

CHAPTER 5

Synthesis and Activity Evaluation of Pyridine Derivatives

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Abstract: Pyridine is a basic heterocyclic organic compound with the chemical formula C_5H_5N . In various characteristics, it can be related to well established and very fundamental aromatic molecule benzene. Benzene with one C-H group replaced by a nitrogen atom. Pyridine has a conjugated system containing six π -electrons that are delocalized over the heterocyclic ring. Pyridine ring system is very widely distributed in nature, especially in plant kingdom. It plays a key role catalysing both biological and chemical systems. In many enzymes of living organisms, it is the prosthetic pyridine nucleotide that is involved in several oxidation–reduction processes. It is used as a precursor to synthesize agrochemicals, pharmaceuticals, photo material along with it is utilized as reactant or reaction intermediate to architect more complex heterocyclic structures. In various reactions it performs role of solvent. It is well known that the pyridine derivatives possess the important biological activity and numerous applications in different fields. In the pharmaceutical industry, pyridine forms the nucleus of over thousands of existing drugs. It is found in vitamins and also in alkaloids.

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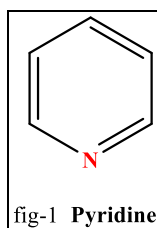
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Introduction

Pyridine is heterocyclic six membered aromatic compound with molecular formula C_5H_5N , an isostere of benzene (fig-1). The name pyridine came from Greek word and is amalgamation of two different words such as “pyr” means fire and “idine” represent aromatic based. In 1846 Anderson at first isolated pyridine motif was isolated from picoline. After certain years Wilhelm Körner in 1869 and James Dewar in 1871 revealed structure of pyridine. In earlier by combination of acetylene and hydrogen cyanide in red hot condition to obtained pyridine-based compound by William Ramsay in 1876. Nature is enriched with pyridine and pyridine based compounds and play vital role in biological system also numerous enzymatic reactions, oxidation–reduction processes, and in various vitamins also play crucial role [1,2].



Pyridine is N-heterocycles compound with diverse pharmacological activity and synthesis of pyridine based heterocycle is also one of strategic method in organic synthesis [3]. Pyridine motif found in many natural products. (fig-2) Pyridine is main component in different pharmacological scaffold having wide pharmacological activity such as anticonvulsant, antidiabetic, antitumor activity, anti-inflammatory, antidepressant, antihypertensive, IKK- β inhibitors, cytotoxic, CNS depressant, antioxidant etc [4-13].

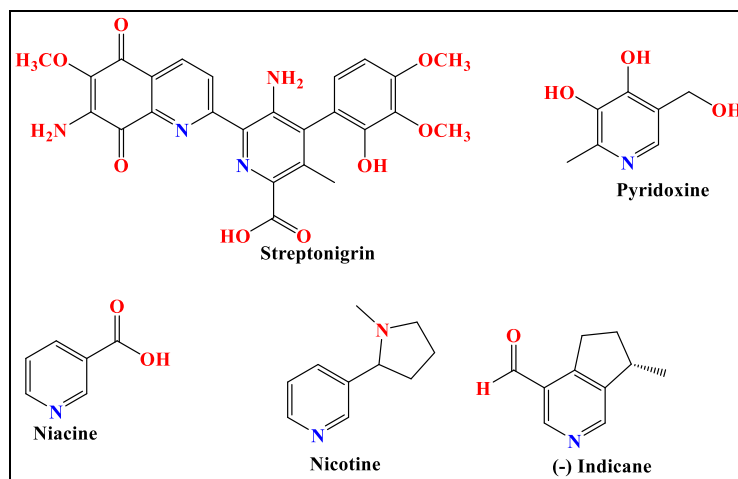


Fig. 2

Several classical methods are employed to synthesised pyridine such as Hantzsch pyridine synthesis by employing β -dicarbonyl compounds in the presence of an aldehyde and ammonia, Friedländer condensation using enaminketones of β -ketoesters with 1,3-diketones, Knoevenagel cyclisation using precursor β -dicarbonyl compounds in the presence of an aldehyde and ammonia [14-16]. In the synthesis of pyridine scaffold main foundation is to insert nitrogen which can be done by using compound containing cyanide with single, boulle and triple bonds [03]. The compound which containing CN group in their structure reacts with carbon-carbon unsaturated compounds, are also extensively employed to synthesize pyridine via transition metal catalysed reaction [17-19]. Some of the pyridine based molecule which is used as drug in commercial market in pharma industries. (Fig-3) In present book chapter we overview about synthesis and activity of different pyridine based compounds.

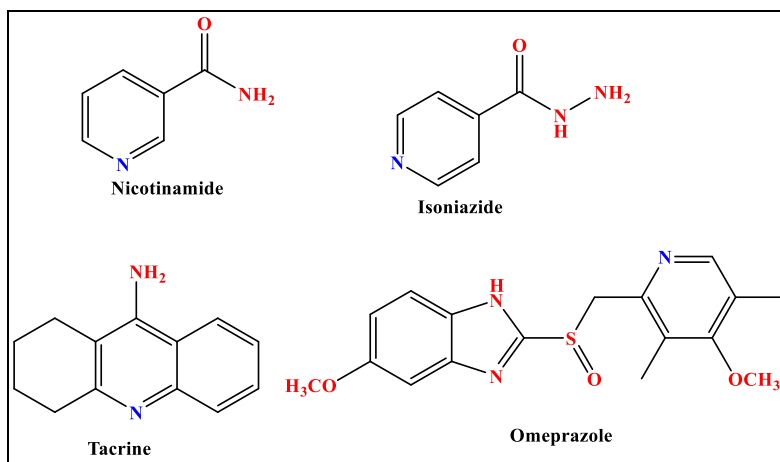


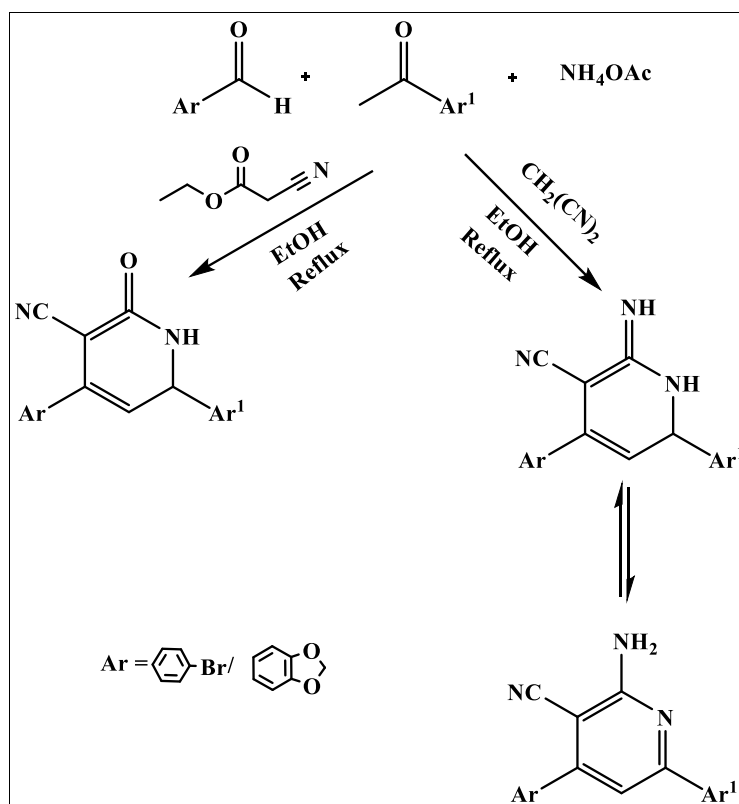
Fig. 3

Along with pharmacological activity, pyridine also play crucial role as insecticides as a part neonicotinoid. It is one of effective and commonly used insecticides applicable for wide range of sucking and certain chewing insects [20-21].

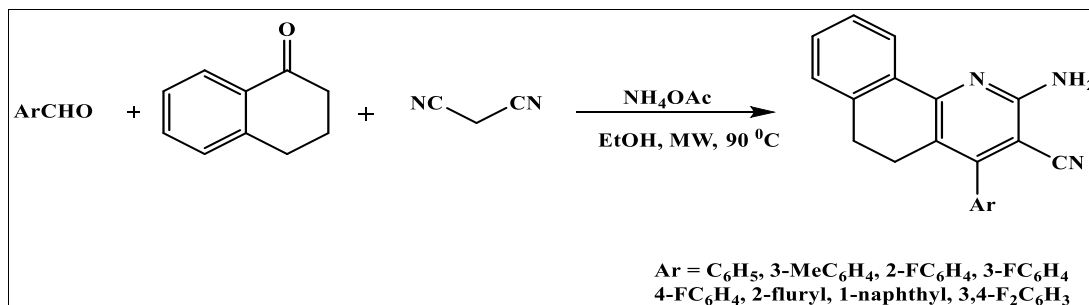
Synthesis of pyridine Derivatives and activity evaluation

Ashraf H. Abadi et al. reported synthesis of 4,6-diaryl-2-imino-1,2-dihydropyridine-3-carbonitriles and 4,6-diaryl-2-oxo-1,2-dihydropyridine-

3-carbonitriles by using p-bromoacetophenone or 3,4-methylenedioxy acetophenone, aldehyde, malononitrile and ammonium acetate refluxed in ethanol for about 18-24 hrs. Obtained product was filter followed by washing with ethanol and recrystallization with DMF/ethanol 1:2 to get desired product. Synthesize compound screen for their in vitro potency to inhibit PDE3A and the growth of the human HT-29 colon adenocarcinoma tumour cell line. Some of the synthesized derivates shows good activity but electronic effects, steric effects, conformational aspects, the H-bonding ability paly crucial role in activity evaluation [22].

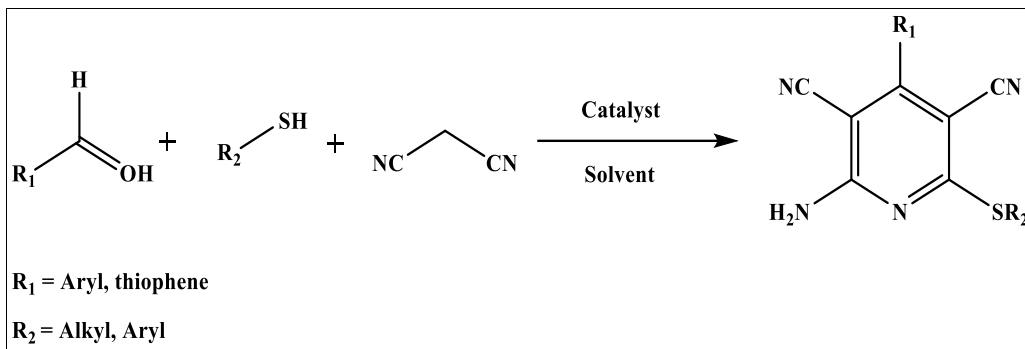


Cheng Guo and co-worker reported synthesis of cyclohexane-fused pyridine derivatives and study their photophysical properties. Synthesis of derivatives was carried out by employing one pot three-component condensation using precursor arylaldehyde, 3,4-dihydro-1(2*H*)-naphthalenone and malononitrile in presence of catalyst ammonium acetate under microwave condition. All the synthesized derivatives show different photophysical properties and study reveals that, group present on aromatic ring along with their position on ring also large impact on fluorescent intensity. TD-DFT helps to understand consequence of excitation on the absorption spectra of compounds [23].

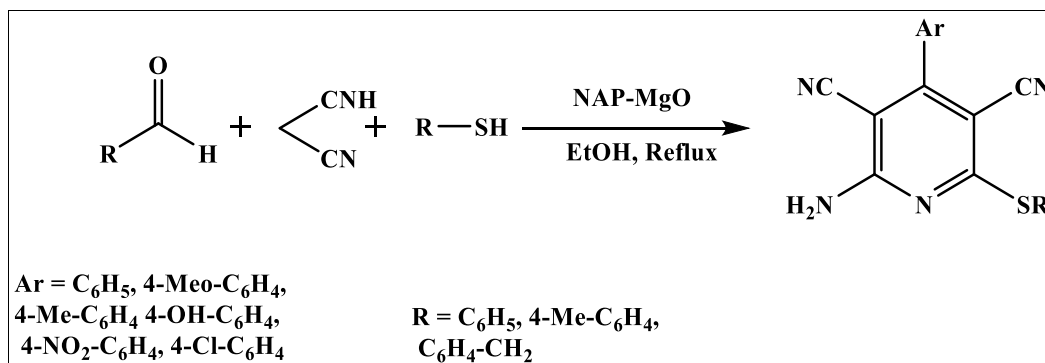


Paweł Kowalczyk et al. reported enzyme catalysed synthesis of pyridine derivatives which is effective against *E. coli* Strains. In this method expected compounds are obtained by using aldehyde,

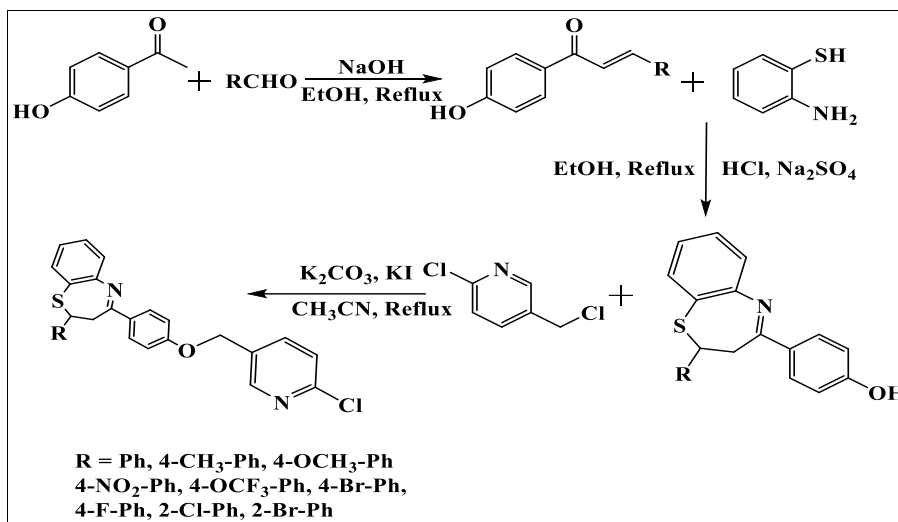
malononitrile, PPL and thiol in presence of solvent ethanol was carried out at 200 rpm at 40 °C for 18 hrs. After completion of reaction by simple filtration using celite to get desired product. Results shows that structure of substituent present on thiol moiety play crucial role of effectiveness of compounds. Results of pyridine compounds possess more cytotoxic in model bacterial cell than most commonly used antibiotics [24].



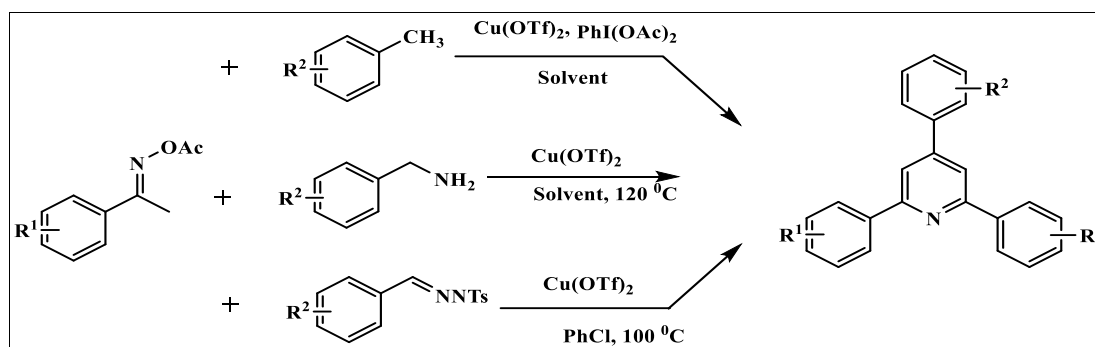
M Lakshmi Kantam et al. synthesized highly substituted pyridine via one pot three component method by using aldehyde, malononitrile in ethanol as solvent, in presence of NAP-MgO as a catalyst. After heating at 50 °C temperature thiol was added at reflux condition. Desire product was obtained after reaction completion followed centrifugation of reaction mixture and column chromatography [25].



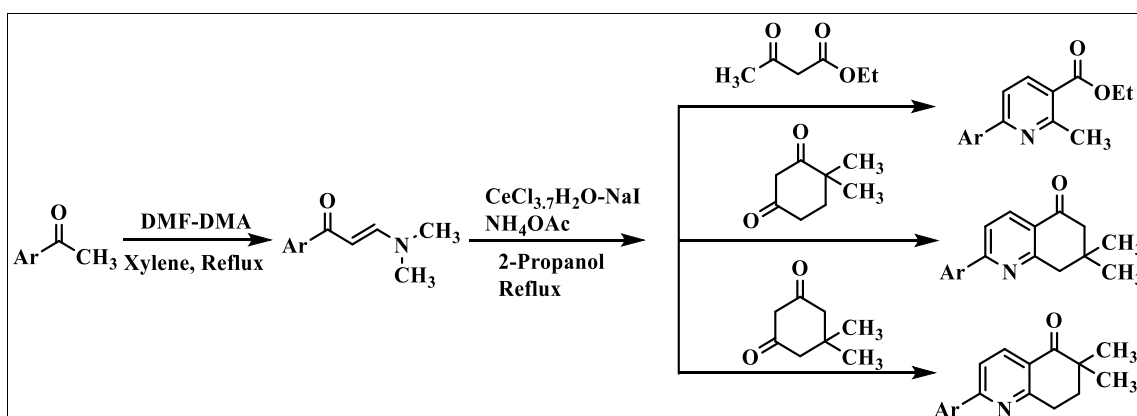
Tianxian Li et al. reported synthesis and antiviral activities of pyridine based 1,5-benzothiazepine compounds by using precursors aromatic aldehydes, hydroxyacetophenone, *o*-aminothiophenol in ethanol and acetonitrile solvent at different reaction condition to get desired product after recrystallization. Prepared derivative shows antiviral activity against TMV in vivo [26].



Baohua Chen et al. introduced synthesis of polyfunctional pyridines by coupling reaction via oxidative Copper-Catalyzed method. Synthesis of pyridine was carried out using precursor oxime acetate, Cu(OTf)₂, PhI(OAc)₂ in toluene as a solvent. Reaction mixture was stirred for an hrs at 100 °C. After completion of reaction, reaction mixture extracted with ethylacetate and dried using sodium sulphate. Desired compound was isolated using silica gel column chromatography [27].



Srinivas Kantevari et al reported synthesis of newer Aryl, Heteroaryl Tethered Pyridines and Dihydro-6H-quinolin-5-ones using variants of Bohlmann_Rahtz Reaction. Synthesis was carried out by employing β -Enaminones, ethyl Acetoacetate, 5,5-dimethylcyclohexane-1,3-dione or 4,4-dimethylcyclohexane-1,3-dione and ammonium acetate which is reflux in 2-propanol to get expected compound. Among entirely the synthesized compound some compound shows excellent antitubercular activity [28].



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