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Review

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Pyrazole-carboxaldehydes as versatile precursors for different pyrazole-substituted heterocyclic systems

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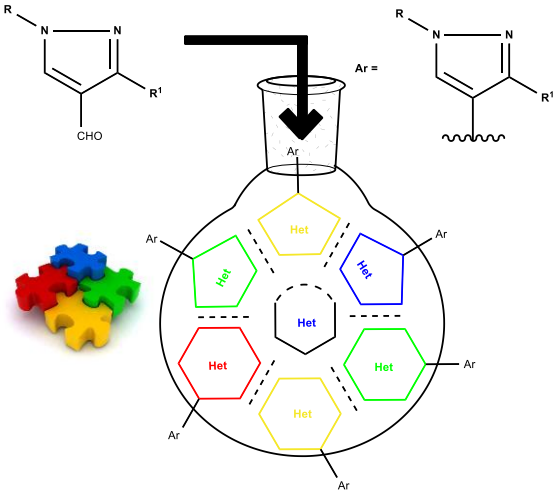
Abstract

In the last decade, interest in pyrazole chemistry has grown considerably due to the discovery of fascinating properties demonstrated by a large number of pyrazole derivatives. They occur in a wide range of natural products, dyes, and as scaffolds in a number of drugs and associated pharmaceutical active substances. Substantial attention has been paid to the creation of hybrid molecules in which two heterocycles are bound in a single molecule to enhance their biological effectiveness and overcome drug resistance. In this regard, this review illustrated various methods for the construction of pyrazole-substituted heterocycles and their corresponding fused derivatives using pyrazole carboxaldehydes as effective precursors. The heterocyclic systems mentioned in this review are categorized according to the type of the heterocyclic systems.



Keywords : Vilsmeier-Haack reaction**,** pyrazole-carboxaldehydes, pyrazole-substituted heterocycles, pyrazole-substituted fused-heterocycles

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1. Introduction

Heterocycles are significant classes of compounds that make up more than half of all known organic compounds. They exist in a wide range of medications, most supplements, many natural products, and biomolecules like hormones, antibiotics, alkaloids, vitamins, etc. The vast majority of commercially available synthetic drugs have a heterocyclic structural component. Many heterocyclic compounds were found to exhibit a wide variety of biological activities including antitumor, antibiotics, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antiviral, antidiabetic, herbicide, and fungicide agents. Many of the heterocycles have also many applications such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. Heterocycles are also of great interest as intermediates, protecting groups, chiral auxiliaries, organic catalysts, and metal ligands. In addition, ionic liquids composed of heterocyclic compounds can serve as green solvents as well as catalyst.[1–20]

Nitrogen-containing heterocycles are among the most active compounds due to their large occurrence in natural products. They are among the core structures of various biologically active compounds and are considered as essential roles in many of the chemical reactions occurring in all organisms.[19] They also show numerous applications in chemistry, biology, and other sciences. In addition, nitrogen-containing heterocycles play a significant role in coordination chemistry.[21]

Among different nitrogen-containing heterocycles, pyrazole derivatives represent an interesting class of five-membered heterocycles.[11] Pyrazole is a motif found in a number of molecules that have a wide range of agricultural and pharmaceutical activities.[12,22]

Pyrazole derivatives exhibited a wide variety of biological profiles, such as anti-tuberculosis, anti-AIDS, anti-malarial, anti-microbial, antitumor, antifungal, anti-hyperglycemic agents, anti-depressant agents, anti-convulsant agents, antipyretic agents, and anti-anxiety agents.[23–29] The pyrazole ring is involved in diverse therapeutic active compounds. In this respect, a variety of well-known drugs belonging to various categories such as celecoxib, rimonabant, fomepizole, and sildenafil have been recently developed.

Some of the pyrazole derivatives have important applications as brightening agents[30] and some exhibit significant solvatochromic and electroluminescence properties.[31] Their application in material chemistry,[32] semiconductors,[33] liquid crystals,[34] and organic light-emitting diodes[35] have been extensively reported.

The diversity in the numerous potential applications of pyrazoles encouraged the continuous investigation of this class of compounds and prompted authors to search for more effective and selective synthetic routes to this type of compounds and allowing the production of a large number of structurally diverse derivatives with various biological profiles.

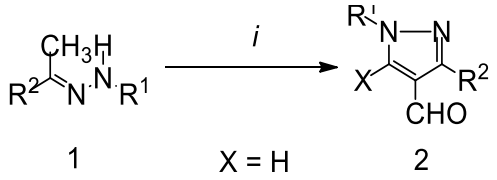
Continuing our interest in reviewing various approaches to heterocyclic system synthesis,[36–51] this review highlights the different synthetic methods for the preparation of pyrazole-carboxaldehydes and their usefulness as versatile precursors for different pyrazole-substituted heterocyclic systems. Based on the size of the heterocyclic ring as well as the position and number of the heteroatoms, heterocyclic compounds mentioned in this review are arranged.

2. Synthesis of Pyrazole-carboxaldehyde

There have been several important routes to synthesize pyrazole-carboxaldehydes, e.g. (*i*) Vilsmeier-Haack reaction of hydrazones, (*ii*) Oxidation of the corresponding alcohols, (*iii*) Reduction of the corresponding nitrile and (*iv*) Miscellaneous methods.

2.1. Vilsmeier-Haack reaction

2.1.1 Vilsmeier-Haack reaction of hydrazine. This method is the most common one to synthesize pyrazole-4-carboxaldehydes **2** *via* the corresponding hydrazonoyl derivatives **1** (Scheme 1, Table 1).

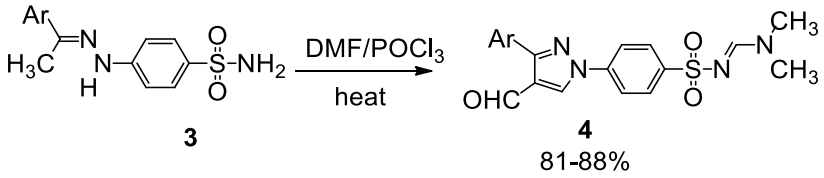


1 2

i = *N*,*N*-dimethyl formamide (DMF)/ phosphorus oxychloride ($POCl_3$)/ heat;[52–78] 2,4,6-trichloro[1,3,5]triazine (TCT)/DMF /r.t/ Na_2CO_3.[79]

Scheme 1. Synthesis of pyrazole-carboxaldehydes by Vilsmeier-Haack reaction of hydrazones.

Phenylsulfonyl-*N,N*-dimethylformimidamide-pyrazole-4-carboxaldehydes **4** were obtained by Vilsmeier-Haack reaction of the corresponding benzenesulfonamide hydrazonoyl derivatives **3** with $POCl_3$ in DMF (Scheme 2).[80,81]



3 **4**
81-88%

Ar = C_6H_5, 4-H_3C-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_4, 4-F-C_6H_4, 2- Thiophene

Scheme 2. Synthesis of phenylsulfonyl-*N,N*-dimethylformimidamide-pyrazole-4-carboxaldehydes **4.**

Table 1. Yields (%) of compounds **2** prepared from hydrazones

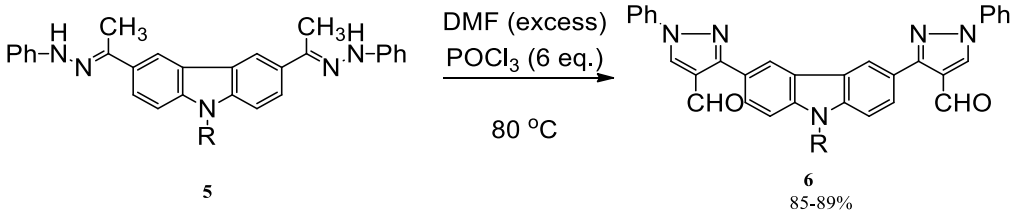
NO.	R^1	R^2	Yield%	Ref.
1	C_6H_5	H, C_6H_5, CH_3, 4-O_2N-C_6H_4, 4-H_3C-C_6H_4, 3-H_3C-C_6H_4, 2-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 2-HO-C_6H_4, 3-HO-C_6H_4, 4-HO-C_6H_4, 3-O_2N-C_6H_4, 2,4-di-Cl-C_6H_3, 3,4,5-tri-H_3CO-C_6H_2, *tert*-Butyl, *iso*-Butyl, 2-oxo-2*H*-chromen-3-yl, 6-Y-2-oxo-2*H*-chromen-3-yl (Y = Cl, Br, O_2N), 6,8-Cl_2-2-oxo-2*H*-chromen-3-yl, 6,8-Br_2-2-oxo-2*H*-chromen-3-yl, 8-H_3CO-2-oxo-2*H*-chromen-3-yl, 2-oxo-2*H*-benzo[*g*]chromen-3-yl, 5-Br-thiophen-2-yl, benzofuran-2-yl, 3-H_3C-benzofuran-2-yl, 4-HO-6-H_3C-2-oxo-2*H*-pyran-3-yl, COOEt, 10*H*-phenothiazin-2-yl	38-95	52,53,62–66,72–76,54,77–79,55–61
2	4-O_2N-C_6H_4	C_6H_5, Benzofuran-2-yl, 3-H_3C-benzofuran-2-yl, 4-HO-6-H_3C-2-oxo-2*H*-pyran-3-yl, Benzofuran-2-yl, 3-	58-94	52,63,75,76

		H_3C-benzofuran-2-yl, 4-HO-6-H_3C-2-oxo-2*H*-pyran-3-yl		

Table 1. Continued

NO.	R^1	R^2	Yield%	Ref.
3	4-Cl-C_6H_4	H, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-HO-6-H_3C-2-oxo-2*H*-pyran-3-yl, COOEt	47-92	53,61,66,67,76
4	4-H_3C-C_6H_4	H, 4-OH-6-H_3C-2-oxo-2*H*-pyran-3-yl, C_6H_5	42-80	61,76,79
5	H	C_6H_5, 4-Cl-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 4-C_2H_5-C_6H_4, 4-$(H_3C)_2HC$-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4, 4-H_5C_2O-C_6H_4, 4-$H_3C(CH_2)_3O$-C_6H_4, 3-F-C_6H_4, 3-Br-C_6H_4, 3-O_2N-C_6H_4, 3- H_3CO-C_6H_4, 3-HO-C_6H_4, 3-H_3C-C_6H_4, 2-F-C_6H_4, 2-H_3CO-C_6H_4, 2,4-$(H_3C)_2$-C_6H_3, 3,4-$(H_3C)_2$-C_6H_3, 2,5-$(H_3C)_2$-C_6H_3, 3,4-$(H_3CO)_2$-C_6H_3, 2,5-$(H_3CO)_2$-C_6H_3, 3-Cl-4-H_5C_2O-C_6H_3, 2- Thienyl	32-87	68
6	2,4-$(O_2N)_2$-C_6H_3	4-OH-6-H_3C-2-oxo-2*H*-pyran-3-yl, CO_2Et	55	69,76
7	isonicotinoyl	4-NO_2-C_6H_4	60	70
8	2,6-Cl_2-4-F_3C-C_6H_2	C_6H_5, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Br-C_6H_4, 3-Br-C_6H_4, 4-H_3CO-C_6H_4, 4-F_3C-C_6H_4, 4-O_2N-C_6H_4, 6-H_3CO-naphthalen-2-yl	81-89	71
9	3-H_3C-C_6H_4	COOEt	73	66
10	4-F-C_6H_4	C_6H_5	82	79

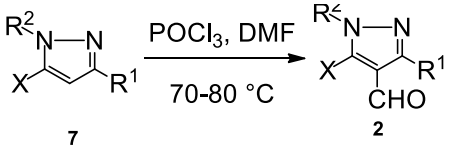
Ramu and Rajagopal[82] reported that the Vilsmeier reaction of the bis-acetyl carbazole hydrazones **5** yielded the corresponding 3,3'-(9-alkyl-carbazole-3,6-diyl)bis(1-phenyl-1*H*-pyrazole-4-carboxaldehyde) **6** in good yield (Scheme 3).



R = CH_3, C_2H_5, *n*-C_4H_9, $H_2CC_6H_5$

Scheme 3. Synthesis of 3,3'-(9-alkyl-carbazole-3,6-diyl)bis(1-phenyl-1*H*-pyrazole-4-carboxaldehyde) **6.**

2.1.2. Vilsmeier-Haack reaction of pyrazole derivatives. 2.1.2.1. Vilsmeier-Haack reaction of pyrazole. Heating of pyrazole **7** with DMF/$POCl_3$ gave the corresponding pyrazole-carboxaldehyde **2** (Scheme 4, Table 2).[76,83–85]



7 2

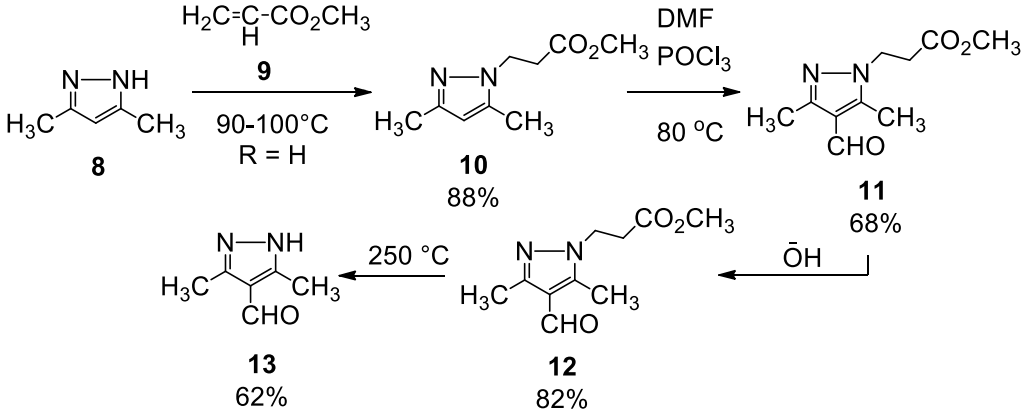
Scheme 4. Synthesis of pyrazole-carboxaldehyde **2** from pyrazole **7.**

Table 2. Yields (%) of compounds **2** prepared from pyrazoles

NO	R^1	R^2	X	Yield%	Ref.
1	BnO	C_6H_5	H	60	[83]
2	CH_3	C_6H_5	Cl	85	[84]
3	4-HO-6-H_3C-2-oxo-2*H*-pyran-3-yl	C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 2,4-$(O_2N)_2$- C_6H_3	H	50	[76]
4	H	C_2H_5	H	77	[85]
5	CH_3	CH_3, C_2H_5, C_3H_7	CH_3	69	[85,86]

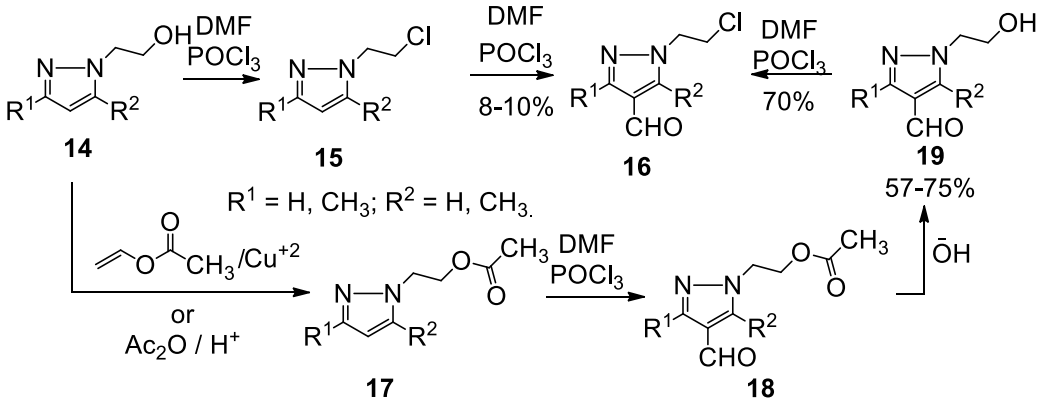
In contrast, 3,5-dimethyl-1*H*-pyrazole **8** did not undergo formylation at position 4 under analogous conditions. However, the protection of compound **8** through its reaction with methyl acrylate **9** affords methyl-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)propanoate **10**. Subsequent reaction of **10** with $POCl_3$/DMF afforded methyl 3-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionate **11** which undergo alkaline hydrolysis to give methyl 3-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propanoate **12.** Subsequent heating of **12** at 250 °C gave 3,5-dimethyl-1*H*-pyrazole-4-carboxaldehyde **13** (Scheme 5).[86]

2-(Pyrazol-1-yl)-ethanoles **14** do not undergo Vilsmeier–Haack formylation and instead *N*-chloroethylpyrazoles **15** were formed. The reaction of *N*-chloroethylpyrazole **15** with Vilsmeier reagent gave *N*-chloroethylpyrazole-4-carboxaldehyde **16** in 8-10% yield. On the other hand, synthesis of 1-(2-hydroxyethyl)-3,5-dimethyl-1*H*-pyrazole-4-carboxaldehyde **17** took place by acylation of **14** with acetic anhydride or vinyl acetate in the presence of a catalytic amount of copper acetate to give acylated products **17** which readily underwent Vilsmeier-Haack formylation to give **18**. Subsequent hydrolysis of **18** afforded **19** which underwent chlorination to give **16** upon treatment of Vilsmeier reagent (Scheme 6) .[87,88]



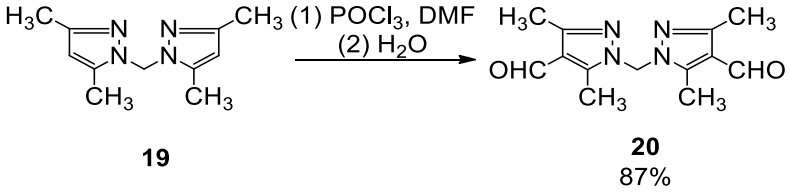
8 **10** 88% **11** 68% **12** 82% **13** 62%

Scheme 5. Synthesis of 3,5-dimethyl-1*H*-pyrazole-4-carboxaldehyde **13.**



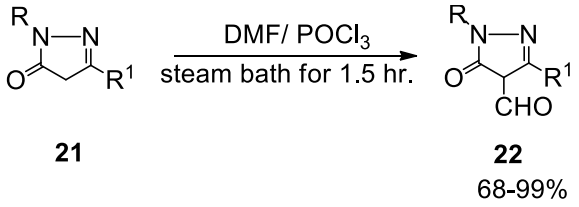
Scheme 6. Synthesis of 2-(4-formyl-1*H*-pyrazol-1-yl)ethyl acetate.

Vilsmeier-Haack reaction of bis(3,5-dimethyl-1*H*-pyrazol-1-yl)methane **19** afforded 1,1'-Methylenebis(3,5-dimethylpyrazole-4-carboxaldehyde) **20** (Scheme 7).[85]



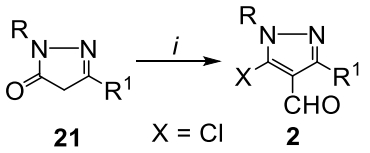
Scheme 7. Synthesis of 1,1'-Methylenebis(3,5-dimethylpyrazole-4-carboxaldehyde) **20.**

2.1.2.2. Vilsmeier-Haack reaction of pyrazolone. Wallace and Straley[89] reported the synthesis of 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde **22** in good yield by treating the pyrazolinone **21** with DMF and $POCl_3$ (Scheme 8).



Scheme 8. Synthesis of 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde **22.**

However, it was reported by others, that pyrazol-5-ones **21** underwent formylation using Vilsmeier-Haack conditions to give the corresponding 5-chloropyrazole-4-carboxaldehydes **2** (Scheme 9, Table 3).[90–93]

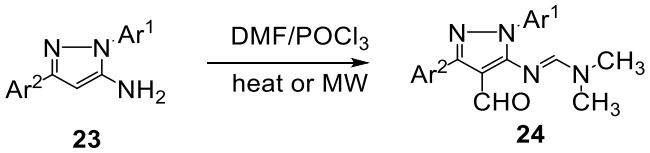


Scheme 9. Synthesis of 5-chloropyrazole-4-carboxaldehydes **2.**

Table 3. Yields (%) of compounds **2** prepared from pyrazolones **21**

Entry	R	R^1	*i*	Yield%	Ref.
1	CH_3	CH_3, C_6H_5	1)DMF/ $POCl_3$ 2) $POCl_3$	94	90
2	C_6H_5	4-H_3C-C_6H_4, CH_3, C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4	BTC(Bis(trichloromethyl) carbonate) / DMF/ Chlorobenzene, 130 °C	57-86	91
3	C_6H_5	C_6H_5, Pyridyl	DMF/ $POCl_3$ / heat	60-75	92,93

2.1.2.3. Vilsmeier-Haack reaction of aminopyrazoles. Vilsmeier-Haack formylation of 5-aminopyrazoles **23** with excess DMF/$POCl_3$ under conventional heating[94] or MW irradiation[95] led to the formation of 4-formyl-pyrazolyl-dimethylimidoformamides **24** (Scheme 10, Table 4).[94,95]

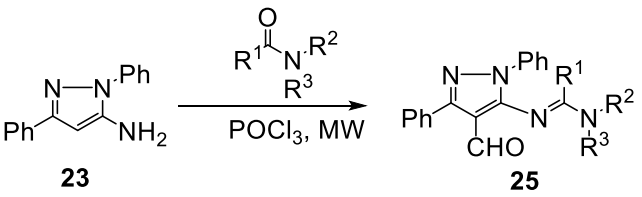


Scheme 10. Synthesis of 4-formyl-pyrazolyl-dimethylimidoformamides **24.**

N-*N*-Disubstituted-*N*`-[1,3-diphenyl-4-formyl-1*H*-pyrazol-5-yl] formimidamides **25** were synthesized by microwave irradiation of 5-amino-1,3-diphenyl-1*H*-pyrazole **23** with various amide solvents in the presence of $POCl_3$ (Scheme 11, Table 5).[95]

Table 4. Yields (%) of compounds **24**

Entry	Ar^1	Ar^2	Cond.	Yield%	Ref.
1	C_6H_5	4-Cl-C_6H_4, 4-Br- C_6H_4, 4-H_3C-C_6H_4	heat	72-78	94
2	C_6H_5, 2-Cl-C_6H_4, 3-H_3C-C_6H_4, 3-Cl-C_6H_4, 3-O_2N-C_6H_4, 4-Br-C_6H_4, 4-H_3CO-C_6H_4	C_6H_5	MW	81-94	95
3	C_6H_5	4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, *t*-Butyl	MW	77-97	95



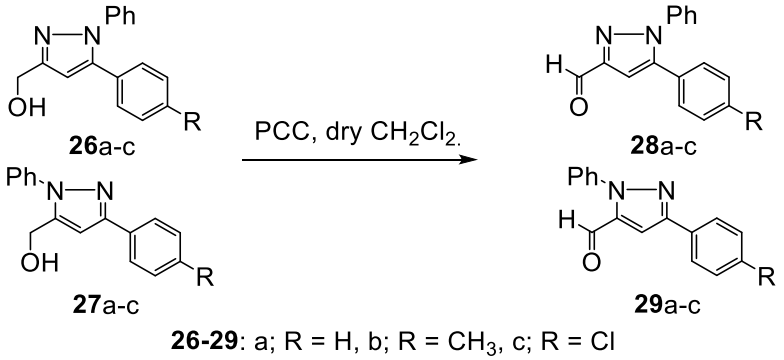
Scheme 11. Synthesis of *N*-*N*-Disubstituted-*N*`-[1,3-diphenyl-4-formyl-1*H*-pyrazol-5-yl]formimidamides **25.**

Table 5. Yields (%) of compounds **25**

	Amide solvents			Yield %
	R^1	R^2	R^3	
3a	H	C_2H_5	C_2H_5	91
3b	H	Pyrrolidinyl		96
3c	H	Piperidinyl		92

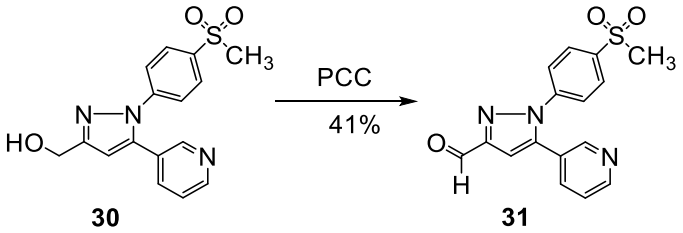
2.2. Oxidation of the corresponding alcohols

Somnath *et al.*[96] reported that the oxidation of hydroxymethylpyrazole derivatives **26a-c** or **27a-c** in the presence of pyridinium chlorochromate (PCC) yielded the corresponding pyrazole-carboxaldehydes **28a-c** and **29a-c**, respectively, in 55-57% and 75-80% yields (Scheme 12).



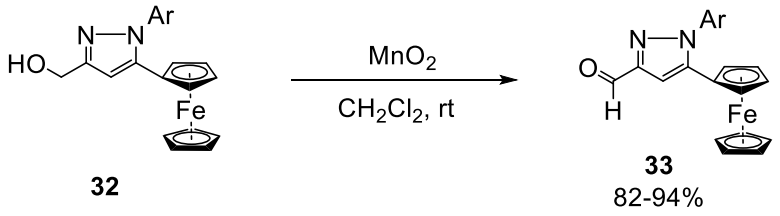
Scheme 12. Synthesis of pyrazole-carboxaldehydes **28a-c** and **29a-c.**

The oxidation of hydroxymethyl-(3-pyridyl)pyrazole derivative **30** with PCC afforded (3-pyridyl)pyrazole-4-carboxaldehyde **31** in 41% yield (Scheme 13).[97]



Scheme 13. Synthesis of (3-pyridyl)pyrazole-4-carboxaldehyde **31.**

Ferrocene-based pyrazole-carboxaldehyde **33** has been formed by oxidation of hydroxymethylpyrazole linked to ferrocene **32** with manganese dioxide (MnO_2) in dichloromethane (Scheme 14).[98]

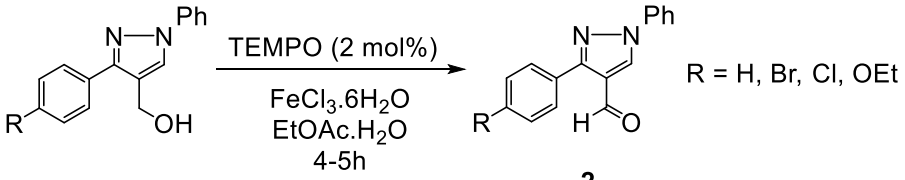


32 **33**
82-94%

Ar = C_6H_5, Naphthalen-1-yl, 4- H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-*tert*-Butyl-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 3-Cl-2-F-C_6H_3, CH_3.

Scheme 14. Synthesis of ferrocene-based pyrazole-carboxaldehyde **33.**

1,3-Diaryl-1*H*-pyrazole-4-carboxaldehydes **2** were prepared in good to excellent yields *via* the oxidation of the corresponding (1,3-diaryl-1*H*-pyrazol-4-yl)methanol **34** by iron(III) chloride hexahydrate $FeCl_3.6H_2O$ catalyzed by a free radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 15).[99]

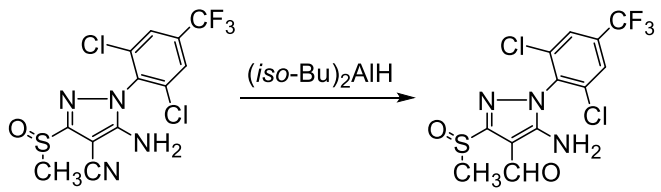


34 **2**
50-85%

Scheme 15. Synthesis of 1,3-diaryl-1*H*-pyrazole-4-carboxaldehydes **2** from alcohol **34.**

2.3. Reduction of the corresponding pyrazolecarbonitrile

The reduction of 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(methylsulfinyl)-1*H*-pyrazole-3-carbonitrile **35** in the presence of di-*iso*-butylaluminium hydride (*iso*-Bu)$_2$AlH afforded the corresponding pyrazole-4-carboxaldehyde **2** (Scheme 16).[100]

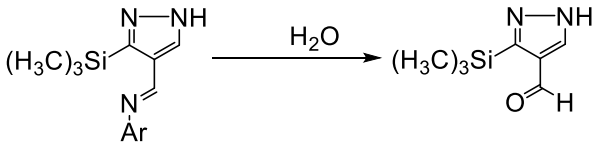


35 **2**

Scheme 16. Synthesis of pyrazole-4-carboxaldehyde **2** by reduction of pyrazolecarbonitrile **35.**

2.4. Hydrolysis of (pyrazolyl)methanimine

Hydrolysis of *N*-aryl-1-(3-(trimethylsilyl)-1*H*-pyrazol-4- yl)methanimine **36** gave 3-(trimethylsilyl)-1*H*-pyrazole-4-carboxaldehyde **37** (Scheme 17).[101]

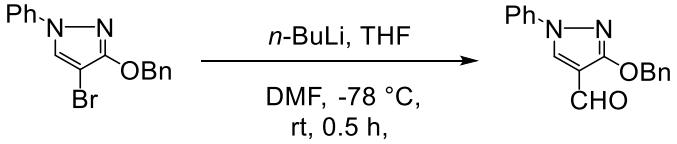


36 **37**

Scheme 17. Synthesis of 3-(trimethylsilyl)-1*H*-pyrazole-4-carboxaldehyde **37.**

2.5. Miscellaneous methods

Arbačiauskienė *et al.*[83] reported that the treatment of 3-(benzyloxy)-4-bromo-1-phenyl-1*H*-pyrazole **38** with *n*-BuLi gave rise to selective bromine-lithium exchange. Subsequent quenching of the intermediate 4-lithiopyrazole with DMF afforded pyrazole-carboxaldehyde **2** (Scheme 18).



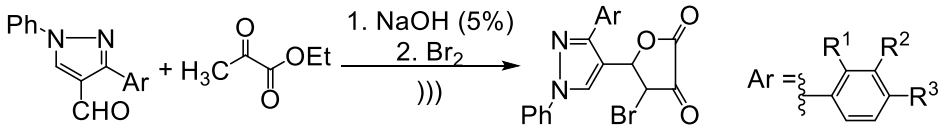
38 **2**
70%

Scheme 18. Synthesis of pyrazole-carboxaldehyde **2.**

3. Synthesis of Pyrazole-substituted Heterocycles

3.1. Pyrazole-substituted monoheterocyclic ring

3.1.1. Monocyclic five-membered with one heteroatom. 3.1.1.1. Furan derivatives. Fekri *et al.*[102] reported that the one-pot multi-component reaction of 4-pyrazole-carboxaldehyde **2**, ethyl pyruvate **39**, and bromine gave 2,3-dihydrofuranediones **40** under ultrasonic irradiation (Scheme 19).



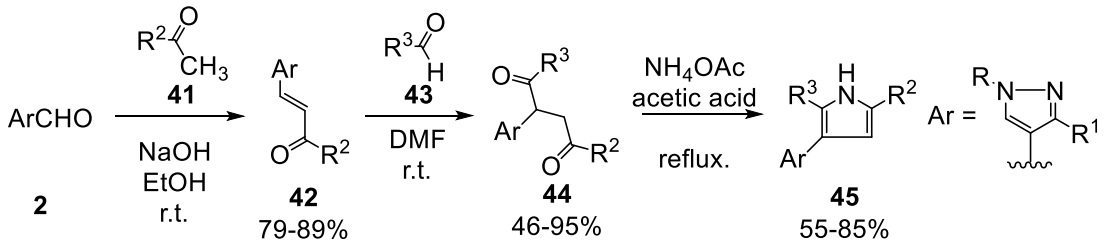
2 **39** **40**
85-92%

R^1 = H, Cl; R^2 = H, NO_2; R^3 = OCH_3, OH, H, Cl.

Scheme 19. Synthesis of 2,3-dihydrofuranediones **40.**

3.1.1.2. Pyrrole derivatives. Ragab *et al.*[67] reported that the Claisene-Schmidt condensation between pyrazole-carboxaldehydes **2** and 4-chloroacetophenone **41** afforded the corresponding chalcones **42** which upon reaction with 4-substituted-benzaldehyde **43** in DMF in the presence of potassium cyanide as a catalyst afforded 1,4-

diketones **44**. Compounds **44** were cyclized using ammonium acetate in acetic acid under Paale-Knorr reaction conditions to yield the corresponding pyrrole derivatives **45** (Scheme 20).

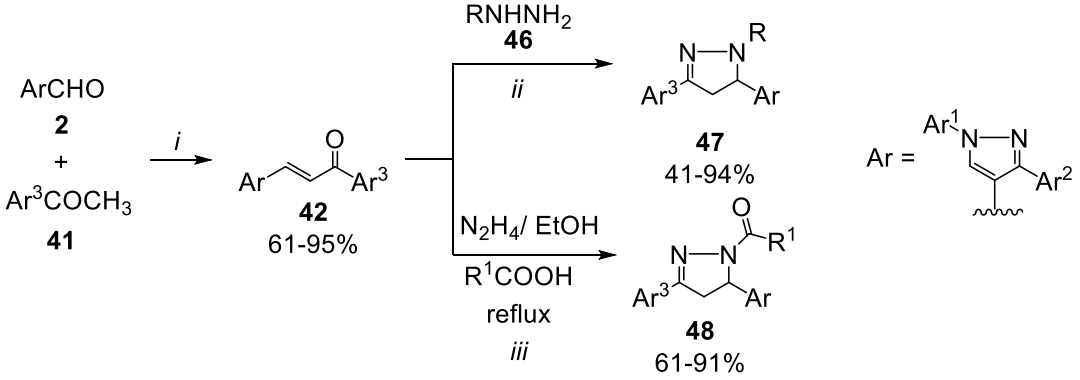


R = 4-Cl-C_6H_4, 4-H_2NO_2S-C_6H_4; R^1 = 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4; R^2 = 4-Cl-C_6H_4; R^3 = 4-H_3CO-C_6H_4, 4-F-C_6H_4.

Scheme 20. Synthesis of pyrrole derivatives **45.**

3.1.2. Monocyclic five-membered with two heteroatoms. 3.1.2.1. Pyrazole derivatives. 3.1.2.1.1. Synthesis of pyrazole derivatives from chalcone carrying pyrazole. Under different reaction conditions, a series of chalcones **42** were synthesized through the Claisen–Schmidt condensation of pyrazole-4-carboxaldehyde **2** with aryl(hetero)methylene ketones **41**.[26,57,59,103–116] The chalcone derivatives **42** were then reacted with hydrazine derivatives **46** to give the corresponding 4,5-dihydro-1*H*-pyrazole **47**.[26,57,113–116,59,103–107,111,112] On the other hand, the reaction of chalcones **42** with hydrazine hydrate in the presence of acid gave the acylated 4,5-dihydro-1*H*-pyrazole **48**[104,107–109,114] (Scheme 21).

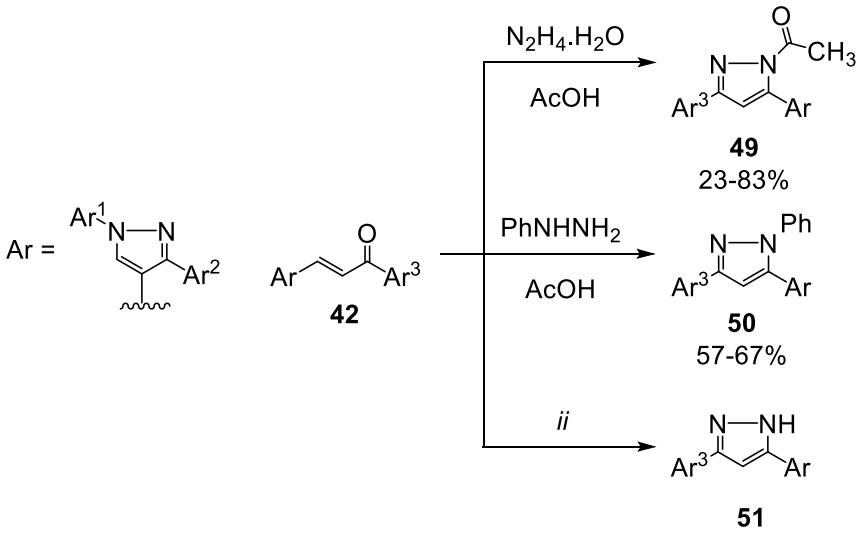
On the other hand, the same reaction of chalcones **42** with hydrazine hydrate or phenylhydrazine in the presence of acetic acid gave the corresponding 1*H*-pyrazoles **49** and **50** respectively.[59] The reaction of chalcones **42** with iodine in dimethyl sulfoxide (DMSO) followed by reaction with hydrazine hydrate afforded pyrazoles **51**[59,106] (Scheme 22).



Ar^1 = C_6H_5, 3-Cl-C_6H_4; Ar^2 = C_6H_5, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-Br-C_6H_4, 4-O_2N-C_6H_4, 3-Br-C_6H_4, 3-O_2N-C_6H_4, Pyridin-3-yl, Thiophen-2-yl, 5-Methylfuran-2-yl, Naphthalen-2-yl; Ar^3 = C_6H_5, 4-O_2N-C_6H_4, 2-O_2N-C_6H_4, 3-O_2N-C_6H_4, 4-H_3C-C_6H_4, 2-H_3C-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-F-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 4-HO-C_6H_4, 2-HO-C_6H_4, 3-HO-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4, 4-H_5C_2-C_6H_4, 5-H_3C-2-HO-C_6H_3, 5-Cl-2-HO-C_6H_3, 4-H_3C-2-HO-C_6H_3, 3-H_3C-2-HO-C_6H_3, 5-H_5C_2-2-HO-C_6H_3, 5-Br-2-HO-C_6H_3, 5-F-2-HO-C_6H_3, 3,5-di-H_3C-2-HO-C_6H_2, 3,5-di-Cl-2-HO-C_6H_2, 4,6-di-H_3C-2-HO-C_6H_2, 5-Cl-3-H_3C-2-HO-C_6H_2, 2,4-di-Cl-C_6H_3, 2,3-di-H_3CO-C_6H_3, Pyridin-3-yl, 10*H*-Phenothiazin-2-yl, Thiophen-2-yl, Benzofuran-2-yl, Furan-2-yl; R = H, C_6H_5, 4-Sulfamoylphenyl, $CSNH_2$, 4-Phenylthiazol-2-yl, 4-Phenyl-5-(phenyldiazenyl)thiazol-2-yl; R^1 = H, CH_3, C_2H_5, C_3H_7; *i*) EtOH/ KOH/ reflux[106,111,112] or grindig,[112] MeOH/ NaOH/ reflux,[113] MeOH/ NaOH r.t. ,[57,110] EtOH/

NaOH;[59,104,114,115] *ii*) two drops AcOH/ stirring r.t. ,[111,116] MeOH/ HCl/ reflux,[113] AcOH/ reflux,[103] H_2SO_4/ AcOH/ reflux[26,112] or grindig,[112] EtOH/ NaOH/reflux,[57,59,104,114] EtOH,[59,104,112] grindig[112] or dioxan.[105]

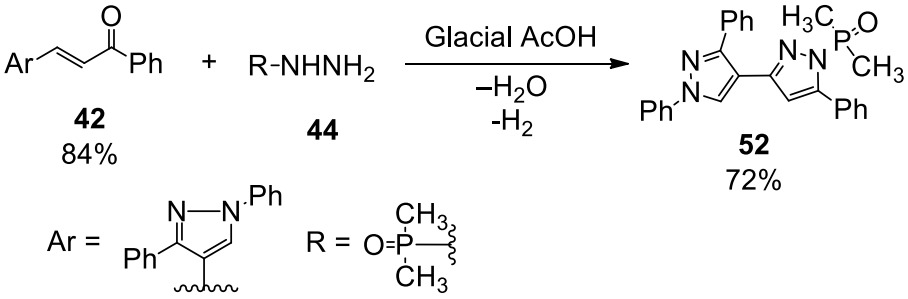
Scheme 21. Synthesis of 4,5-dihydro-1*H*-pyrazole **47** and 4,5-dihydro-1*H*-pyrazole **48.**



Ar^1 = C_6H_5; Ar^2 = C_6H_5, Naphthalen-2-yl; Ar^3 = 5-H_3C-2-HO-C_6H_3, 5-Cl-2-HO-C_6H_3, 4-H_3C-2-HO-C_6H_3, 3-H_3C-2-HO-C_6H_3, 5-H_5C_2-2-HO-C_6H_3, 5-Br-2-HO-C_6H_3, 5-F-2-HO-C_6H_3, 3,5-di-H_3C-2-HO-C_6H_2, 3,5-di-Cl-2-HO-C_6H_2, 4,6-di-H_3C-2-HO-C_6H_2, 5-Cl-3-H_3C-2-HO-C_6H_2, 10*H*-Phenothiazin-2-yl; *i*) EtOH/ KOH/ reflux,[106] EtOH/ NaOH;[59] *ii*) (1)I_2/ DMSO 2) N_2H_4/ EtOH)[106] or N_2H_4/ EtOH.[59]

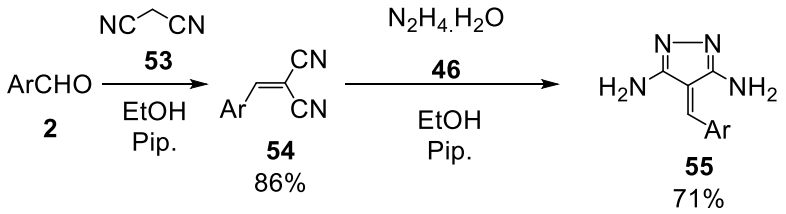
Scheme 22. Synthesis of 1*H*-pyrazoles **49, 50** and **51.**

Ali[117] reported the synthesis of 1-(dimethylphosphoryl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-phenyl-1*H*-pyrazole **52** by reaction of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one **42** with *p*,*p*-dimethylphosphinic hydrazide **46** in the presence of acetic acid (Scheme 23).



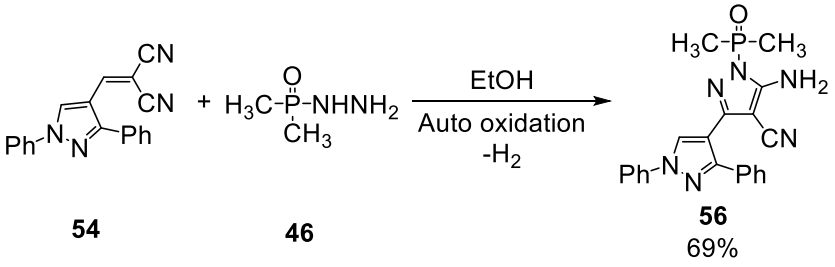
Scheme 23. Synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-phenyl-1*H*-pyrazole **52.**

3.1.2.1.2. Synthesis of pyrazole derivatives from arylidene malononitrile carrying pyrazole. Ismail *et al*.[118] reported the synthesis of 2-((1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)malononitrile **54** by heating of pyrazole-4-carboxaldehyde **2** and malononitrile **53**. Heating of **54** at reflux with hydrazine hydrate **46** in ethanol/ piperidine gave 4-((1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)-4*H*-pyrazole-3,5-diamine **55** (Scheme 24).



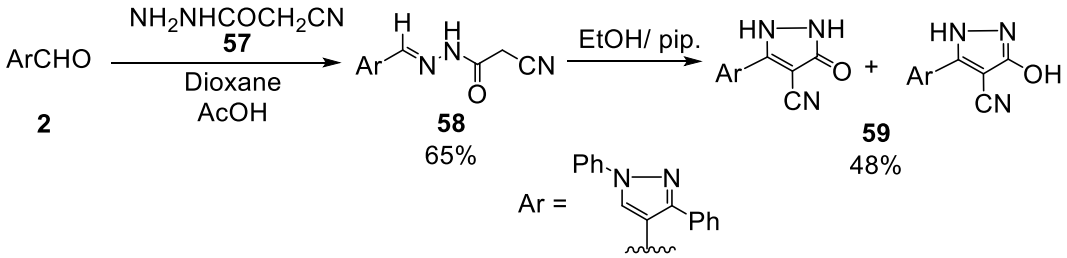
Scheme 24. Synthesis of 4-((1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)-4*H*-pyrazole-3,5-diamine **55**.

On the other hand, the reaction of 2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)malononitrile **54** with *p,p*-dimethylphosphinic hydrazide afforded 5-amino-1-(dimethylphosphoryl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-pyrazole-4-carbonitrile **56**[117] (Scheme 25).



Scheme 25. Synthesis of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-pyrazole-4-carbonitrile **56.**

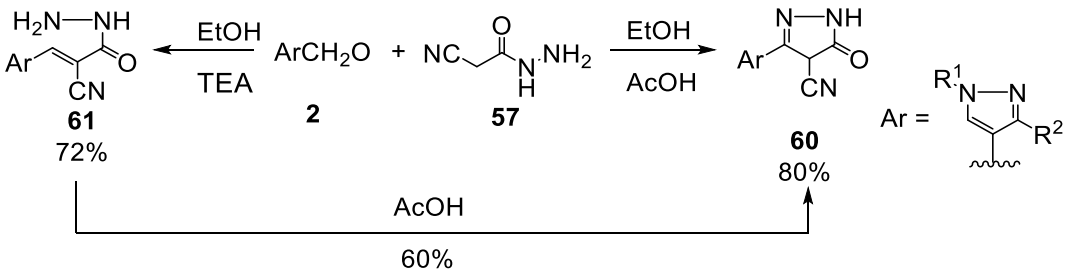
3.1.2.1.3. Synthesis of pyrazole derivatives from cyanoacetohydrazide carrying pyrazole. Atta-Allah *et al*.[119] reported that treatment of the pyrazole-4-carboxaldehyde **2** with cyanoacetohydrazide **57** in dioxane at reflux gave 2-cyano-*N*'-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]acetohydrazide **58**. Heating *N*-condensation product **58** in ethanol in the presence of a catalytic amount of piperidine, gave a mixture of pyrazolone and hydroxyl pyrazole derivatives **59** in a ratio of 2:3 (Scheme 26).



Scheme 26. Synthesis of a mixture of pyrazolone and hydroxyl pyrazole derivatives **59.**

3.1.2.1.4. Synthesis of pyrazole derivatives from cyanoacrylohydrazide carrying pyrazole. Fahmy *et al*.[120] reported that heating of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde **2** with cyanoacetohydrazide **57** in ethanol containing a few drops of acetic acid gave pyrazolinone derivative **60**. Stirring of pyrazole-carboxaldehyde **2** and cyanoacetohydrazide **57** in ethanol containing few drops of triethylamine

gave 3-[1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]-2-cyanoacrylohydrazide **61**. Heating of **61** at reflux in acetic acid afforded compounds **60** (Scheme 27).

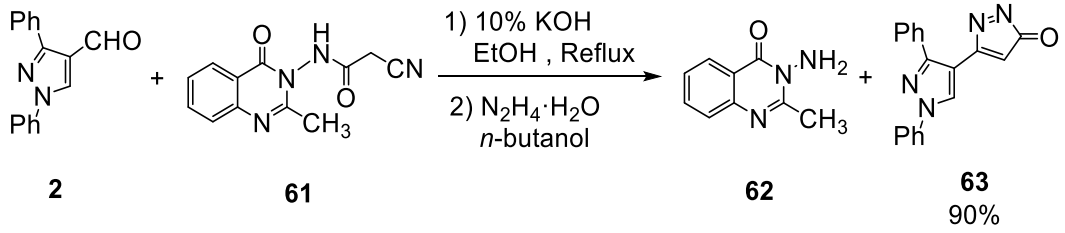


R^1 = 3-Cl-C_6H_4; R^2 = 4-H_3CO-C_6H_4.

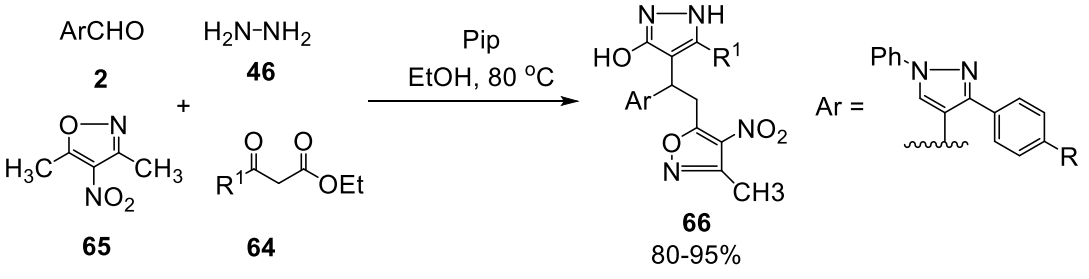
Scheme 27. Synthesis of pyrazolinone derivatives **60.**

3.1.2.1.5. Miscellaneous methods. Youssef *et al*.[121] reported that heating of quinazolinone derivative **61** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** in ethanol at reflux followed by heating with hydrazine hydrate at reflux gave 5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3*H*-pyrazol-3-one **63** and 3-amino-2-methylquinazolin-4(3*H*)-one **62** as a by-product (Scheme 28).

Muthineni *et al*.[122] reported that the four-component reaction of hydrazine hydrate **46,** ethylacetate derivative **64,** pyrazole-carboxaldehyde **2,** and 3,5-dimethyl isoxazole **65** afforded the corresponding 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5yl)-1-arylethyl)-1*H*-pyrazol-3-oles **66** (Scheme 29).



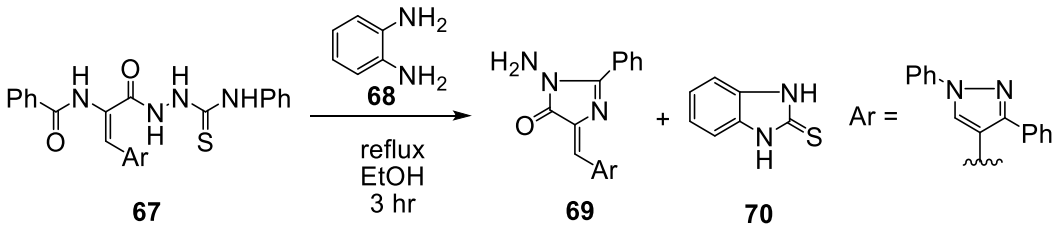
Scheme 28. Synthesis of 3-amino-2-methylquinazolin-4(3*H*)-one **62** and 5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3*H*-pyrazol-3-one **63.**



R = H, CH_3, OCH_3, F, Cl, Br, NO_2; R^1 = CH_3, C_6H_5.

Scheme 29. Synthesis of 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5yl)-1-arylethyl)-1*H*-pyrazol-3-oles **66.**

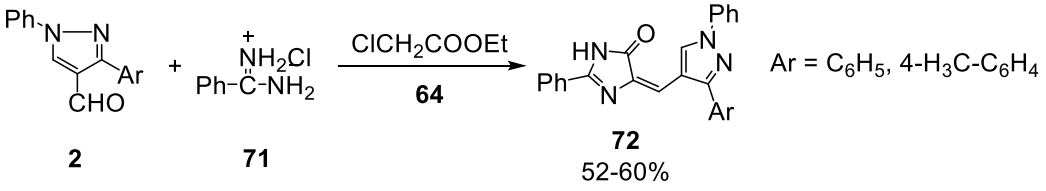
3.1.2.2. Imidazole derivatives. Abou Elmagd *et al.*[123] reported that heating of *N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-oxo-3-(2-((phenyl-l2-azaneyl)carbonothioyl) hydrazineyl) prop-1-en-2-yl)benzamide **67**[124] with *o*-phenylenediamine **68** in ethanol at reflux produced a mixture of 3-amino-5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one **69** and 1,3-dihydro-2*H*-benzo[*d*]imidazole-2-thione **70** (Scheme 30).



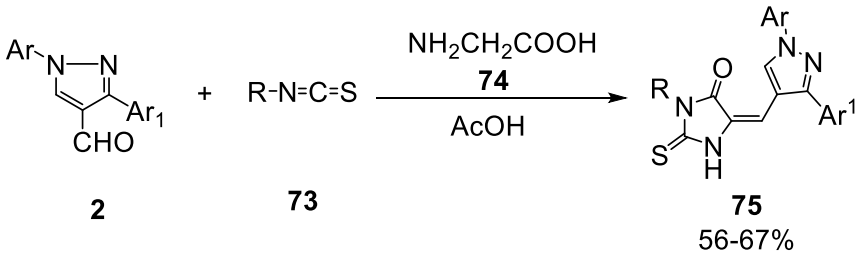
Scheme 30. Synthesis of 3,5-dihydro-4*H*-imidazol-4-one **69** and 2*H*-benzo[*d*]imidazole-2-thione **70.**

Aly *et al*.[125] reported that heating of 3-aryl-1-phenyl-1*H*-pyrazole-4-carboxaldehydes **2** with benzamidine hydrochloride **71** and ethyl chloroacetate **64** gave dihydroimidazolone derivatives **72** (Scheme 31).

Heating of pyrazole-4-carboxaldehyde **2** with the appropriate isothiocyanate **73** and glycine **74** in glacial acetic acid at reflux afforded thioxoimidazolidin-4-ones **75**[118,126] (Scheme 32).



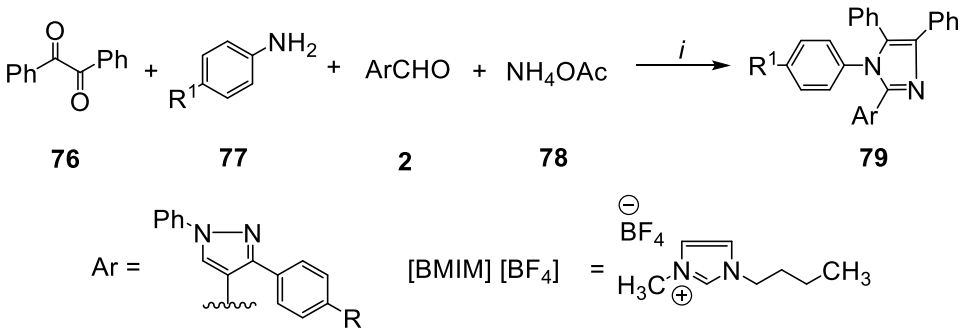
Scheme 31. Synthesis of dihydroimidazolone derivatives **72.**



Ar = C_6H_5, 3-Cl-C_6H_4; Ar^1 = 4-H_3CO-C_6H_4, H_5C_6-CH_2O-C_6H_5; R = C_6H_5, 3-Cl-C_6H_4, 4-H_3CO-C_6H_4.

Scheme 32. Synthesis of thioxoimidazolidin-4-ones **75.**

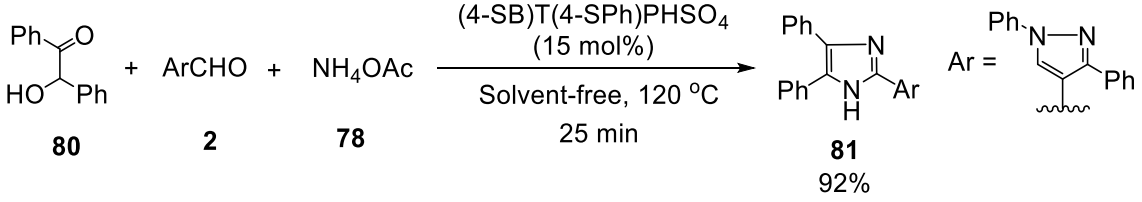
Shirole *et al*.[127] reported that imidazoles **79** were synthesized by a multi-component reaction of benzil **76**, aniline derivatives **77**, 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carboxaldehyde **2** and ammonium acetate **78** in the presence of 1-butyl-3-methyl-1-imidazolium tetrafluoroborate [BMIM][BF_4] as a catalyst (Scheme 33).



R = CH_3, H, F, Cl, Br, NO_2; R^1 =H, Cl; ***i*** = Conventional Method: Reflux 14-15 h / [BMIM] [BF_4]/Ethanol (68- 78%); Green Method: MW at 240 W/ [BMIM][BF4]/Solvent Free 10-12 min (84- 89%).

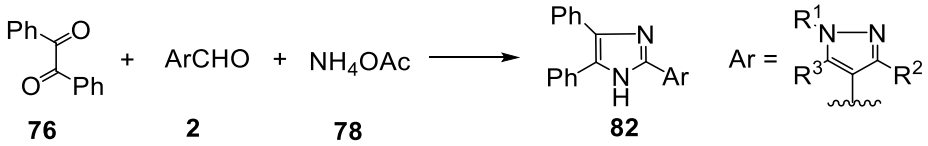
Scheme 33. Synthesis of imidazoles **79.**

Banothu *et al.*[128] reported that 1,3-diphenyl-4-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-pyrazoles **81** were synthesized by the condensation of benzoin **80** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** and ammonium acetate **78** using Brønsted acidic ionic liquid, (4-sulfobutyl)tris(4-sulfophenyl) phosphonium hydrogen sulfate [(4-SB)T(4-SPh)$PHSO_4$] as a catalyst (Scheme 34).



Scheme 34. Synthesis of 1,3-diphenyl-4-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-pyrazoles **81.**

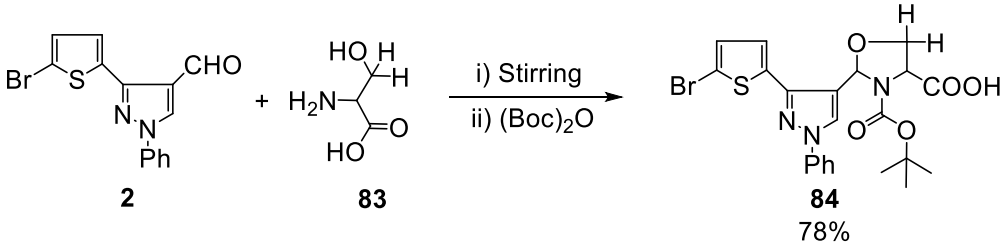
Under different reaction conditions, a series of imidazolylpyrazoles **82** was synthesized by the multicomponent reaction of pyrazole-4-carboxaldehydes **2**, benzil **76,** and ammonium acetate **78**[128–132] (Scheme 35).



Reaction conditions; **a:** NH_4OAc / Acetic acid / Reflux (69-95%),[129–131] **b:** NH_4OAc / Acetic acid / MW (84-91%),[129] **c:** NH_4OAc / Glutamic acid / ethanol / Reflux (85-94%),[129] **d:** NH_4OAc / 120 °C using Brønsted acidic ionic liquid, [(4-SB)T(4-SPh)$PHSO_4$] (98%),[128] **e:** NH_4OAc/ Reflux 4- 4.5hrs/ [BMIM] [BF_4]/ Ethanol (68-72%),[132] **f:** NH_4OAc/ Ultra-sonication (80-90 min)[BMIM] [BF_4]/ Ethanol (78-80%),[132] **g:** NH_4OAc/ MW irradiation 240 watt (7-9 min) [BMIM][BF4]/ Solvent Free (80-86%);[132] R^1 = C_6H_5, 4-O_2N-C_6H_4; R^2 = C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 3-O_2N-C_6H_4, 4-(H_5C_6)-C_6H_4, 3,4-diCl-C_6H_3, 3,4-diF-C_6H_3, 2-Thienyl, 2-Fluorobenzyl, CH_3, Coumarinyl, 6-Br-coumarinyl; R^3 = H, CH_3.

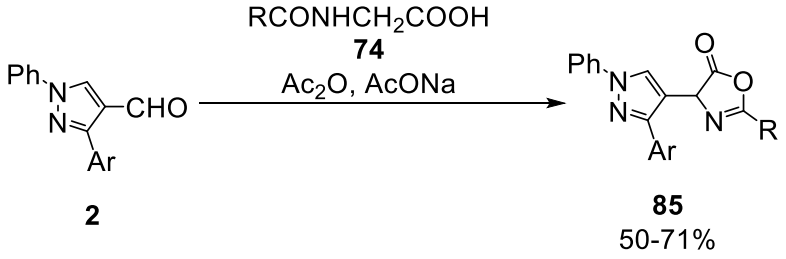
Scheme 35. Synthesis of imidazolylpyrazoles **82.**

3.1.2.3. Oxazole derivatives. Bekhit and Fahmy[133] reported the synthesis of oxazolidine-3-carboxylate **84** *via* reaction of 3-(5-bromo-2-thienyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde **2** with *L*-serine **83**, followed by *N*-protection using di-*tert*-butyl dicarbonate $(Boc)_2O$ (Scheme 36).



Scheme 36. Synthesis of oxazolidine-3-carboxylate **84.**

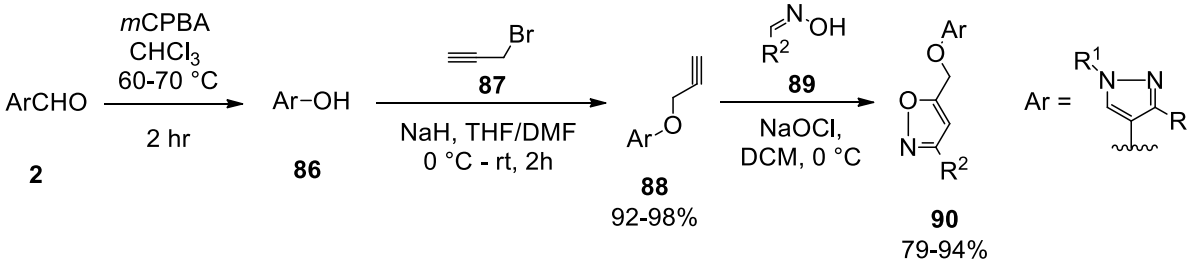
Aly *et al*.[125] reported that heating of 3-aryl-1-phenyl-1*H*-pyrazole-4-carboxaldehydes **2** with glycine derivatives **74** and sodium acetate in acetic anhydride afforded the corresponding 4-(3-aryl-1-phenyl-1*H*-pyrazole-4-ylmethylene)-2-substituted oxazol-5-(4*H*)-ones **85** (Scheme 37).



Ar = C_6H_5, 4-H_3C-C_6H_4, Pyridyl; R = C_6H_5, CH_3.

Scheme 37. Synthesis of 2-substituted oxazol-5-(4*H*)-ones **85.**

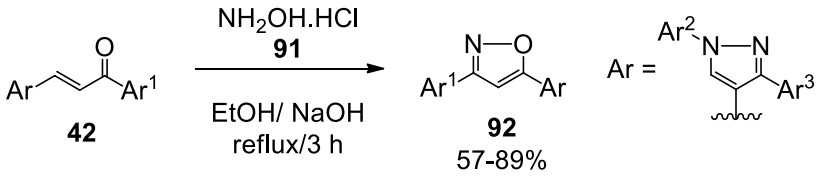
3.1.2.4. Isoxazole derivatives. Madhavilatha *et al*.[134] reported that pyrazole-carboxaldehydes **2** was converted to 4-hydroxypyrazoles **86** upon treatment with *meta*-chloroperoxybenzoic acid (*m*CPBA). Next, 4-hydroxypyrazoles **86** reacted with propargyl bromide **87** in tetrahydrofuran (THF)/ DMF using NaH as a base to give *O*-propargylated pyrazole derivative **88**. The reaction of **88** with aryl aldoximes **89** afforded isoxazole functionalized pyrazole derivatives **90** (Scheme 38).



R = H, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4; R^1 = 4-H_3C-C_6H_4, C_6H_5, 4-F-C_6H_4; R^2 = 4-H_3CO-C_6H_4, 3,4,5-tri-H_3CO-C_6H_2, 4-F-C_6H_4; DCM: Dichloromethane

Scheme 38. Synthesis of isoxazole functionalized pyrazole derivatives **90.**

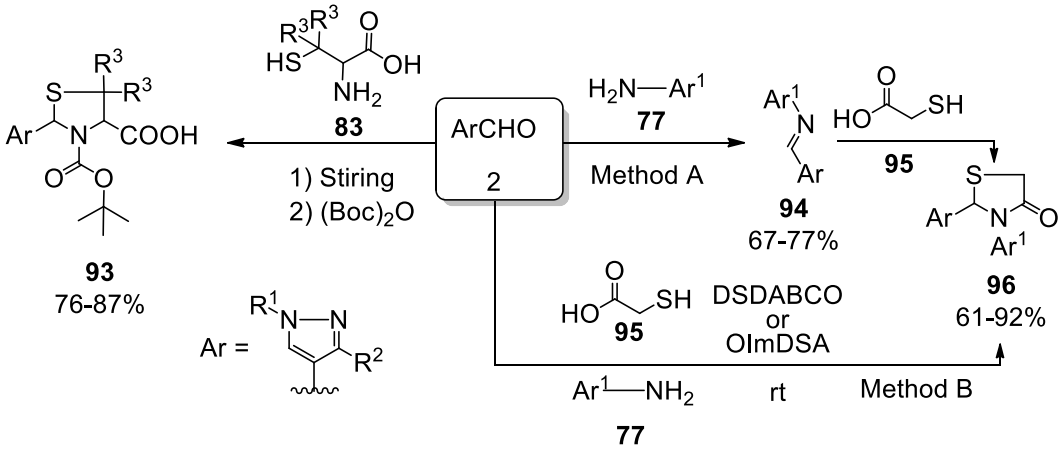
Reaction of *α*,*β*-unsaturated ketones **42** with an aqueous solution of hydroxylamine hydrochloride **91,** and sodium acetate in ethanol at reflux gave isoxazole derivatives **92**[59,104,114,135] (Scheme 39).



Ar^1 = C_6H_5, 4-H_2N-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 2-HO-C_6H_4, 4-HO-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, Thiophen-2-yl, 10*H*-Phenothiazin-2-yl; Ar^2 = C_6H_5, 3-Cl-C_6H_4; Ar^3 = C_6H_5, 2-H_3CO-C_6H_4, 4-H_3CO-C_6H_4

Scheme 39. Synthesis of isoxazole derivatives **92.**

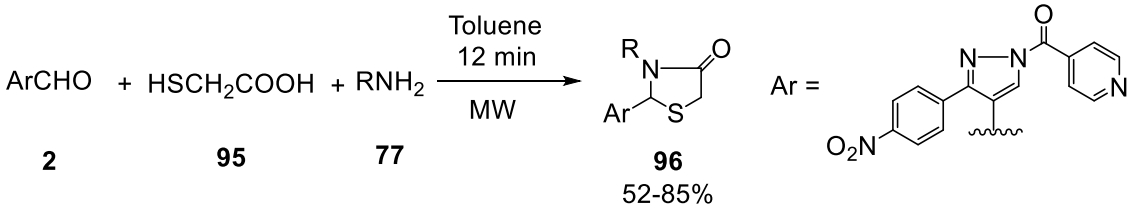
3.1.2.5. Thiazole derivatives. Heating a solution of pyrazole-carboxaldehyde **2** with *L*-cysteine (R^3 = H) or *L*-penicillamine (R^3 = CH_3) **83** followed by *N*-protection using $(Boc)_2O$ provided thiazolidine-4-carboxylic acid **93**.[133,136] Condensation of pyrazole-4-carboxaldehyde **2** with arylamine **77** gave Schiff's bases **94** which reacted with thioglycolic acid **95** to give the thiazolidinedione derivatives **99**[136,137] (Method A). Taherkhorsand *et al*.[138] and Nikpassand *et al*.[139] reported also the synthesis of 2-pyrazole-3-phenyl-1,3-thiazolidine-4-ones **96** *via* a multi-component reaction of pyrazole-carboxaldehydes **2**, arylamine **77**, thioglycolic acid **95** in the presence of DSDABCOC[138] or OImDSA[139] (Method B) (Scheme 40).
DSDABCOC: ionic liquid 1,4-disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride
OImDSA: 2-oxoimidazolidine-1,3-disulfonic acid



R^1 = C_6H_5, 5-Bromothiophen-2-yl; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 3-O_2N-C_6H_4, 4-HO-C_6H_4; R^3 = H, CH_3; Ar^1 = 4-H_3CO-C_6H_4, 2-H_3C-4-O_2N-C_6H_3, C_6H_5, 4-O_2N-C_6H_4, 4-H_3C-C_6H_4, 4-Fluorobenzyl, 4-(4-Chlorophenyl)thiazol-2-yl.

Scheme 40. Synthesis of 2-pyrazole-3-phenyl-1,3-thiazolidine-4-ones **96.**

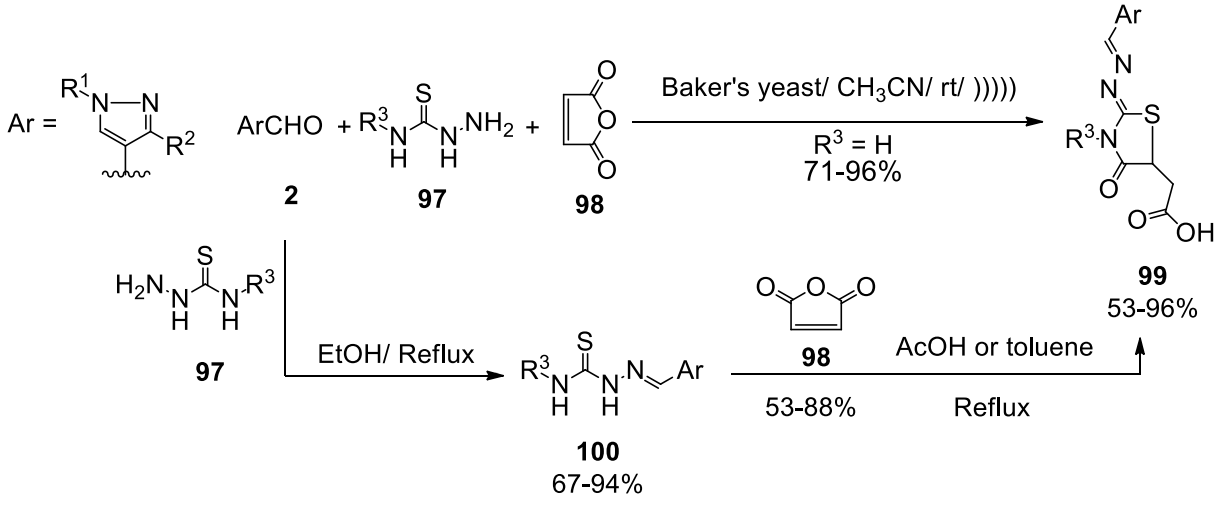
Visagaperumal *et al.*[70] reported that thiazolidin-4-ones **96** has been synthesized by stirring of pyrazole-4-carboxaldehyde **2** with 2-mercaptoacetic acid **95** and different substituted aromatic amines **77** in dry toluene under the effect of microwave heating for 12 min (Scheme 41).



R = C_6H_5, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-C_7H_7O, 4-C_7H_7, 4-C_8H_7O, 4-$C_7H_5O_2$, 3-O_2N-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4.

Scheme 41. Synthesis of thiazolidin-4-ones **96.**

One-pot multi-component cyclocondensation of pyrazole-4-carboxaldehydes **2**, thiosemicarbazide **97,** and maleic anhydride **98** using baker's yeast as a catalyst afforded pyrazol-4-yl substituted thiazoles **99**.[140] Thiazoles **99** were also synthesized via two-steps-reactions. Thus, cyclocondensation reaction of pyrazole-4-carboxaldehydes **2** with substituted thiosemicarbazide derivatives **97** afforded the corresponding thiosemicarbazone derivatives **100**[62,103,126,141–147] which underwent cyclization with maleic anhydride **98** to furnish thiazole derivatives **99**[144,146] (Scheme 42).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4; R^3 = H, C_6H_5, 4-H_3CO-C_6H_4, 4-F-C_6H_4, Cyclohexane.

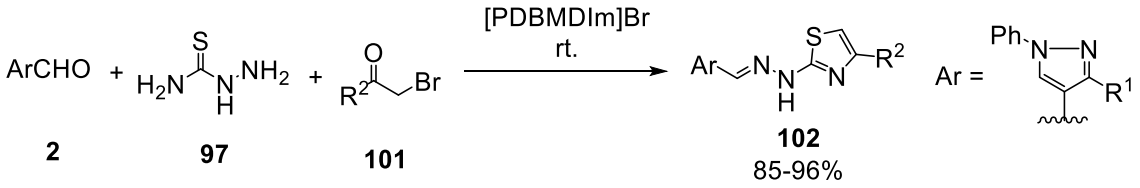
Scheme 42. Synthesis of thiazole derivatives **99.**

Nikpassand *et al.*[148] reported that stirring a mixture of a pyrazole-carboxaldehyde **2**, thiosemicarbazide **97**, bromoacetophenone **101** in the presence of [PDBMDIm]Br as a catalyst at room temperature afforded 2-hydrazonyl-4-phenylthiazoles **102** (Scheme 43).

Cyclization of thiosemicarbazone derivatives **100** either by ethyl chloroacetate,[141] methyl *α*-bromopropionate,[141] ethyl bromoacetate,[62,142,143] chloroacetic acid,[149] diethyl-2-bromomalonate[146] or methyl bromoacetate[126] **64** furnished the thiazole derivatives **103** (Scheme 44).

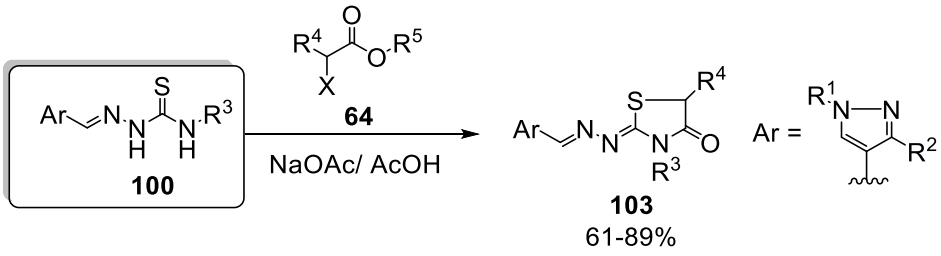
Similarly, Some 4-arylthiazol-2-yl-hydrazines derivatives **104**[62,126,141–144,146,147] were prepared by reaction of the appropriate α-haloketones **101** with the corresponding thiosemicarbazone **100**. The reaction of thiosemicarbazone derivatives **100** with the appropriate hydrazonoyl halides **105** gave 5-phenylazo-thiazol-2-yl-

hydrazine derivative **106**.[103] Compounds **106** were alternatively obtained by reaction of ω-bromoacetophenone **101** with **100** to give 1-((1,3-diphenyl-1*H*-pyrazol-4- yl)methylene)-2-(4-phenylthiazol-2-yl)hydrazine **107**[103] followed by reaction with benzenediazonium chloride **108**[103] (Scheme 45).



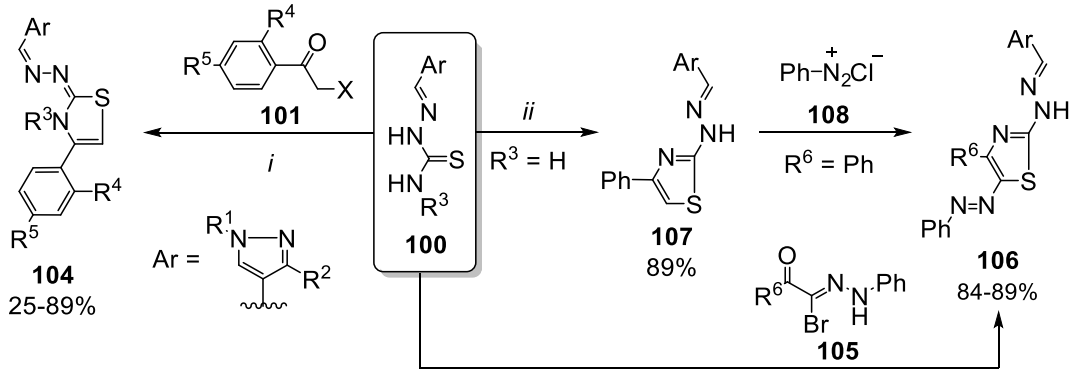
[PDBMDIm]Br = 3,3′-(pentane-1,5-diyl)bis(1,2-dimethyl-1*H*imidazol-3-ium)bromide
R^1 = 4-H_3C-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, C_6H_5, 4-HO-C_6H_4, 4-HO-C_6H_4; R^2 = 2-HO-C_6H_4, C_6H_5, 2-Br-C_6H_4, 2-H_3CO-C_6H_4, 3-O_2N-C_6H_4, 3-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-HO-C_6H_4.

Scheme 43. Synthesis of 2-hydrazonyl-4-phenylthiazoles **102.**



R^1 = C_6H_5, 4-H_2NO_2S-C_6H_4, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 5-Bromothiophen-2-yl; R^3 = H, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-H_3CO-C_6H_4, Cyclohexane; R^4 = H, CH_3, COOEt; R^5 = H, CH_3, C_2H_5; X = Br, Cl.

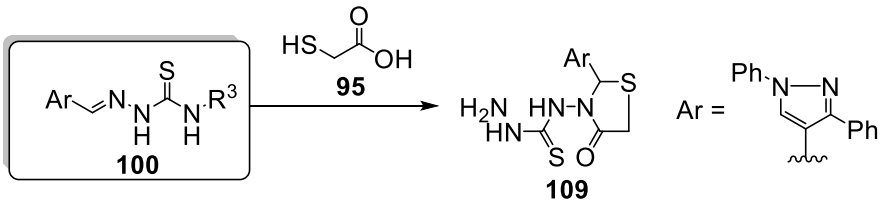
Scheme 44. Synthesis of thiazole derivatives **103.**



R^1 = C_6H_5, 3-H_3C-C_6H_4, 4-H_2NO_2S-C_6H_4, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-HO-C_6H_4, 4-O_2N-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-(C_6H_5-CH_2-O)-C_6H_4, 5-Bromothiophen-2-yl; R^3 = H, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-H_3CO-C_6H_4, Cyclohexane; R^4 = H, F, NO_2, OCH_3, OH; R^5 = H, SO_2CH_3, F, Cl, Br, CH_3, NO_2, C_6H_5; R^6 = H, CH_3, C_6H_5, 2-C_8H_5O; X = Cl, Br; *i* = PEG-400/ stir. at r. t.,[147] ethanol/ sodium acetate/ reflux,[146] dry ethanol/ reflux ;[142] *ii* = $PhCOCH_2Br$/ ethanol/ sodium acetate/ reflux.[103]

Scheme 45. Synthesis of thiazol-2-yl-hydrazines derivatives **104** and **106.**

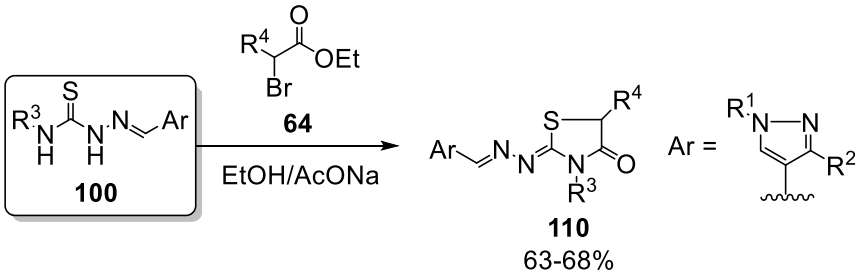
On the other hand, treatment of pyrazolyl hydrazone derivative **100** with thioglycolic acid **95** acid gave the corresponding thiazolidinedione derivative **109**[145] (Scheme 46).



Scheme 46. Synthesis of thiazolidinedione derivatives **109.**

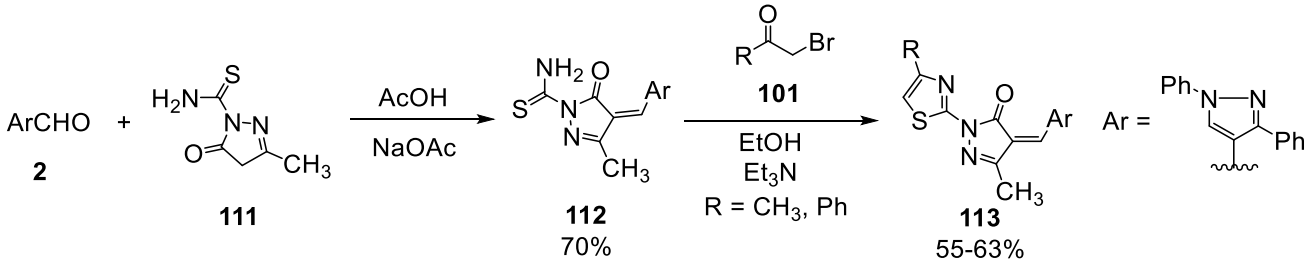
Treatment of thiosemicarbazone derivatives **100** with ethyl bromoacetate[142] or diethyl-2-bromomalonate[146] **64** in the presence of sodium acetate led to the corresponding thiazolidinediones **110**[142,146] (Scheme 47).

Gaffer *et al.*[150] reported that condensation of pyrazolin-5-one derivative **111** with Pyrazole-carboxaldehyde **2** in acetic acid and fused sodium acetate yielded the corresponding condensation product **112** which underwent further heterocyclization reaction with bromoacetone and phenacyl bromide **101** to give the corresponding thiazolyl-pyrazole derivatives **113** (Scheme 48).



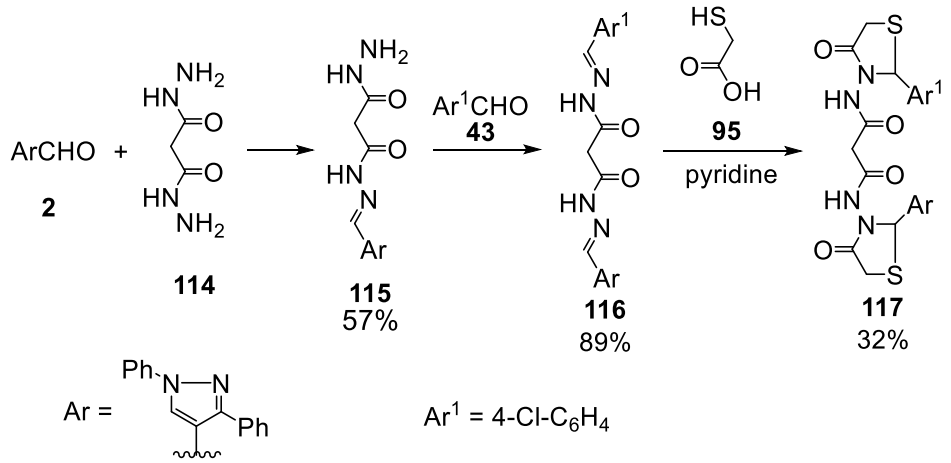
R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = 4-H_3OC-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4; R^3 = H, C_6H_5; R^4 = H, COC_2H_5

Scheme 47. Synthesis of thiazolidinediones **110.**



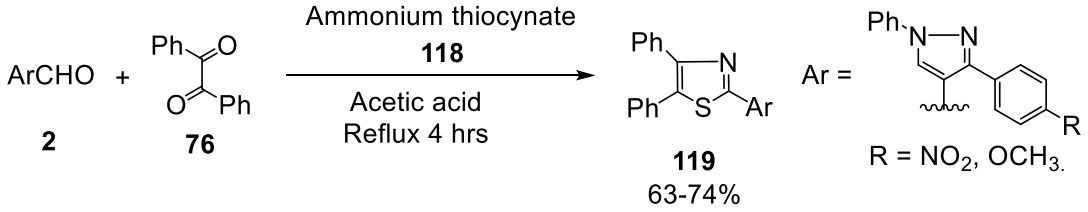
Scheme 48. Synthesis of thiazolyl-pyrazole derivatives **113.**

Treatment of pyrazole-carboxaldehyde **2** with malonic acid hydrazide **114** afforded pyrazolyl malonohydrazone derivative **115** which reacted with *p*-chlorobenzaldehyde **43** to give the corresponding benzylidene derivative **116**. The reaction of **116** with thioglycolic acid **95** gave the dithiazolidinone derivative **117**[145] (Scheme 49).



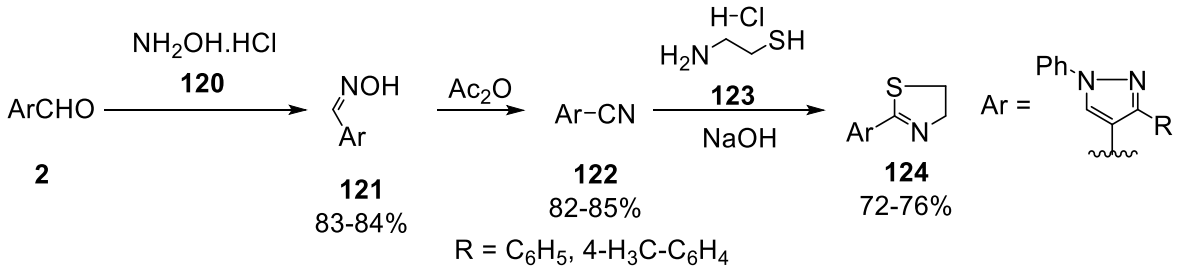
Scheme 49. Synthesis of dithiazolidinone derivative **117.**

Bhatt and Sharma[130] reported the synthesis of tri-substituted thiazoles derivatives **119** by the reaction of benzil **76** with pyrazole-4-carboxaldehydes **2** and ammonium thiocyanate **118** (Scheme 50).



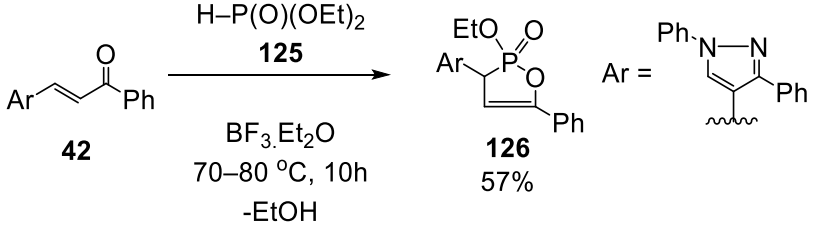
Scheme 50. Synthesis of tri-substituted thiazoles derivatives **119.**

Bekhit *et al.*[136] reported that 3-aryl-1-phenyl-1*H*-pyrazole-4-aldoximes **121** were obtained by the condensation of 3-aryl-1-phenyl-1*H*-pyrazole-4-carboxaldehydes **2** with hydroxylamine hydrochloride **120** in ethanol containing anhydrous sodium acetate. Dehydration of the oximes **121** with acetic anhydride (Ac_2O) afforded the cyano derivatives **122**. Cyclization of the cyano derivatives **122** with cysteamine hydrochloride **123** in the presence of sodium hydroxide afforded thiazolidine derivatives **124** (Scheme 51).



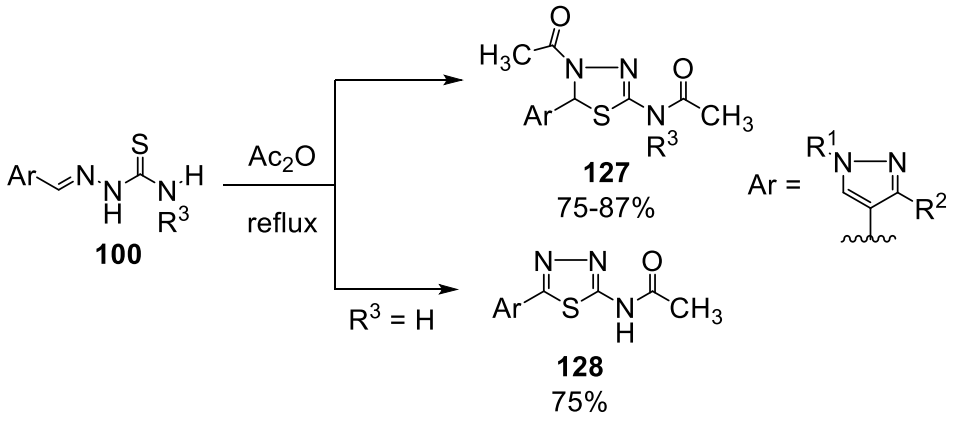
Scheme 51. Synthesis of thiazolidine derivatives **124.**

3.1.2.6. 1,2-Oxaphosphole derivatives. Ali[117] reported that heating of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one **42**[116] with diethylphosphite **125** in boron trifluoride etherate ($BF_3.Et_2O$) afforded 4-(2-ethoxy-2-oxido-5-phenyl-2,3-dihydro-1,2-oxaphosphol-3-yl)-1,3-diphenyl-1*H*-pyrazole **126** (Scheme 52).



Scheme 52. Synthesis of 1,3-diphenyl-1*H*-pyrazole **126.**

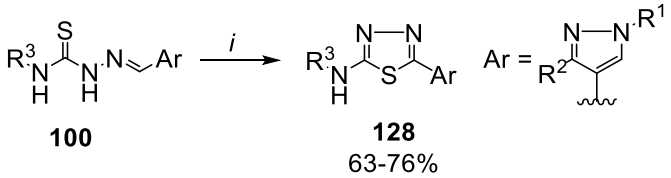
3.1.3. Monocyclic five-membered with three heteroatoms. 3.1.3.1. 1,3,4-Thiadiazole derivatives. Heating of thiosemicarbazone derivatives **100** in acetic anhydride at reflux gave the corresponding 3-acetyl-2,3-dihydro-1,3,4-thiadiazole derivatives **127**[62,142,143] or corresponding 1,3,4-thiadiazole derivatives **128**[126] (Scheme 53).



R^1 = C_6H_5, 4-(H_2NO_2S)-C_6H_4; R^2 = 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3CO-C_6H_4, C_6H_5, 4-($H_5C_6H_2CO$)-C_6H_4; R^3 = H, C_6H_5, 4-Cl-C_6H_4.

Scheme 53. Synthesis of 1,3,4-thiadiazole derivatives **128.**

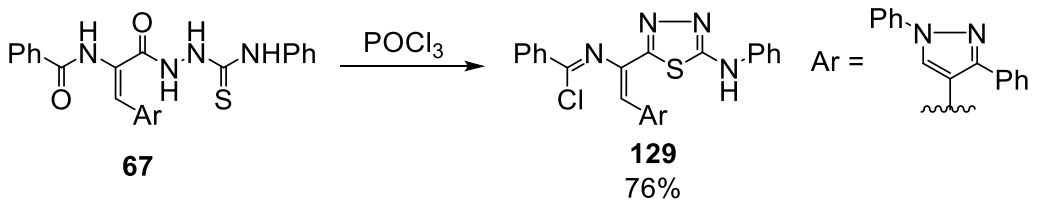
Oxidative cyclization of the thiosemicarbazones **100** afforded the corresponding 1,3,4-thiaoxadiazoles **128**[151, 143] (Scheme 54).



R^1 = C_6H_5, 2-H_3CO-C_6H_4, 2-H_3C-C_6H_4, 4-Cl-C_6H_4, 2,4-di(O_2N)-C_6H_3, 4-(H_2NO_2S)-C_6H_4; R^2 = C_6H_5, 7-HO-4-H_3C-2-oxo-2*H*-chromen-8-yl; R^3 = H, C_6H_5, 4-Cl-C_6H_4; *i* = Br_2/ CH_3COOH,[151] $FeCl_3$/ (Dioxane/ ethanol)/ Reflux.[143]

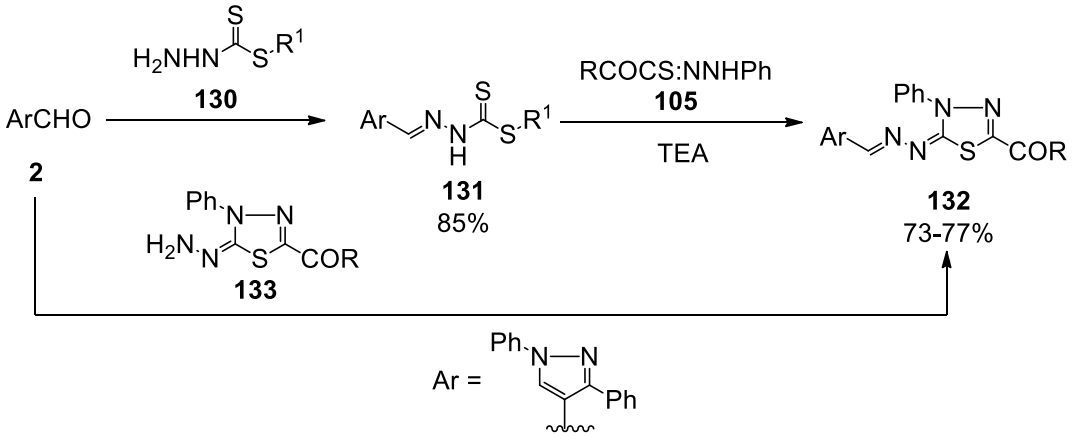
Scheme 54. Synthesis of 1,3,4-thiaoxadiazoles **128.**

Abou Elmagd *et al.*[123] reported that heating of thiosemicarbazide **67**[124] with phosphoryl trichloride at reflux afforded 1,3,4-thiadiazole derivatives **129** (Scheme 55).



Scheme 55. Synthesis of 1,3,4-thiadiazole derivatives **129.**

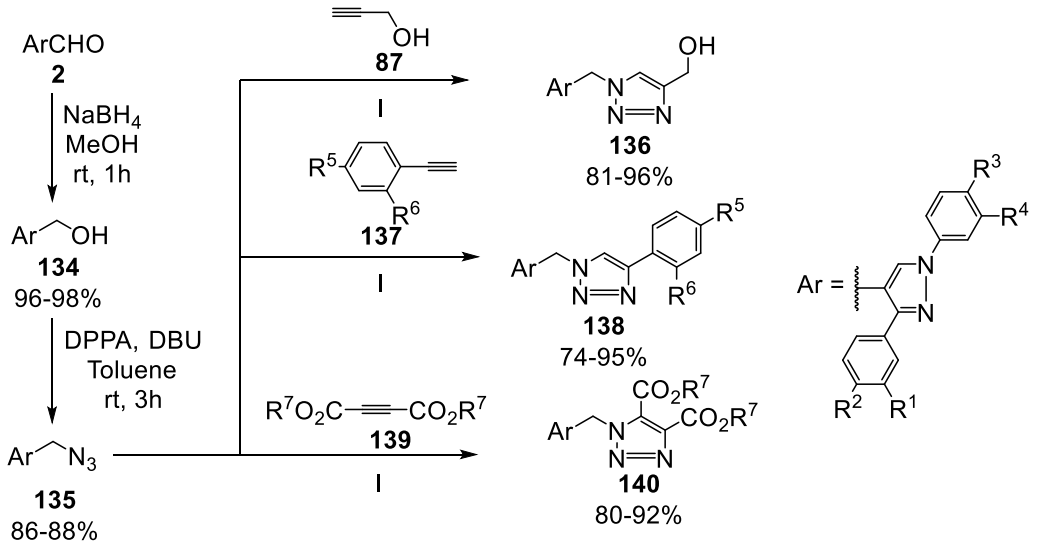
Treatment of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** with the appropriate methyl(benzyl)carbodithioate **130** in 2-propanol gave the corresponding alkyl carbodithioates **131**. The reaction of the appropriate hydrazonoyl halides **105** with alkyl carbodithioates **131** in ethanol containing triethylamine (TEA) afforded 2,3-dihydro-1,3,4-thiadiazoles **132**. Compounds **132** were alternatively obtained by the reaction of ethyl 2-hydrazono-3-phenyl-1,3,4-thidiazoline-5-carboxylate **133** with pyrazole-carboxaldehyde **2**[103] (Scheme 56).



R = CH_3, C_6H_5, 2-C_8H_5, OC_2H_5, NHC_6H_5; R^1 = CH_3, $H_2CC_6H_5$.

Scheme 56. Synthesis of 2,3-dihydro-1,3,4-thiadiazoles **132.**

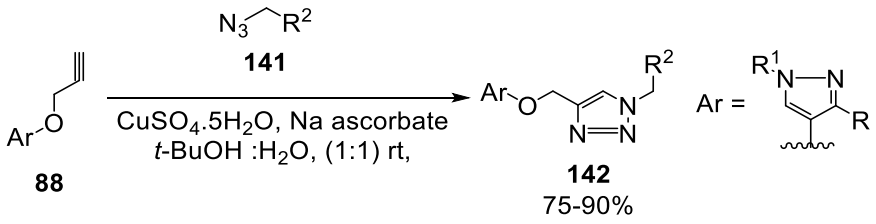
3.1.3.2. 1,2,3-Triazole derivatives. Dayakar *et al*.[152] reported that reduction of pyrazole-carboxaldehydes **2** using sodium borohydride ($NaBH_4$) provided the corresponding alcohols **134** which was converted to the corresponding azides **135** in the presence of diphenyl phosphoryl azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Reaction of azides **135** with propargyl alcohol **87**, phenyl acetylenes **137** and dimethyl/ diethyl acetylene dicarboxylate **139** in the presence of copper(II) sulfate pentahydrate ($CuSO_4.5H_2O$)/ sodium ascorbate in aqueous alcohol medium provided the corresponding pyrazolyl-1*H*-1,2,3-triazolyl alcohols **136**, pyrazolyl-1*H*-1,2,3-triazoles **138** and pyrazolyl-1*H*-1,2,3-triazolyl carboxylates **140**, respectively (Scheme 57).



R^1 = H, Cl; R^2 = H, Cl, CH_3, OCH_3; R^3 = H, Cl, CH_3; R^4 = H, CH_3; R^5 =H, CF_3, NH_2, $N(CH_3)_2$, F, Cl, Br, CH_3, OCH_3, OCH_3; R^6 = H, CF_3, CH_3; R^7 = CH_3, C_2H_5.

Scheme 57. Synthesis of pyrazolyl-1*H*-1,2,3-triazoles **136**, **138** and **140.**

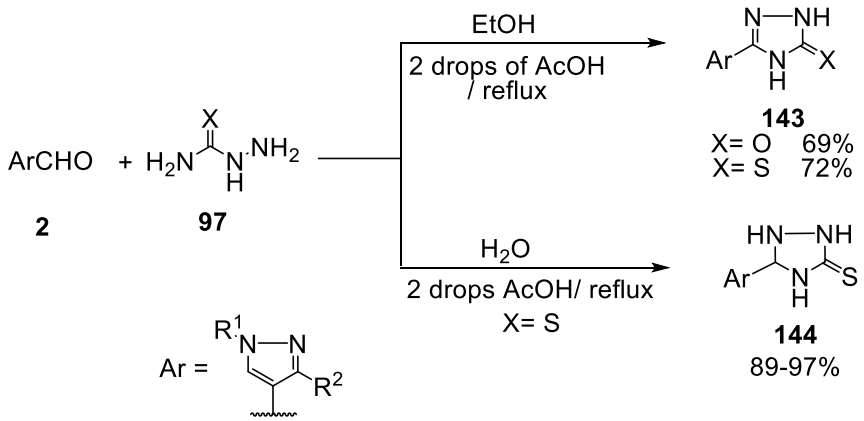
The reaction of aryl azides **141** with *O*-propargylated pyrazole derivatives **88** afforded the corresponding 1,4-disubstituted-1,2,3-triazole-linked pyrazole hybrids **142**[134] (Scheme 58).



R = H, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4; R^1 = 4-H_3C-C_6H_4, C_6H_5, 4-F-C_6H_4, 4-F-C_6H_4; R^2 = C_6H_5, 2-Cl-C_6H_4, 2-Br-C_6H_4, 2-F-C_6H_4, 3-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4.
t-BuOH: *tert*-Butyl alcohol; NaH: Sodium hydride.

Scheme 58. Synthesis of 1,4-disubstituted-1,2,3-triazole-linked pyrazole hybrids **142.**

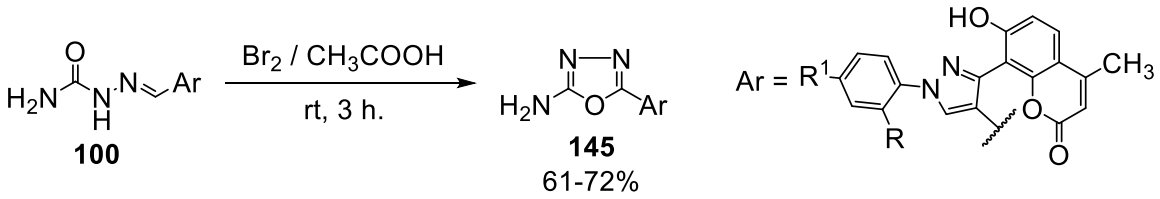
3.1.3.3. 1,2,4-Triazole derivatives. Heating of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde **2** with semicarbazide hydrochloride or thiosemicarbazide **97** in absolute ethanol at reflux in the presence of few drops of glacial acetic acid afforded 1,2,4-triazole-3(4*H*)-one **143**.[120] On the other hand, heating of pyrazole-carboxaldehyde **2** with thiosemicarbazide **97** in water as a green solvent afforded the 5-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1,2,4-triazolidine-3-thiones **144**[111] (Scheme 59).



R^1 = 3-Cl-C_6H_4; R^2 = 4-H_3CO-C_6H_4, C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4.

Scheme 59. Synthesis of 5-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1,2,4-triazolidine-3-thiones **144.**

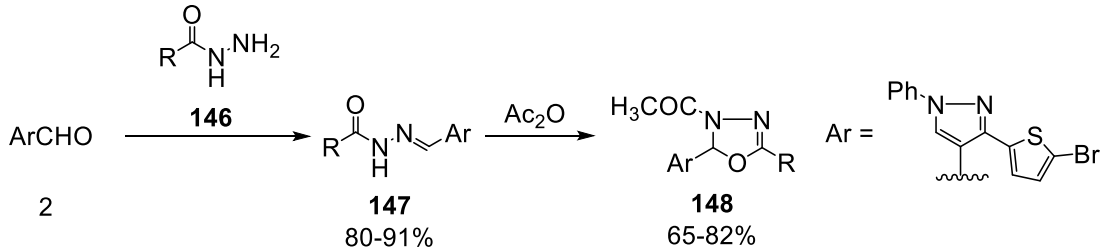
3.1.3.4. 1,3,4-Oxadiazole derivatives. Renuka *et al.*[151] reported that the oxidative cyclization of semicarbazones **100** using bromine as an oxidant in acetic acid at room temperature yielded the corresponding 1,3,4-oxadiazoles **145** (Scheme 60).



R = H, Cl, NO_2; R^1 = H, OCH_3, CH_3, NO_2.

Scheme 60. Synthesis of 1,3,4-oxadiazoles **145.**

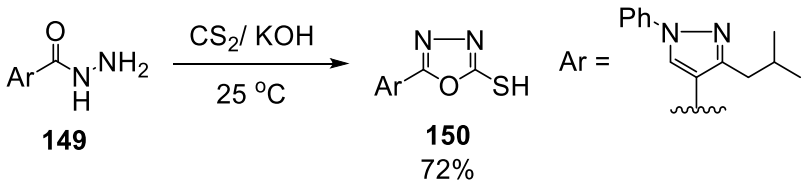
Farghaly *et al.*[62] reported the synthesis of aroylhydrazones **153** by heating the pyrazole-carboxaldehyde **2** with acid hydrazide **152** in ethanol. Cyclization of aroylhydrazones **153** upon treatment with acetic anhydride gave the corresponding oxadiazoline derivatives **154** (Scheme 61).



R = C_6H_5, $H_2CC_6H_5$, 4-Pyridyl

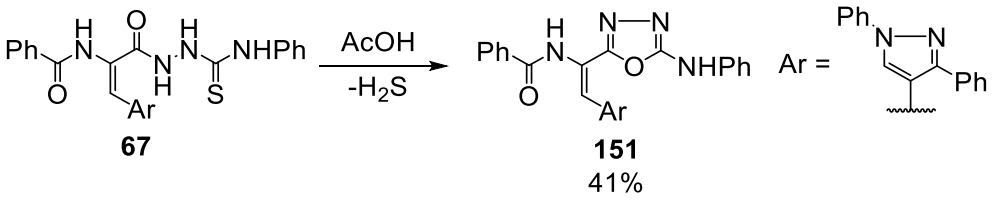
Scheme 61. Synthesis of oxadiazoline derivatives **154.**

Abu-Zaied *et al.*[65] reported that 5-(3-*iso*butyl-1-phenyl-1*H*-pyrazole-4-yl)-1,3,4-oxadiazole-2-thiol **150** was prepared by the reaction of ethanolic potassium hydroxide solution of 3-*iso*butyl-1-phenyl-1*H*-pyrazole-4-carbohydrazide **149** with carbon disulfide (CS_2) (Scheme 62).



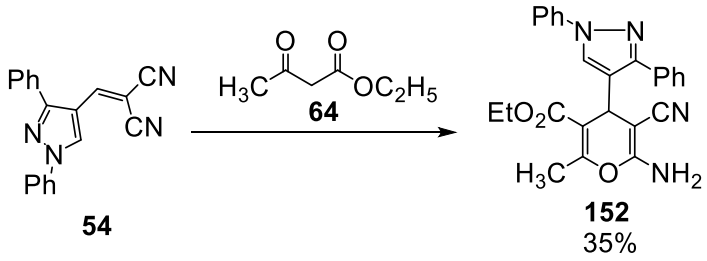
Scheme 62. Synthesis of 5-(3-*iso*butyl-1-phenyl-1*H*-pyrazole-4-yl)-1,3,4-oxadiazole-2-thiol **150.**

Abou Elmagd *et al.*[123] reported that heating of thiosemicarbazide derivative **67** in glacial acetic acid at reflux afforded the oxazolone derivative **151** (Scheme 63).



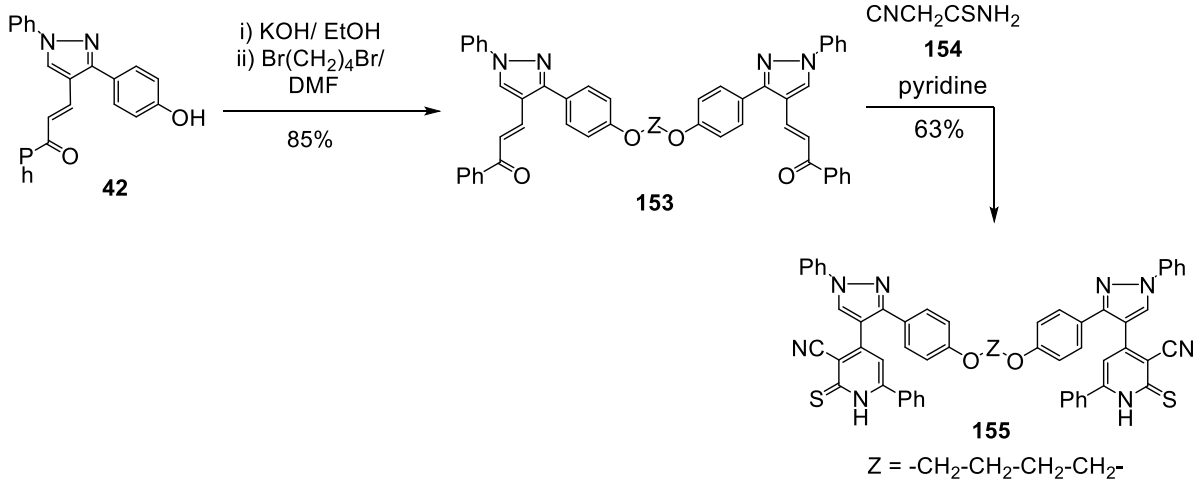
Scheme 63. Synthesis of oxazolone derivative **151.**

3.1.4. Monocyclic six-membered with one heteroatom. 3.1.4.1. Pyran derivatives. Heating of 2-((1,3-diphenylpyrazol-4-yl)methylene)malononitrile **54** with ethyl acetoacetate **64** in methylene chloride at reflux in the presence of triethylamine gave the ethyl 6-amino-5-cyano-4-(1,3-diphenylpyrazol-4-yl)-2-methyl-4*H*-pyran-3-carboxylate derivative **152**[141] (Scheme 64).



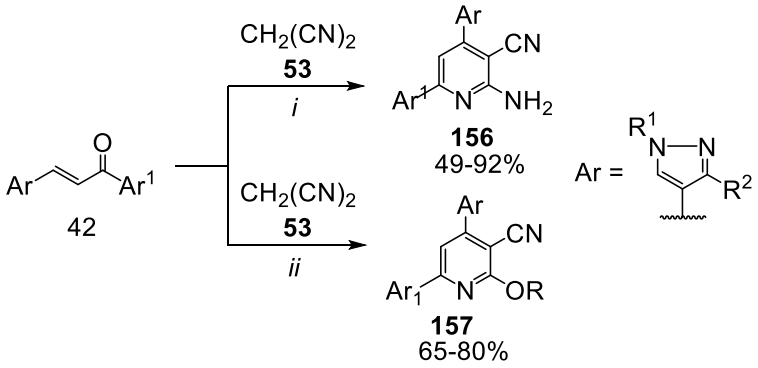
Scheme 64. Synthesis of ethyl 6-amino-5-cyano-4-(1,3-diphenylpyrazol-4-yl)-2-methyl-4*H*-pyran **152.**

3.1.4.2. Pyridine derivatives. 3.1.4.2.1. Synthesis of pyridine derivatives from chalcone carrying pyrazole. Hawass *et al*.[153] reported that the potassium salt of unsaturated carbonyl compounds **42** reacted with 1,4-dibromobutane to afford bis-unsaturated carbonyl compound **153**. Cyclocondensation of compound **153** with 2-cyanoethanethioamide **154** in pyridine at reflux gave bis(pyridine-2(1*H*)-thione) derivative **155** (Scheme 65).



Scheme 65. Synthesis of bis(pyridine-2(1*H*)-thione) derivative **155.**

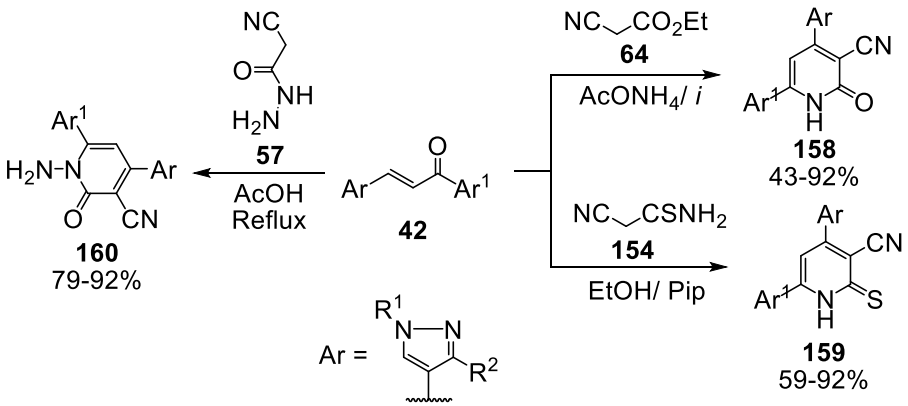
The reaction of *α*,*β*-unsaturated ketones **42** with malononitrile **53** in ethanol at reflux in the presence of ammonium acetate afforded the corresponding 2-amino-3-cyano-pyridine derivatives **156.**[112,114,154] On the other hand, a reaction of **42** with **53** in the presence of either sodium methoxide/ methanol or sodium ethoxide/ ethanol gave the corresponding 2-alkoxynicotinonitriles **157**[155] (Scheme 66).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3CO-C_6H_4; Ar^1 = C_6H_5, Benzofuran-2-yl, 2-Thienyl, 4-Br-C_6H_4, 4-H_3CO-C_6H_4; R^3 = CH_3, C_2H_5; ***i*** = Grinding 92%,[112] traditional 75%,[112] CH_3COONH_4/ ethanol/ reflux; [114,154] ***ii*** **=** RONa / ROH/ stirring/ r.t..

Scheme 66. Synthesis of 2-amino-3-cyano-pyridine derivatives **156** and 2-alkoxynicotinonitriles **157.**

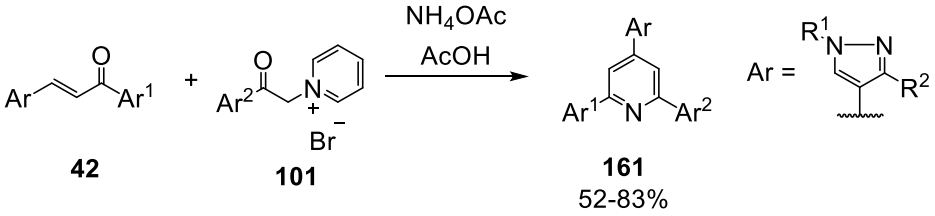
Heterocyclization of chalcones carrying pyrazole **42** with ethyl cyanoacetate **64** and ammonium acetate gave the corresponding 2-oxo-1,2-dihydropyridine-3-carbonitrile **158.**[112,114,135,141,156,157] On the other hand, heating chalcones **3** with cynothioacetamide **154** in ethanol at reflux afforded the corresponding 3-cyano-pyridine-2(1*H*)-thiones **159.**[112,141,153,157] Moreover, reaction of chalcones **42** with 2-cyanoacetohydrazide **57** afforded 1-amino-2-oxo-1,2-dihydropyridine-3-carbonitrile **160**[112] (Scheme 67).



R^1 = 4-Cl-C_6H_4, 4-H_3C-C_6H_4, C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 2-H_3CO-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-HO-C_6H_4; Ar^1 = C_6H_5, 4-H_2N-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 2-HO-C_6H_4, 4-HO-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, 2-Thienyl, Benzofuran-2-yl; ***i*** = ethanol/ reflux,[114,135,156] AcOH/ reflux,[112] Oil path (150 °C).[141,157]

Scheme 67. Synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile **158** and 3-cyano-pyridine-2(1*H*)-thiones **159.**

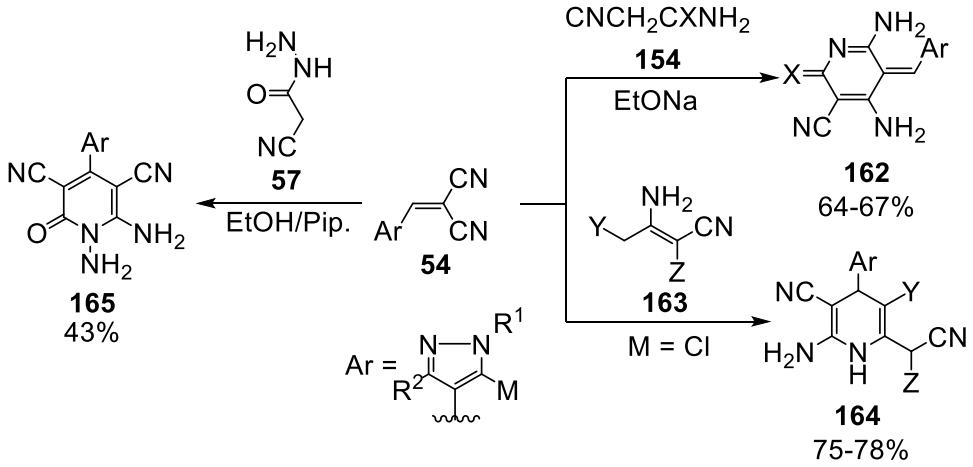
Heating of *α*,*β*-unsaturated ketones **42** with different phenacyl pyridium bromides **101** in acetic acid at reflux in the presence of ammonium acetate under Kröhnke's conditions gave the pyridinyl pyrazoles **161**[158–160] (Scheme 68).



R^1 = 2,4-di-F-C_6H_3, C_6H_5; R^2 = 4-Br-C_6H_4, C_6H_5, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4; Ar^1 = C_6H_5, 4-Br-C_6H_4, 4-H_3C-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 2-oxo-2*H*-chromen-3-yl, 8-H_3CO-2-oxo-2*H*-chromen-3-yl; Ar^2 = C_6H_5, 4-Cl-C_6H_4, 4-Methyl-2-oxo-3-phenyl-2*H*-chromen-6-yl, 8-H_3C-2-oxo-2*H*-chromen-3-yl, 8-Br-2-oxo-2*H*-chromen-3-yl, 2-oxo-2*H*-chromen-3-yl, 8-H_3CO-2-oxo-2*H*-chromen-3-yl, 3-oxo-3*H*-benzo[*f*]chromen-2-yl.

Scheme 68. Synthesis of pyridinyl pyrazoles **161.**

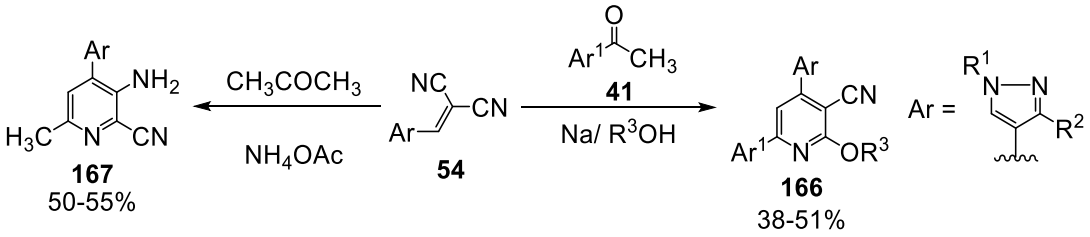
3.1.4.2.2. Synthesis of pyridine derivatives from aryliden malononitrile carrying pyrazole. The reaction of pyrazol-4-ylmethylene-malononitrile **54** and 2-cyanoacetamide or 2-cyanothioacetamide **154** in sodium ethoxide at reflux afforded 4,6-diamino-5-((1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methylene)-2,5-dihydro-2-oxo(thioxo)pyridine-3-carbonitriles **162.**[118] Reaction of pyrazol-4-ylmethylene-malononitrile **54** with malononitrile dimer, ethyl cyanoacetate dimer or ethyl-3-amino-2,4-dicyanobut-2-enoate **163** gave the corresponding dihydropyridine derivatives **164.**[161,162] On the other hand, reaction of **54** with 2-cyanoacetohydrazide **57** in ethanol in the presence of piperidine gave 1,6-diamino-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **165**[119] (Scheme 69).



R^1 = 3-Cl-C_6H_4, C_6H_5; R^2 = 4-H_3CO-C_6H_4, C_6H_5, 4-H_3C-C_6H_4; M = H, Cl; X = S, O; Y = CN, CO_2Et; Z = CN, CO_2Et.

Scheme 69. Synthesis of dihydropyridine derivatives **162** and **164.**

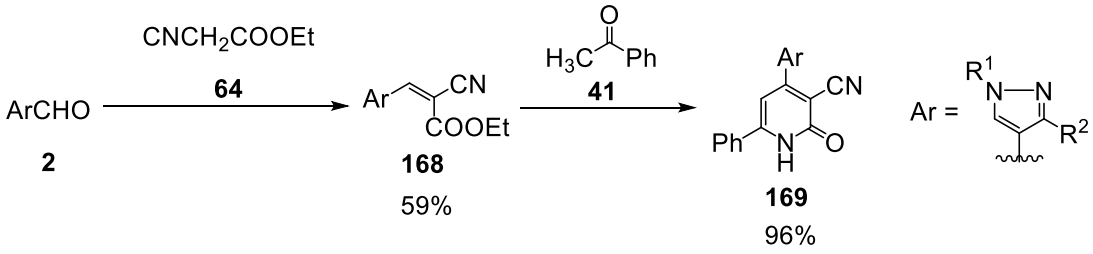
Condensation of pyrazol-4-ylmethylene malononitrile **54** with different aryl ketones **41** in the presence of sodium methoxide/ ethoxide gave the corresponding 2-alkyloxypyridine-3-carbonitriles **166**.[163] On the other hand, pyrazol-4-ylmethylene malononitrile **54**[125,164] could be cyclized with acetone and ammonium acetate to give the corresponding 3-amino-6-methylpyridine-2-carbonitriles **167**[125] (Scheme 70).



R^1 = 3-Cl-C_6H_4; R^2 = Pyren-1-yl; Ar^1 = C_6H_5, 2-Thienyl, 2-Pyridinyl, 2-Furanyl, 2-Pyrrolyl; R^3 = CH_3, C_2H_5.

Scheme 70. Synthesis of pyridine-2/3-carbonitriles **166** and **167.**

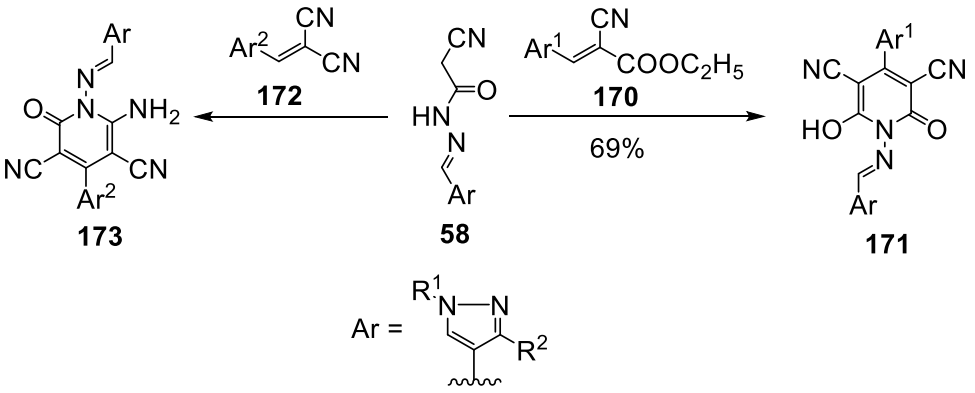
3.1.4.2.3. Synthesis of pyridine derivatives from ethyl arylidencyanoacetate linked to pyrazole moiety. The Knoevenagel condensation reaction of pyrazole-4-carboxaldehyde **2** with ethyl cyanoacetate **64** gave ethyl-2-cyano-acrylate derivative **168** which was then reacted with acetophenone **41** to afford 2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile **169**[165] (Scheme 71).



R^1 = C_6H_5; R^2 = 2-HO-3,4-di-H_3CO-C_6H_2.

Scheme 71. Synthesis of 2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carbonitrile **169.**

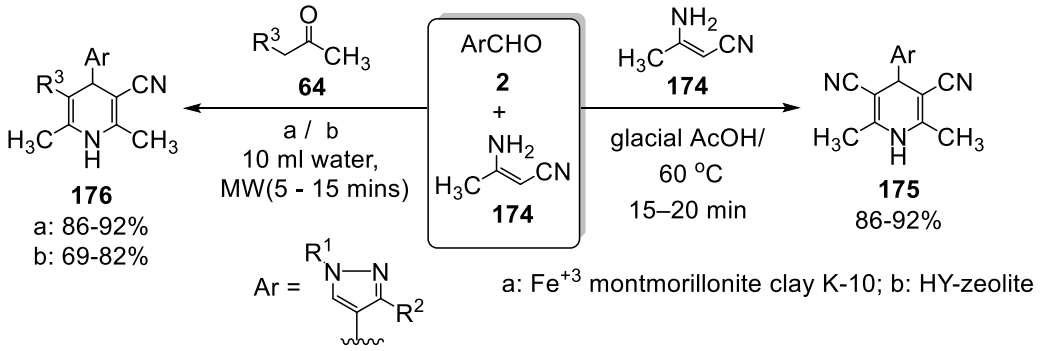
3.1.4.2.4. Synthesis of pyridine derivatives from hydrazone carrying pyrazole. Treatment of hydrazone derivative **58** with ethyl-2-cyano-3-arylacrylate **170** yielded pyridinone **171**.[166] On the other hand, the reaction of **58** with 2-arylidenemalononitrile derivatives **172** afforded 6-amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **173**[167,168] (Scheme 72).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3CO-C_6H_4; Ar^1 = 4-F-C_6H_4; Ar^2 = C_6H_5, 2-HO-C_6H_4, 4-HO-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-C1-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 3,4,5-$(H_3CO)_3$-C_6H_2, 2-O_2N-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, 2-Br-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 2-F_3C-C_6H_4, 4-F_3C-C_6H_4, 4-*iso*-Propyl-C_6H_4.

Scheme 72. Synthesis of pyridinones **171** and **173.**

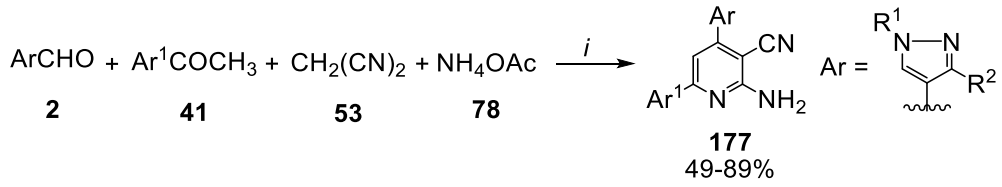
3.1.4.2.5. Synthesis of pyridine derivatives from reaction of pyrazole-carboxaldehyde with 3-aminocrotononitrile. The pseudo-multicomponent reaction of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** with two equivalent of 3-aminocrotononitrile **174** in glacial acetic acid afforded 3,5-dicyano-2,6-dimethyl-1,4-dihydropyridines **175**.[169] On the other hand, the one-pot multicomponent reaction of pyrazole-4-carboxaldehyde **2**, 3-aminocrotononitrile **174** and ethyl acetoacetate (EAA) or/ methyl acetoacetate (MAA) **64** in the presence of Fe^{+3} montmorillonite clay K-10 or HY-zeolite under microwave irradiation in aqueous medium afforded the corresponding 1,4-dihydropyridine derivatives **176**[170] (Scheme 73).



R^1 = C_6H_5; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 2-HO-C_6H_4, 2-H_3CO-C_6H_4, 3-O_2N-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 2-HO-C_6H_4, 4-F_3C-C_6H_4, 3-Cl-C_6H_4, 4-H_3CO-C_6H_4, 3-HO-C_6H_4; R^3 = $COOCH_3$, $COOC_2H_5$.

Scheme 73. Synthesis of 1,4-dihydropyridine derivatives **175** and **176.**

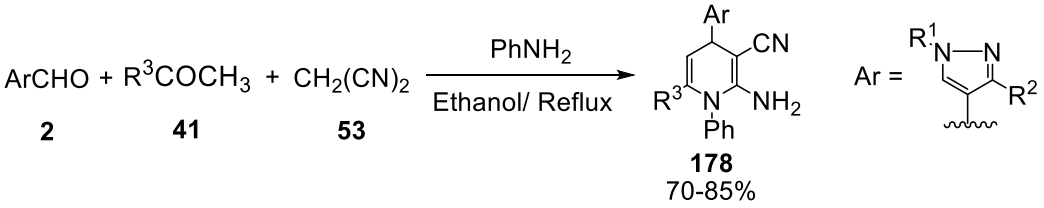
3.1.4.2.6. Synthesis of pyridine derivatives *via* one-pot reaction of pyrazole-carboxaldehyde. One-pot reaction of pyrazole-4-carboxaldehyde **2** with an appropriate aromatic ketone **41** and malononitrile **53** in the presence of ammonium acetate **78** furnished 2-amino-nicotinonitrile **177**[120,155,171,172] (Scheme 74).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, Pyren-1-yl, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 2-HO-C_6H_4, 2-CH_3O-C_6H_4, 3-O_2N-C_6H_4, 4-F-C_6H_4 4-OH-C_6H_4, 3-O_2N-C_6H_4, 4-H_2N-C_6H_4 ; Ar^1 = C_6H_5, 4-Cl-C_6H_4, 4-HO-C_6H_4, 4-H_3C-C_6H_4, 2-Thienyl, 2-F-C_6H_4, 2-H_3CO-C_6H_4, 2-Br-C_6H_4, 2-O_2N-C_6H_4, 4-HO-2-oxo-2*H*-chromen-3-yl, 4-HO-8-H_3C-2-oxo-2*H*-chromen-3-yl, 4-HO-5,8-di-H_3C-2-oxo-2*H*-chromen-3-yl, (4-H_3C-2-oxo-2*H*-chromen-7-yl)oxy, Benzofuran-2-yl. ***i*** = Ethanol/ reflux,[120,155] (Fe^{+3} K-10 clay or HY-zeolite)MW irradiation,[171] Ac_2O,[172] butanol/ reflux.[155]

Scheme 74. Synthesis of 2-amino-nicotinonitriles **177.**

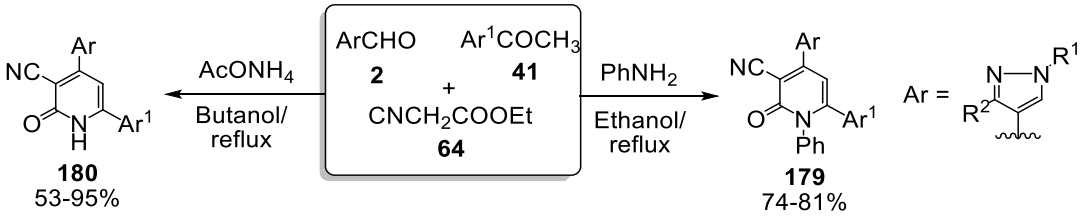
On the other hand, the reaction of equimolecular amounts of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2**, appropriate aromatic ketone **41** and malononitrile **53** in the presence of aniline afforded the corresponding pyridine-3-carbonitriles **178**[155] (Scheme 75).



R^1 = C_6H_5; R_2 = C_6H_5; R^3 = C_6H_5, 2-Thienyl; R^4 = C_6H_5, 4-H_3C-C_6H_4, 2-Thienyl.

Scheme 75. Synthesis of pyridine-3-carbonitriles **178.**

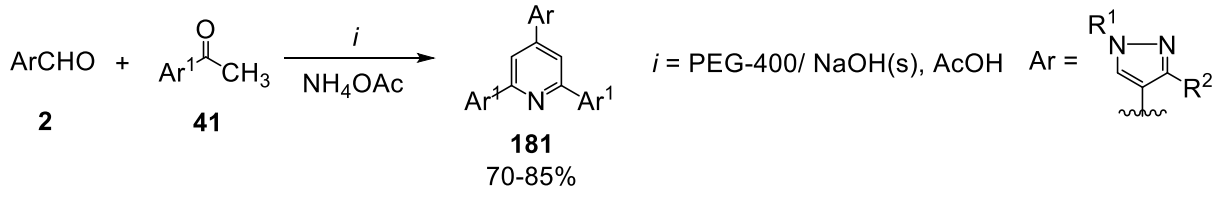
Heating pyrazole-4-carboxaldehyde **2** with aromatic ketone **41** and ethyl cyanoacetate **64** in the presence of ammonium acetate afforded 2-oxo-1,2-dihydropyridine-3-carbonitrile **179.**[120,155,173] Moreover, a mixture of pyrazole-4-carboxaldehyde **2** with aromatic ketone **41** and ethyl cyanoacetate **72** in the presence of aniline afforded the corresponding 2-oxo-1,2-dihydropyridine- oxo-1-phenyl-3-carbonitrile **180**[155] (Scheme 76).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-H_3CO-C_6H_4, Pyren-1-yl; Ar^1 = C_6H_5, 4-Cl-C_6H_4, 4-HO-C_6H_4, 4-H_3C-C_6H_4, 2-Thienyl, 2-F-C_6H_4, 2-H_3CO-C_6H_4, 2-Br-C_6H_4, 2-O_2N-C_6H_4.

Scheme 76. Synthesis of 1,2-dihydropyridine-3-carbonitriles **179** and **180.**

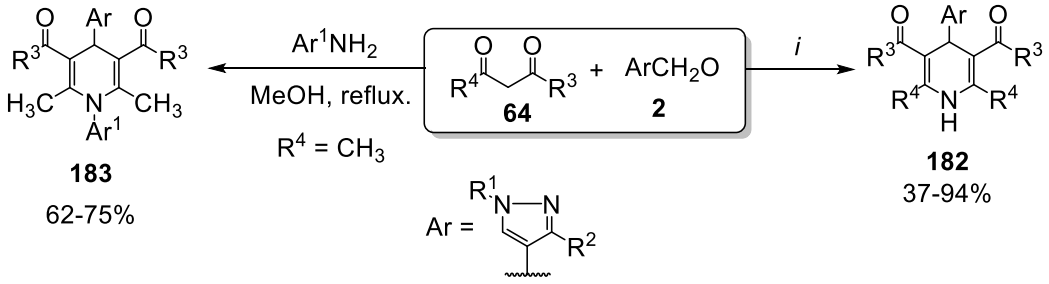
One-pot condensation of substituted pyrazol-4-carboxaldehydes **2**, two equivalents of acetophenones **41** and ammonium acetate in the presence of solid sodium hydroxide and using polyethylene glycol (PEG-400) as a green solvent[174] or acetic acid[175] afforded the corresponding 2,4,6-triaryl substituted pyridines (Krohnke pyridines) **181**[174,175] (Scheme 77).



R^1 = C_6H_5; R^2 = 4-Cl-C_6H_4, 4-HO-C_6H_4, C_6H_5; Ar^1 = 5-Cl-2-HO-C_6H_3, 3-Br-5-Cl-2-HO-C_6H_2, 3-I-5-Cl-2-HO-C_6H_2, 3-I-5-H_3C-2-HO-C_6H_2, 3-I-4-H_3C-2-HO-C_6H_2, 2-Mercapto-4-methyl-1-phenyl-1*H*-imidazol-5-yl.

Scheme 77. Synthesis of 2,4,6-triaryl-substituted pyridines.

Under various conditions, the Hantzsch condensation reaction of pyrazole-4-carboxaldehyde **2** with *β*-ketoester **64** and ammonium acetate or ammonia afforded the corresponding dihydropyridines **182.**[131,176–183] Similarly, *N*-aryl-1,4-dihydropyridines **183** were prepared by heating the 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2**, ethyl acetoacetate/acetylacetone **64** and substituted anilines[184] in methanol at reflux (Scheme 78).

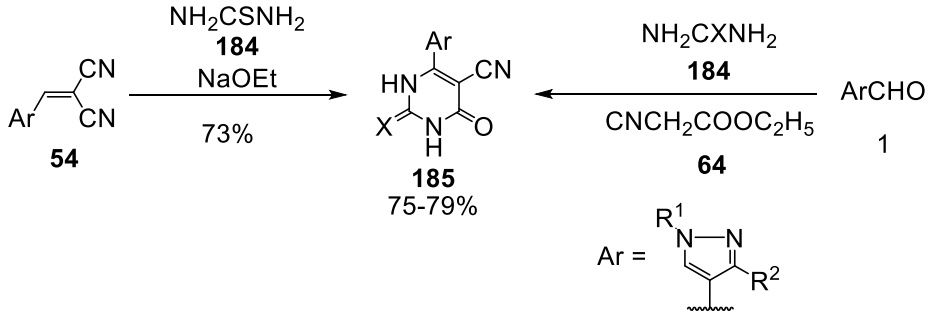


R^1 = C_6H_5, H; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-O_2N-C_6H_4, 3-H_3CO-C_6H_4, 4-H_3CO_2S-C_6H_4, 2-O_2N-C_6H_4, 4-H_3CS-C_6H_4, 3-O_2N-4-Cl-C_6H_3, Pyrazin-2-yl, 4-HO-C_6H_4, 3,4-di-Cl-C_6H_3, 3,4-di-F-C_6H_3; R^3 = OC_2H_5, OCH_3, CH_3; R^4 = CH_3, C_2H_5; Ar^1 = C_6H_5, 2-H_3C-C_6H_4, 3-H_3C-C_6H_4, 4-H_3C-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2-H_3CO-C_6H_4, 3-H_3CO-C_6H_4, 4-H_3CO-C_6H_4; ***i*** = NH_4OAc/ EtOH/ reflux,[176] NH_4OAc/ 20 mol% SA / EtOH/ reflux,[177] NH_4OAc/ MgO nanotube/ Acetonitrile, reflux,[178] NH_3 dropwise/ CH_3OH/ reflux,[179] NH_4OAc/ heat 80 °C/ silica 10 mol%,[180] NH_4OAc/ w. b / EtOH,[131] NH_4OAc/ Bismuth tungstate (Bi_2WO_6) 5 mol%,[181] NH_4OAc/ Gu.HCl/ 25-30°C,[182] NH_4OAc/ Acetonitrile, reflux, 40 °C, 300 W, 30 °C).[183]

Scheme 78. Synthesis of 1,4-dihydropyridines **182** and **183.**

3.1.5. Monocyclic six-membered with two heteroatoms. 3.1.5.1. Pyrimidine derivatives. Condensation of pyrazol-4-ylmethylene malononitrile **54** with thiourea **184** in the presence of sodium ethoxide solution at reflux gave the corresponding pyrimidine derivatives **195**.[165] Also, it was reported that the cyclocondensation of pyrazole-carboxaldehyde **2** with urea[120] or thiourea **184**[120,185] and ethyl cyanoacetate **64** in the presence of

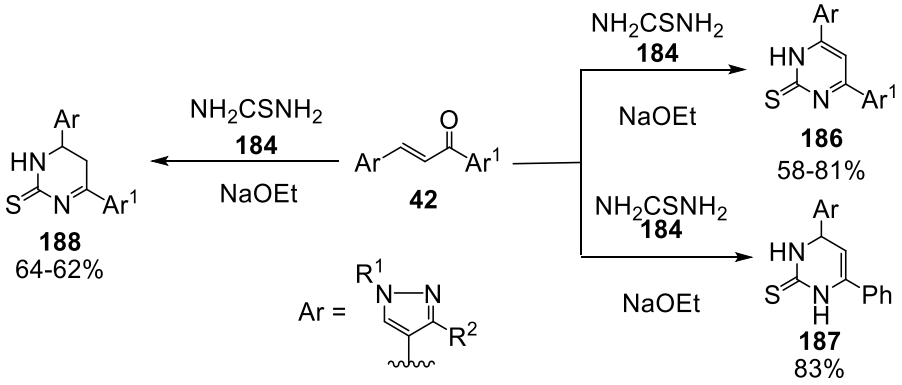
sodium ethoxide[120] or potassium carbonate[185] gave the corresponding 2-oxo(thioxo)pyrimidine derivatives **185** (Scheme 79).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = 2-HO-3,4-di-H_3CO-C_6H_2, 4-H_3CO-C_6H_4, C_6H_5; X = O, S

Scheme 79. Synthesis of 2-oxo(thioxo)pyrimidine derivatives **185.**

The reaction of *α,β*-unsaturated ketone **42** with thiourea **184** in the presence of sodium ethoxide solution at reflux was reported to give either the corresponding pyrimidine derivatives **186**,[104,114,115,165] **187**,[141,157] or **188**[186] (Scheme 80).

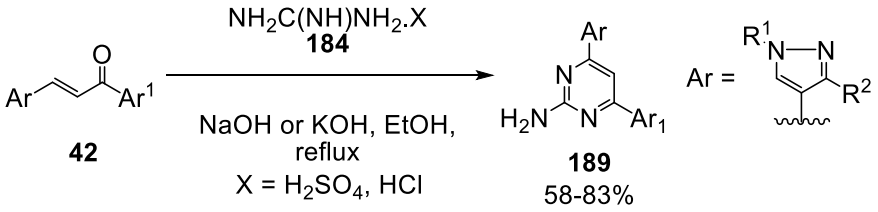


R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = 2-HO-3,4-di-H_3CO-C_6H_2, 4-H_3CO-C_6H_4, C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-HO-C_6H_4, 2,4-di-O_2N-C_6H_3, 2,4-di-H_3CO-C_6H_3, 2-HO-C_6H_4, Ar^1 = C_6H_5, 2-Oxo-2*H*-chromen-3-yl, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-HO-C_6H_4, 2-HO-C_6H_4, 4-O_2N-C_6H_4, 4-Br-C_6H_4, 2-Thienyl.

Scheme 80. Synthesis of pyrimidinethione derivatives **186**, **187** and **188.**

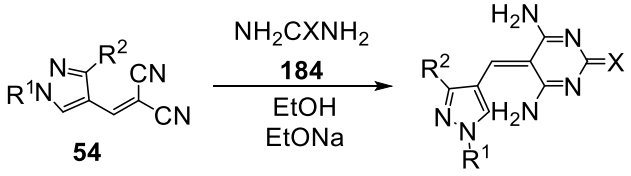
On the other hand treatment of chalcones **42** with guanidine hydrochloride or guanidine sulfate **184** at reflux afforded pyrimidin-2-amines **189**[104,109,114,115] (Scheme 81).

Ismail *et al*.[118] reported that the reaction of pyrazol-4-ylmethylene malononitrile **54** with urea or thiourea **184** afforded 4,6-diamino-5-benzylidenepyrimidin-2(5*H*)-ones/(thiones) **190** (Scheme 82).



R^1 = C_6H_5, 3-Cl-C_6H_4; R^2 = C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 3-Br-C_6H_4, 4-Br-C_6H_4, 3-O_2N-C_6H_4, 4-O_2N-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4; Ar^1 = Pyridin-3-yl, Thiophen-2-yl, C_6H_5, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-HO-C_6H_4, 2-HO-C_6H_4, 4-O_2N-C_6H_4, 4-Br-C_6H_4.

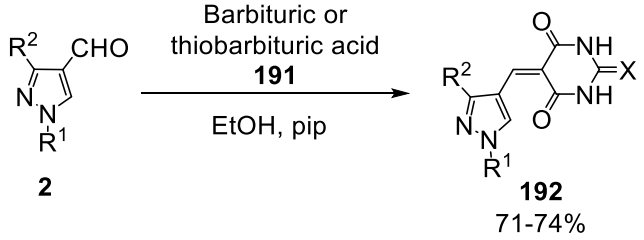
Scheme 81. Synthesis of pyrimidin-2-amines **189.**



R^1 = 3-Cl-C_6H_4; R^2 = 4-H_3CO-C_6H_4; X = O, S

Scheme 82. Synthesis of 4,6-diamino-5-benzylidenepyrimidin-2(5*H*)-ones/(thiones) **190.**

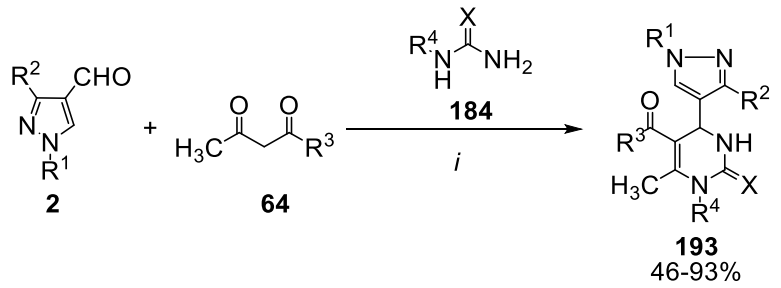
Knovenagel condensation of pyrazole-carboxaldehyde **2** with barbituric acid, thiobarbituric acid **191** afforded the corresponding pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione **192**[118,126] (Scheme 83).



R^1 = 3-Cl-C_6H_4, C_6H_5; R^2 = 4-H_3CO-C_6H_4, 4-($H_5C_6H_2CO$)-C_6H_4; X = O , S

Scheme 83. Synthesis of dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione **192.**

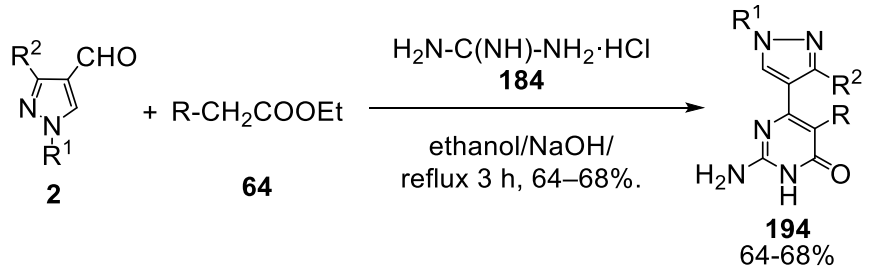
Under various conditions multi-component reaction of pyrazole-4-carboxaldehyde **2** with ethylacetoacetate,[120,131,187–189] methylacetoacetate,[131,187] acetylacetone[120,131] or butanamides[64,190,191] **64** and urea,[64,120,131,187,189–191] thiourea,[64,103,120,187,188,191] guanidine[187] or 1-methylurea[189] **184** afforded the corresponding 2-oxo (thioxo) pyrazole substituted pyrimidine derivatives **193** (Scheme 84).
TEAA = triethylammonium acetate; *p*-TsOH = *p*-toluenesulfonic acid



R^1 = C_6H_5, 3-Cl-C_6H_4, 4-F-C_6H_4, 2,4-di-F-C_6H_3; R^2 = 3,4-di-Cl-C_6H_3, 3,4 di-F-C_6H_3, 4-H_3CO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-O_2N-C_6H_4, 4-H_3C-C_6H_4, C_6H_5, 2,4-di-Cl-5-F-C_6H_2, 3-Br-C_6H_4, 3-O_2N-C_6H_4, CH_3, C_2H_5, 4-HO-C_6H_4, 2-HO-C_6H_4; R^3 = OC_2H_5, OCH_3, CH_3, Pyridin-2-yl-NH, (5-H_3C-pyridin-2-yl)-NH, (5-Br-pyridin-2-yl)-NH, C_6H_5NH, NH-(4-H_3C-C_6H_4), NH-(4-H_3CO-C_6H_4), NH-(4-Cl-C_6H_4), NH-(2-Cl-C_6H_4), NH-(4-O_2N-C_6H_4), NH-(2-F-C_6H_4), NH-(3-F-C_6H_4), NH-(3-Cl-C_6H_4), NH-(2-O_2N-C_6H_4), NH-(2-F-C_6H_4), NH-(3-O_2N-C_6H_4); R^4 = H, CH_3; X = S, O, NH. ***i*** = HCl/ EtOH,[103,120,131,187,188] TEAA,[190] *p*-TsOH 40 mol %/ EtOH,[64] CH_3OH/ HCl,[191] $FeCl_3.6H_2O$,[192] Phosphotungstic acid.[189]

Scheme 84. Synthesis of 2-oxo (thioxo) pyrazole substituted pyrimidine derivatives **193.**

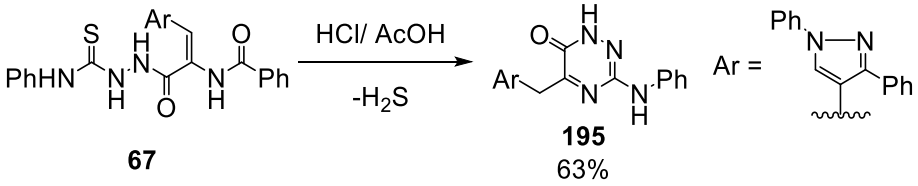
On the other hand condensation of 1-(3-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxaldehyde **2** with ethyl cyanoacetate or ethyl acetoacetate **64** in the presence of guanidine hydrochloride **184** gave 2-amino-5-cyano/acetyl-6-hydroxy-4-aryl pyrimidines **194**[104] (Scheme 85).



R^1 = 3-Cl-C_6H_4; R^2 = 4-H_3CO-C_6H_4; R = CN, CH_3CO

Scheme 85. Synthesis of 2-amino-5-cyano/acetyl-6-hydroxy-4-aryl pyrimidines **194.**

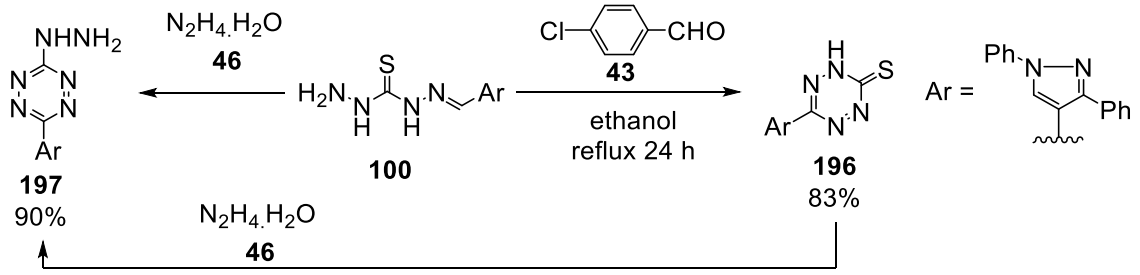
3.1.6. Monocyclic six-membered with three heteroatoms. 3.1.6.1. Triazine derivatives. Heating a solution of thiosemicarbazide derivative **67** in acetic acid and HCl at reflux produced 5-((1,3-diphenyl-1*H*-pyrazole-4-yl)methyl)-3-(phenylamino)-1,2,4-triazin-6(1*H*)-one **195**[123] (Scheme 86).



Scheme 86. Synthesis of 5-((1*H*-pyrazole-4-yl)methyl)-3-(phenylamino)-1,2,4-triazin-6(1*H*)-one **195.**

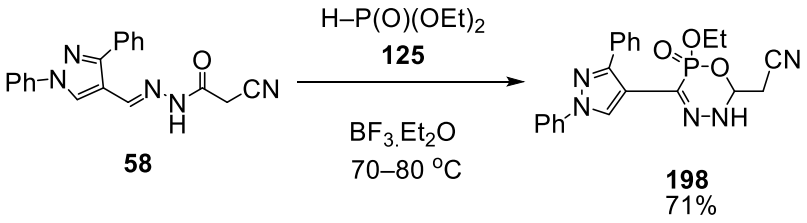
3.1.7. Monocyclic six-membered with four heteroatoms. 3.1.7.1. Tetrazine derivatives. El-Bordany *et al*.[145] reported that the reaction of pyrazolyl thiocarbohydrazone derivative **100** with 4-chlorobenzaldehyde **43** in

ethanol at reflux gave instead of a condensation product, the cyclized adduct pyrazolyl-tetrazinethione derivative **196**. Reaction of **100** with hydrazine hydrate **46** in ethanol at reflux afforded corresponding 1,2,4,5-tetrazine derivative **197.** Compound **197** was alternatively obtained by reaction of **196** with hydrazine hydrate **46** in ethanol at reflux (Scheme 87).



Scheme 87. Synthesis of pyrazolyl-tetrazinethione derivatives **196** and **197.**

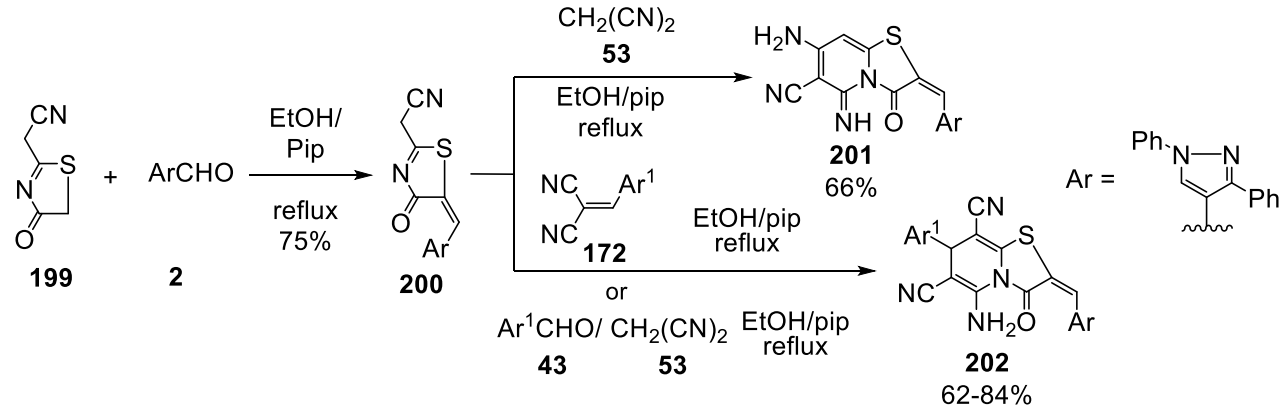
3.1.7.2. Oxadiazaphosphinin derivatives. Ali [117] reported that heating of 2-cyano-*N*-[1,3-diphenyl-1*H*-pyrazol-4-ylmethylidene]acetohydrazide **58** with diethyl phosphite **125** and boron trifluoride etherate afforded [2-ethoxy-2-oxido-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2*H*-1,4,5,2-oxadiazaphosphinin-6-yl]acetonitrile **198** in good yield (Scheme 88).



Scheme 88. Synthesis of [3-(1*H*-pyrazol-4-yl)-2*H*-1,4,5,2-oxadiazaphosphinin-6-yl]acetonitrile **198.**

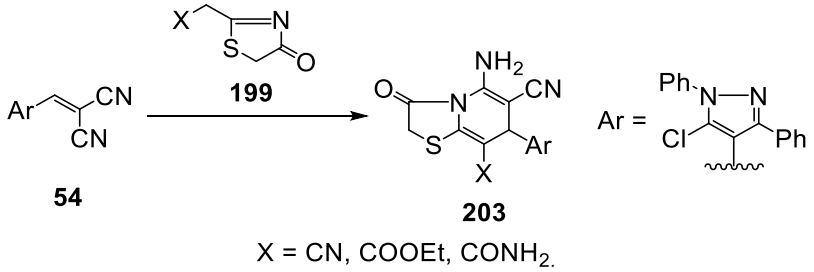
3.2. Pyrazole-substituted fused heterocyclic system

3.2.1. Pyrazole-substituted bicyclic systems. 3.2.1.1. Fused [5-6] system with two heteroatoms. 3.2.1.1.1. Thiazolo[3,2-*a*]pyridine derivative. El-Emary *et al.*[166] reported that condensation of 2-cyanomethyl-4-thiazolinone **199** with 1,3-diphenyl-pyrazole-4-carboxaldehyde **2** yielded 2-(5-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile **200**. Heating of **200** with malononitrile in ethanol at reflux gave the corresponding thiazolo[3,2-*a*]pyridine derivative **201**. On the other hand, treatment of compound **201** with arylidenemalononitriles **172** gave the thiazolo[3,2-*a*]pyridine derivatives **202**. Thiazolo[3,2-*a*]pyridines **202** were also synthesized *via* a multi-component reaction of compound **200** with aromatic aldehyde **43** and malononitrile **53** in ethanol containing piperidine at reflux (Scheme 89).



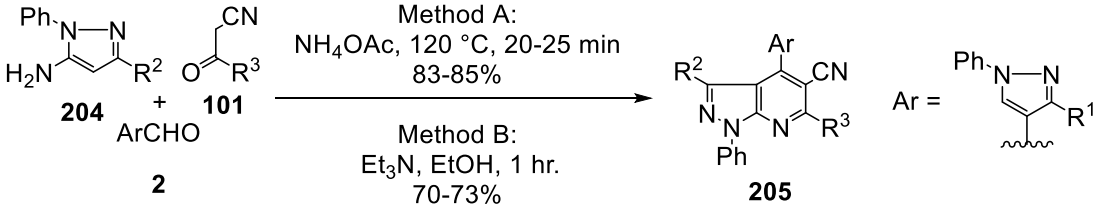
Scheme 89. Synthesis of thiazolo[3,2-*a*]pyridine derivatives **201** and **202.**

Abdel Hafiz *et al.*[162] reported that the formation of 5-amino-3-oxo-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile **203** was performed by the reaction of pyrazol-4-ylmethylene malononitrile **54** with thiazol-4(5*H*)-one derivatives **199** (Scheme 90).



Scheme 90. Synthesis of 5-amino-3-oxo-tetrahydro-5*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile **203.**

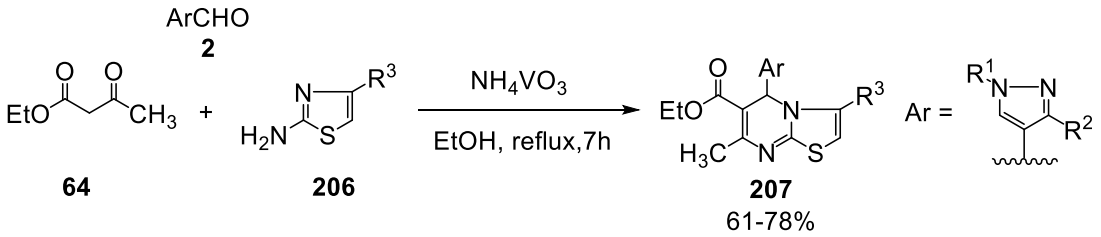
3.2.1.1.2. Fused [5-6] system with three heteroatoms. 3.2.1.1.2.1. Pyrazolo[3,4-*b*]pyridine derivatives. Jachak *et al.*[193] reported that pyrazolo[3,4-*b*]pyridine derivatives **205** were synthesized by one-pot cyclocondensation of 5-amino-3-aryl-1*H*-phenylpyrazoles **204**, *p*-substituted benzoylacetonitriles **101,** and pyrazole-4-carboxaldehydes **2** using ammonium acetate or triethylamine as a catalyst (Scheme 91).



Scheme 91. Synthesis of pyrazolo[3,4-*b*]pyridine derivatives **205.**

3.2.1.1.2.2. Thiazolo[3,2-*a*]pyrimidine derivatives. Sahu *et al.*[194] reported the synthesis of a series thiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives **207** through a multi-component reaction of ethyl acetoacetate **64**,

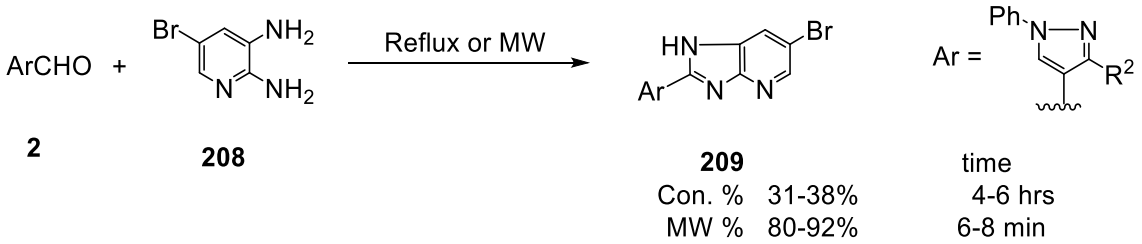
pyrazole-4-carboxaldehydes **2,** and an excess amount of substituted aminothiazole **206** using ammonium metavanadate (NH_4VO_3) as a catalyst (Scheme 92).



R^1 = C_6H_5, H; R^2 = C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4; R^3 = C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4; X = O, S.

Scheme 92. Synthesis of thiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives **207.**

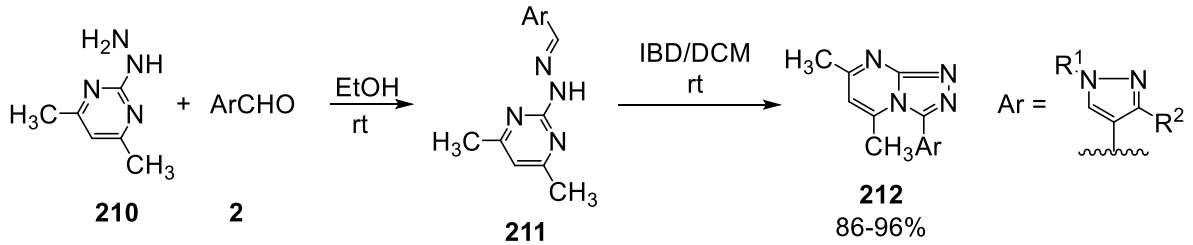
3.2.1.1.2.3. 1*H*-Imidazo[4,5-*b*]pyridine derivatives. Kumbar *et al*.[195] reported the synthesis of 6-bromo-1*H*-imidazo[4,5-*b*]pyridines **209** by condensation of 6-bromo-pyridine-2,3-diamine **208** with pyrazole-4-carboxaldehydes **2** in ethanol at reflux or under microwave irradiation (Scheme 93).



R^2 = 2-Oxo-3,8a-dihydro-2*H*-chromen-3-yl, 6-Cl-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl, 6-Br-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl, 8-H_3CO-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl.

Scheme 93. Synthesis of 6-bromo-1*H*-imidazo[4,5-*b*]pyridines **209.**

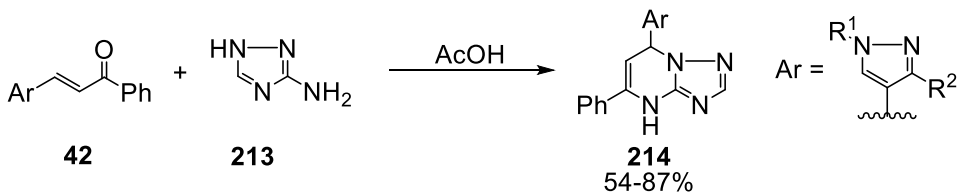
3.2.1.1.3. Fused [5-6] system with four heteroatoms. 3.2.1.1.3.1. [1,2,4]Triazolo[4,3-*a*]pyrimidine derivatives. Kamal *et al*.[196] reported that hydrazone derivatives **211** were obtained by heating the 2- hydrazino-4,6-dimethylpyrimidine **210** with the appropriate pyrazole-4-carboxaldehyde derivatives **2** in ethanol at reflux. [1,2,4]Triazolo[4,3-*a*]-pyrimidines **212** were obtained by oxidation of hydrazone derivatives **211** using iodobenzebediacetate (IBD) in dichloromethane (DCM) at room temperature (Scheme 94).



R^1 = C_6H_5; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 2-H_3CO-C_6H_4, 4-O_2N-C_6H_4, 3-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 2-Naphthyl.

Scheme 94. Synthesis of [1,2,4]triazolo[4,3-*a*]-pyrimidines **212.**

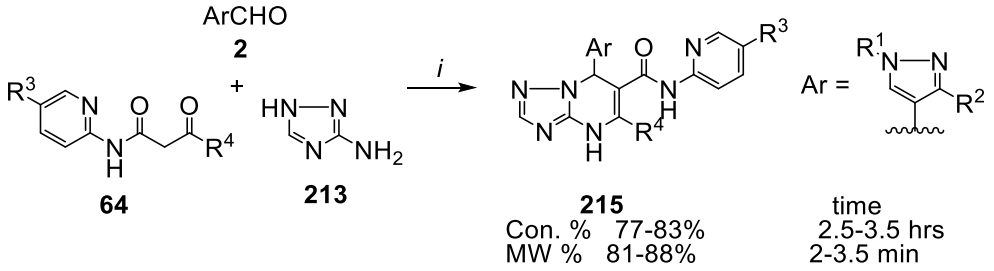
3.2.1.1.3.2. Triazolo[1,5-*a*]pyrimidine derivatives. Shejale *et al*.[157] and El-Emary and Bakhite[141] reported that the reaction of chalcones **42** with 3-amino-*s*-triazole **213** in acetic acid at reflux afforded 4,7-dihydro-7-{1-phenyl-3-(substituted phenyl)-1*H*-pyrazol-4-yl}-5-phenyl-s-triazolo[1,5-*a*]pyrimidine **214** (Scheme 95).



R^1 = C_6H_5; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4.

Scheme 95. Synthesis of 7-{1*H*-pyrazol-4-yl}-5-phenyl-*s*-triazolo[1,5-*a*]pyrimidines **214.**

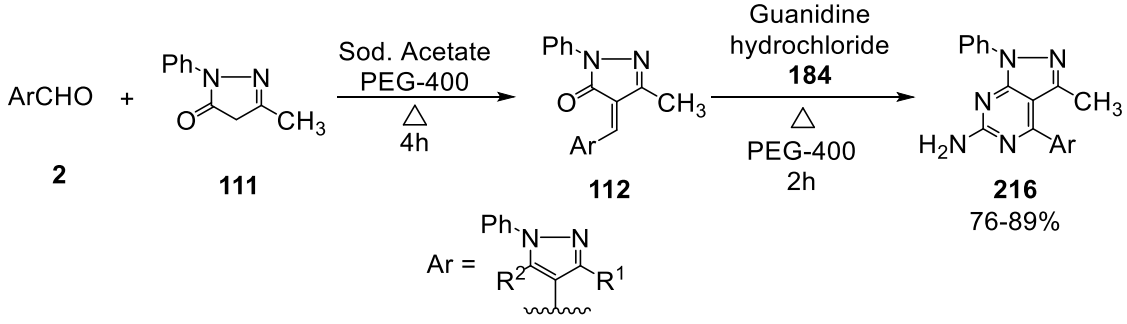
Bhatt *et al.*[197] reported the synthesis of 4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidine-6-carboxamides **215** *via* Biginelli reaction of 1-phenyl-3-aryl-1*H*-pyrazol-4-carboxaldehyde **2**, 1*H*-1,2,4-triazol-3-amine **213** and acetoacetanilide derivatives **64** under conventional and microwave irradiation conditions (Scheme 96).



i = Conventional heating or MW irradiation/ solvent of reaction in the both conditions [DMF, EtOH, (EtOH, HCl), (EtOH, PTSA), TEAA]; R^1 = C_6H_5; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4; R^3 = H, CH_3, Br; R^4 = -CH_3, -$HC(CH_3)_2$.

Scheme 96. Synthesis of 4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidine-6-carboxamides **215.**

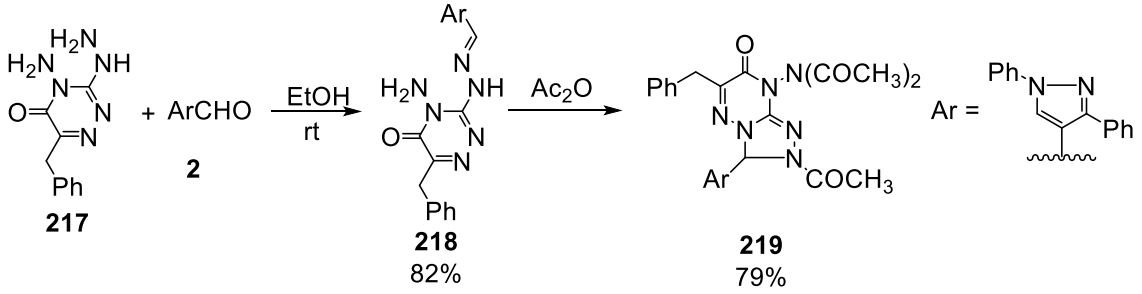
3.2.1.1.3.3. Pyrazolo[3,4-*d*]pyrimidine derivatives. The reaction of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **111** with pyrazol-4-carboxaldehyde **2** in the presence of sodium acetate and PEG-400 as a solvent gave the corresponding 4-(arylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5-ones **112**. The reaction of **112** with guanidine hydrochloride **184** and sodium hydroxide in the presence of PEG-400 afforded the corresponding pyrazolo[3,4-*d*]pyrimidin-6-amine derivatives **216**[198] (Scheme 97).



R^1 = CH_3, 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-F-C_6H_4; R^2 = Cl, H.

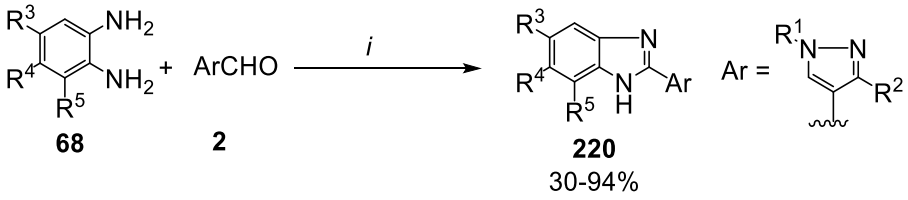
Scheme 97. Synthesis of pyrazolo[3,4-*d*]pyrimidin-6-amine derivatives **216.**

3.2.1.1.4. Fused [5-6] system with five heteroatoms. 3.2.1.1.4.1. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazine derivatives. Hamama *et al*.[199] reported that the condensation of 4-amino-6-benzyl-3-hydrazineyl-1,2,4-triazin-5(4*H*)-one **217** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** afforded the corresponding Schiff bases **218**. Treatment of compound **218** with acetic anhydride gave *N*-acetyl-*N*-(2-acetyl-6-benzyl-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-7-oxo-2,3-dihydro-1,2,4-triazolo[4,3-*b*] 1,2,4-triazin-8(7*H*)-yl)acetamide **219** (Scheme 98).



Scheme 98. Synthesis of 3-(1*H*-pyrazol-4-yl)-1,2,4-triazolo[4,3-*b*]-1,2,4-triazin-8(7*H*)-yl)acetamide **219.**

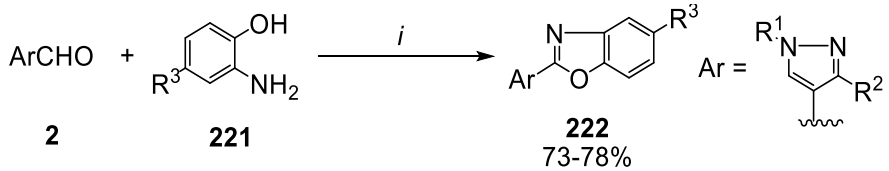
3.2.1.1.5. Fused [6-5] system with two heteroatoms. 3.2.1.1.5.1. Benzo[*d*]imidazole derivatives. Condensation of *o*-phenylenediamines derivatives **68** with pyrazole-4-carboxaldehydes **2** afforded the corresponding 2-(pyrazol-4-yl) benzo[*d*]imidazoles **220**[195,200–204] (Scheme 99).



R^1 = C_6H_5, Pyridin-2-yl, 4-H_2NO_2S-C_6H_4; R^2 = C_6H_5, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_4, 4-Cl-C_6H_4, 4-HO-C_6H_4, 4-H_2N-C_6H_4, 4-H_3C-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 3,4,5-tri-H_3CO-C_6H_2, 2-HO-C_6H_4, 2-oxo-3,8a-dihydro-2*H*-chromen-3-yl, 6-Cl-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl, 6-Br-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl, 8-H_3CO-2-oxo-3,8a-dihydro-2*H*-chromen-3-yl; R^3 = CH_3, H, Cl, NO_2, F, Br, OCH_3, CF_3; R^4 = CH_3, H, Cl, NO_2; R^5 = CH_3, H. ***i*** = $ZnCl_2$/ CH_3CN,[200], visible light/ Rose Bengal (2mol%)/ CH_3CN,[201] EtOH/ PCl_3/ 60 °C,[202] Oxone/ DMF/ H_2O,[203] EtOH/ $Na_2S_2O_5$/ 50 °C-60 °C,[204] reflux or MW.[195]

Scheme 99. Synthesis of 2-(pyrazol-4-yl) benzo[*d*]imidazoles **220.**

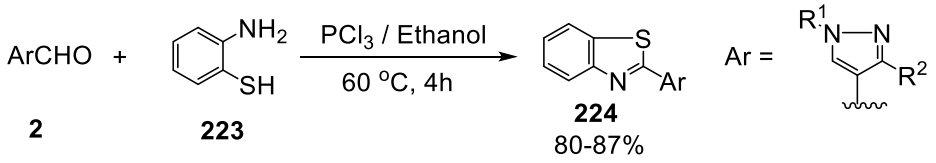
3.2.1.1.5.2. Benzo[*d*]oxazole derivatives. Condensation of pyrazole-4-carboxaldehydes **2** with 2-aminophenol derivatives **221** under different conditions led to the formation of the corresponding benzo[*d*]oxazole derivatives **222**[72,202,205] (Scheme 100).



R^1 = C_6H_5, Pyridin-2-yl; R^2 = 2-HO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4; R^3 = H, Cl; ***i*** = EtOH/ Phosphorus trichloride (PCl_3)/ 60 °C,[202] NH_4Cl:70 mol% O_2 Air/ CH_3OH: H_2O (15:1,V:V) rt,[205] (1) CH_3OH (2) $PhI(OAc)_2$.[72]

Scheme 100. Synthesis of benzo[*d*]oxazole derivatives **222.**

3.2.1.1.5.3. Benzo[*d*]thiazole derivatives. The reaction of pyrazole-4-carboxaldehyde **2** with 2-aminobenzenethiol **223** in the presence of PCl_3 in ethanol afforded the corresponding benzo[*d*]thiazole **224**[202] (Scheme 101).

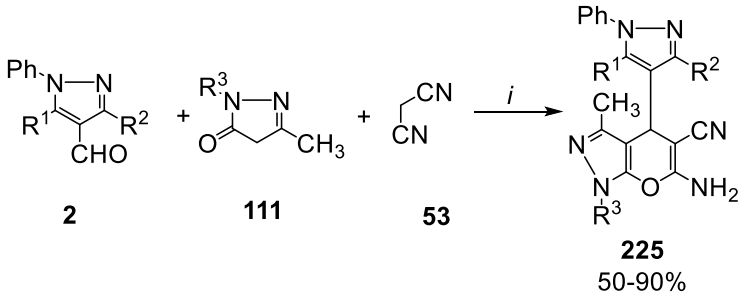


2 **223** **224** 80-87%

R^1 = C_6H_5, Pyridin-2-yl; R^2 = 2-HO-C_6H_4, C_6H_5.

Scheme 101. Synthesis of benzo[*d*]thiazoles **224.**

3.2.1.1.6. Fused [6-5] system with three heteroatoms. 3.2.1.1.6.1. Pyrano[2,3-*c*]pyrazole derivatives. Pyrano[2,3-*c*]pyrazole derivatives **225** were prepared *via* the one-pot cyclocondensation reaction of pyrazolone **111**, substituted pyrazole-4-carboxaldehydes **2** and malononitrile **53** in polyethylene glycol (PEG-400) as a green solvent[206,207] or in ethanol at reflux in the presence of piperidine[208] (Scheme 102).

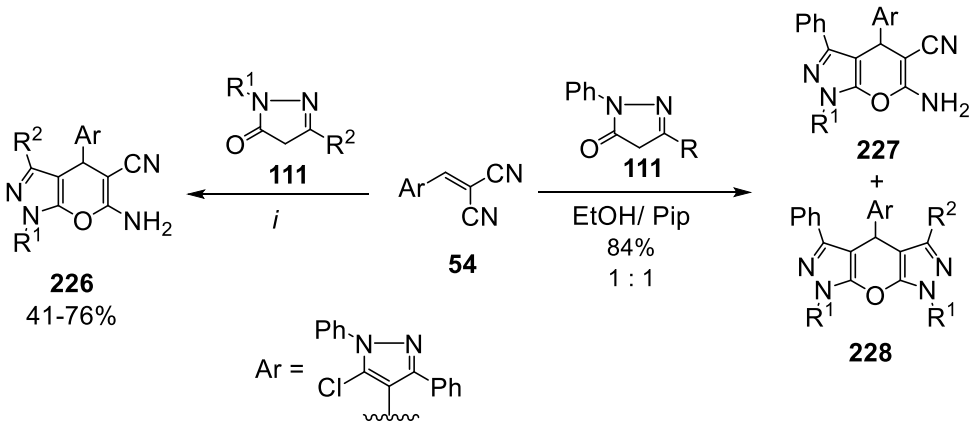


2 **111** **53** **225** 50-90%

R^1 = H, Cl; R^2 = C_6H_5, 4-Br-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-HO-C_6H_4, 4-O_2N-C_6H_4, CH_3, 2-Thienyl; R^3 = H, C_6H_5; ***i*** = PEG-400/ Stirr 40 °C 2hrs, EtOH/ Pip. / reflux

Scheme 102. Synthesis of pyrano[2,3-*c*]pyrazole derivatives **225.**

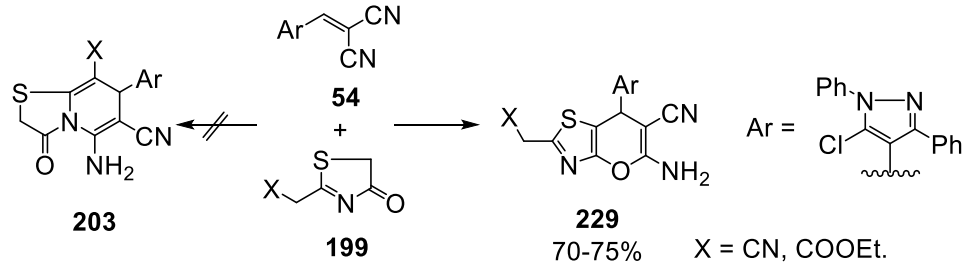
Reaction of pyrazolone derivatives **111** with 2-((5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)malononitrile **54** afforded the corresponding 6-amino-1-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **226**[161,162]. On the other hand, *Abderazek et al.*[161] reported that heating of pyrazolone derivatives **111** with **54** in ethanol containing piperidine afforded a mixture of 6-amino-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **227** and 1,7-diphenyl-4,7-dihydro-1*H*-pyrano[2,3-*c*;6,5-*c*9]dipyrazoles **228** (Scheme 103).



R^1 = H, C_6H_5; R^2 = CH_3, C_6H_5; ***i*** = EtOH/ Pip. /Reflux 3hr,[161, 162] EtOH/ NaOEt.[161]

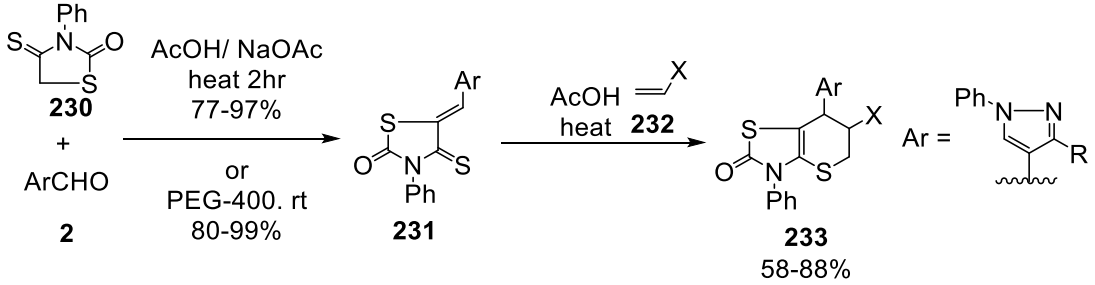
Scheme 103. Synthesis of a mixture of pyrano[2,3-*c*]pyrazoles **227** and pyrano[2,3-*c*;6,5-*c*9]dipyrazoles **228.**

3.2.1.1.6.2. Pyrano[2,3-*d*]thiazole derivatives. Abdelrazek *et al.*[161] reported that the reaction of 2-((5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)malononitrile **54** with substituted thiazolin-4-ones **199** afforded pyrano[2,3-*d*]thiazole derivatives **229** but not thiazolo[3,2-*a*]pyridine derivatives **203** (Scheme 104).



Scheme 104. Synthesis of pyrano[2,3-*d*]thiazole derivatives **229.**

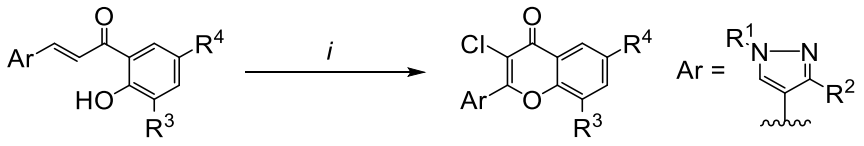
3.2.1.1.6.3. Thiopyrano[2,3-*d*]thiazole derivatives. Metwally *et al.*[209] reported that the knöevenagel condensation of 3-phenyl-4-thioxo-2-thiazolidinone **230** with 1-phenyl-3-aryl-1*H*-pyrazole-4-carboxaldehydes **2** in glacial acetic acid at reflux or in PEG-400 at room temperature without a catalyst afforded the corresponding 5-pyrazolylmethylene derivatives **231**. [4+2] Cycloaddition reaction of compounds **231** with acrylonitrile and ethyl acrylate **232** afforded the corresponding thiopyrano[2,3-*d*]thiazole derivatives **233** (Scheme 105).



R = C_6H_5, 4-H_3C-C_6H_5, 4-H_3CO-C_6H_5, 4-Cl-C_6H_5; X = CN, CO_2Et.

Scheme 105. Synthesis of thiopyrano[2,3-*d*]thiazole derivatives **233.**

3.2.1.1.7. Fused [6-6] system with one heteroatom. 3.2.1.1.7.1. Chromene derivatives. Oxidative cyclization of pyrazolylpropenones **42** using copper chloride in DMSO[105,210] or hydrogen peroxide (H_2O_2) in potassium hydroxide solution in methanol by Algar Flynn Oymanda (AFO) reaction[211] gave chlorochromones **234** (Scheme 106).



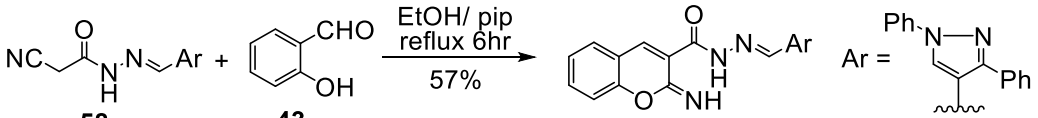
42 **234** 41-63%

i = DMSO/ excess $CuCl_2$/ Reflux, KOH/ CH_3OH/ H_2O_2

R^1 = C_6H_5, CH_3; R^2 = C_6H_5, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_5, 4-F-C_6H_4; R^3 = H, CH_3; R^4 = H, Cl, CH_3, Br, F.

Scheme 106. Synthesis of chlorochromones **234.**

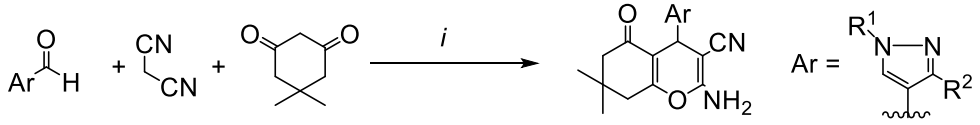
El-Emary *et al.*[166] reported that the treatment of hydrazone derivative **58** with salicylaldehyde **43** yielded chromene **235** (Scheme 107).



58 **43** **235**

Scheme 107. Synthesis of chromene **235.**

A series of 4-pyrazolyl-4*H*-benzopyranes **237** has been synthesized *via* a one-pot three-component cyclocondensation reaction of 1-phenyl-3-(het)aryl-pyrazole-4-carboxaldehyde **2**, malononitrile **53,** and dimedone **236** in the presence of (diacetoxyiodo)benzene[212] or piperidine as catalysts[208] (Scheme 108).

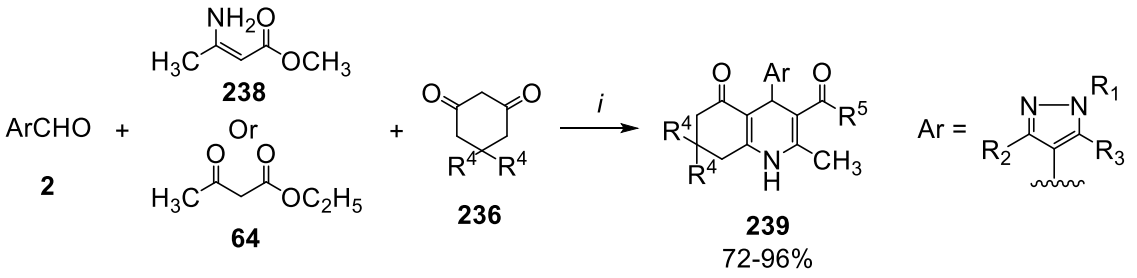


2 **53** **236** **237** 58-90%

R^1 = C_6H_5; R^2 = C_6H_5, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4- H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 2-Thienyl; ***i*** = (diacetoxyiodo)benzene (5mol %)/ EtOH/ reflux,[212] EtOH/ Pip. /reflux.[208]

Scheme 108. Synthesis of 4-pyrazolyl-4*H*-benzopyranes **237.**

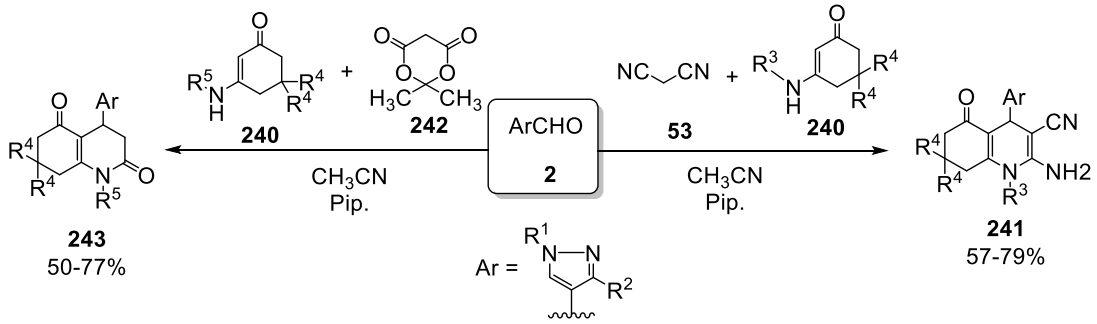
3.2.1.1.7.1.2. Quinoline derivatives. Multi-component reaction of pyrazole-4-carboxaldehydes **2**, dimedone[213–215] or 1,3-cyclohexanedione[215] **236** and methyl-3-aminobut-2-enoate[213] **238** or ethylacetoacetate[214,215] **64** under various conditions afforded hexahydroquinoline derivatives **239** (Scheme 109).



R^1 = C_6H_5, H, 2,4-di-O_2N-C_6H_3; R^2 = CH_3, 4-Cl-C_6H_4, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4; R^3 = Cl, H; R^4 = H, CH_3; R^5 = OCH_3,[213] OC_2H_5;[214, 215] ***i*** = Pip. / EtOH,[213] NH_4OAc/ Poly(4-vinylpyridinium)hydrogen sulfate [P(4-VPH)HSO_4]/ H_2O/ reflux 5-15 min,[214] NH_4OAc/ Cellulose-sulforic acid/ EtOH/ reflux.[215]

Scheme 109. Synthesis of hexahydroquinoline derivatives **239.**

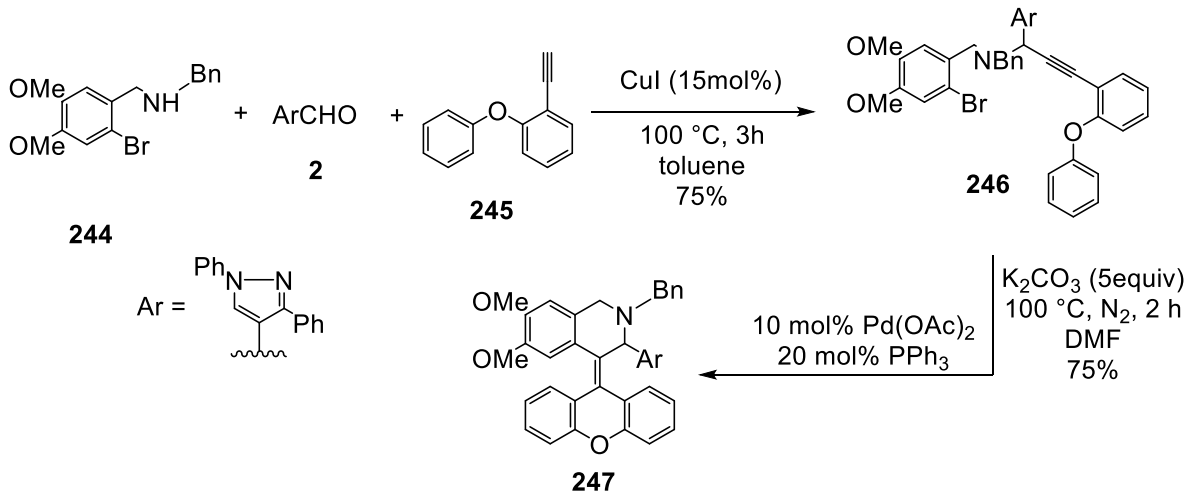
Heating a mixture of pyrazole-4-carboxaldehyde **2**, malononitrile **53**, and the appropriate *β*-enaminones **240** in acetonitrile containing piperidine at reflux led to the formation of the corresponding 2-amino-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **241**[216]. Moreover, the reaction of pyrazole-4-carboxaldehyde **2**, Meldrum's acid **242,** and the appropriate *β*-enaminones **240** in acetonitrile containing few drops of piperidine at reflux afforded the corresponding 7,7-disubstituted-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione **243**[217] (Scheme 110).



R^1 = C_6H_5; R^2 = C_6H_5, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-H_3CO-C_6H_4, 4-H_3C-C_6H_4, 4-O_2N-C_6H_4, 2-Thienyl; R^3 = 4-(4-F-C_6H_4)thiazol-2-yl, 4-F-C_6H_4; R^4 = H, CH_3; R^5 = 4-(4-F-C_6H_4)thiazol-2-yl.

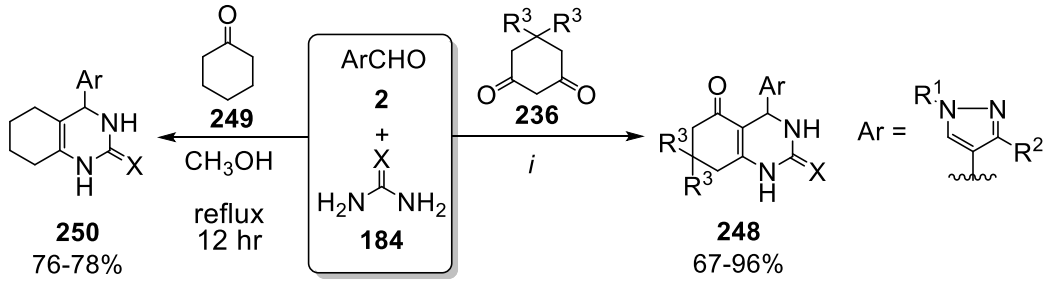
Scheme 110. Synthesis of hexahydroquinoline-3-carbonitriles **241** and tetrahydroquinoline-2,5-diones **243.**

3.2.1.1.7.1.3. Isoquinoline derivatives. Nandakumar and Perumal[218] reported that the coupling reactions of *N*-benzyl-1-(2-bromo-4,5-dimethoxyphenyl)methanamine **244**, 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** and 1-ethynyl-2-phenoxybenzene **245** using copper(I) iodide (CuI) as a catalyst afforded propargyl amine derivative **246** which underwent intramolecular carbocyclization to give tetrahydroisoquinoline derivative **247** (Scheme 111).



Scheme 111. Synthesis of tetrahydroisoquinoline derivative **247.**

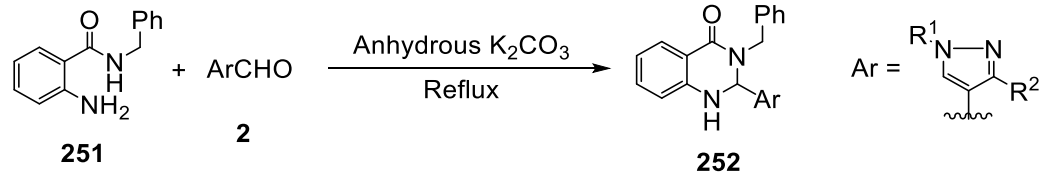
3.2.1.1.8. Fused [6-6] system with two heteroatoms. 3.2.1.1.8.1. Quinazoline derivatives. Biginelli condensation of cyclohexane-1,3-dione[120,219] or 5,5-dimethyl-1,3-cyclohexanedione[220] **236**, (thiourea or urea **184**) and pyrazole-4-carboxaldehyde **2** in methanol at reflux afforded 2,3,4,6,7,8-hexahydroquinazolin-5(1*H*)-one or 4,6,7,8-tetrahydroquinazoline-2,5(1*H*,3*H*)-dione derivatives **248**.[120,219,220] Similarly, condensation of cyclohexanone **249**, (thiourea or urea **184**) and 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** in methanol at reflux afforded 3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thione or 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one analogues **250**[219] (Scheme 112).



R^1 = C_6H_5, 3-Cl-C_6H_4, H; R^2 = C_6H_5, 4-H_3CO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4; R^3 = H, CH_3; X = O, S; ***i*** = reflux/ methanol,[219] drops of HCl/ EtOH, refux,[120] *p*-TsOH/ H_2O/reflux.[220]

Scheme 112. Synthesis of hexahydroquinazolin-5(1*H*)-ones and hexahydroquinazoline-2(1*H*)-thiones **248** and **250.**

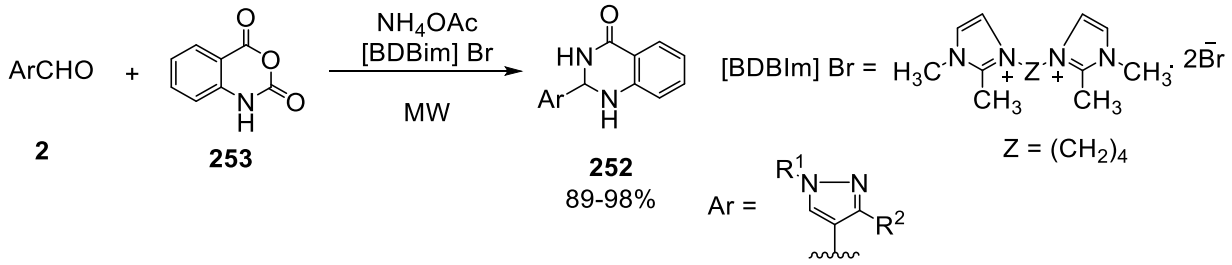
Kamble *et al.*[68] reported the synthesis of 3-benzyl-2,3-dihydro-2-(1-phenyl-3-substituted-1*H*-pyrazol-4-yl)quinazolin-4(1*H*)-ones **252** *via* the reaction of 3-(substituted)-1-phenyl-1*H*-pyrazole-4-carboxaldehydes **2** with aminobenzamide **251** upon heating in methanol at reflux in the presence of potassium carbonate (Scheme 113).



R^1 = C_6H_5; R^2 = C_6H_5, 3-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-O_2N-C_6H_4, Pyridine-3-yl, Thiophen-2-yl.

Scheme 113. Synthesis of 3-benzyl-2-(1-phenyl-3-substituted-1*H*-pyrazol-4-yl)quinazolin-4(1*H*)-ones **252.**

Nikpassand *et al.*[221] reported that pyrazolyl-substituted quinazolinones **252** were obtained *via* a three-component condensation of pyrazole-4-carboxaldehyde **2** with isatoic anhydride **253** and ammonium acetate under microwave irradiation in the presence of [BDBIm] Br as a catalyst which could be recovered easily and reused without appreciable loss of reactivity (Scheme 114).

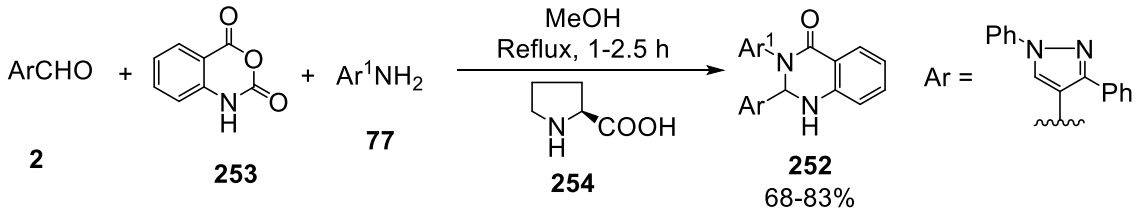


[BDBIm] Br: 3,3′-(butane-1,4-diyl)bis(1,2-dimethyl-1*H*-imidazol-3-ium) dibromide.

R^1 = C_6H_5; R^2 = 4-H_3CO-C_6H_4, 4-HO-C_6H_4, 4-Cl-C_6H_4, 2-HO-C_6H_4, C_6H_5.

Scheme 114. Synthesis of pyrazolyl-substituted quinazolinones **252.**

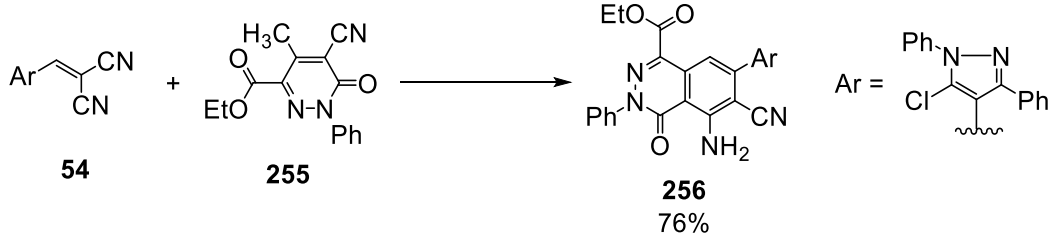
Mehta *et al.*[222] reported the synthesis of a series of quinazolin-4(3*H*)-one derivatives **252** containing a (1,3-diph0enyl-1*H*-pyrazol-4-yl) substituent at the position-2 and aromatic or heteroaromatic substituents at the position-3 by using *l*-proline **254** to catalyze the one-pot multi-component reaction of 1-phenyl-3-aryl-1*H*-pyrazole-4-carboxaldehyde **2**, isatioc anhydride **253**, aromatic amines **77** in methanol at reflux (Scheme 115).



Ar^1 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-O_2N-C_6H_4, 4-Pyr.

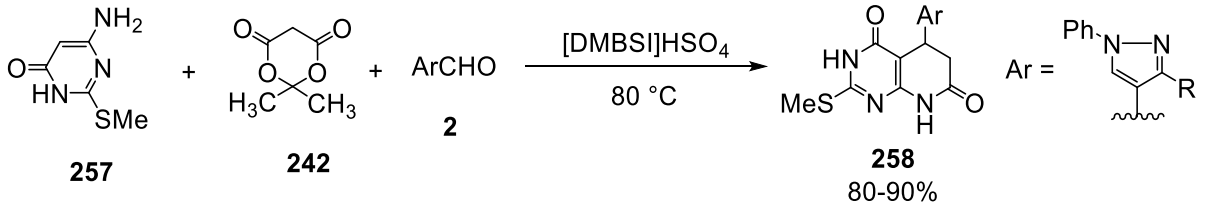
Scheme 115. Synthesis of pyrazolyl-substituted quinazolinones **252.**

3.2.1.1.8.2. Phthalazine derivatives. The reaction of ethyl-5-cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate **255** with pyrazolylmethylene malononitrile **54** gave the phthalazinone derivative **256**[161,162] (Scheme 116).



Scheme 116. Synthesis of phthalazinone derivative **256.**

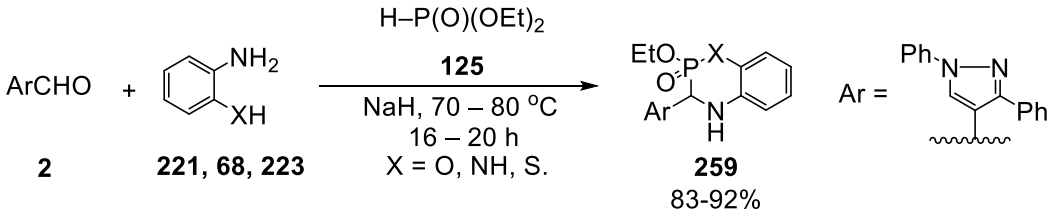
3.2.1.1.9. Fused [6-6] system with three heteroatoms. 3.2.1.1.9.1. Pyridopyrimidine derivatives. Nia *et al*.[223] reported that stirring equimolar amounts of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one **257**, Meldrum's acid **242,** and pyrazole-4-carboxaldehydes **2** with a catalytic amount of 1,2–dimethyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate [DMBSI]HSO_4 in an oil bath led to the formation of the corresponding pyridopyrimidine derivatives **258** (Scheme 117).



R = C_6H_5, 4-H_3CO-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 3-O_2N-C_6H_4.

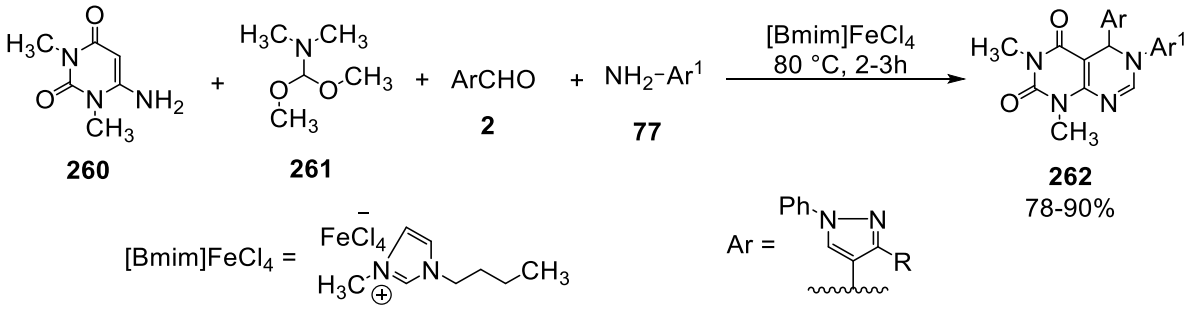
Scheme 117. Synthesis of pyridopyrimidine derivatives **258.**

3.2.1.1.9.2. Benzo[*e*][1,4,2](ox/ di/ thi)azaphosphinine derivatives. Reaction of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** with 2-aminophenol **221**, 1,2-phenylenediamine **68** and 2-aminothiophenol **223** in the presence of diethyl phosphite H-P(O)$(OEt)_2$ **125** and sodium hydride gave 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-ethoxy-3,4-dihydrobenzo[*e*][1,4,2](ox/ di/ thi)azaphosphinine-2-oxide derivatives **259** (Scheme 118) .[117]



Scheme 118. Synthesis of 3-(1*H*-pyrazol-4-yl)-3,4-dihydrobenzo[*e*][1,4,2](ox/di/thi)azaphosphinine-2-oxide derivatives **259.**

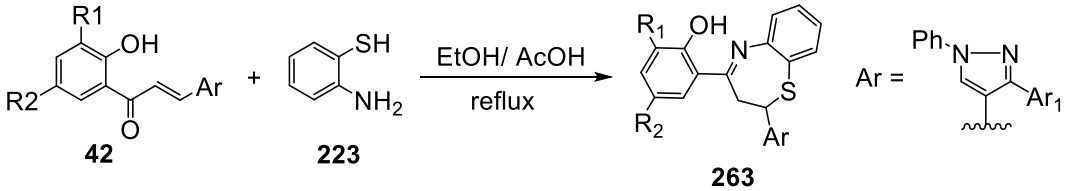
3.2.1.1.10. Fused [6-6] system with four heteroatoms. 3.2.1.1.10.1. Pyrimido[4,5-*d*]pyrimidine derivatives. Suresh *et al*.[224] reported that a four-component reaction of 6-amino-1,3-dimethyluracil **260**, *N*,*N*-dimethylformamide dimethyl acetal **261**, 1-phenyl-3-(4-substituted-phenyl)-4-formyl-1*H*pyrazoles **2** and aromatic amines **77** in the presence of 1-butyl-3-methylimidazolium tetrachloroferrate [Bmim]$FeCl_4$ ionic liquid as a promoting medium gave pyrazolopyrimido[4,5-*d*]pyrimidines derivatives **262** (Scheme 119).



R = 4-O_2N-C_6H_4, 4-Cl-C_6H_4, 4-H_3C-C_6H_4, C_6H_5, Thiophene; Ar^1 = C_6H_5, 4-Cl-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 3-O_2N-C_6H_4.

Scheme 119. Synthesis of pyrazolopyrimido[4,5-*d*]pyrimidines derivatives **262.**

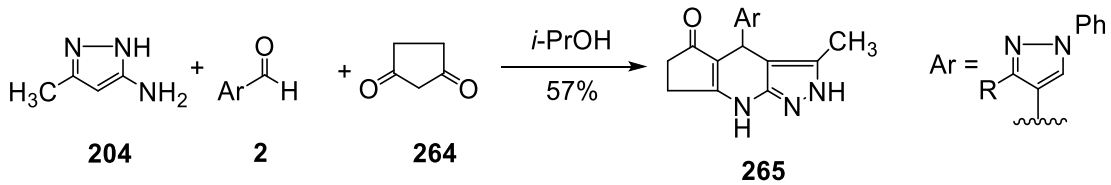
3.2.1.1.11. Fused [6-7] system with two heteroatoms. 3.2.1.1.11.1. Benzo[*b*][1,4]thiazepine derivatives. Karale *et al*.[210] reported that the condensation of pyrazolylpropenones **42** with 2-aminothiophenol **223** in ethanol containing acetic acid at reflux gave benzothiazepines **263** (Scheme 120).



R^1 = H, CH_3; R^2 = Cl, CH_3, Br; Ar^1 = C_6H_5, 4-H_3C-C_6H_4.

Scheme 120. Synthesis of benzothiazepines **263.**

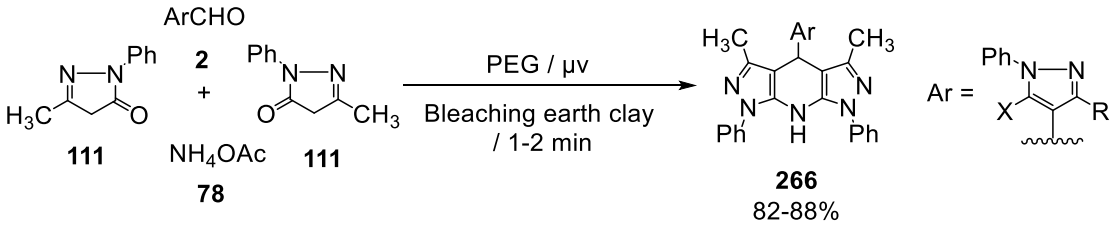
3.2.2. Pyrazole-substituted tricyclic system. 3.2.2.1. Fused [5-5-6] system with three heteroatoms. 3.2.2.1.1. Cyclopenta[*b*]pyrazolo[4,3-*e*]pyridine derivatives. Lipson *et al.*[225] reported that heating of equimolar quantities of 3-methyl-1*H*-pyrazol-5-amine **204**, pyrazole-4-carboxaldehyde **2**, and cyclopentane-1,3-dione **264** in 2-propanol at reflux led to the formation of the corresponding 3-methyl-4,6,7,8-tetrahydrocyclopenta[*b*]pyrazolo[4,3-*e*] pyridin-5(2*H*)-one **265** (Scheme 121).



R = 4-H_3CO-C_6H_4.

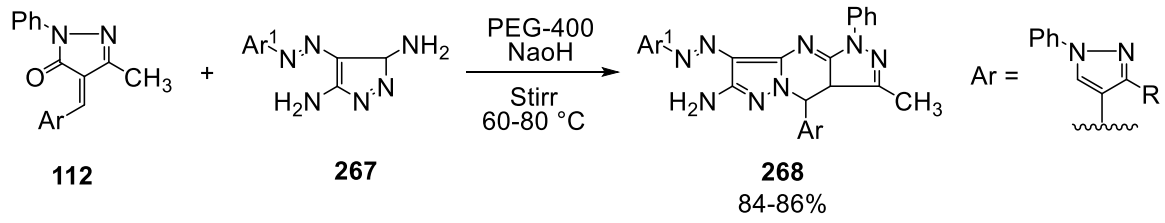
Scheme 121. Synthesis of 3-methyltetrahydrocyclopenta[*b*]pyrazolo[4,3-*e*] pyridin-5(2*H*)-one **265.**

3.2.2.2. Fused [5-5-6] system with five heteroatoms. 3.2.2.2.1. Dipyrazolo[3,4-*b*:4',3'-*e*]pyridine derivatives. Dawane *et al.*[226] reported that the microwave irradiation of pyrazolone **111**, pyrazole-4-carboxaldehydes **2,** and ammonium acetate **78** dissolved in PEG-400 afforded the corresponding 3,5-dimethyl-1,7-diphenyl-1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4',3'-*e*]pyridines **266** (Scheme 122).



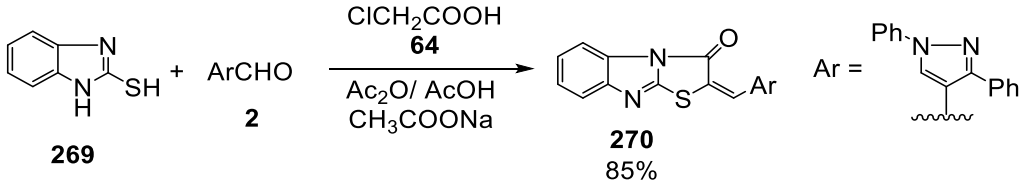
Scheme 122. Synthesis of 1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4',3'-*e*]pyridines **266.**

3.2.2.2.2. Dipyrazolo[1,5-*a*:3',4'-*d*]pyrimidine derivatives. Chobe *et al.*[227] reported that condensation of 4-(arylidene)-3-methyl-1-phenyl-1*H*-pyrazol-5-ones **112** with 4-((4-chlorophenyl)diazenyl)-3*H*-pyrazole-3,5-diamine **267** in PEG-400 afforded pyrazolo[1,5-*a*]pyrimidines **268** (Scheme 123).



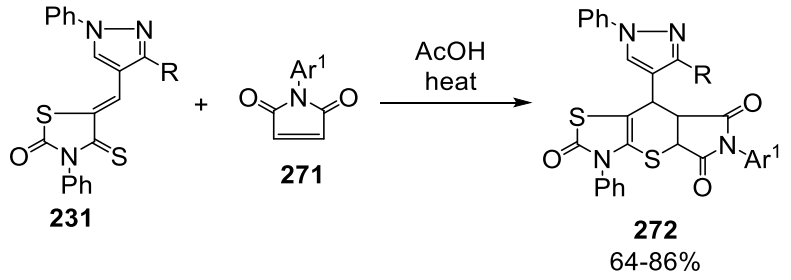
Scheme 123. Synthesis of pyrazolo[1,5-*a*]pyrimidines **268.**

3.2.2.3. Fused [5-6-5] system with three hetero atoms. 3.2.2.3.1. [1,3]Thiazolo[3,2-*a*]benzimidazole derivatives. One-pot three-component reaction of 1,3-dihydro-2*H*-benzimidazole-2-thione **269** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** and chloroacetic acid **64** in glacial acetic acid and acetic anhydride in the presence of sodium acetate afforded 2-[1*H*-pyrazol-4-yl-methylene][1,3]thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one **270**[228] (Scheme 124).



Scheme 124. Synthesis of 2-[1*H*-pyrazol-4-yl-methylene][1,3]thiazolo[3,2-*a*]benzimidazolone **270.**

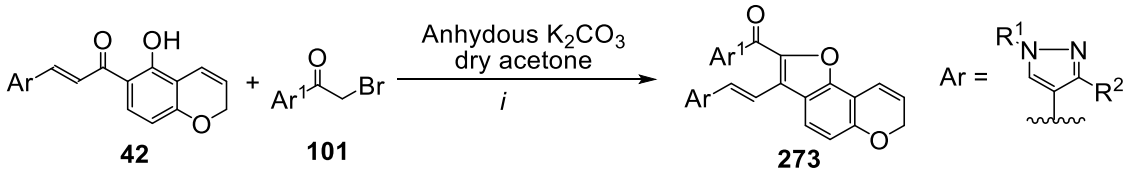
3.2.2.3.2. Pyrrolo[3',4':5,6]thiopyrano[2,3-*d*]thiazole derivatives. [4+2] Cycloaddition reaction of 5-pyrazolylmethylene derivatives **231** with *N*-arylmaleimides **271** in acetic acid at reflux afforded pyrrolo[3',4':5,6]thiopyrano[2,3-*d*]thiazole derivatives **272** (Scheme 125). [209]



R = C_6H_5, 4-H_3C-C_6H_5, 4-H_3CO-C_6H_5, 4-Cl-C_6H_5; Ar^1 = C_6H_5, 4-H_3C-C_6H_5, 4-H_3CO-C_6H_5, 4-Cl-C_6H_5.

Scheme 125. Synthesis of pyrrolo[3',4':5,6]thiopyrano[2,3-*d*]thiazole derivatives **272.**

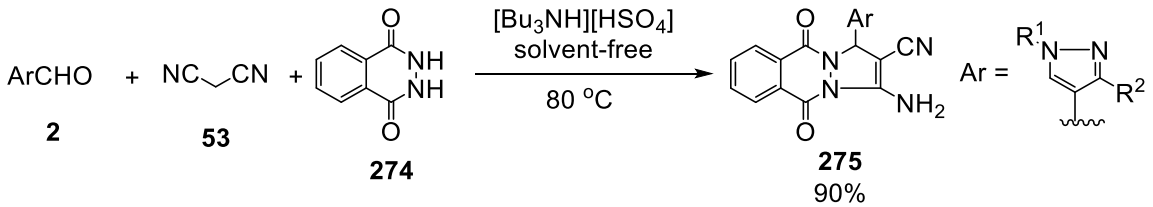
3.2.2.4. Fused [5-6-6] system with two heteroatoms. 3.2.2.4.1. Furo[2,3-*f*]chromene derivatives. Ashok *et al.*[229] reported the synthesis of {3-[2-(3-aryl-1-phenyl-1*H*pyrazol-4-yl)vinyl]-7*H*-furo[2,3-*f*]chromen-2-yl}-(4-bromophenyl) methanones **273** by the reaction of 2-bromo-1-(4-bromophenyl)ethanone **101** with 2-hydroxychalcones **42** in acetone containing K_2CO_3 under conventional heating, microwave irradiation or ultrasonication (Scheme 126).



R^1 = C_6H_5; R^2 = C_6H_5, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 4-H_5C_2O-C_6H_4, 3,4-di-$(H_3CO)_2$-C_6H_3, Naphth-2-yl; Ar^1 = 4-Br-C_6H_4; ***i*** = Conventional 54-61%; Ultrasound 64-74%; MW 79-85%

Scheme 126. Synthesis of {3-[2-(1*H*pyrazol-4-yl)vinyl]-7*H*-furo[2,3-*f*]chromen-2-yl}-(4-bromophenyl) methanones **273.**

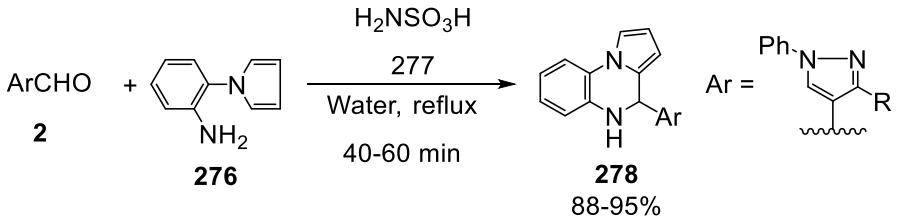
3.2.2.4.2. Pyrazolo[1,2-*b*]phthalazine derivatives. Shaikh *et al*.[230] prepared 3-amino-5,10-dioxo-1-(1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-5,10-dihydro-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile **275** by the reaction of 1-phenyl-3-(p-tolyl)-1*H*-pyrazole-4-carboxaldehyde **2**, malononitrile **53** and phthalhydrazide **274** catalyzed by 20 mol% of tributylammonium sulfate $[Bu_3NH][HSO_4]$ under solvent-free condition (Scheme 127).



R^1 = C_6H_5; R^2 = 4-H_3C-C_6H_4.

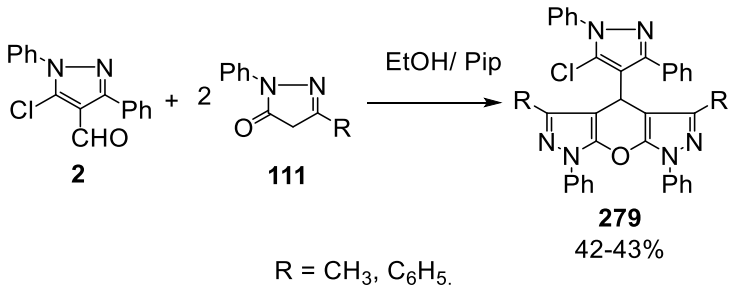
Scheme 127. Synthesis of 1-(1*H*-pyrazol-4-yl)-5,10-dihydro-1*H*-pyrazolo[1,2-b]phthalazine-2-carbonitrile **275.**

3.2.2.4.3. Pyrrolo[1,2-*a*]quinoxalines derivatives. Kamal *et al.*[231] reported that heating of 1-(2-aminophenyl)pyrrole **276**, pyrazole-4-carboxaldehydes **2**, and sulfamic acid **277** in H_2O at reflux afforded dihydropyrrolo[1,2-*a*]quinoxalines derivatives **278** (Scheme 128).



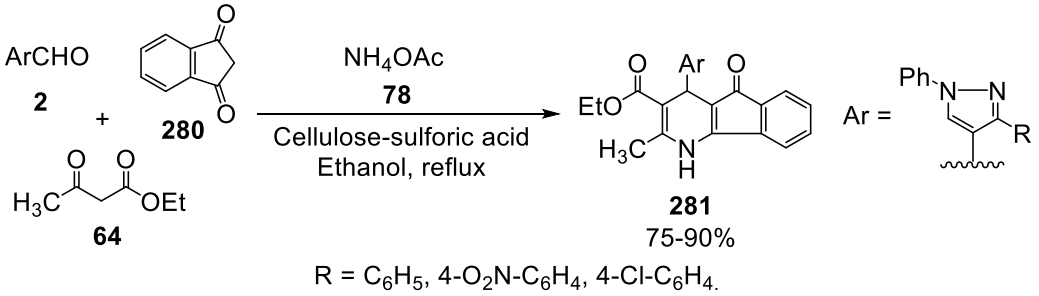
Scheme 128. Synthesis of dihydropyrrolo[1,2-*a*]quinoxalines derivatives **278.**

3.2.2.5. Fused [6-5-5] system with five heteroatoms. 3.2.2.5.1. Pyrano[2,3-*c*:6,5-*c*']dipyrazole derivatives. Abdelrazek *et al.*[161] reported that the reaction of two equivalents of 2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones **111** with 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** afforded the corresponding 1,7-diphenyl-4,7-dihydro-1*H*-pyrano[2,3-*c*:6,5-*c*']dipyrazoles **279** (Scheme 129).



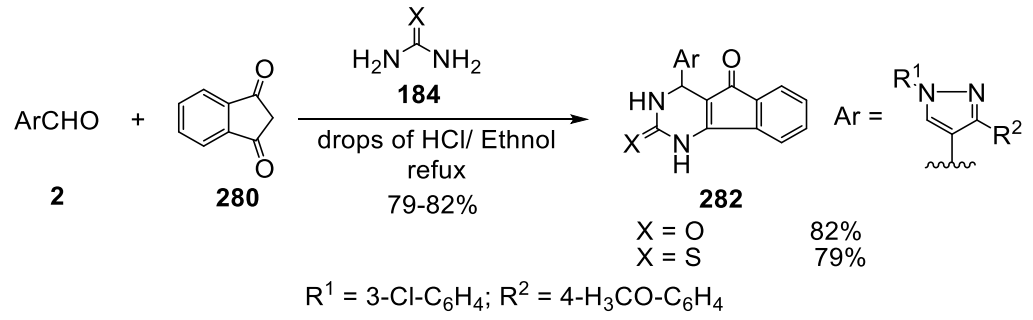
Scheme 129. Synthesis of 1,7-diphenyl-4,7-dihydro-1*H*-pyrano[2,3-*c*:6,5-*c*']dipyrazoles **279.**

3.2.2.6. Fused [6-5-6] system with one heteroatom. 3.2.2.6.1. Indeno[1,2-*b*]pyridine derivatives. Mamaghani *et al*.[215] reported that heating a mixture of 3-aryl-4-formylpyrazole **2**, indanedione **280**, ethyl acetoacetate **64,** and ammonium acetate **78** in the presence of cellulose-sulfuric acid in ethanol at reflux furnished 4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carboxylates **281** (Scheme 130).



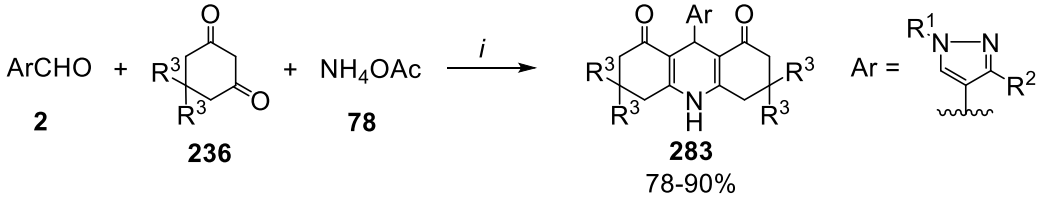
Scheme 130. Synthesis of 4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carboxylates **281.**

3.2.2.7. Fused [6-5-6] system with two heteroatom. 3.2.2.7.1. Indeno[1,2-*d*]pyrimidine derivatives. Fahmy *et al.*[120] reported that the reaction of 1,3-indanedione **280** with urea or thiourea **184** and pyrazole-4-carboxaldehydes **2** gave indeno[1,2-*d*]pyrimidine-2-oxo(thioxo) derivatives **282** (Scheme 131).



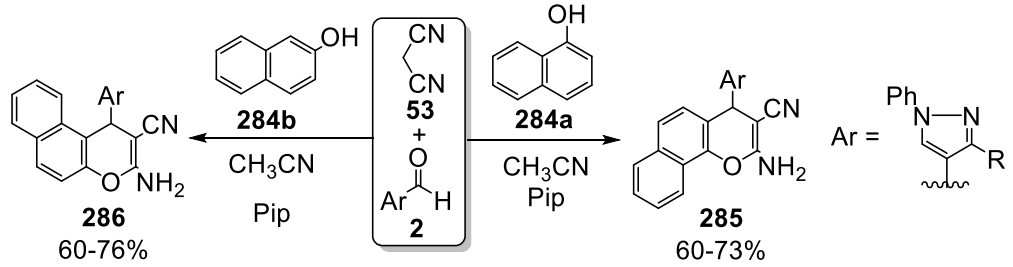
Scheme 131. Synthesis of indeno[1,2-*d*]pyrimidine-2-oxo (thioxo) derivatives **282.**

3.2.2.8. Fused [6-6-6] system with one heteroatom. 3.2.2.8.1. Acridine derivatives. The reaction of pyrazole-4-carboxaldehydes **2**, dimedone[232,233] or 1,3-cyclohexanedione[233] **236**, NH_4OAc **78** and a catalytic amount of magnetic iron oxide nanocrystals (nano Fe_3O_4) in a water bath under ultrasound irradiation[232] or using environmentally friendly poly(4-vinylpyridinium)hydrogen sulfate P-(4-VPH)HSO_4 as a catalyst in aqueous medium[233] afforded the corresponding 3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione derivatives **283** (Scheme 132).



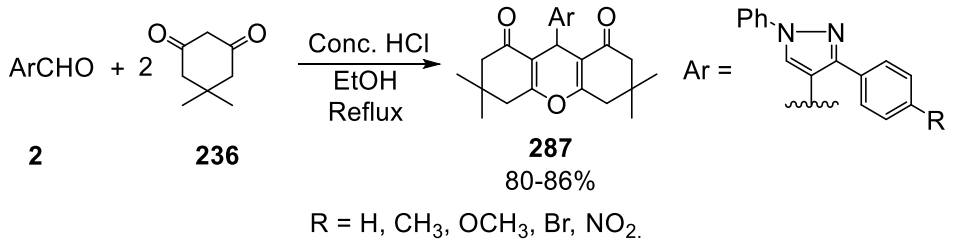
Scheme 132. Synthesis of 3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione derivatives **283.**

3.2.2.8.2. Benzo[*h*]chromene and benzo[*f*]chromene. Thumar and Patel[208] reported the synthesis of a series of 4-pyrazolyl-4*H*-naphthopyran derivatives **285** and **286** by one-pot three-component cyclocondensation reactions of pyrazole-4-carboxaldehydes **2**, malononitrile **53,** and naphthols **284a** or **284b**, respectively, in the presence of piperidine as a catalyst (Scheme 133).



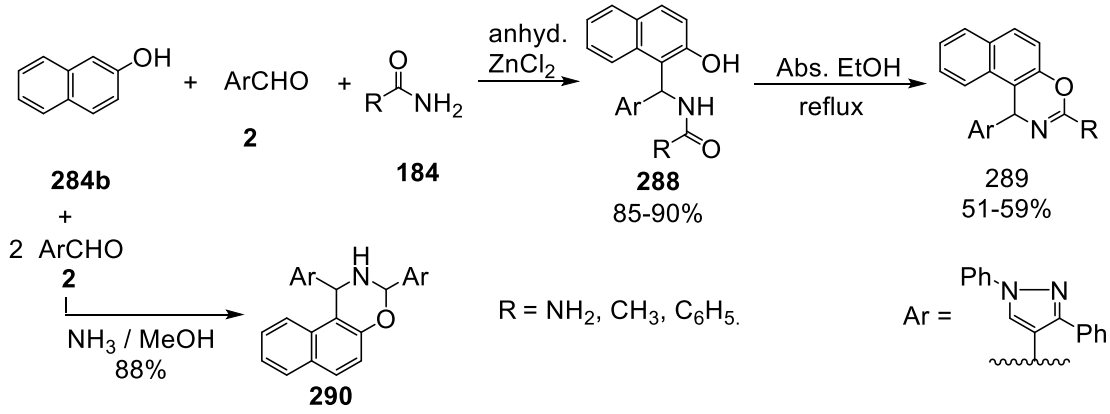
Scheme 133. Synthesis of 4-pyrazolyl-4*H*-naphthopyran derivatives **285** and **286.**

3.2.2.8.3. Xanthene derivatives. Neena *et al.*[234] reported that heating of 1-phenyl-3-aryl-1*H*-pyrazole-4-carboxaldehyde **2** with two equivalents of dimedone **236** in ethanol solution containing a catalytic amount of concentrated HCl at reflux afforded 3,3,6,6-tetramethyl-9-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(*2H*)-diones **287** (Scheme 134).



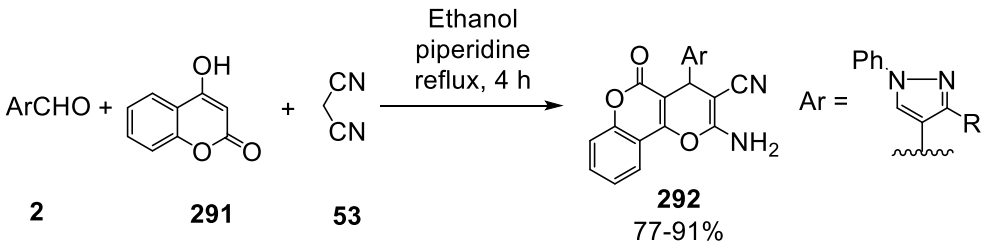
Scheme 134. Synthesis of 9-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)hexahydro-1*H*-xanthene-1,8(*2H*)-diones **287.**

3.2.2.9. Fused [6-6-6] system with two heteroatoms. 3.2.2.9.1. Naphtho[1,2-*e*][1,3]oxazine derivatives. Abou-Elmagd and Hashem[235] reported the preparation of 1-amidoalkyl-2-naphthols **288** *via* a one-pot condensation reaction of 1,3-diphenyl-pyrazole-4-carboxaldehyde **2**, naphthalen-2-ol **284b** and amides **184** in the presence of anhydrous zinc chloride under solvent-free conditions. Ring closure of **288** in ethanol at reflux gave the pyrazol-4-ylnaphtho[1,2-e][1,3]oxazine derivatives **289**. On the other hand, the reaction of 2-naphthol **284b** with two mole equivalents of 1,3-diphenyl-pyrazole-4-carboxaldehyde **2**, and ammonia solution gave 1,3-bis(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine **290** (Scheme 135).



Scheme 135. Synthesis of pyrazol-4-ylnaphtho[1,2-*e*][1,3]oxazine derivatives **289** and **290.**

3.2.2.9.2. Pyrano[3,2-*c*]chromene derivatives. Heating of 4-hydroxy coumarin **291** with substituted pyrazole-4-carboxaldehydes **2** and malononitrile **53** in ethanol at reflux in the presence of piperidine as base catalyst afforded 2-amino-4- (3-(4-substituted)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitriles **292**[172] (Scheme 136).

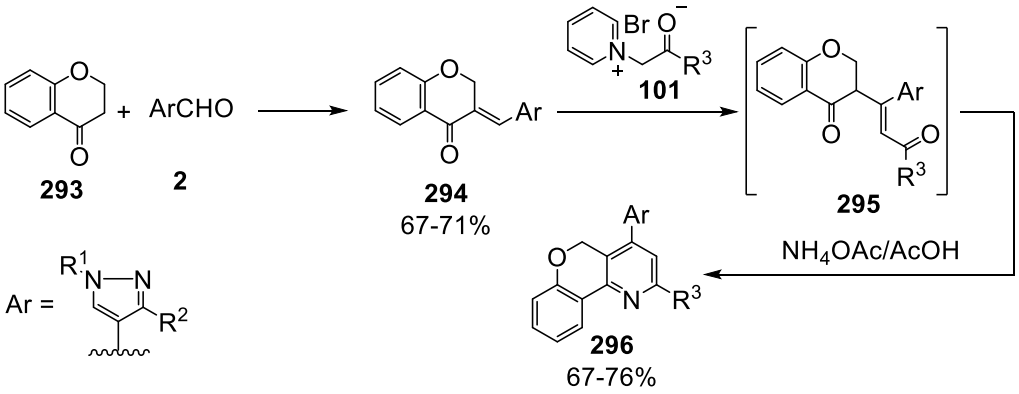


2 **291** **53** **292**
77-91%

R = 4-HO-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-O_2N-C_6H_4, 4-H_2N-C_6H_4.

Scheme 136. Synthesis of (1*H*-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitriles **292.**

3.2.2.9.3. Chromeno[4,3-*b*]pyridine derivatives. Reddy and Rao[236] reported that the reaction of pyrazole-4-carboxaldehydes **2** with chroman-4-one **293** gave *α,β*-unsaturated ketone system **294**. Initial Michael addition of phenacylpyridinim bromide **101** with compound **294** gave 1,5-dicarbonyl system **295** which subsequently underwent cyclization in the presence of NH_4OAc/ acetic acid to give chromeno[4,3-*b*]pyridines **296** (Scheme 137).

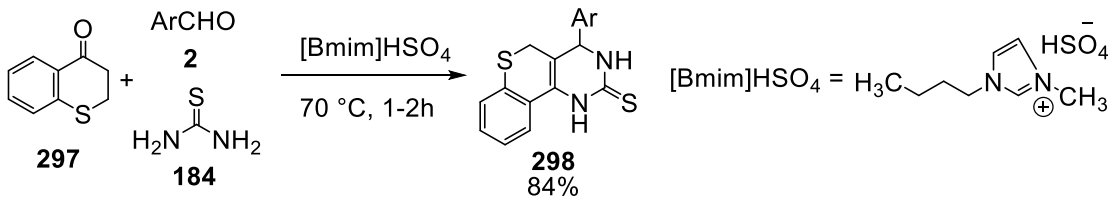


293 **2** **294**
67-71%
295
296
67-76%

R^1 = 4-H_3C-C_6H_4, 4-F-C_6H_4, 3-H_3C-C_6H_4, 2-F-C_6H_4; R^2 = 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-H_3C-C_6H_4; R^3 = C_6H_5, 4-Cl-C_6H_4.

Scheme 137. Synthesis of chromeno[4,3-*b*]pyridines **296.**

3.2.2.10. Fused [6-6-6] system with three heteroatoms. 3.2.2.10.1. Thiochromeno[3,4-*d*]pyrimidine derivatives. Suresh *et al*.[237] reported the synthesis of thiochromeno[3,4-*d*]pyrimidine derivatives **298** *via* a one-pot three-component reaction of thiochrome-4-one **297**, pyrazole-4-carboxaldehydes **2,** and thiourea **184** in the presence of 1-butyl-3-methylimidazolium hydrogen sulfate [Bmim]HSO_4 (Scheme 138).

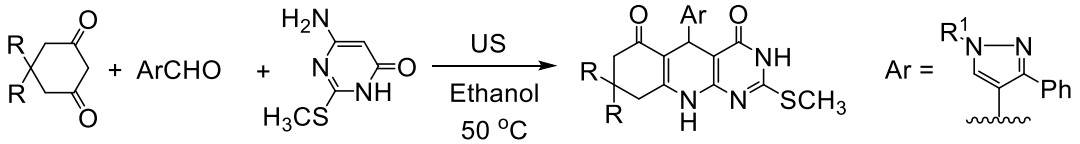


297 **184** **298**
84%

Ar = Pyrazole, 4-O_2N-Pyrazole, 4-Cl-Pyrazole, 4-H_3CO-Pyrazole.

Scheme 138. Synthesis of thiochromeno[3,4-*d*]pyrimidine derivatives **298.**

3.2.2.10.2. Pyrimido[4,5-*b*]quinoline derivatives. Jourshari *et al.*[238] reported that 5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione derivatives **299** were synthesized by one-pot three-component reaction of pyrazole-4-carboxaldehydes **2**, dimedone or cyclohexanedione **236** and 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one **257** in ethanol under ultrasonic irradiation in excellent yields (94-99%) (Scheme 139).



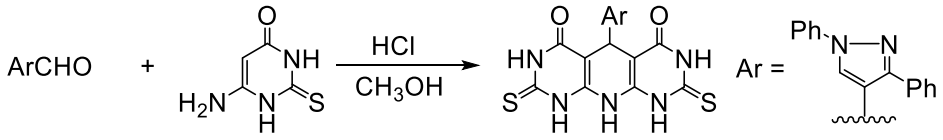
236 **2** **257** **299**

94-99%

R = H, CH_3; R_1 = C_6H_5, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4.

Scheme 139. Synthesis of tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,7*H*)-dione derivatives **299.**

3.2.2.11. Fused [6-6-6] system with five heteroatoms. 3.2.1.2.11.1. Pyrido[2,3-*d*:6,5-*d*']dipyrimidine derivatives. Abdel-Aziem *et al.*[239] reported that the reaction of two equivalents of 6-aminothiouracil **260** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** in methanol containing few drops of hydrochloric acid led to the formation of 5-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,8-dithioxo-2,3,5,8,9,10-hexahydropyrido [2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,7*H*)-dione **300** (Scheme 140).

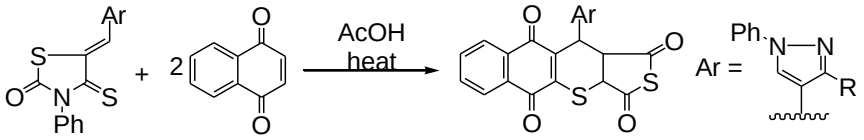


2 **260** **300**

75%

Scheme 140. Synthesis of 5-(1*H*-pyrazol-4-yl)hexahydropyrido [2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,7*H*)-dione **300.**

3.2.3. Pyrazole-substituted tetracyclic system. 3.2.3.1. Fused [6-5-6-6] system with two heteroatoms. 3.2.3.1.1. Benzo[*g*]thieno[3,4-*b*]thiochromene derivatives. Metwally *et al.*[209] reported that [4+2] cycloaddition reaction of 5-pyrazolylmethylene derivatives **231** with 1,4-naphthoquinone **301** afforded benzo[g]thieno[3,4-*b*]thiochromenes **302** (Scheme 141).



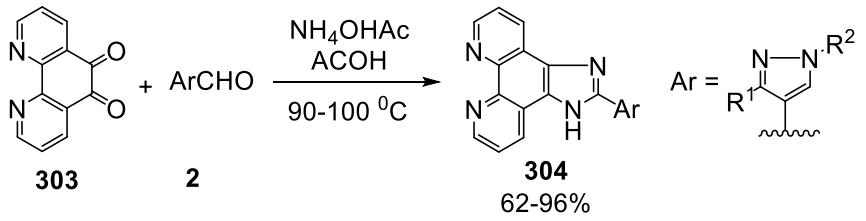
231 **301** **302**

59-70%

R = C_6H_5, 4-H_3C-C_6H_5, 4-H_3CO-C_6H_5, 4-Cl-C_6H_5.

Scheme 141. Synthesis of benzo[*g*]thieno[3,4-*b*]thiochromenes **302.**

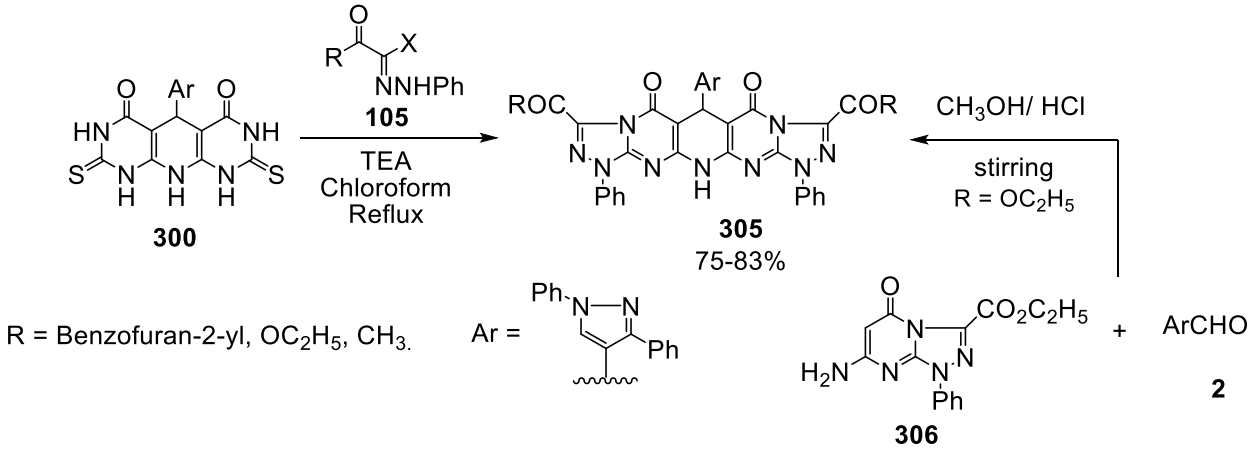
3.2.3.2. Fused [6-5-6-6] system with four heteroatoms. 3.2.3.2.1. Imidazo[4,5-*f*][1,10]phenanthroline derivatives. Liu *et al*.[240] reported that heating a mixture of 1,10-phenanthroline-5,6-dione **303**, ammonium acetate **78** and pyrazole-carboxaldehydes **2** in glacial acetic acid gave Imidazo[4,5-*f*][1,10]phenanthroline derivatives **304** (Scheme 142).



R^1 = 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3C-C_6H_4; R^2 = H, CH_3, -H_2C-C_6H_5, -$(H_2C)_3$-$N(CH_3)_2$, 2,4-O_2N-C_6H_4, 6-chloropyridazin-3-yl.

Scheme 142. Synthesis of Imidazo[4,5-*f*][1,10]phenanthroline derivatives **304.**

3.2.4. Pyrazole-substituted pentacyclic system. 3.2.4.1. Fused [6-5-5-6-6] system with nine heteroatoms. 3.2.4.1.1. Pyrido[2,3-*d*:6,5-*d*']ditriazolopyrimidine derivatives. Abdel-Aziem *et al.*[239] reported that the reaction of hexahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-4,6(1*H*,7*H*)-dione **300** with hydrazonoyl halides **105** in boiling chloroform gave ditriazolo[4,3-*a*]pyrimidin-5(1*H*)-one-dihydropyridine **305**. Compound **305** was alternatively obtained by the reaction of ethyl-7-amino-5-oxo-1-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate **306** with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde **2** in the presence of hydrochloric acid (Scheme 143).



Scheme 143. Synthesis of ditriazolo[4,3-*a*]pyrimidin-5(1*H*)-one-dihydropyridines **305.**

Conclusions

Heterocycles, in particular nitrogen-containing heterocycles, have been found to show a range of important applications in various fields. Among the different nitrogen-containing heterocycles, pyrazole derivatives are the most active class of five-member heterocycles due to their wide variety of important applications. This review highlighted the different synthetic methods for the preparation of pyrazole-carboxaldehydes and their

utility as versatile precursors for various pyrazole-substituted heterocyclic systems as hybrid molecules. The heterocyclic compounds described in this review are arranged on the basis of the size of the heterocyclic ring as well as the location and number of heteroatomes. We hope that this analysis will be useful not only for synthetic organic chemists, but also for researchers interested in medicinal and biological chemistry.

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