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A concise review on some synthetic routes and applications of pyridine scaffold compounds

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A B S T R A C T

Different methods for the synthesis of pyridine derivatives as well as the chemical reactivity profiles and structures of these substances are reviewed. The utility of these compounds as precursors is emphasized in the synthesis of many heterocycles that are pharmacologically active organic compounds and agrochemicals. This review results from a literature survey containing some synthetic methods and applications of pyridine derivatives.

1. Introduction

Pyridine derivatives are an important class of azaheterocycles found in many natural products, active pharmaceuticals and functional materials.[1-8] Synthetic routes appeared from the latter half of the 19th century although pyridine derivatives were of little commercial importance for decades and required quantities could be obtained from coal tar distillation.

Pyridines came to prominence in the 1930s with the recognition of the importance of niacin **1** for the prevention of dermatitis and dementia. In the 1940s a new major application was discovered for 2-vinylpyridine **2** as a constituent in latex. Demand for 2-picoline **3** for latex production outstretched its availability from coal tar sources and so researchers at Reilly industries developed an industrial

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synthesis of 2- and 4-picolines **3**, **4** by vapour phase catalytic reactions. The demand for pyridine and its derivatives has further increased over the last 50 years by the discovery of many bioactive pyridine-containing compounds (**Fig. 1**).[9,10]

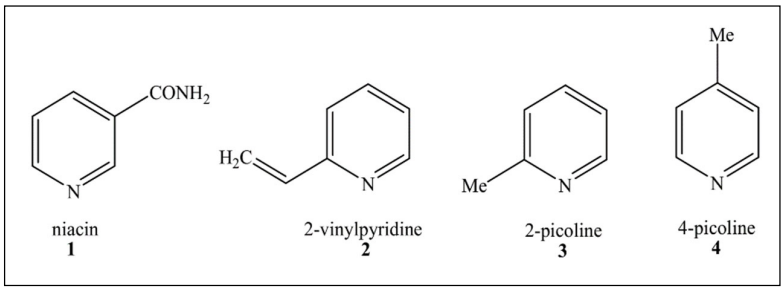


Fig. 1. Structure of compounds **1**-**2**.

Many pyridine-based alkaloid natural products are derivatives of nicotinic acid **5**.[11] Nicotine **6** is formed by the incorporation of a pyrrolidine moiety derived from L-ornithine onto the molecular frame work of nicotinic acid. Like nicotine, similar alkaloids, including anabasine **7**, ricinine **8**, and arecoline **9**, all originate from nicotinic acid (**Fig. 2**).[11]

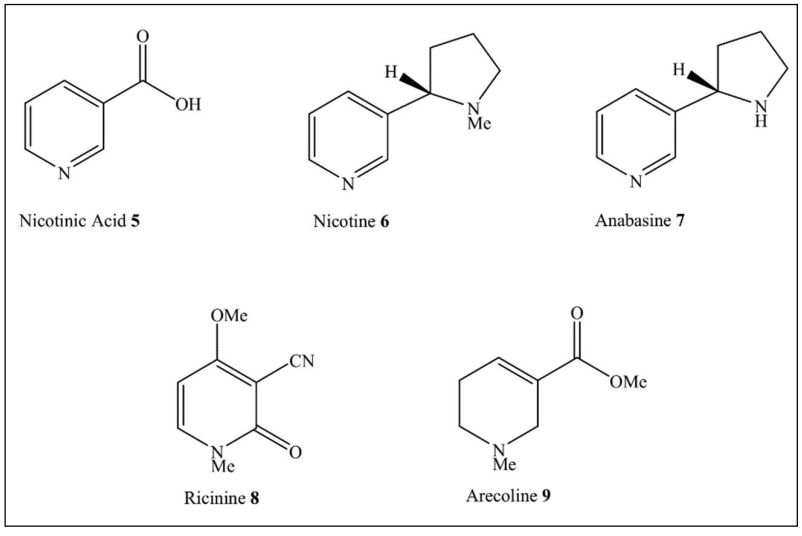


Fig. 2. Structure of compounds **5**-**9**.

A large number of reports concerning the chemistry and applications of numerous pyridines as well as their condensed derivatives have been published during the last five decades,[12-15] and a very lengthily review will be required to cover them. So, this work will be focused only on special interesting aspects related the synthesis and applications of pyridine derivatives.

2. Synthesis of pyridine derivatives

2.1 From reactions of 1,3-dicarbonyl compounds.

The reaction of 1,3-dicarbonyl compounds and 3-aminoenones, 3-aminoacrylates or 3-aminoacrylonitrile is one of the most versatile and useful reactions, since it allows the construction of substituted pyridines from relatively simple precursors. Thus, the reaction of 3-methylpentane-2,4-dione (**10**) with 3-aminoenones **11** gave penta-substituted pyridine **12**. 1,3-Dialdehyde equivalents can also be used, but only in the form of their acetal enol ethers such as **13** which upon treatment with **14** produced pyridine derivative **15**.[16] 3-Aminoenone **11** and acrylate **14** are readily available from the reaction of ammonia with 1,3-diketone or 3-ketoester (**Fig. 3**).

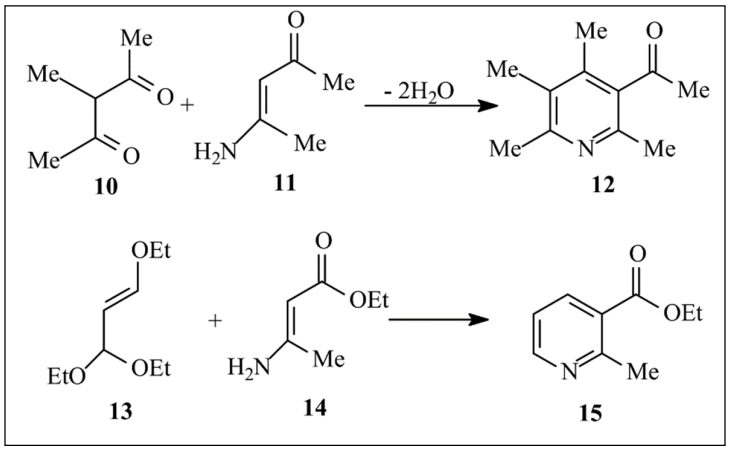


Fig. 3. Synthsis of compounds **10**-**15**.

Henecke reported that the reaction of 2,4-diketoester **16** with triethyl orthoformate gave an ester enol ether **17** which cyclo-condensed with 3-aminonitrile **18** to furnish tetrasubstituted pyridine **19** (**Fig. 4**).[16,17]

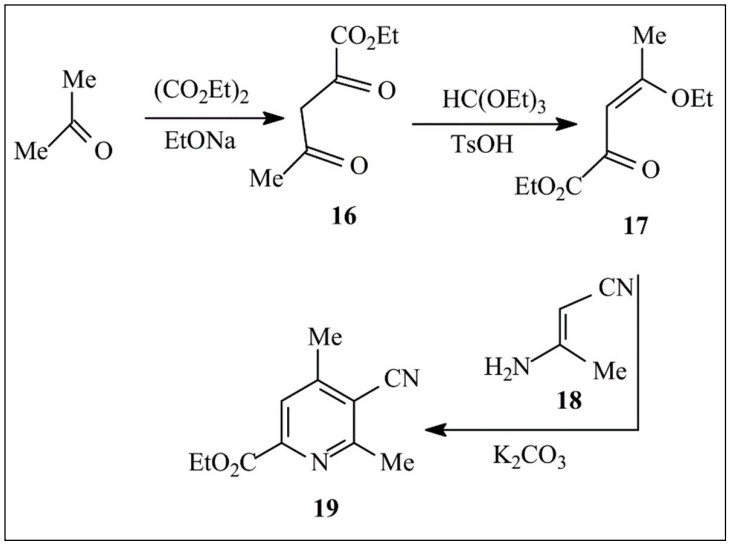


Fig. 4. Synthsis of compounds **16**-**19**.

Also, 1,3-dicarbonyl compounds are extensively utilized for the synthesis of 2-pyridones as well as their thioxo analogs. Thus, the reaction of 2-phenylmalonodialdehyde (**20**) with cyanothioacetamide in the presence of β-diethylaminoethanol, as a basic catalyst, gave 3-cyano-5-phenylpyridine-2(*1H*)-thione (**21**) (**Fig. 5**).[18]

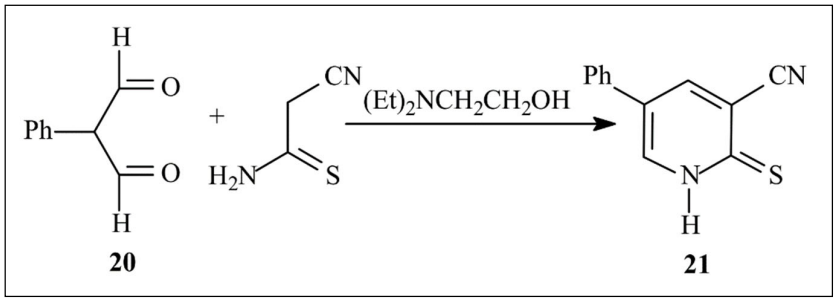


Fig. 5. Synthsis of compounds **20**-**21**.

The reaction of β-ketobutyraldehyde dimethylacetal (**22**) with cyanothioacetamide gave 3-cyano-6-methylpyridine-2(*1H*)-thione (**23**) (**Fig. 6**).[19]

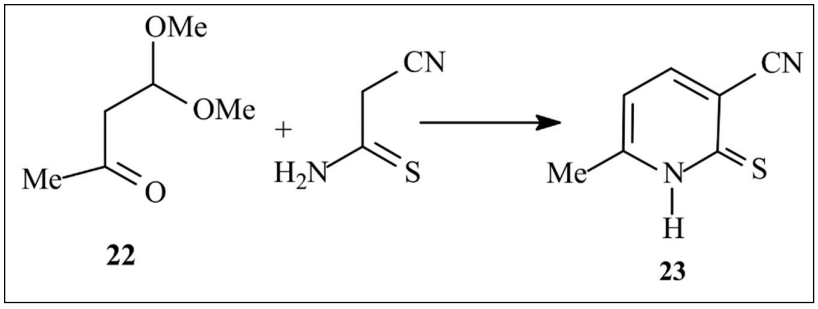


Fig. 6. Synthsis of compounds **22**-**23**.

The cyclocondensation of acetylacetone **24** with cyanothioacetamide in the presence of a basic catalyst produced the corresponding 3-cyanopyridine derivatives **25**.[20] Treatment of **25** with benzylidenernalononitrile resulted in the formation of monoarylidene derivatives that formulated as **26**.[20] Attempted addition of another molecule of benzylidenemalononitrile to **26** resulted in the formation of dibenzylidene derivative **27**, which was assumed to occur via addition of the C-4 methyl function to the activated double bond and subsequent elimination of malononitrile (**Fig. 7**).[20]

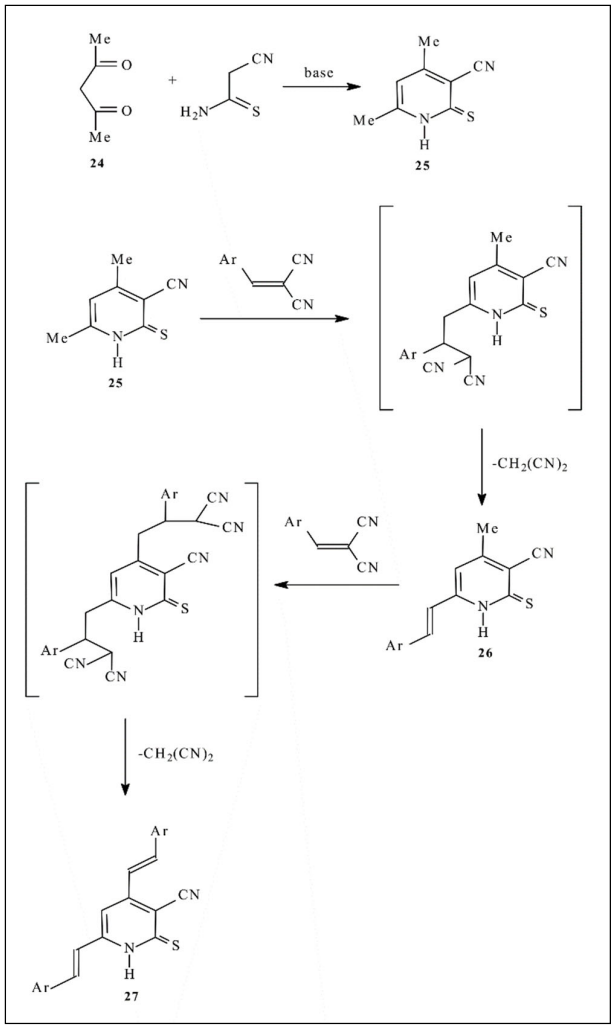


Fig. 7. Synthsis of compounds **25**-**27**.

Similarly, the interaction of arylhydrazone derivatives **28** with cyanothioacetamide in the presence of sodium ethoxide furnished the corresponding 3-cyanopyridine-2(*1H*)-thiones **29** (**Fig. 8**).[21,22]

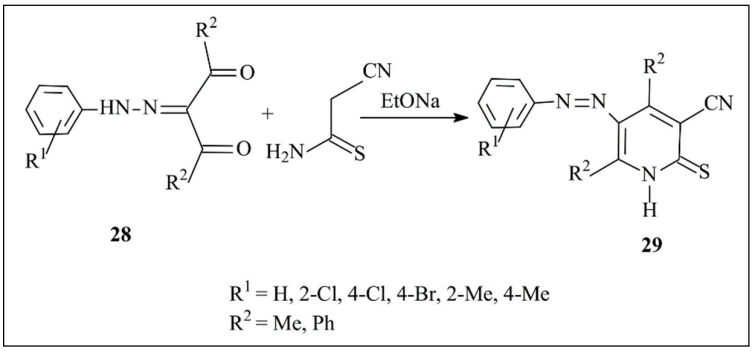


Fig. 8. Synthsis of compound **29**.

The reaction of 1-ethoxy-2,4-dioxopentane (**30**) with ethyl β-amino-β-ethoxyacrylate (**31**) and ammonia is reported to give ethyl 2-amino-4-ethoxymethyl-6-methylnicotinate (**32**) (**Fig. 9**).[23]

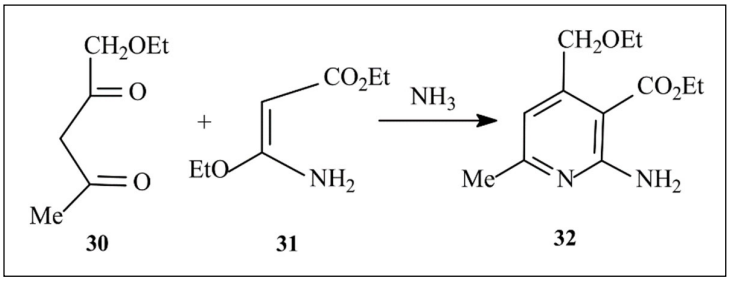


Fig. 9. Synthsis of compound **32**.

When malonamide was heated with an excess amount of ethyl β-acetylpyruvate (**33**) at 130-140°C, the imide of 2-hydroxy-6-methylpyridine-3,4-dicarboxylic acid (**34**) was obtained (**Fig. 10**).[24]

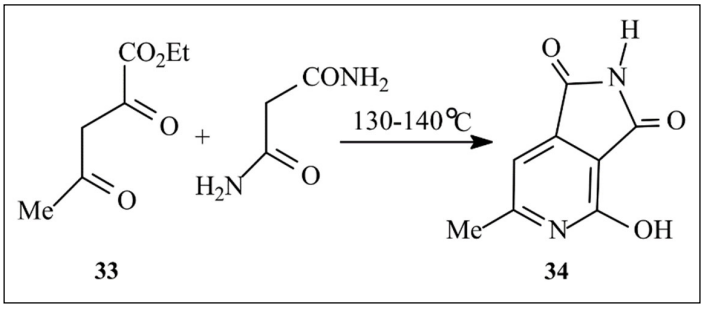


Fig. 10. Synthsis of compound **34**.

2.2 From α,β-unsaturated carbonyl compounds.

α,β-Unsaturated carbonyl compounds were extensively utilized for the synthesis of several functionally substituted pyridines. Thus, the reaction of compound **35** with the enamines **36-38** gave the pyridine derivatives **39-41** in moderate yields, with an average purity of greater than 85% by HPLC (**Fig. 11**).[25]

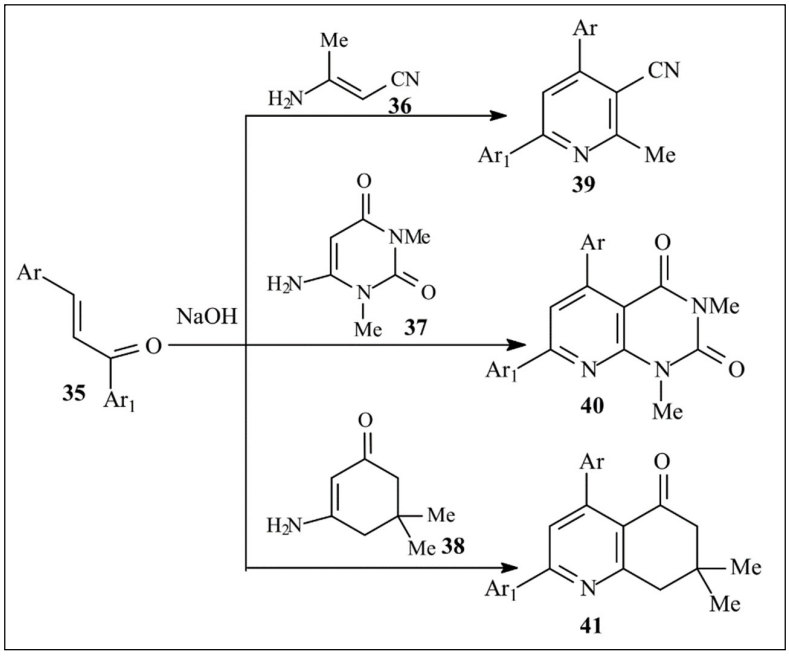


Fig. 11. Synthsis of compounds **39-41**.

Katritzky and co-workers in 1997 employed (1-benzotriazolyl)acetonitrile **42** as a nucleophile for Michael addition onto α,β-unsaturated carbonyl **43**. Nucleophilic attack onto the nitrile **44** by a secondary amine then initiated condensation followed by aromatisation, *via* **45**, to yield the desired 2,4,6-trisubstituted pyridine **46** in a good yield (64 %) (**Fig. 12**).[26]

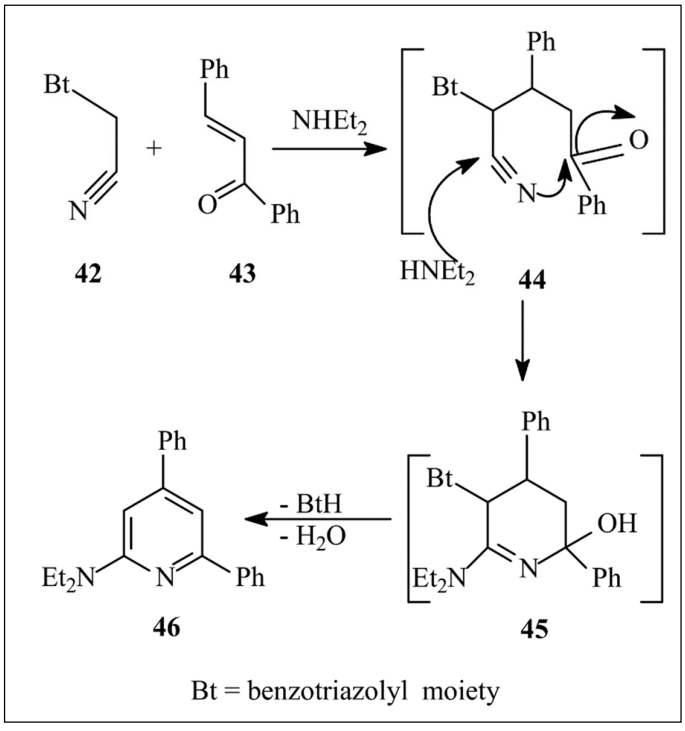


Fig. 12. Synthsis of compounds **44-46**.

The reactions of chalcones **47** with cyanothioacetamide gave the corresponding 3-cyanopyridine-2(*1H*)-thiones **48** (**Fig. 13**).[27]

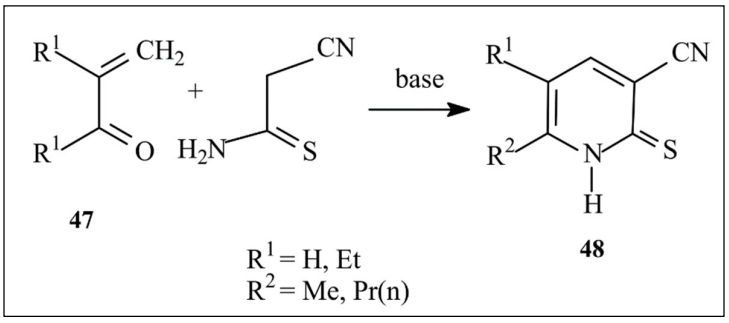
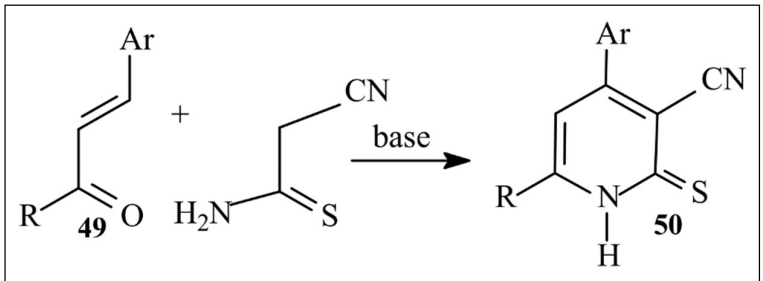


Fig. 13. Synthsis of compound **48**.

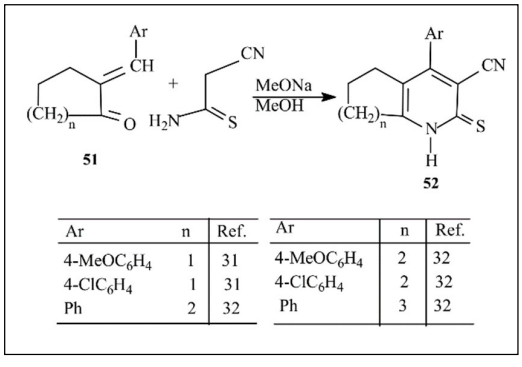
Similarly, the reactions of chalcones **49** with cyanothioacetamide were reported to give the corresponding 3-cyanopyridine-2(*1H*)-thiones **50** (**Fig. 14**).[28-30]



R	Ar	Ref.
Me	4-ClC_6H_4	28
Me	2-furyl	28
Ph	2-furyl	29
Ph	2-thienyl	29
PhCH=CH-	Ph	30
4-$MeOC_6H_4CH$=CH-	4-$MeOC_6H_4$	30
4-ClC_6H_4CH=CH-	4-ClC_6H_4	30

Fig. 14. Synthsis of compound **50**.

Moreover, 4-aryl-3-cyanocycloalka[*b*]pyridine-2(*1H*)-thiones (**52**) were synthesized *via* the interaction of 2-arylmethylene-cycloalkanones (**51**) with cyanothioacetamide in the presence of sodium methoxide as a basic catalyst (**Fig. 15**).[31,32]



Ar	n	Ref.
4-$MeOC_6H_4$	1	31
4-ClC_6H_4	1	31
Ph	2	32

Ar	n	Ref.
4-$MeOC_6H_4$	2	32
4-ClC_6H_4	2	32
Ph	3	32

Fig. 15. Synthsis of compound **52**.

The reaction of compound **53** with enamine **54** followed by a ring closure in the presence of a dehydrating agent, gave ethyl 2-methylnicotinate (**55**) (**Fig. 16**).[33]

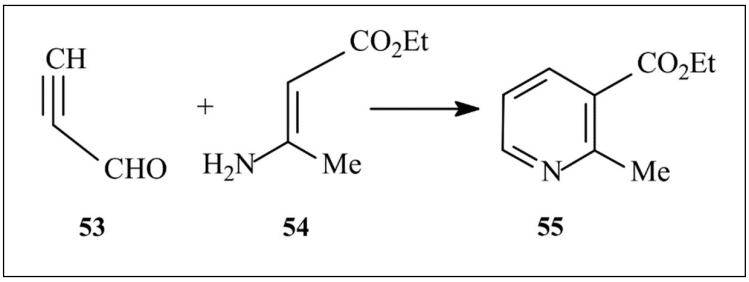


Fig. 16. Synthsis of compound **55**.

2.3 From conjugated nitriles.

1,6-Addition of ammonia to the conjugated nitrile **56** by Perveev and Koshmina in 1968 gave the 2-aminopyridine derivative **58** *via* **57** in a good yield (70–80%) (**Fig. 17**).[5,34]

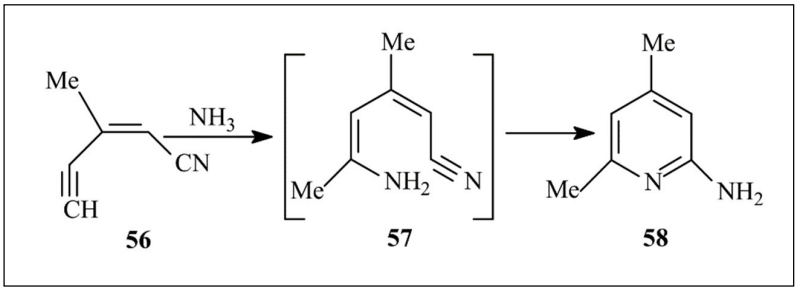


Fig. 17. Synthsis of compound **58**.

In 1999, Katritzky *et. al.* reported that the reaction of a Vilsmeier-type reagent **62** with a dienamine **61** gave pyridine derivative **63**. The intermediate **61** was easily synthesized from ketones such as **59** and β-aminocrotononitrile **60** (**Fig. 18**).[35]

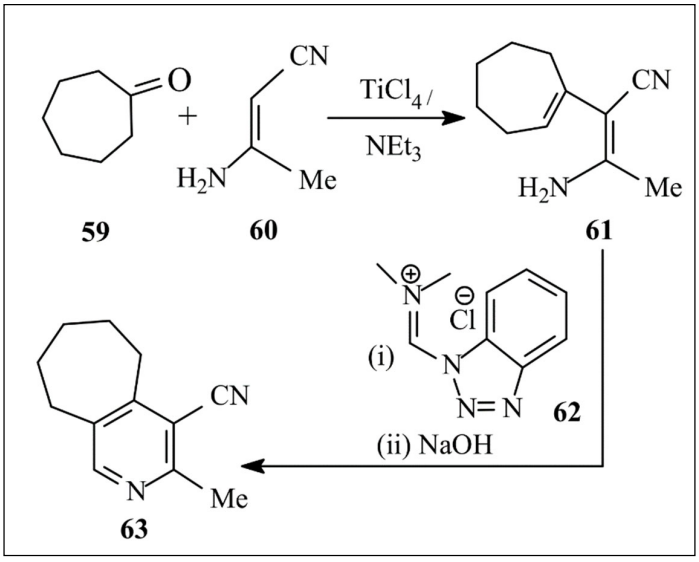


Fig. 18. Synthsis of compound **63**.

The reaction of β-substituted-α-thiocarbamoylacrylonitriles with active methylene compounds provided a good method for synthesizing a variety of 3-cyanopyridine-2(*1H*)-thione derivatives. Thus, the reaction of β-aryl-α-thiocarbamoylacrylonitriles (**64**) with some cycloalkanones was reported to give the corresponding 4-aryl-3-cyanocycloalka[*b*]pyridine-2(*1H*)-thiones (**65**) (**Fig. 19**).[36]

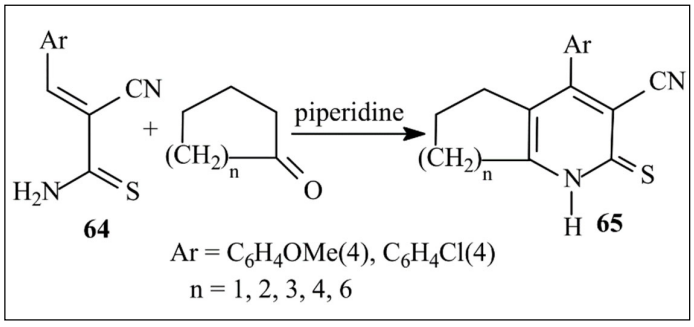


Fig. 19. Synthsis of compound **65**.

The reaction of β-aryl-α-thiocarbamoylacrylonitriles (**64**) with acetylacetone gave contradictory results. Thus, whereas many authors[37-39] reported that the reaction products were pyridine-2(*1H*)-thiones **66**, others[40,41] reported that dihydropyridine-2(*1H*)-thiones **67** were the only isolated reaction products. This reaction was reinvestigated by Eldin,[42] who proved that its products were a mixture of **66** and **67** (**Fig. 20**).

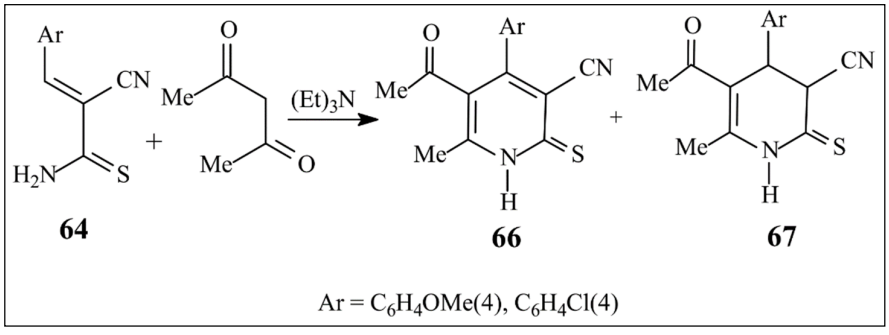


Fig. 20. Synthsis of compound **67**.

The reaction of **64** with ethyl acetoacetate was reported to give the corresponding pyridinethiones **68** (**Fig. 21**).[43]

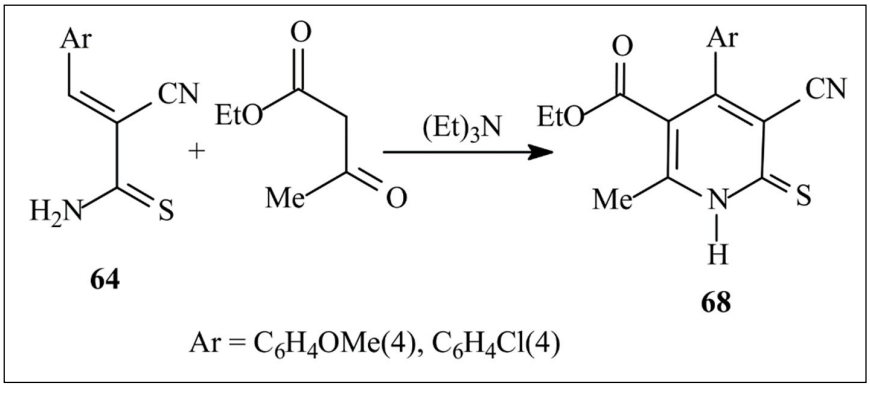


Fig. 21. Synthsis of compound **68**.

2.4 From Diels-Alder reaction.

Janz and Monaghan in 1964 reported that the 1,3-dienes e. g. **69** undergoes Diels–Alder reaction upon treatment with activated nitriles such as **70** to give moderate to excellent yields of pyridines (**71,** 99%). High temperatures (~ 400°C) are necessary, except in reactions involving the most electrophilic of nitriles, for example, RSO_2CN (**Fig. 22**).[5,44]

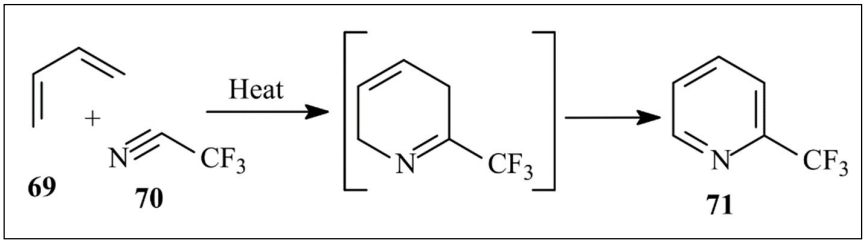


Fig. 22. Synthsis of compound **71**.

Pyrones such as **72** can be an attractive replacement for the 1,3-dienes **69** in the Diels–Alder reaction, as shown by Jaworski and Kwiatkowski in 1970.[5,45] Also, pyronecarbonitrile **75** has the potential to act as an electrophile towards amine **76** to form pyridine deivative **77** in a low yield (40 %) by an alternative mechanism, as shown by Farhanullah and co-workers in 2003 (**Fig. 23**).[46]

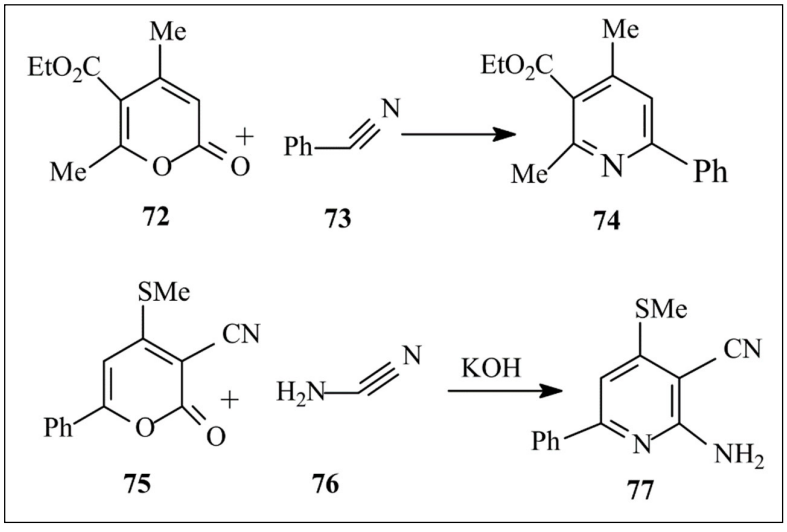


Fig. 23. Synthsis of compounds **74** and **75**.

The addition of a dienophile e.g. acrylic acid **78** to oxazole derivative **79** was reported by Kondrat'eva and Huan in 1965, where the subsequent extrusion of the oxazole oxygen gave the target pyridine **80** in a good yield (70 %) (**Fig. 24**).[16,47]

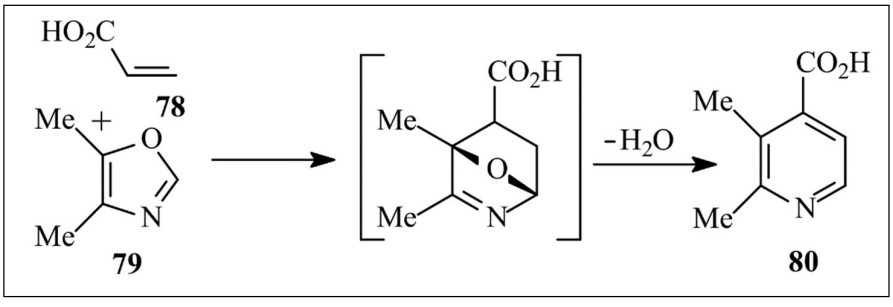


Fig. 24. Synthsis of compound **80**.

Similarly, 1,2,4-triazines (e. g. **81**) undergo inverse-type Diels–Alder reactions with electron-rich and angle-strained dienophiles such as **82** to give pyridine derivatives (e. g. **83)**, after extrusion of molecular nitrogen, in 64–90% yield, as shown by Sauer and co-workers in 1998 (**Fig. 25**).[48]

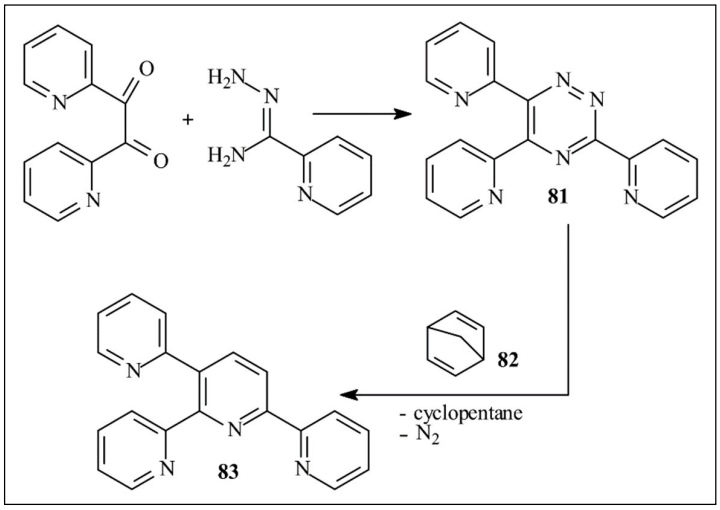


Fig. 25. Synthsis of compound **83**.

2.5 From other ring system.

Pyrylium salts, for example, **84**, were efficiently converted into the 2,4,6-trisubstituted pyridine **85**, as shown by Balaban in 1969 (**Fig. 26**).[49]

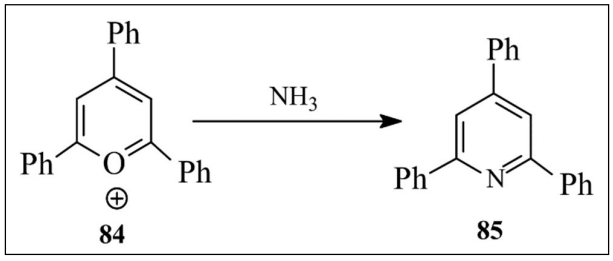


Fig. 26. Synthsis of compound **85**.

Transformation of 2-amino-*4H*-pyrans **86** into the corresponding 2-pyridinones **65** was achieved when the pyrans were allowed to react with nitrosylsulfuric acid in acetic acid solution. The reaction can be understood by assuming the formation of an open chain intermediate **87** due to the nucleophilic attack of water to the protonated pyran ring followed by cyclization and spontaneous dehydrogenation to furnish the product **88** (**Fig. 27**).[50]

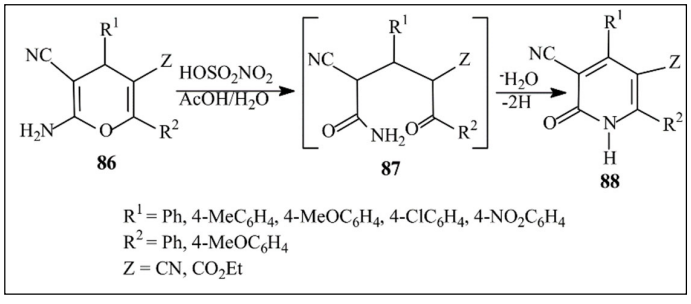
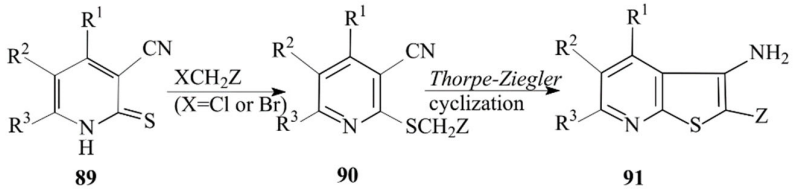


Fig. 27. Synthsis of compound **88**.

2.6 From 3-cyanopyridine-2(1H)-thiones.

Substituted 3-cyanopyridine-2(1*H*)-thiones were used extensively in the synthesis of a large number of functionally substituted thieno[2,3-*b*]pyridines. Thus, thieno[2,3-*b*]pyridine derivatives **91** were prepared from the reaction of **89** with the respective halo compounds followed by cyclization of the resulting intermediates **90** (**Fig. 28**).[51-61]



89 **90** **91**

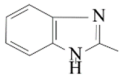
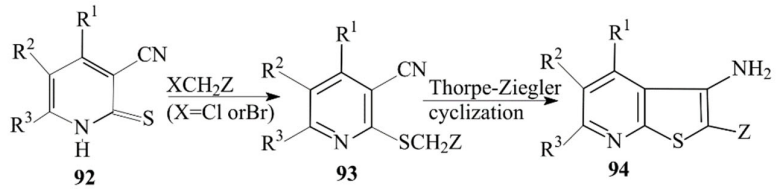
R^1	R^2	R^3	Z	Ref.
H	Et	Me	CO_2Et, $CONH_2$, CN	51
Me	H	Me	$CONH_2$, CONHPh,	52
CH_2OMe	H	Me	COPh, $CONH_2$, CONHPh	53
Ph	H	Ph	COPh, CO_2Et, CO_2H	54
Me	H	CH_2OH	COPh, CO_2Et, $CONH_2$	55
4-ClC_6H_4	H	Me	$CONH_2$, CONHPh	56
Ph	H	Styryl	COMe	57
Furyl	H	Me	COPh, $CONH_2$	58
CF_3	H	2-thienyl	$CONH_2$, CONHPh,	59
Ph	H		COMe, CO_2Et, CONHPh	60
SMe	COAr	H	CO_2Et, $CONH_2$	61

Fig. 28. Synthsis of compound **91**.

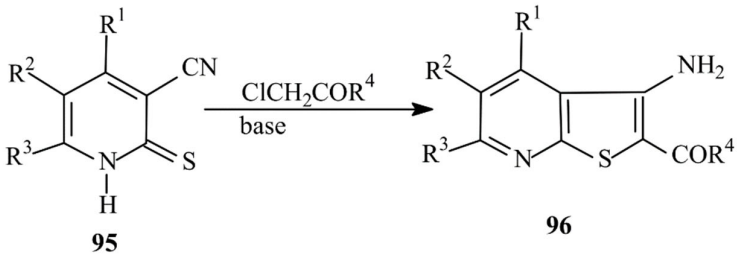
Also, the reaction of trisubstituted 3-cyanopyridine-2(1*H*)-thiones of the type **92** with the appropriate α-haloketones, α-haloesters, chloroacetamide or chloroacetonitrile produced the pentasubstituted thiopyridines **93**. When the latter compounds were heated with strong base such as potassium hydroxide or sodium alkoxide, they underwent intramolecular Thorpe-Ziegler cyclization to give thieno[2,3-*b*]pyridine derivatives **94** (**Fig. 29**).[62-70]



R^1	R^2	R^3	Z	Ref.
Et	PhNHCO	Me	2-thenoyl	62
Me	Me	Me	$CONH_2$, CN	63
Ph	CO_2Et	Me	CO_2Me	64
Ar	CO_2Et	Ph	COMe, COPh	65
2-furyl	CO_2Et	Me	COMe, $CONH_2$	66
Ar	COMe	Me	CO_2Et,$CONH_2$, COAr,	67
			CONHAr	68
2-furyl	PhNHCO	Me	$COC_6H_3Cl_2$(3,4),	69
Ph	CN	OEt	CN	70

Fig. 29. Synthsis of compound **94**.

When the reaction of 3-cyanopyridine-2(1*H*)-thiones **95** or **97** with some α-haloketones or alkyl chloroacetate was carried out in high boiling point solvent such as pyridine or in the presence of relatively strong base such as K_2CO_3, KOH or sodium alkoxide, the corresponding thieno[2,3-*b*]pyridine derivatives **96** [21,22,71-77] and **98** [71,78,79] were directly obtained (**Fig. 30** and **Fig. 31**).



95 **96**

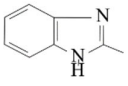
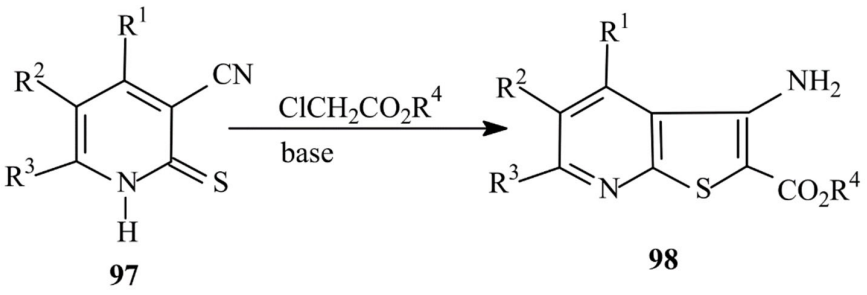
R^1	R^2	R^3	R^4	Ref.
H	H	Me	Me	71
Me	H	Me	Me	71
Styryl	H	styryl	Me	71
Styryl	H	Ph	Me	71
H	H	Ph	Ph	72
Me	H	NH_2	Ph	72
Me	H	NH_2	Ph	73
Et	CN	Me	Ph	74
CO_2Et	H	Me	Me or Bu^t	75
CO_2Et	H	Me	Ph	75
Me	PhN=N	Me	Ph	21
Ph	ArN=N	Ph	Ph	22
Aryl	H		Ph	76
Ph	H	Ph	2-naphthyl	77

Fig. 30. Synthsis of compound **96**.

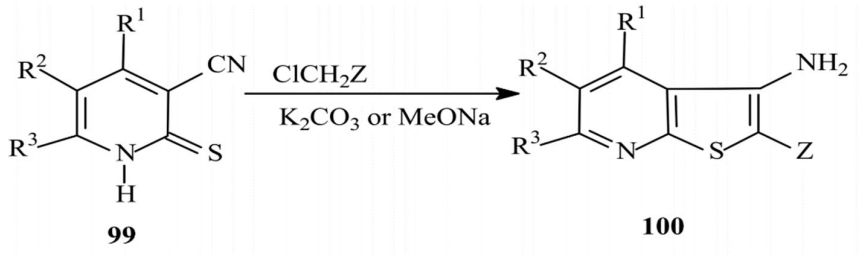


97 **98**

R^1	R^2	R^3	R^4	Ref.
H	H	Me	Et	71
Me	H	Me	Et	78
styryl	H	Me	Et	71
styryl	H	styryl	Et	71
H	H	Ph	Et	79
Me	H	Ph	Et	79
Me	Me	Me	Et	79
Me	$PhCH_2$	Me	Et	79
4-BrC_6H_4	H	Me	Me	79
Me	H	4-BrC_6H_4	Me	79

Fig. 31. Synthsis of compound **98**.

Similarly, the compounds **99** were reacted with chloroacetonitrile and/or chloroacetamide in the presence of potassium carbonate or sodium methoxide to give the target 2-functionalized 3-aminothieno[2,3-*b*]pyridines **100** (**Fig. 32**).[71,80-82]



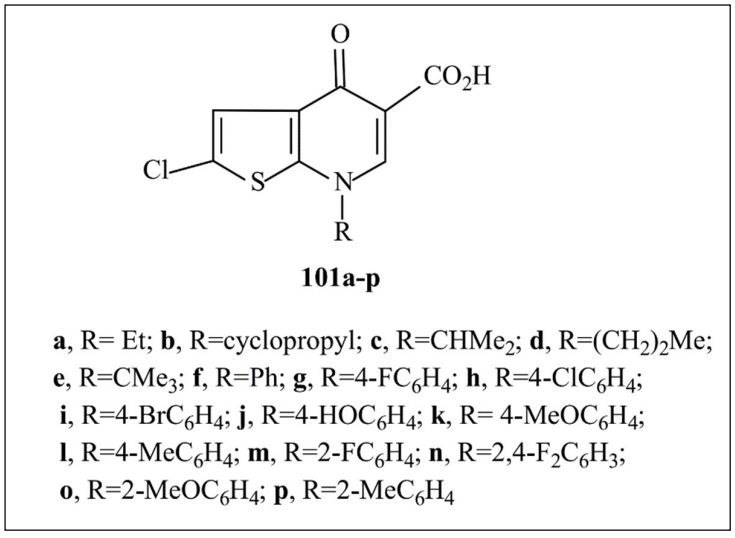
R^1	R^2	R^3	Z	Ref.
Me	H	Me	CN	71
Styryl	H	Me	CN	71
Styryl	H	styryl	CN	71
Ph	H	Me	$CONH_2$	80
Ph	H	Me	CN	80
Me	H	Ph	CN	80
Ph	H	Ph	CN	80
Me	H	4-ClC_6H_4	CN	80
4-ClC_6H_4	H	Me	CN	80
4-ClC_6H_4	H	Ph	$CONH_2$	80
4-ClC_6H_4	H	4-ClC_6H_4	$CONH_2$	80
4-ClC_6H_4	H	4-ClC_6H_4	CN	80
4-BrC_6H_4	H	Me	$CONH_2$	80
Me	H	4-BrC_6H_4	$CONH_2$	80
Me	Me	Me	$CONH_2$	80
Me	Me	Me	CN	80
Me	CH_2Ph	Me	$CONH_2$	80
H	Me	Me	$CONH_2$	81
Ph	CN	OEt	$CONH_2$	82

Fig. 32. Synthsis of compound **100**.

3. Applications of pyridine derivatives

Thieno[2,3-*b*]pyridines systems -as an example of pyridine derivatives- are proved to be an interesting class of heterocycles. Most of them are reported to possess anticipated biological activities.

Some of them are known to exhibit a variety of medicinal and industrial applications. For example, 2-chloro-7-alkyl- or aryl-4,7-dihydro-4-oxothieno[2,3-*b*] pyridine-5-carboxylic acids (**101a-p)** are reported to possess good antibacterial activities especially against *Escherichia coli* (**Fig. 33**).[83-85]

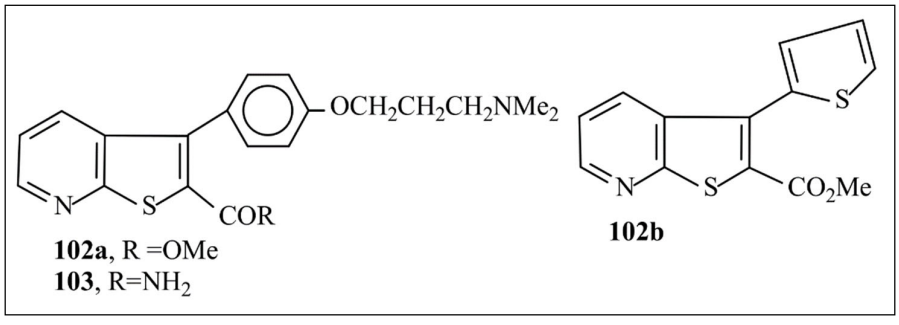


101a-p

a, R= Et; **b**, R=cyclopropyl; **c**, R=$CHMe_2$; **d**, R=$(CH_2)_2Me$;
e, R=CMe_3; **f**, R=Ph; **g**, R=4-FC_6H_4; **h**, R=4-ClC_6H_4;
i, R=4-BrC_6H_4; **j**, R=4-HOC_6H_4; **k**, R= 4-$MeOC_6H_4$;
l, R=4-MeC_6H_4; **m**, R=2-FC_6H_4; **n**, R=2,4-$F_2C_6H_3$;
o, R=2-$MeOC_6H_4$; **p**, R=2-MeC_6H_4

Fig. 33. Structure of compound **101a-p**.

Compounds **102a** and **103** are useful as hematinics, antitumor agents and as immunostimulants.[86] Compound **102b** was used for compacting phytopathogenic fungi (**Fig. 34**).[87]

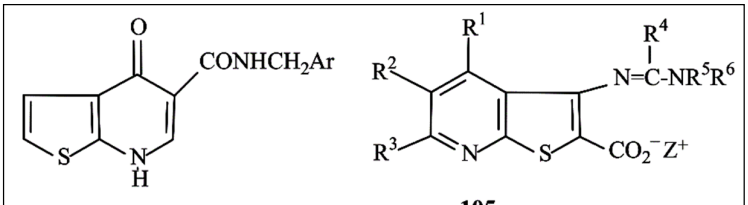


102a, R =OMe
103, R=NH_2

102b

Fig. 34. Structure of compounds **102a**, **102b**, and **103**.

The 4,7-dihydrothieno[2,3-*b*]pyridine derivative **104** showed a considerable antiviral activity.[88] Most of the compounds **105** showed inhibitory activity against different lipoxygenases (**Fig. 35**).[89]



104, Ar = 4-ClC_6H_4

105

R^1= H, Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, R_2 = H
R^3 = Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4; R_4=Me, Et
NR^5R^6= piperidino, morpholino;
Z^+ = piperidinium, morpholinium

Fig. 35. Structure of compounds **104** and **105**.

Thieno[2,3-*b*]pyridine derivatives **106** are used as anti-inflammatory agents, particularly agents for treating arthritis and bone resorption inhibiting agents (**Fig. 36**).[90]

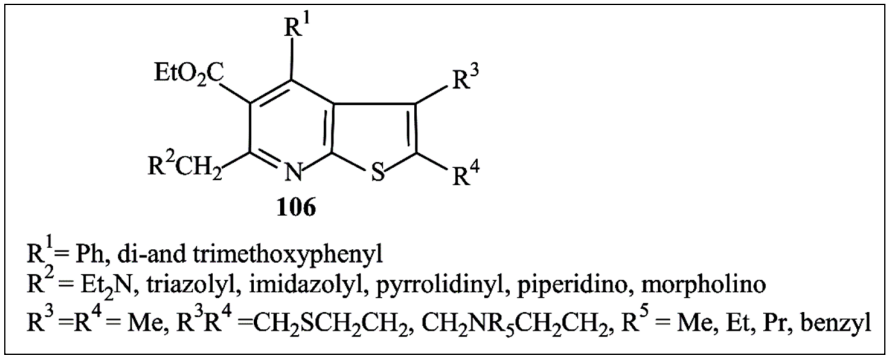


Fig. 36. Structure of compound **106**.

The pyridine derivative **107** is useful as an anti-inflammatory drug particularly as a remedy for arthritis (**Fig. 37**).[91]

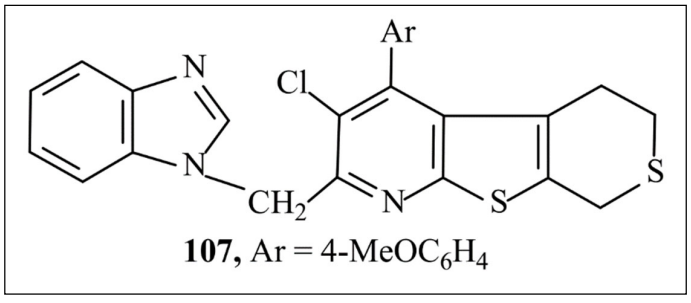


Fig. 37. Structure of compound **107**.

On the other hand, the azo dyes **108** and **109** were applied to polyesters and polyamide fibers, and their spectral and fastness properties were measured (**Fig. 38**).[92]

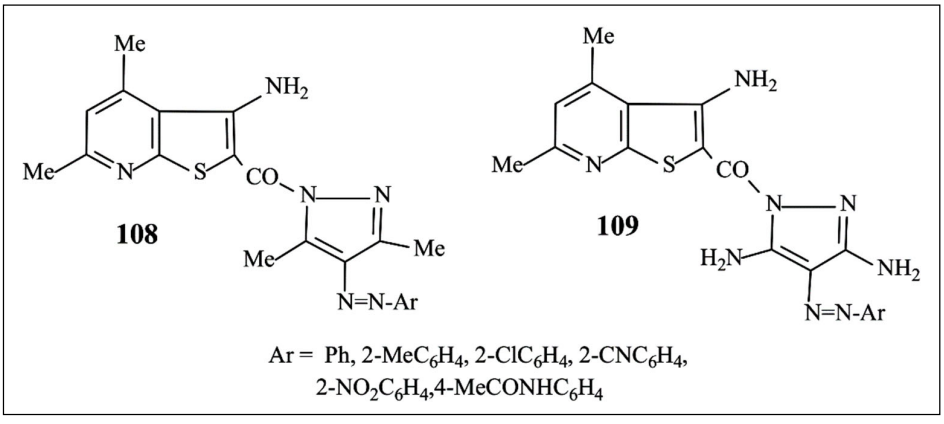


Fig. 38. Structure of compounds **108** and **109**.

Compound **110** was reported to possess a good antimicrobial activity (**Fig. 39**).[93]

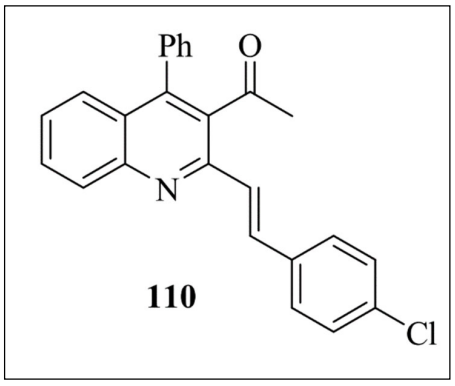


Fig. 39. Structure of compound **110**.

Also, pyridine derivatives are used widely in agrochemicals.[94] Some of these chemicals (**111–120)** and their applications are shown below (**Fig. 40**), which confirms the importance of organic compounds in the field of agrochemicals.[94-105]

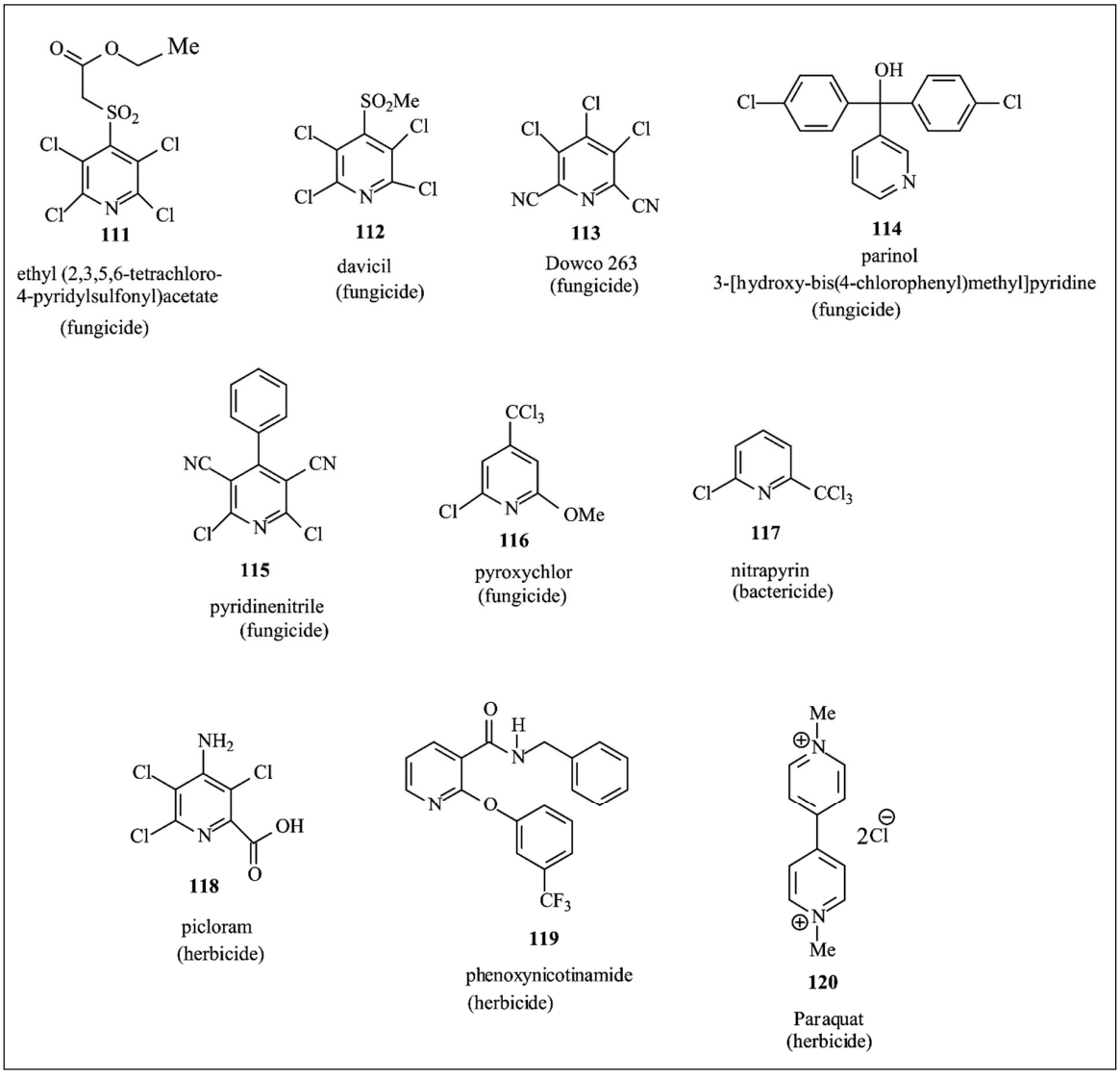


Fig. 40. Structure of compounds **111-120**.

4. Conclusions

Pyridine, a six membered nitrogen bearing heterocyclic scaffold, can be found in a number of pharmacologically efficient structures. There has been an increasing attention in the development of bioactive compounds, bearing the heterocyclic, pyridine. The data studied in this review obviously determine the great synthetic potential of pyridine scaffold. This recommends that pyridine scaffold can be principally encouraging synthons in synthesis of novel greatly effective pharmaceuticals.

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