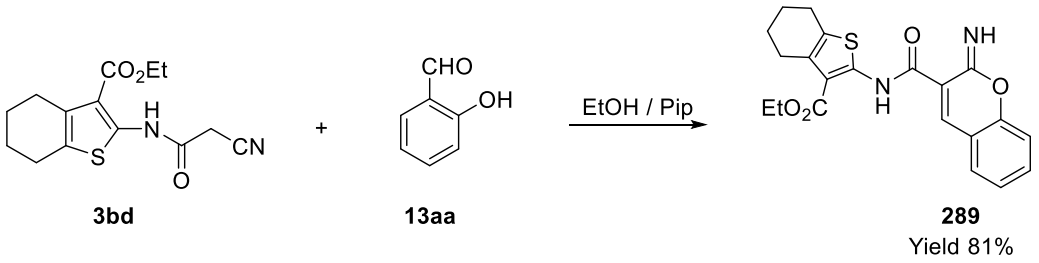
Entry	Product	X	Yield (%)
3em	**287a**	F	94
3en	**287b**	H	94
3eo	**287c**	OCH_3	97
3ep	**287d**	CN	86

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

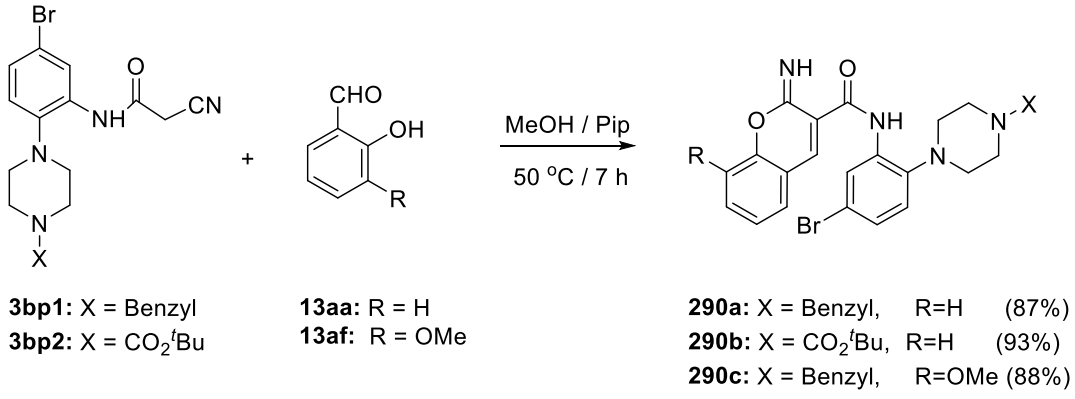


Scheme 130

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



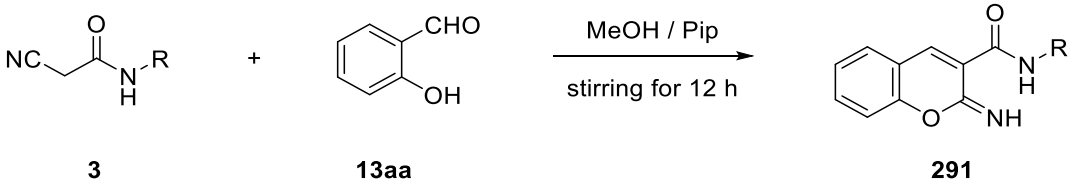
Scheme 131



Scheme 132

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]

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]



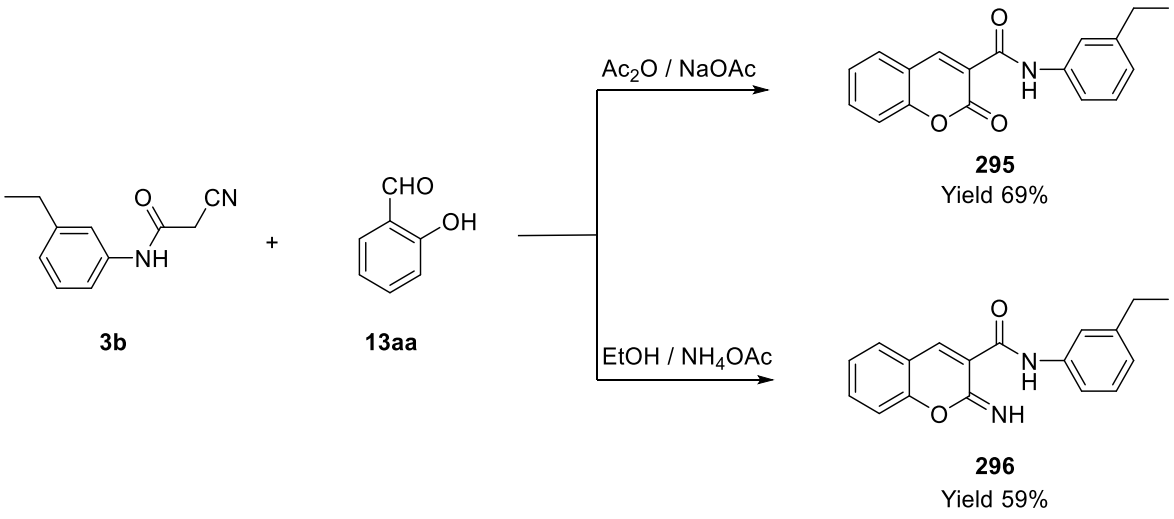
3 **13aa** **291**

Scheme 133

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

Entry	Product	R	Yield (%)
3bj	**291a**	4-$NO_2C_6H_5$	81
3bi	**291b**	4-BrC_6H_5	82
3bk	**291c**	3,4-$Cl_2C_6H_5$	88
3bh	**291d**	3-$NO_2C_6H_5$	85
3bl	**291e**	4-FC_6H_5	76
3bm	**291f**	3-$CF_3C_6H_5$	78
3bn	**291g**	3,4-$MeO_2C_6H_5$	79

The reaction of **3b** with salicyladehyde **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]

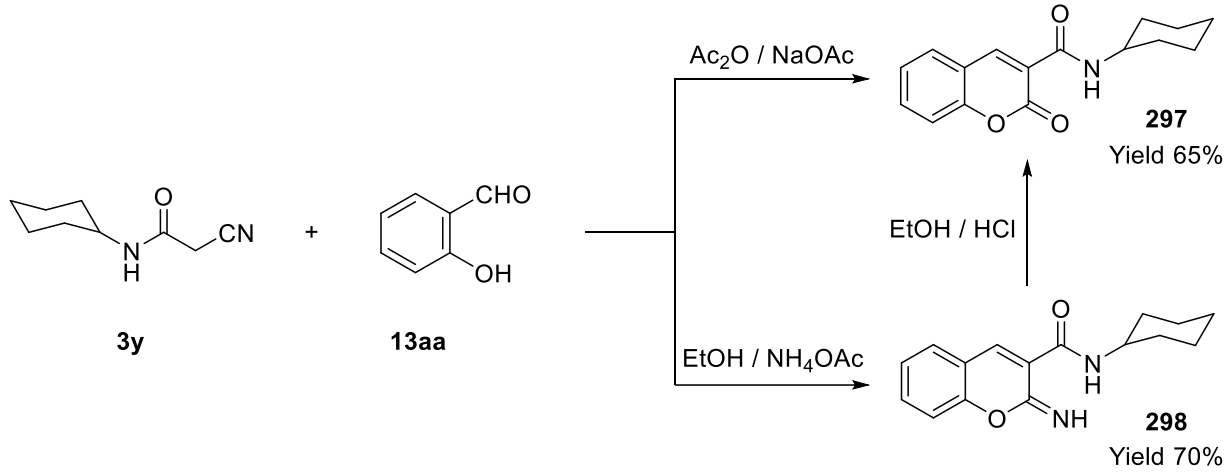


3b **13aa** **295** Yield 69% **296** Yield 59%

Scheme 134

Cyclocondensation of cyanoacetamide derivative **3y** with salicylaldehdye **13aa** in acetic anhydride containing fused sodium acetate at reflux furnished coumanrin derivative **297**. While, heating the reaction

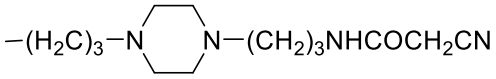
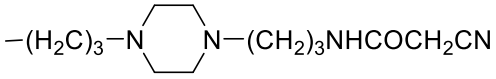
mixture in ethanol containing ammonium acetate at reflux afforded 2-iminocoumarin derivative **298**. Acid hydrolysis of **298** gave readily **297** (Scheme 135).[137]

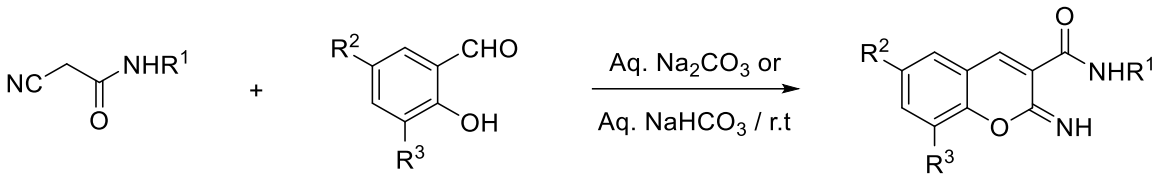


Scheme 135

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]

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

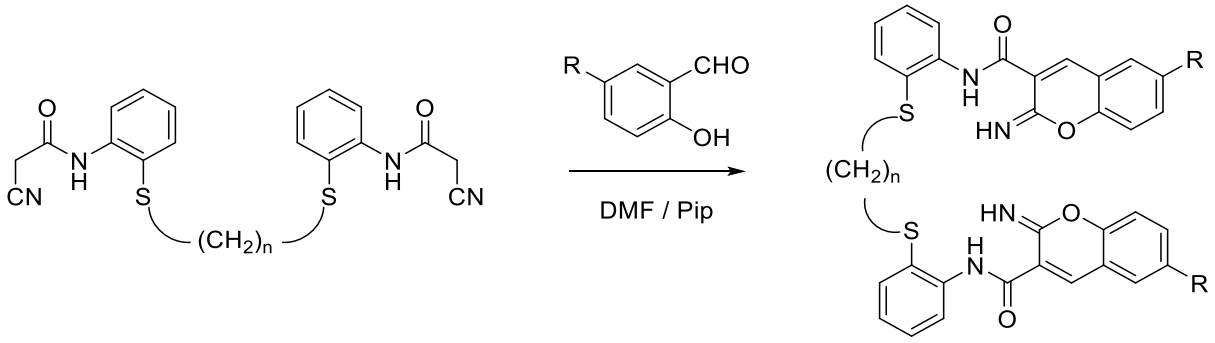
Entry	R^1	Entry	R^3	R^2	Product	Yield (%)
3eq	—$CH_2CH_2OCH_3$	**13ag**	H	MeO	**299a**	100
3er	—CH_2CH_2OH	**13ag**	H	MeO	**299b**	84
3es	—$CH(CH_2CH_3)CH_2OH$	**13ag**	H	MeO	**299c**	87
3et	—$CH_2CH(Ph)OH$	**13ag**	H	MeO	**299d**	81
3eu	—$CH_2CH(OCH_2CH_3)_2$	**13ag**	H	MeO	**299e**	100
3ev		**13ag**	H	MeO	**299f**	100
3ew	—$CH_2CH(OH)CH_2OH$	**13ah**	H	OH	**299g**	not reported
3eq	—$CH_2CH_2OCH_3$	**13aa**	H	H	**299h**	93
3es	—$CH(CH_2CH_3)CH_2OH$	**13aa**	H	H	**299i**	91
3ew	—$CH_2CH(OH)CH_2OH$	**13aa**	H	H	**299j**	not reported
3ev		**13aa**	H	H	**299k**	not reported
3eq	—$CH_2CH_2OCH_3$	**13ai**	Cl	H	**299l**	83
3ew	—$CH_2CH(OH)CH_2OH$	**13ai**	Cl	H	**299m**	not reported
3es	—$CH(CH_2CH_3)CH_2OH$	**13ai**	Cl	H	**299n**	84
3eq	—$CH_2CH_2OCH_3$	**13aj**	Br	H	**299o**	99
3ew	—$CH_2CH(OH)CH_2OH$	**13aj**	Br	H	**299p**	not reported
3et	—$CH_2CH(Ph)OH$	**13aj**	Br	H	**299q**	not reported
3eu	—$CH_2CH(OCH_2CH_3)_2$	**13aj**	Br	H	**299r**	99



3 **13** **299a-r**

Scheme 136

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]



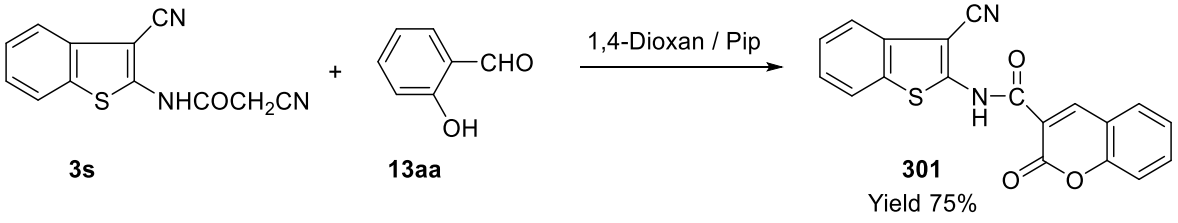
3ex: n = 3
3ey: n = 4

13aa: R = H
13ad: R = Cl

300a: R = H, n = 3 (51%)
300b: R = Cl, n = 3 (45%)
300c: R = H, n = 4 (49%)
300d: R = Cl, n = 4 (45%)

Scheme 137

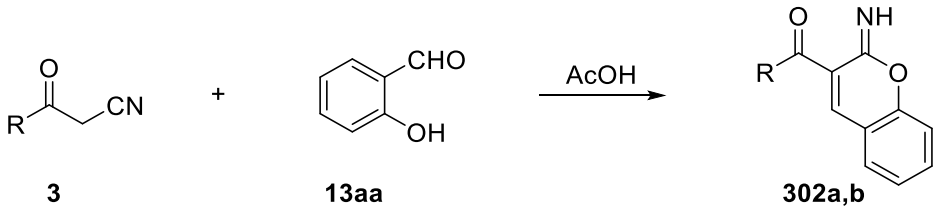
Cyanoacetamide 3s was reacted with salicylaldehyde 13aa to yield the coumarin product 301 (Scheme 138).[25]



3s **13aa** **301**
Yield 75%

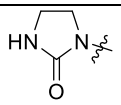
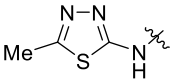
Scheme 138

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]

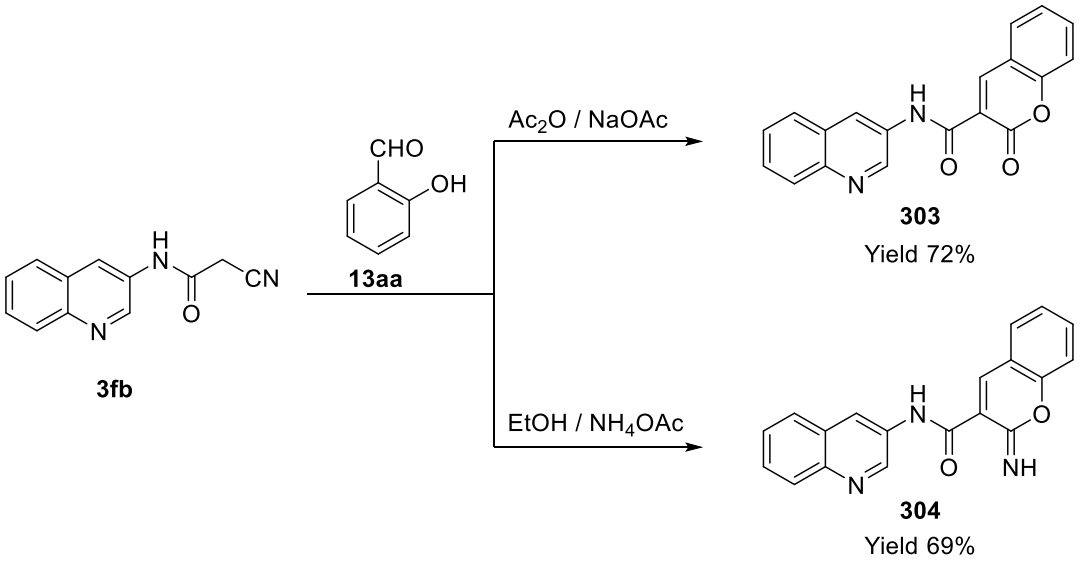


Scheme 139

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

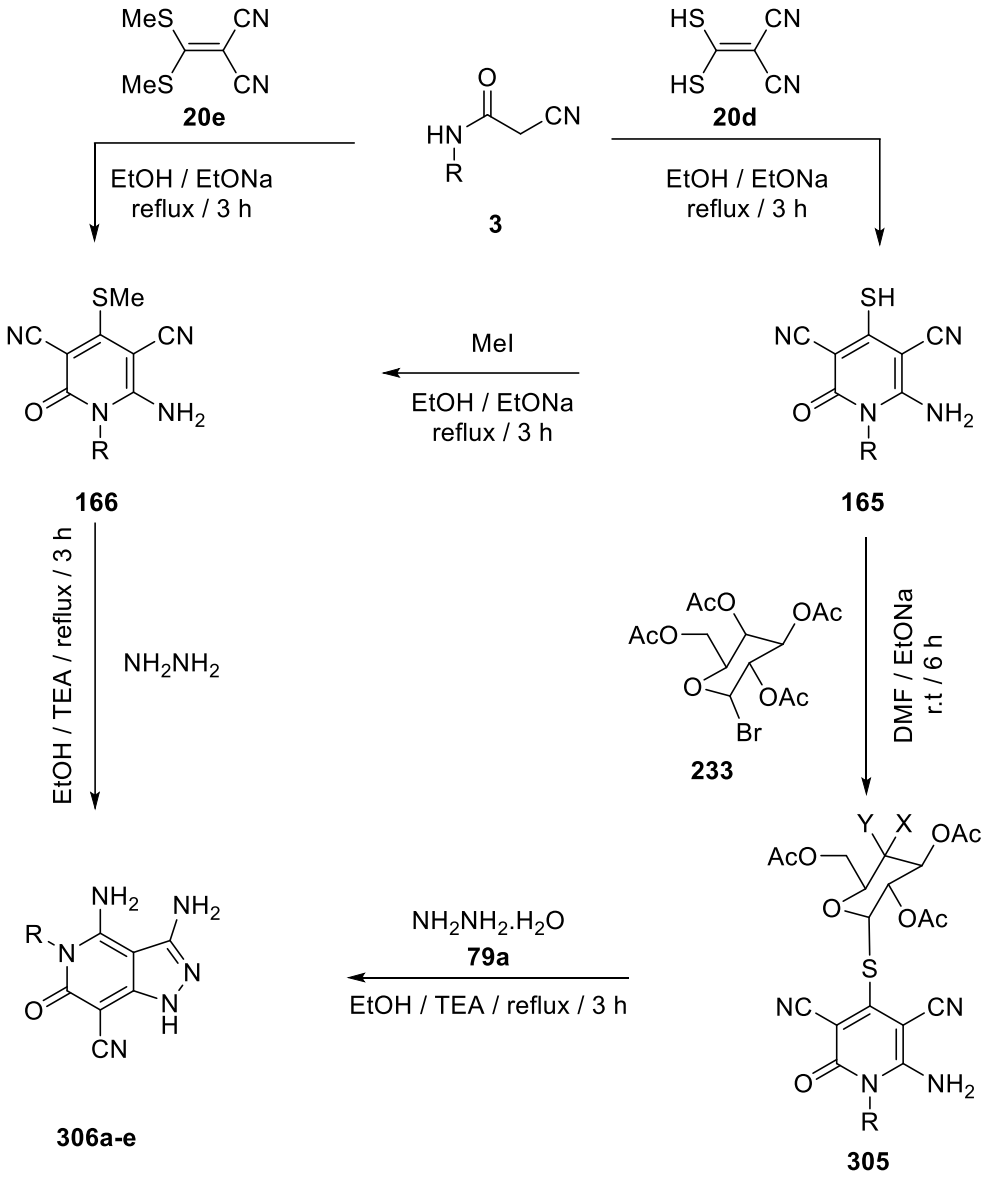
Entry	Product	R	Yield (%)
3ez	**302a**		55
3fa	**302b**		60

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]

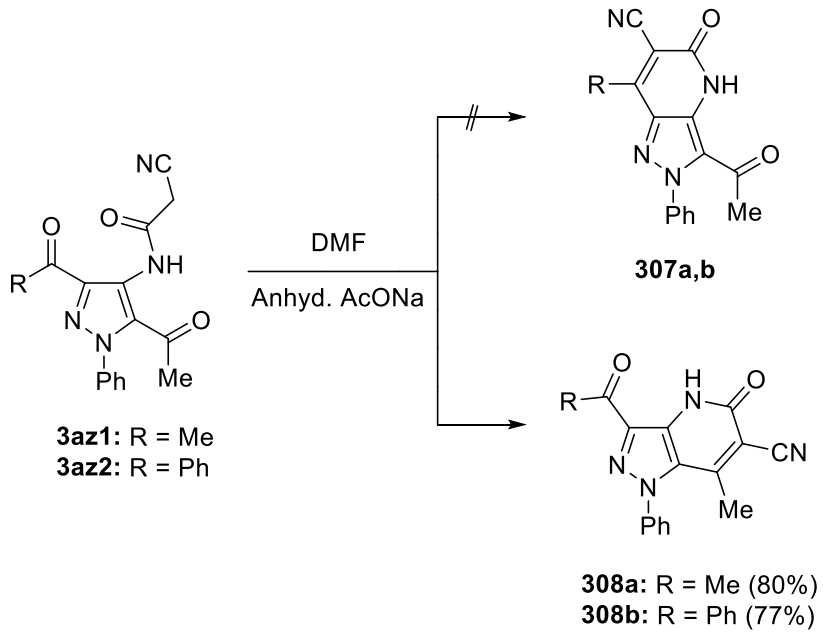


Scheme 141

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

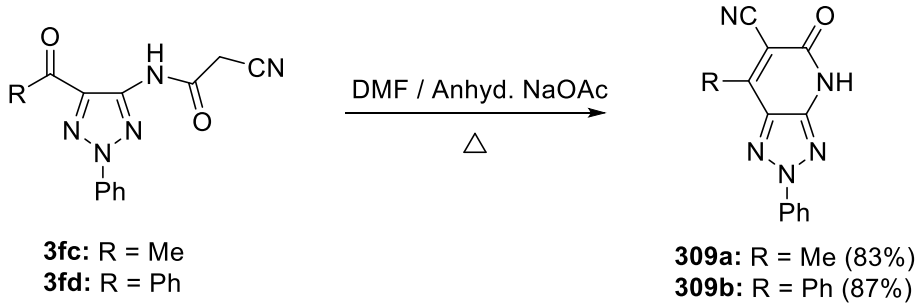
Entry	Product	Ar	Yield (%)
3a	**306a**	Ph	30
3bz	**306b**	4-MeC_6H_4	27
3by	**306c**	4-MeOC_6H_4	31
3co	**306d**	4-ClC_6H_4	30
3cx	**306e**	1-Naphthyl	29

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 ^{13}C-NMR (Scheme 142).[43]



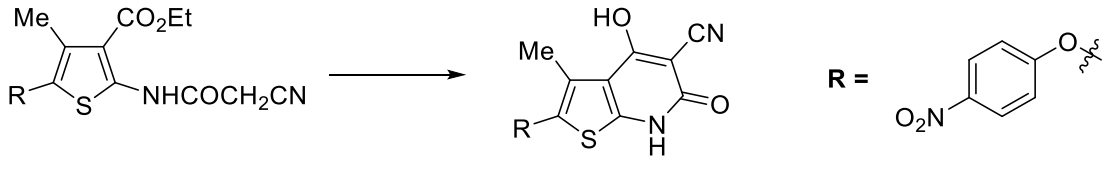
Scheme 142

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

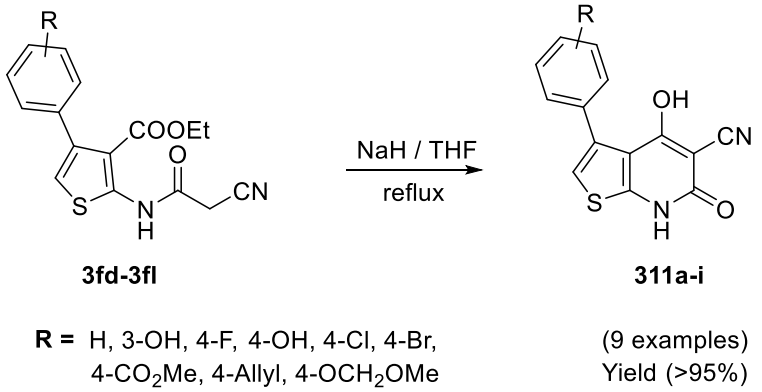
3.2.2.1.3 6,7-Dihydrothieno[2,3-*b*]pyridine. The cyanoacetamide derivative **3u** is cyclized by heating in ethanolic solution of sodium ethoxide at reflux to give thieno[2,3-*b*]pyridine-5-carbonitrile derivative **310** (Scheme 144).[27]



3u **310**
Yield 70%

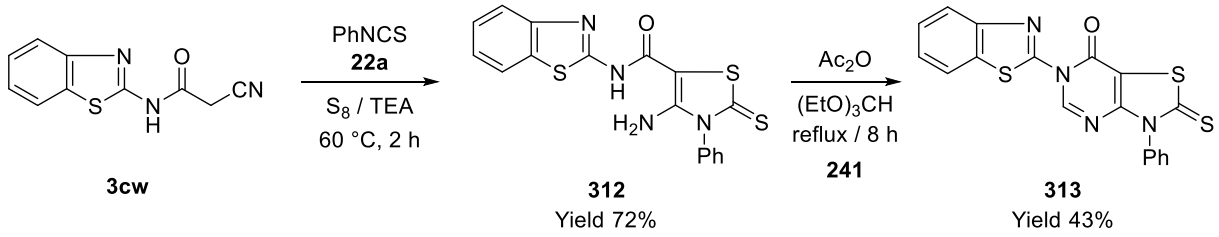
Scheme 144

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).



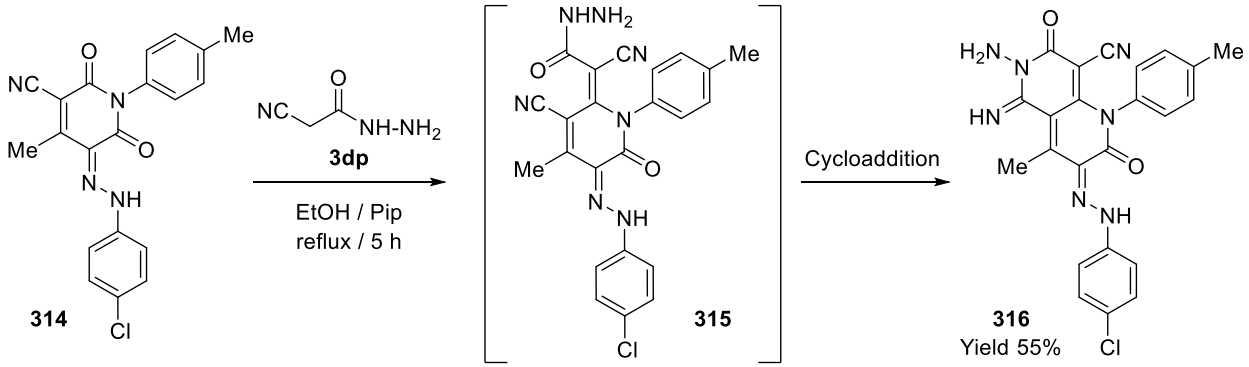
Scheme 145

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]



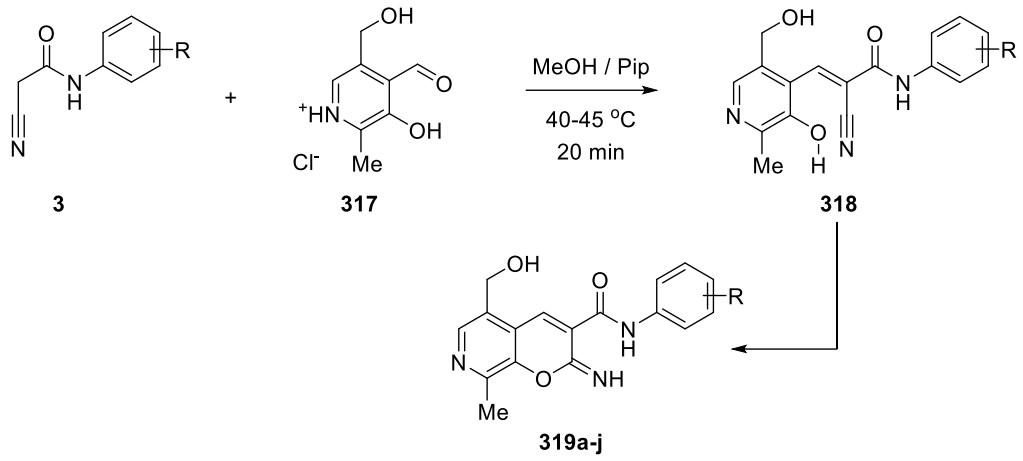
Scheme 146

3.2.2.2 Fused [6-6] system. 3.2.2.2.1. 1,6-Naphthyridine. Cyanoacethydrazide **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*-arylacetamides **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]

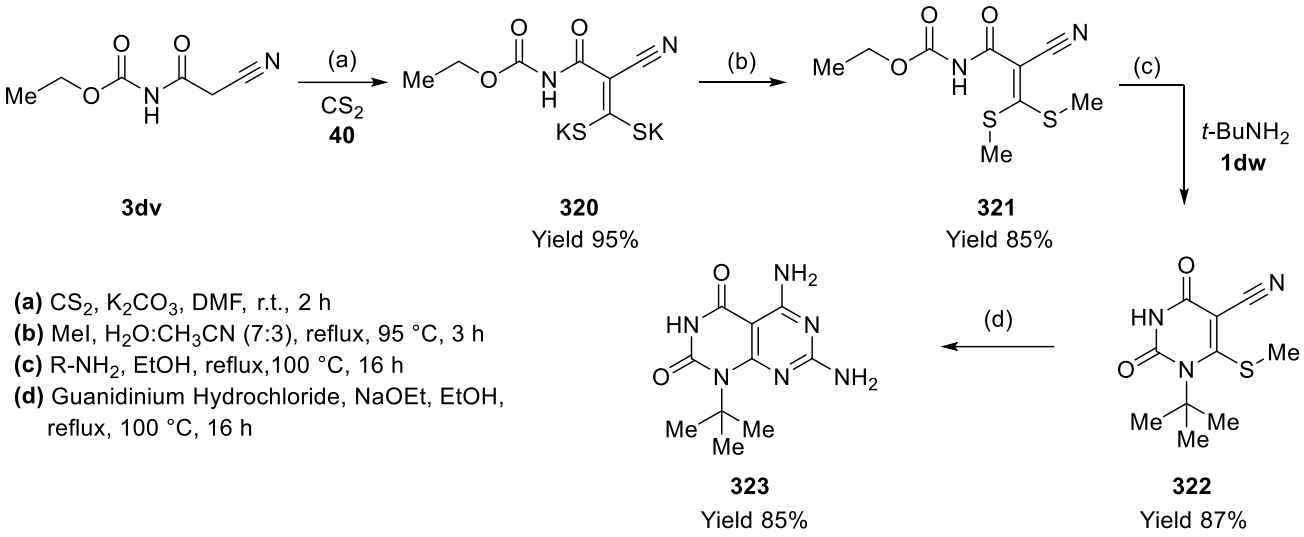


Scheme 148

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

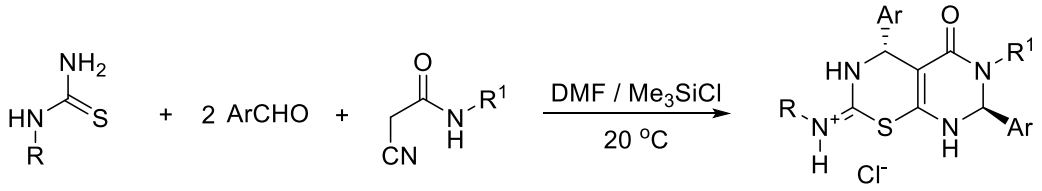
Entry	Product	R	Yield (%)
3a	**319a**	H	56-88%
3cu	**319b**	2-Me	
3di	**319c**	3-Me	
3bz	**319d**	4-Me	
3dk	**319e**	2-Et	
3dr	**319f**	4-Et	
3by	**319g**	4-OMe	
3ek	**319h**	2,4-di-OMe	
3el	**319i**	3,5-di-OMe	
3cq	**319j**	2-F	

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]

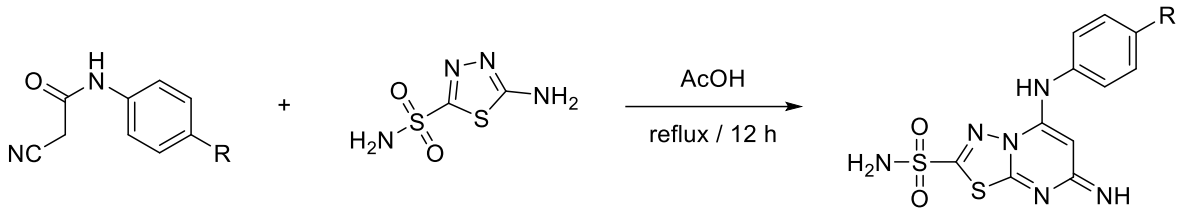


Scheme 150

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_6H_4	**13w**	4-ClC_6H_4	**324g**	92
237d	Ph	**3co**	4-ClC_6H_4	**13x**	4-$MeOC_6H_4$	**324h**	86
237e	$(CH_2)_2MeO$	**3fm**	$(CH_2)_2MeO$	**13k**	Ph	**324i**	72
237f	CH_2THF	**3fm**	$(CH_2)_2MeO$	**13k**	Ph	**324j**	59
237g	$(CH_2)_2OEt$	**3fn**	$(CH_2)_2OEt$	**13k**	Ph	**324k**	64
237g	$(CH_2)_2OEt$	**3fn**	$(CH_2)_2OEt$	**13k**	Ph	**324l**	59
237f	CH_2THF	**3fn**	$(CH_2)_2OEt$	**13k**	Ph	**324m**	56

3.2.3 Two heterocycles with one hetero atom as bridgehead. 3.2.3.1 Fused [5-6] system. 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 Shaaban[146] to give [1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives **325a,b** (Scheme 151).



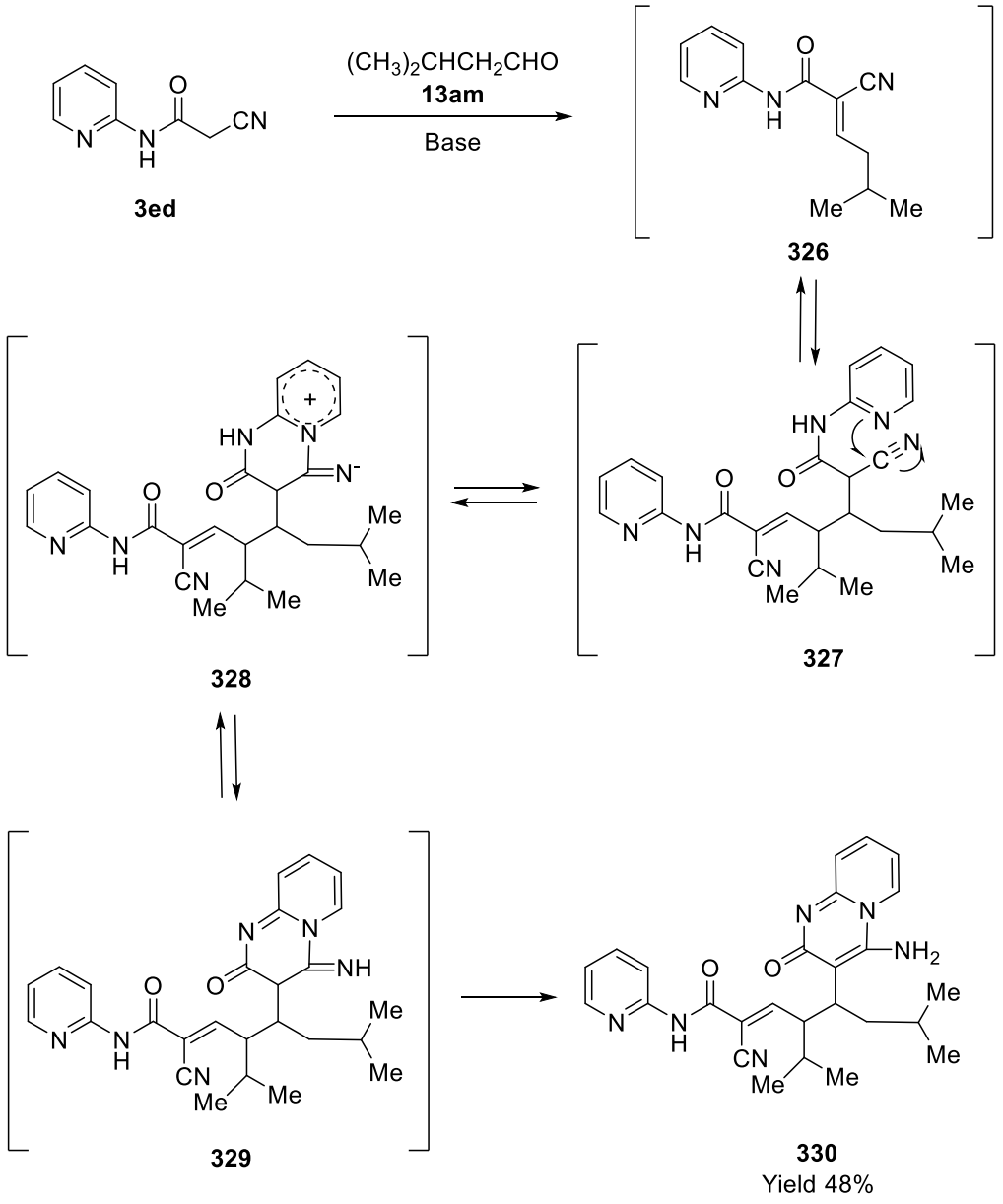
3bi: R = Br
3bz: R = Me

1fo

325a: R = Br (70%)
325b: R = Me (65%)

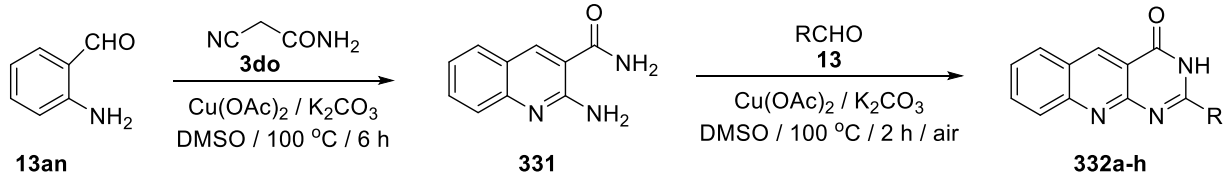
Scheme 151

3.2.3.2 Fused [6-6] system. 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 $Cu(OAc)_2$ 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]

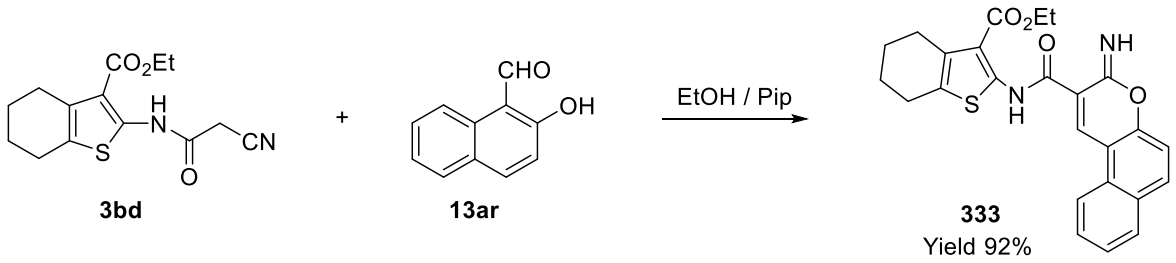


Scheme 153

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

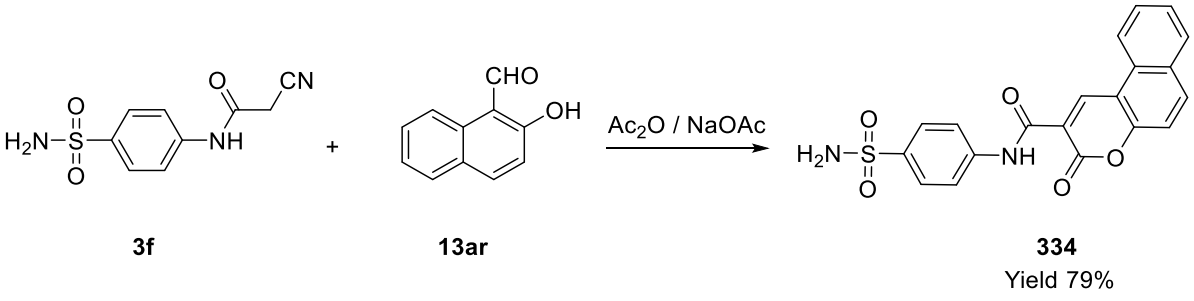
Entry	Product	R	Yield (%)
13ao	**332a**	C_3H_7	44
13k	**332b**	Ph	46
13ap	**332c**	2-MeC_6H_5	55
13o	**332d**	4-MeC_6H_5	46
13l	**332e**	4-$MeOC_6H_5$	54
13w	**332f**	4-ClC_6H_5	45
13y	**332g**	3-ClC_6H_5	44
13aq	**332h**	2-FC_6H_5	60

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]



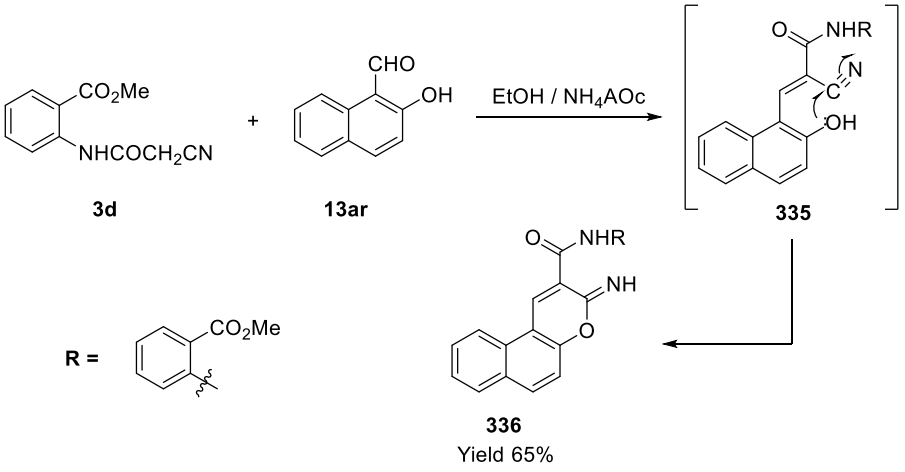
Scheme 154

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]



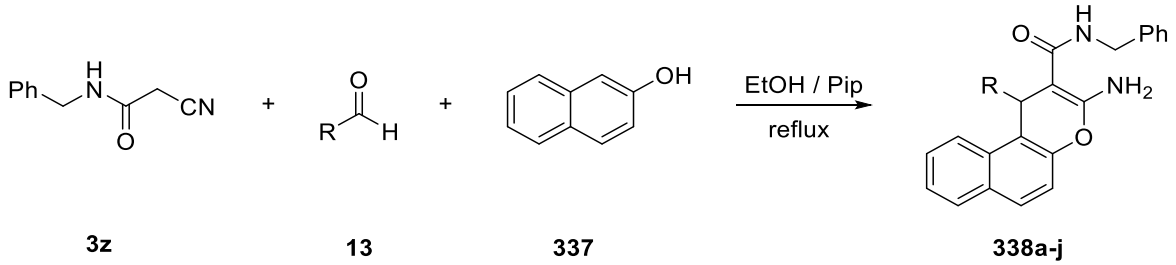
Scheme 155

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]



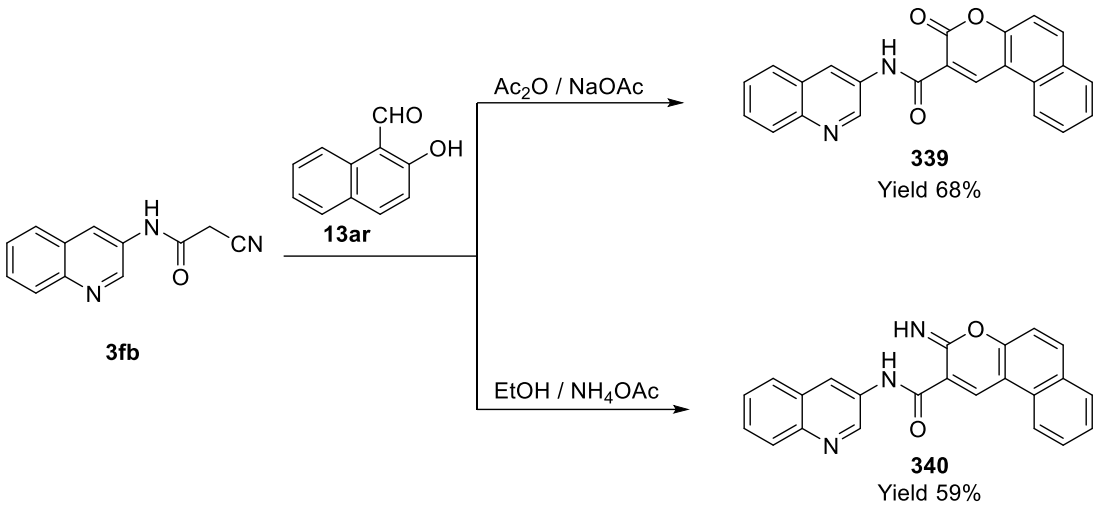
Scheme 157

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

Entry	Product	R	Yield (%)	Entry	Product	R	Yield (%)
13k	**338a**	Ph	75	**13o**	**338f**	4-MeC_6H_4	60
13w	**338b**	4-ClC_6H_4	70	**13x**	**338g**	4-$MeOC_6H_4$	68
13z	**338c**	4-BrC_6H_4	70	**13as**	**338h**	2,4-$Cl_2C_6H_4$	78
13m	**338d**	4-$NO_2C_6H_4$	80	**13r**	**338i**	3-$MeOC_6H_4$	65
13p	**338e**	3-$NO_2C_6H_4$	75	**13i**	**338j**	4-OHC_6H_4	70

3.2.4.1.2.2 Synthesis *via* Perkin reaction

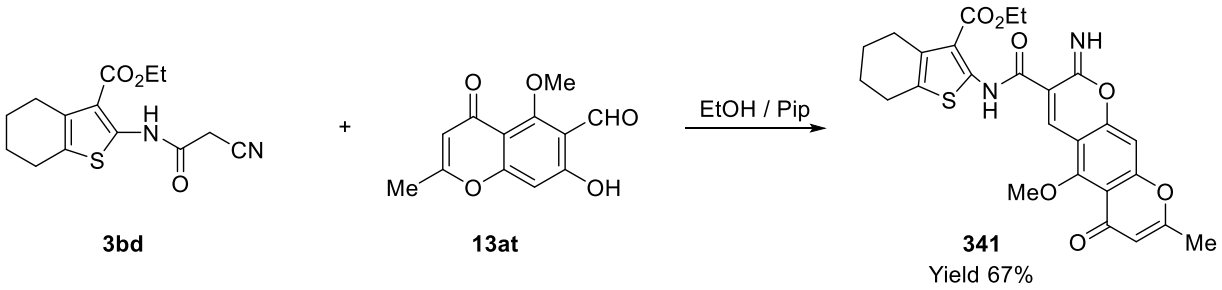
The reaction of 2-hydroxy-1-naphthaldehyde **13ar** with cyanoacetamide **3fb** in acetic anhydride containing sodium acetate gave the benzochromene-2-one **339**. However, performing the same reaction in ethanol containing ammonium acetate afforded 2-iminobenzochromene **340** (Scheme 158).[140]



Scheme 158

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

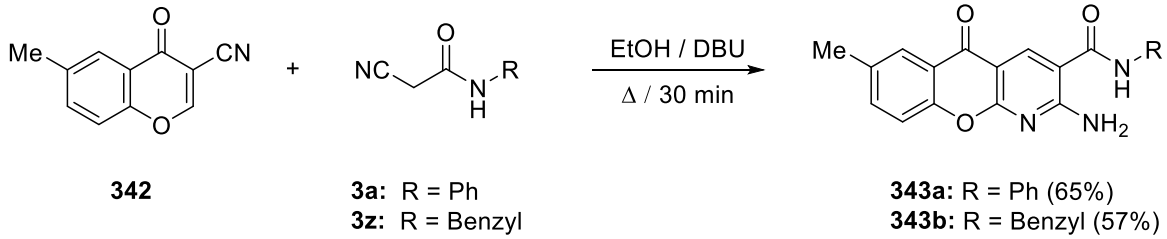
The reaction of **3bd** with chromene-6-carbaldehyde derivative **13at** in ethanol containing piperidine afforded pyrano[3,2-*g*]chromene-3-carboxamide derivative **341** (Scheme 159).[48]



Scheme 159

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

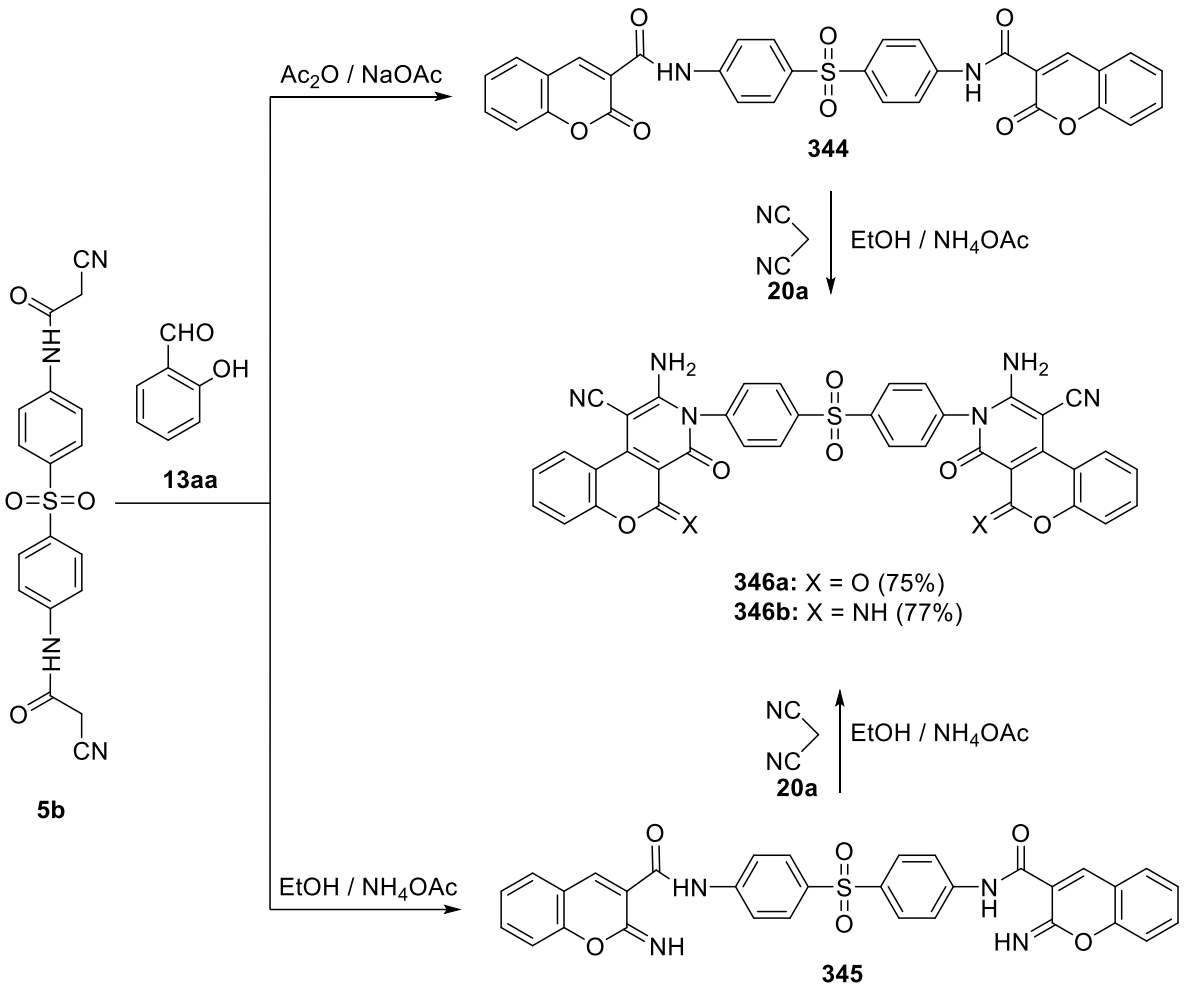
The reaction of nitrile **342** with cyanoacetamide derivatives **3a** and **3z** furnished 2-aminochromeno[2,3-*b*]pyridine-3-carboxamide derivatives **343** in moderate yields (Scheme 160). [150]



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

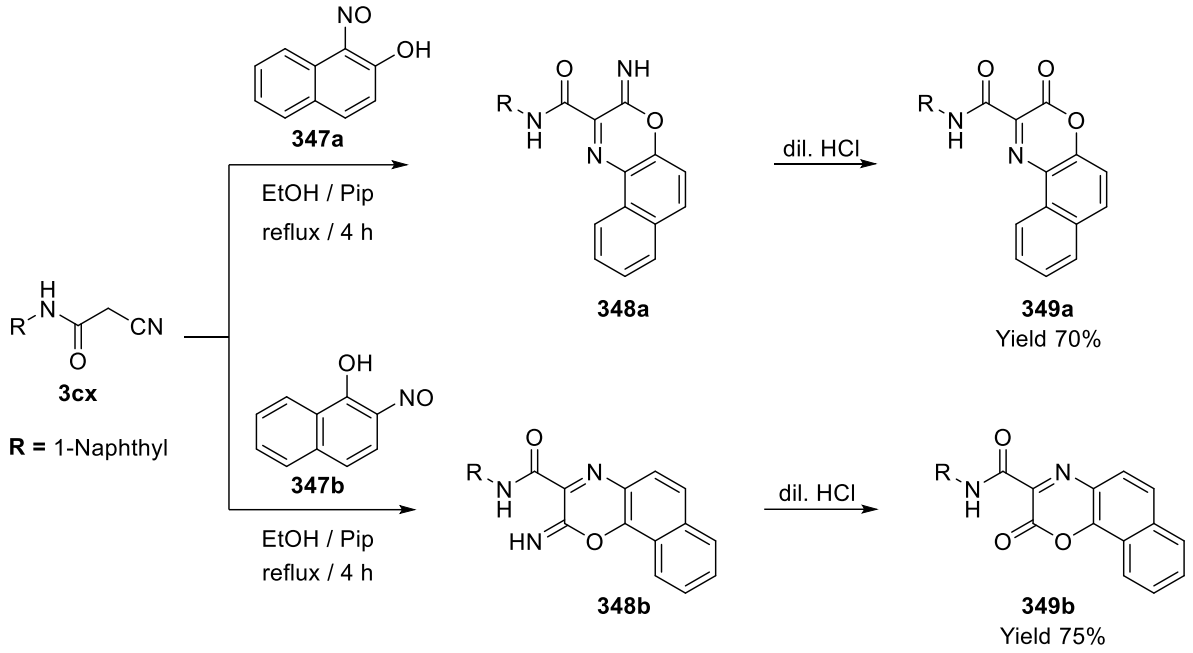
presence of ammonium acetate afforded 2-iminochromene derivative **345**. Reacting either of **344** or **345** with malononitrile in ethanol containing ammonium acetate gave the corresponding bis(4*H*-chromeno[3,4-*c*]pyridines), **346a,b** (Scheme 161). [34]



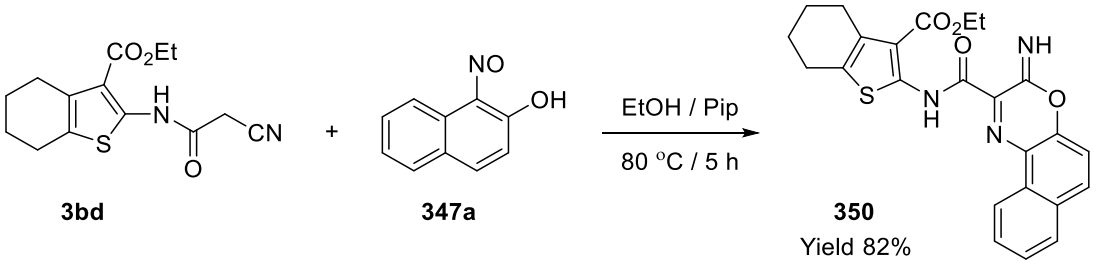
Scheme 161

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]

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

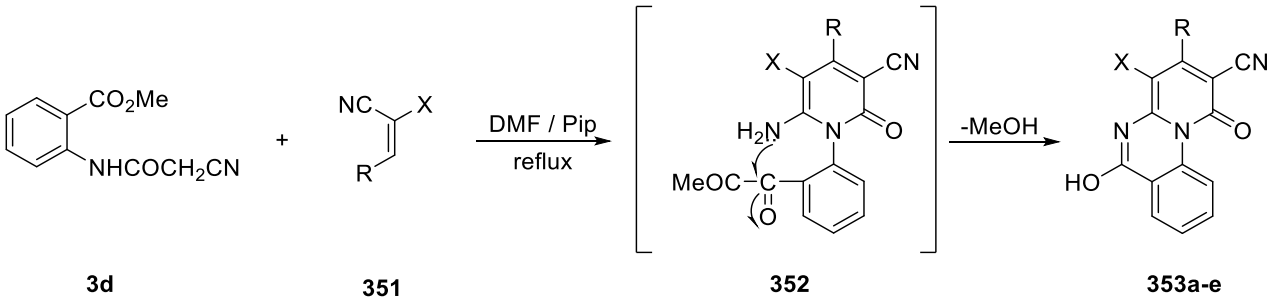


Scheme 162



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 cinnamonitriles **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]

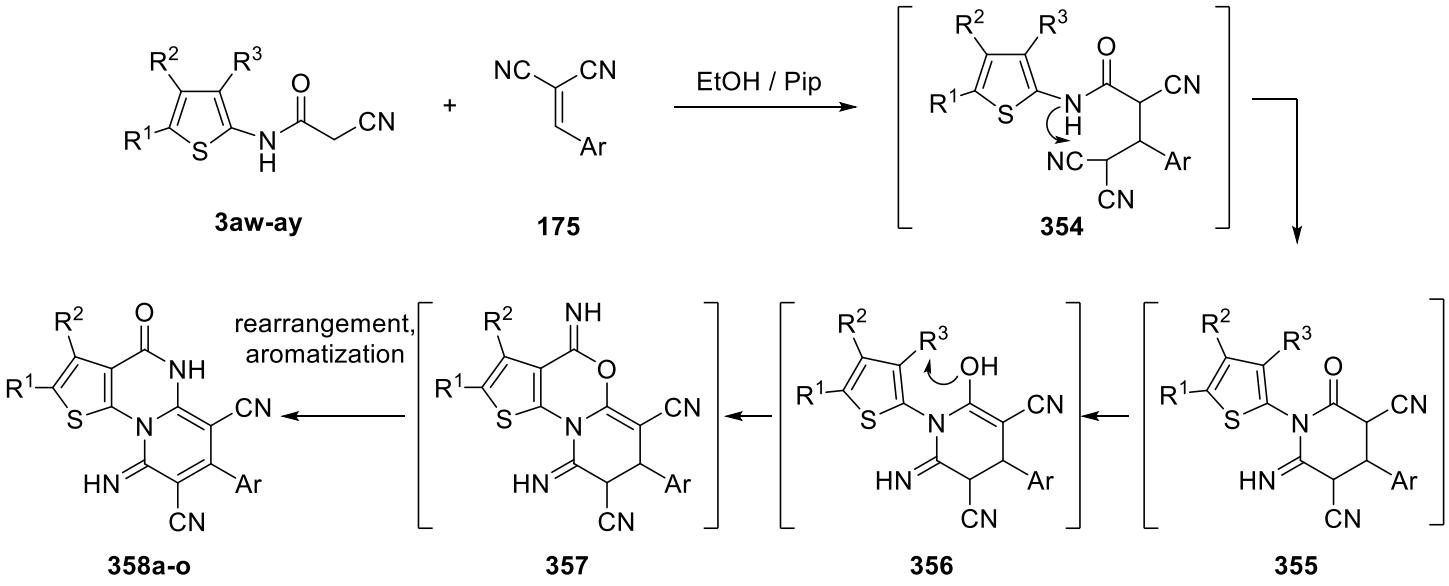


Scheme 164

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

Entry	Product	R	X	Yield (%)
351a	**353a**	2,4-$Cl_2C_6H_3$	$CONH_2$	71
351b	**353b**	2-ClC_6H_3	$CONH_2$	63
351c	**353c**	4-$N(Me)_2C_6H_4$	$CONH_2$	65
351d	**353d**	2-ClC_6H_3	CO_2Et	51
351e	**353e**	4-$N(Me)_2C_6H_4$	CO_2Et	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 ethanol[42] or pyridine[4] 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

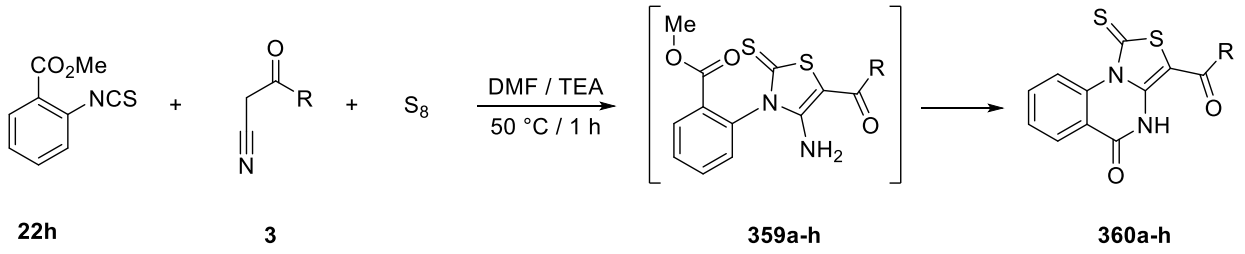
Table 58. Synthesis and % yields of **358a-o**

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_6H_4	**358b**	91
3aw	H	Ph	CN	**175d**	4-$MeOC_6H_4$	**358c**	88
3aw	H	Ph	CN	**175e**	4-$NO_2C_6H_4$	**358d**	84
3aw	H	Ph	CN	**175g**	4-ClC_6H_4	**358e**	90
3aw	H	Ph	CN	**175h**	C_4H_3S	**358f**	81
3ax	H	4-ClC_6H_4	CN	**175c**	Ph	**358g**	89
3ax	H	4-ClC_6H_4	CN	**175f**	4-MeC_6H_4	**358h**	85
3ax	H	4-ClC_6H_4	CN	**175d**	4-$MeOC_6H_4$	**358i**	89
3ax	H	4-ClC_6H_4	CN	**175e**	4-$NO_2C_6H_4$	**358j**	86
3ax	H	4-ClC_6H_4	CN	**175g**	4-ClC_6H_4	**358k**	88

Table 58. Continued

Entry	R^1	R^2	R^3	Entry	Ar	Product	Yield (%)
3ax	H	4-ClC_6H_4	CN	**175h**	C_4H_3S	**358l**	85
3ay	Me	CO_2Et	CN	**175c**	Ph	**358m**	90
3ay	Me	CO_2Et	CN	**175f**	4-MeC_6H_4	**358n**	81
3ay	Me	CO_2Et	CN	**175g**	4-ClC_6H_4	**358o**	85
3fp	CO_2Et	Me	CO_2Et	**175c**	Ph	**358p**	81
3fq	CO_2Et	Me	CO_2Et	**175f**	4-MeC_6H_4	**358q**	76
3fr	CO_2Et	Me	CO_2Et	**175d**	4-$MeOC_6H_4$	**358r**	77
3fs	CO_2Et	Me	CO_2Et	**175e**	4-$NO_2C_6H_4$	**358s**	72
3ft	CO_2Et	Me	CO_2Et	**175g**	4-ClC_6H_4	**358t**	85
3fu	CO_2Et	Me	CO_2Et	**175k**	4-$CH(CH_3)_2C_6H_4$	**358u**	87
3fv	CO_2Et	Me	CO_2Et	**175l**	3,4-$OCH_2OC_6H_4$	**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]



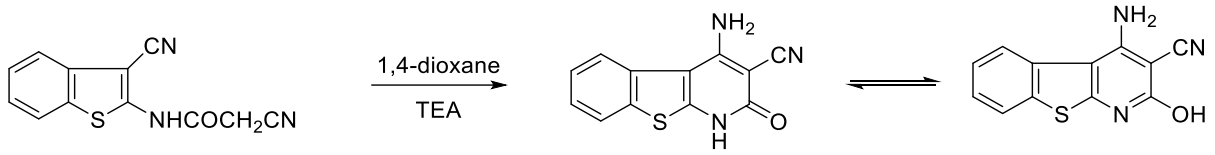
Scheme 166

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_6H_4	67
3cd	**360d**	NH-n-C_5H_{11}	77
3cq	**360e**	NH(2-F)C_6H_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. Synthesis *via* Michael addition reactions

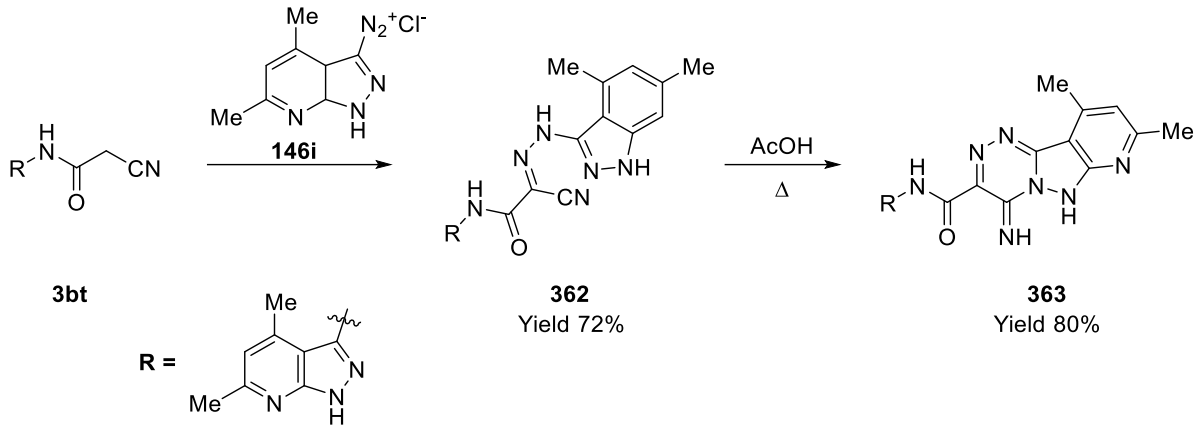
Heating compound **3s** in 1,4-dioxane containing triethylamine affected cyclization into the tetrahydrobenzo[4,5]thieno[2,3-*b*]pyridine derivative **361** (Scheme 167).[25]



3s **361**
Yield 65%

Scheme 167

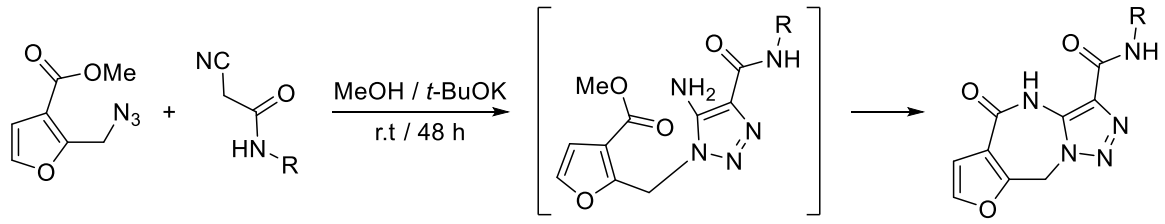
3.2.4.3.2 Pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine. Synthesis *via* coupling reactions. Coupling of **3bt** with 4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-diazonium chloride **146i** in pyridine at 0-5 °C furnished the hydrazono compound **362**. When compound **362** is boiled in acetic acid, it was cyclized into **363**. (Scheme 168).[59]



3bt **362**
Yield 72%
363
Yield 80%

Scheme 168

3.2.4.4 Fused [5-7-5] system. 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).



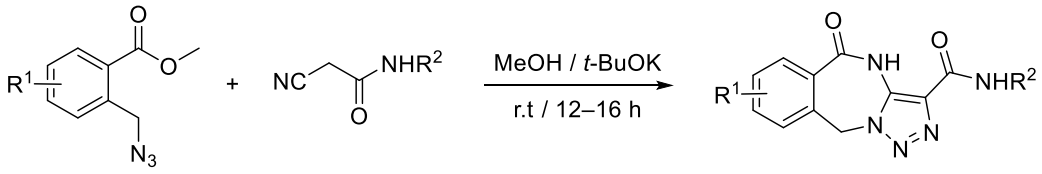
364 **3** **365a-d** **366a-d**

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-$MeOC_6H_4$	79

3.2.4.5 Fused [5-7-6] system. 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]



367a: R^1 = H
367b: R^1 = 3-Br
367c: R^1 = 5-Br

3

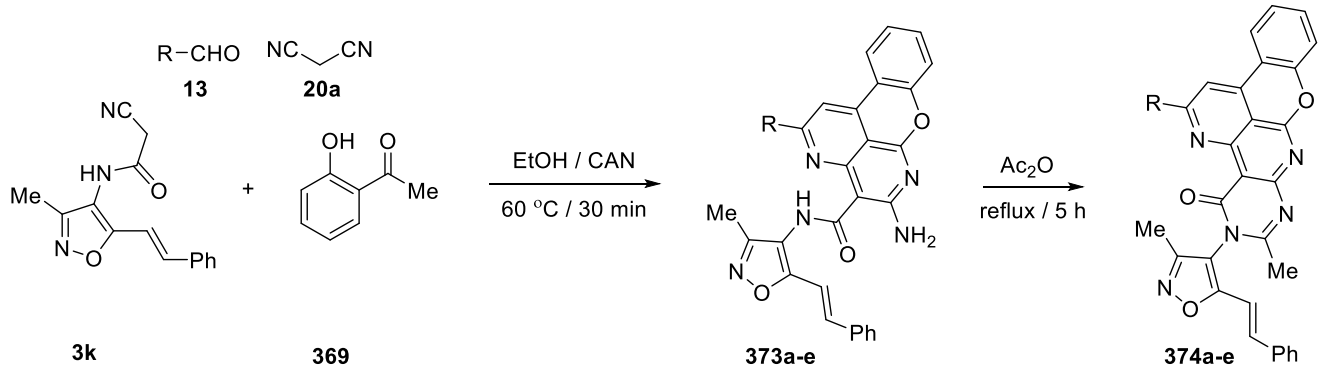
368a-j

Scheme 170

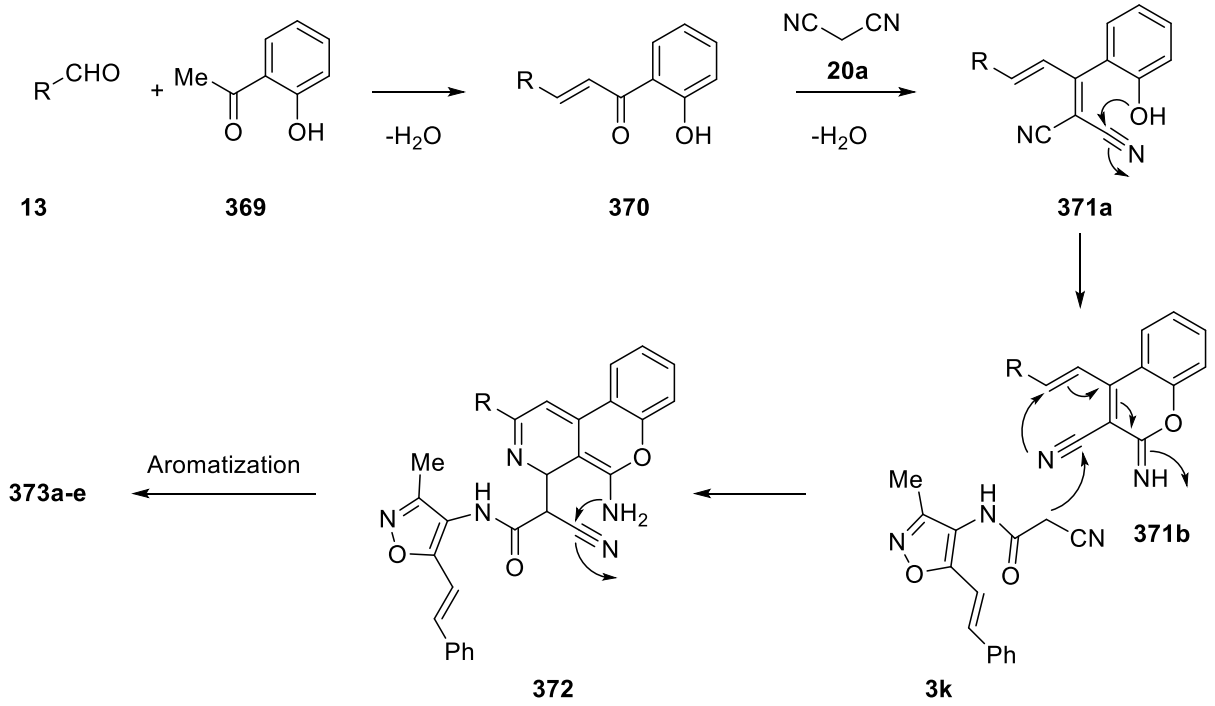
Table 61. Synthesis and % yields of **368a-j**

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_6H_4	**368e**	48
367a	H	**3by**	4-$MeOC_6H_4$	**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-$MeOC_6H_4$	**368j**	48

3.2.5 Four and Five fused heterocycles. 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]napthyridines **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

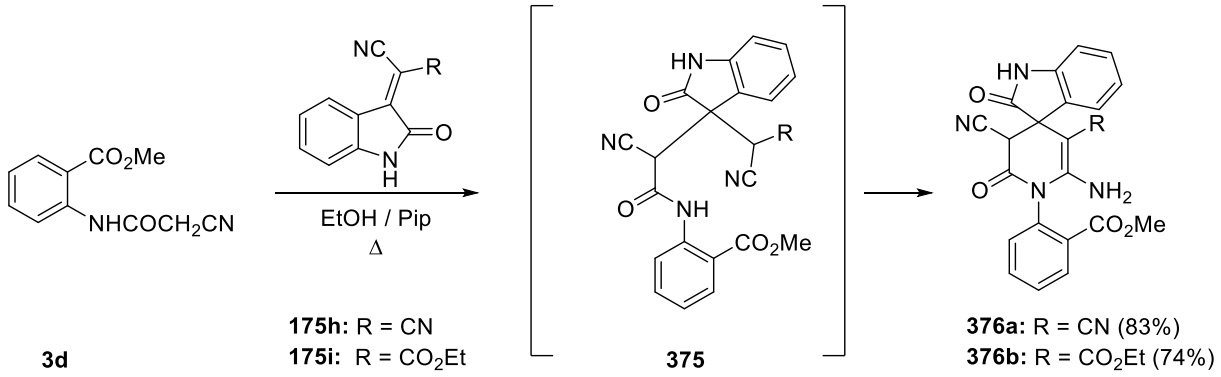


Scheme 172

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

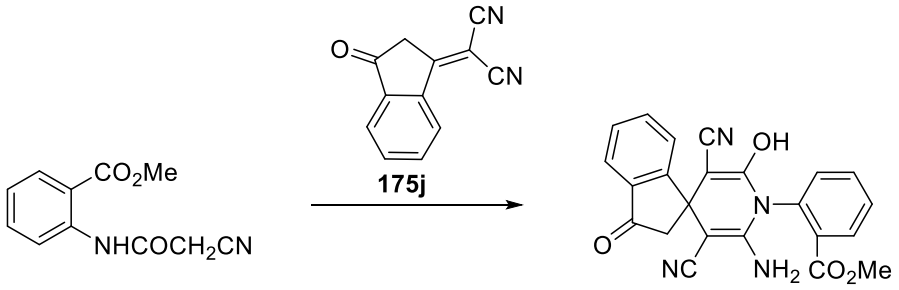
Entry	R	Product	Yield (%)	Product	Yield (%)
13k	Ph	**373a**	60	**374a**	61
13t	2-ClC_6H_4	**373b**	66	**374b**	65
13au	2-BrC_6H_4	**373c**	67	**374c**	68
13o	4-MeC_6H_4	**373d**	61	**374d**	61
13av	2-$MeOC_6H_4$	**373e**	59	**374e**	63

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]



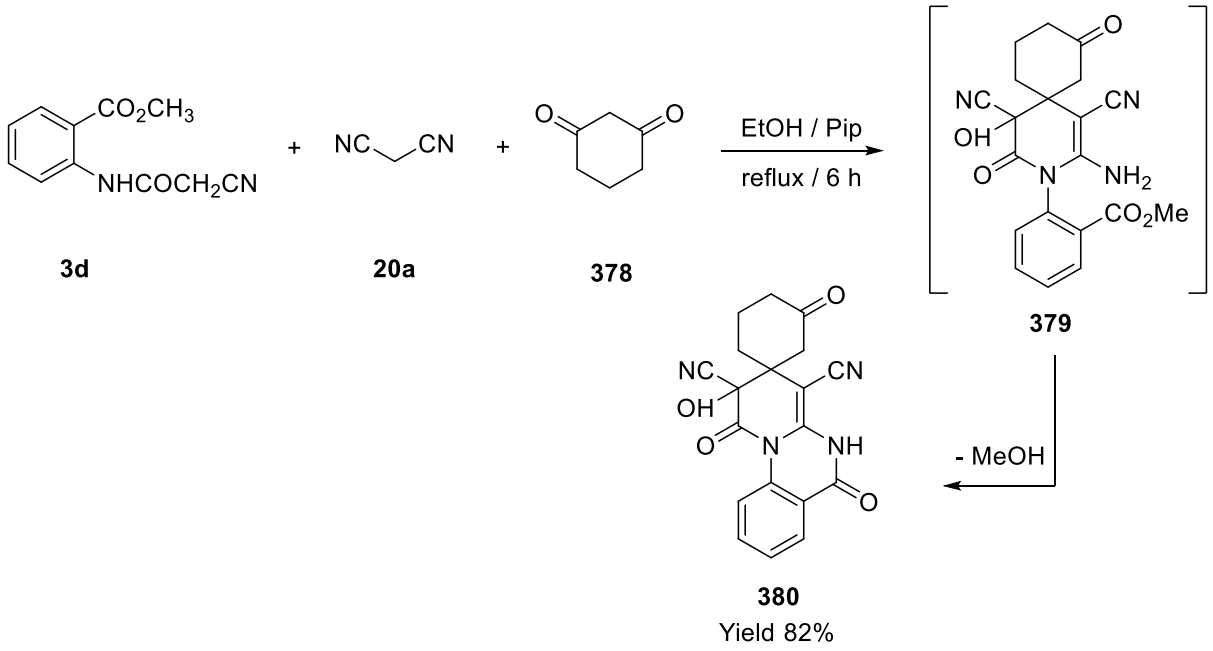
Scheme 173

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]



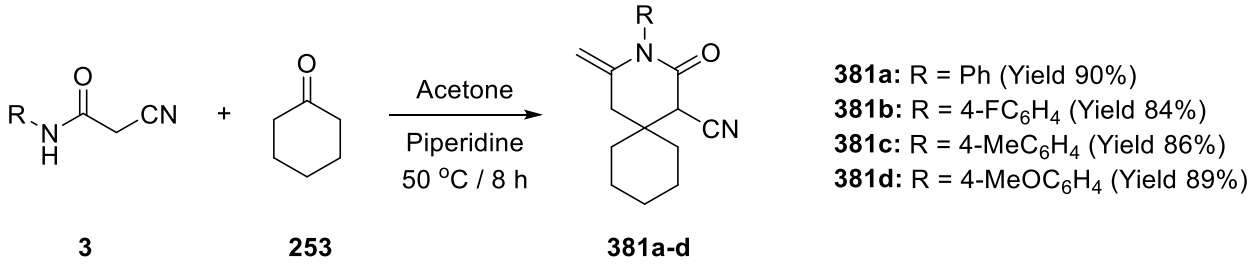
Scheme 174

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]



Scheme 176

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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