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

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ABSTRACT

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. 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
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.](image)

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.](image)

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 lengthy 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. Synthesis 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. Synthesis 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. Synthesis of compounds 20-21.
The reaction of \( \beta \)-ketobutyraldehyde dimethylacetal (22) with cyanothioacetamide gave 3-cyano-6-methylpyridine-2(1H)-thione (23) (Fig. 6).19

![Chemical structure of 22 and 23](image)

**Fig. 6. Synthesis 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 benzylidenemalononitrile 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

![Chemical structures of 24, 25, 26, and 27](image)

**Fig. 7. Synthesis 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).\textsuperscript{21,22}

\[ \text{Fig. 8. Synthesis of compound 29.} \]

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).\textsuperscript{23}

\[ \text{Fig. 9. Synthesis of compound 32.} \]

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).\textsuperscript{24}

\[ \text{Fig. 10. Synthesis of compound 34.} \]

2.2 \textit{From }\alpha,\beta\textit{-unsaturated carbonyl compounds.}

\alpha,\beta\textit{-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).}\textsuperscript{25}
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

The reactions of chalcones 47 with cyanothioacetamide gave the corresponding 3-cyanopyridine-2(1H)-thiones 48 (Fig. 13).²⁷
Similarly, the reactions of chalcones 49 with cyanothioacetamide were reported to give the corresponding 3-cyanopyridine-2\((1H)\)-thiones 50 (Fig. 14).28-30

![Diagram of compound 48 synthesis](image)

**Fig. 13.** Synthesis of compound 48.

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![Diagram of compound 50 synthesis](image)

**Fig. 14.** Synthesis 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

![Diagram of compound 52 synthesis](image)

**Fig. 15.** Synthesis 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. Synthesis of compound 55.](image)

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. Synthesis of compound 58.](image)

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. Synthesis of compound 63.](image)
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. Synthesis of compound 65.](image)

The reaction of β-aryl-α-thiocarbamoylacrylonitriles (64) with acetylacetone gave contradictory results. Thus, whereas many authors37-39 reported that the reaction products were pyridine-2(1H)-thiones 66, others40,41 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. Synthesis of compound 67.](image)

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

![Fig. 21. Synthesis of compound 68.](image)
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, RSO₂CN (Fig. 22).

![Fig. 22. Synthesis of compound 71.](image)

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. Also, pyronecarbonitrile 75 has the potential to act as an electrophile towards amine 76 to form pyridine derivative 77 in a low yield (40%) by an alternative mechanism, as shown by Farhanullah and co-workers in 2003 (Fig. 23).

![Fig. 23. Synthesis of compounds 74 and 75.](image)

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).

![Fig. 24. Synthesis of compound 80.](image)
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

![Synthesis of compound 83](image)

**Fig. 25.** Synthesis 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

![Synthesis of compound 85](image)

**Fig. 26.** Synthesis 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

![Synthesis of compound 88](image)

**Fig. 27.** Synthesis of compound 88.
2.6 From 3-cyanopyridine-2(1H)-thiones.

Substituted 3-cyanopyridine-2(1H)-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

![Fig. 28. Synthesis of compound 91.](image)

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Also, the reaction of trisubstituted 3-cyanopyridine-2(1H)-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
Fig. 29. Synthesis of compound 94.

When the reaction of 3-cyanopyridine-2(1H)-thiones 95 or 97 with some α-halo ketones 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).
**Fig. 30.** Synthesis of compound 96.

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Fig. 31. Synthesis 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).\textsuperscript{71,80-82}
3. Applications of pyridine derivatives

Thieno[2,3-\textit{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).\(^{83-85}\)

![Fig. 33. Structure of compound 101a-p.](image)

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

![Fig. 34. Structure of compounds 102a, 102b, and 103.](image)

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).\(^{89}\)

![Fig. 35. Structure of compounds 104 and 105.](image)
354

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.](image)

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.](image)

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.](image)

Compound 110 was reported to possess a good antimicrobial activity (Fig. 39).93
Also, pyridine derivatives are used widely in agrochemicals,\textsuperscript{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.\textsuperscript{94-105}

Fig. 39. Structure of compound 110.

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.

References


tetrahydroquinolines and tetrahydrothieno[2,3-b]quinolines. 


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(89) Vieweg H., Leistner S., Prantz J., Bohm N., & Wagner G. (1992) Synthesis of N-(2-carboxythieno(2,3-b)pyridin-3-yl)-amidines by the reaction with 4-oxo-4H-pyrido (3',2':4,5)-thieno(3,2-d)-1,3-oxazines with secondary cycloaliphatic amines. Pharmazie, 47(11) 841-845.


