FEF3-CATALYZED SYNTHESIS OF PYRIDINE DERIVATIVES IN PEG-400 VIA FOUR-COMPONENT REACTION

[1]Patil Suraksha Kesarinath, [2]Dr. Subrata Nath
[1]Research Scholar, [2]Supervisor
[1-2] Department of Chemistry, Arunodaya University, Itanagar, Arunachal Pradesh, India

Abstract
In this study, a novel and environmentally benign method for the synthesis of 2-amino-3-cyano pyridine derivatives has been developed via a FeF_3-catalyzed four-component reaction in polyethylene glycol-400 (PEG-400) under ultrasound irradiation. Pyridine derivatives are privileged N-heterocycles found in numerous biologically active compounds and pharmaceutical agents with antiviral, anticancer, anti-inflammatory, and neuroprotective properties. Traditional methods for synthesizing these scaffolds often involve harsh conditions, extended reaction times, and toxic solvents. The current approach offers significant advantages including shorter reaction times, high yields, mild reaction conditions, and the use of a green solvent system. Iron(III) fluoride (FeF_3), which has been comparatively underexplored in organic synthesis, demonstrates excellent catalytic efficiency and reusability, while the application of ultrasound facilitates energy-efficient and waste-minimizing transformations. This method aligns with green chemistry principles and represents, to our knowledge, the first successful use of FeF_3 as a catalyst in ultrasound-assisted multicomponent synthesis of 2-amino-3-cyano pyridine derivatives.
Keywords: FeF_3, multicomponent reaction (MCR), pyridine derivatives, ultrasound-assisted synthesis, PEG-400, green chemistry, 2-amino-3-cyano pyridines, eco-friendly catalysis, nitrogen heterocycles, bioactive scaffolds.

Introduction:

As wide spread N-heterocycle known for its occurrence in many of bioactive compounds and natural products[1] the pyridine ring is considered to be one of the privileged structures in medicinal chemistry and pyridine drug discovery.

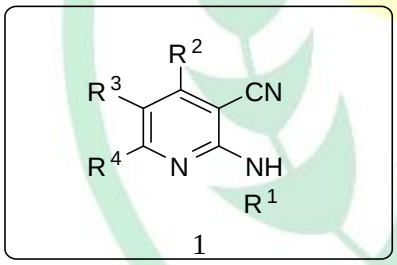


Figure 1: pyridine derivatives

The framework of pyridine (see Figure 1) represents a category of man-made substances that encompass numerous natural products and medicinal compounds.[2] A fundamental framework of the pyridine scaffold is found in various compounds that exhibit biological activity against hepatitis B virus[3], bacteria[4], and possess anti-cancer[5] properties[6]. These libraries have been suggested as possible treatments for Parkinson's disease, asthma, and prion disorders.[7-9] Over the last ten years, numerous synthetic approaches have been utilised for the multi-component synthesis of the pyridine framework, incorporating well-known reactions like the Hantzsch and Chichibabin reactions.[10-11]

Thus, in view to obtain biologically more potent heterocyclic systems, our aim was focused on the prologue of chemical diversity in the molecular framework to synthesize pharmacologically interesting compounds of different

composition by green protocol.

Development of environmentally benign and cost effective multicomponent reactions (MCRs) is great importance in both medicinal and organic chemistry as these methods provide quick and easy access to the diversity having combinatorial library of small molecules and these are very useful for the efforts of new drug discovery. One of the most important features of multi component reactions is that they provide extremely rapid and convergent routes to highly functionalized organic molecules. Moreover, these techniques do not involve the isolation and purification of intermediates and thereby reducing the cost, time and more importantly reduction of waste generation.[12-16] Therefore, multi component reactions have attracted significant attention of researchers particularly working in the area of pharmaceutical / medicinal / organic chemistry. Indeed, multi component reactions have been used extensively to generate the diversity based library of small organic molecules.[17-18]

In recent times, numerous endeavours have been dedicated to creating more effective techniques for synthesising pyridine derivatives, including the utilisation of gold. silver[19] and transition metal catalyst like Iron(III) chloride ($FeCl_3$),[20] montmorillonite K-10[21] and Tin(II)chloride dehydrate [22] However, due to the several drawbacks associated with these previously reported methods including moderate yields, longer reaction time and limited substrate scope a faster method has been developed recently for synthesis of pyridine derivatives..

The role of Iron(III) fluoride (FeF3) in organic synthesis has garnered significant interest recently, particularly when compared to its counterparts such as Iron(III) chloride (FeCl3), Iron(III) bromide (FeBr3), and Iron(III) iodide (FeI3). This is largely due to its remarkable stability and its effective use as a catalyst in a wide array of organic synthesis processes. Recently, alongside its commercial application in ceramic manufacturing, Iron(III) fluoride has garnered interest in the realm of organic synthesis. Salts derived from Iron(III) fluoride appear to hold significant promise and merit investigation for their potential role as catalysts in multicomponent reactions.

Additionally, the use of polyethylene glycol 400 (PEG-400) as an inexpensive and environmental friendly and its non-hazardous nature solvent in commercially available and stable Iron(III)fluoride catalysed reaction has also been explored. This is remarkable as the use of large volumes of volatile hazardous organic solvents in industrial processes posed a serious threat to the environment. Thus, procedures involving alternative benign solvents in reaction, isolation and purification are of high priority in industry. This encouraged us to explore Iron(III)fluoride as a convenient and suitable pre-catalyst for the synthesis of the pyridine derivatives via multi component reaction. Iron(III)fluoride is found to be an effective and environmentally benign catalyst for a number of organic transformations.[23-31]

. Biological importance:

Pyridine derivatives are very important class of compounds found in co- enzyme vitamin-B6 family, numerous natural products such as nicotine and its analogues, quinoline and isoquinoline alkaloids.[32-34] (Figure 2)

Pyridine derivatives have wide range biological against variety of pathogens such as hepatitis B virus, [35] prions [36] and bacteria.[37] Pyridine derivatives were proposed as possible potential therapies for many kidney diseases, hypoxia, epilepsy, Parkinson's disease, cancer, asthma and Creutzfeldt-Jakob disease.[38-40]

2-amino-3-cyanopyridine derivatives were identified as aurora A kianse inhibitors,[41] anti-herbicidal,[42]anti-tuberculosis,[43] anti-inflammatory,[44] and IKK-β-inhibitors.[45] Moreover, these compounds also act as anti-microbial,[46] A_{2A} adenosine antagonists[47] and antitumor.[48] In addition to above activity, these compounds are very important and useful intermediates in the preparation of wide variety of heterocyclic biological active compounds[49]. Therefore, the preparation of the 2-amino-3-cyano pyridines and its derivatives have attracted much attention in field of medicinal and organic chemistry

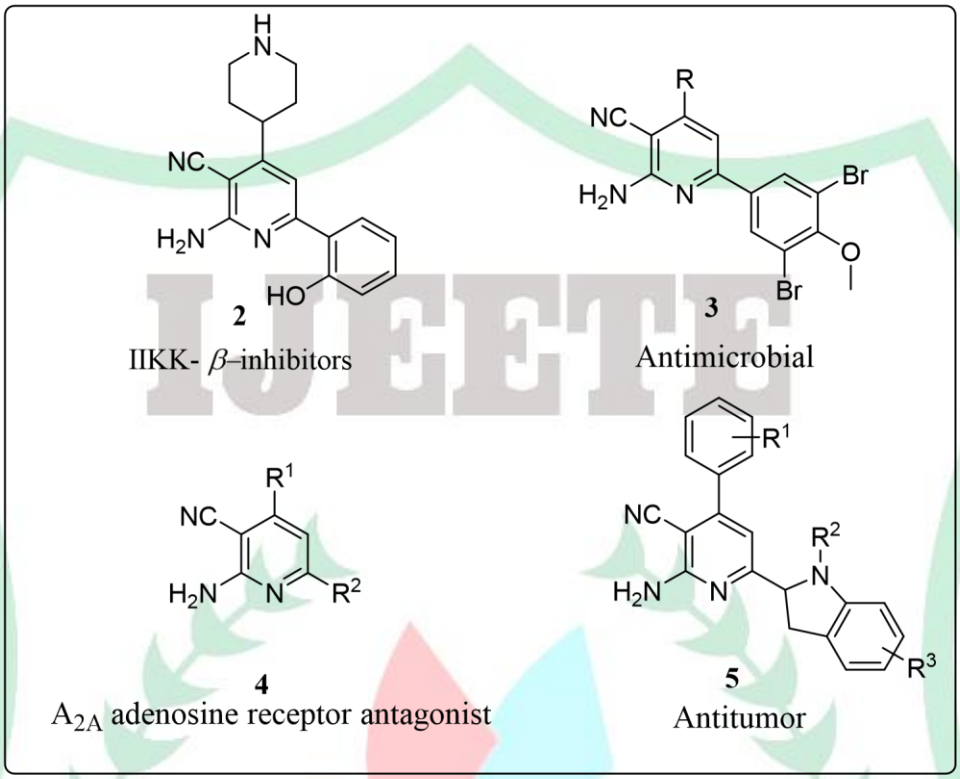


Figure 2: Some biologically active 2-amino, 3-cyano pyridine derivatives

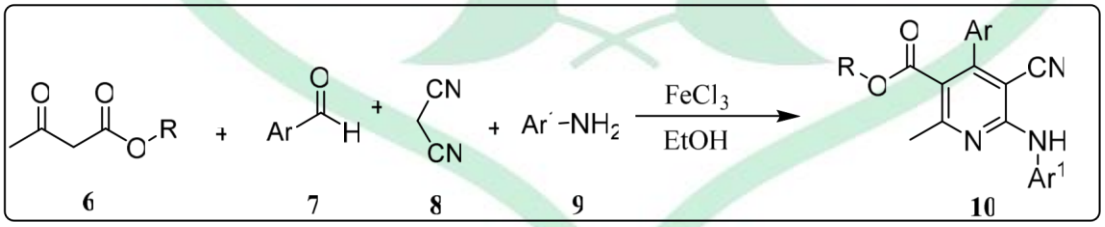
Few literature routes for synthesis of 2-amino, 3- cyano pyridine derivatives

The most commonly used synthetic methods for accessing have been reported to synthesize the 2-amino, 3- cyano pyridine derivatives.

(i) Shang et al., Approach. [50]

Shang and co-authors were reported synthesis of substituted 2- amino, 3-cyano pyridine derivatives by four component coupling of aromatic amine, β-Ketoesters and corresponding aldehyde in presence of Iron(III)chloride and ethanol at 70°C

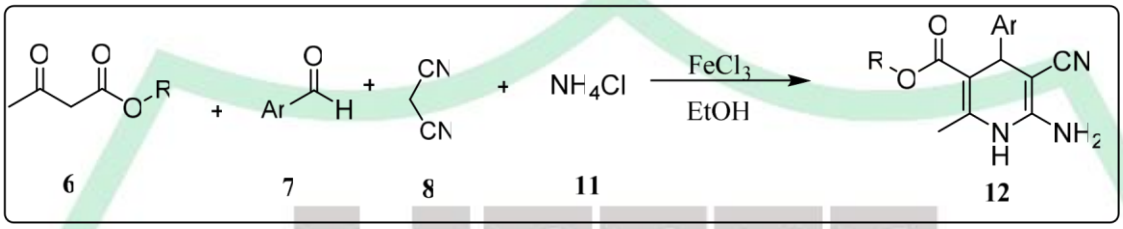
(Scheme 1).



Scheme 1: Iron(III)chloride catalysed synthesis of substituted 2- amino, 3-cyanopyridine derivatives.

Shang et al. also synthesized one pot synthesis of 2-Amino, 3-cyano -1,4dihydropyridine derivatives of Malononitrile,

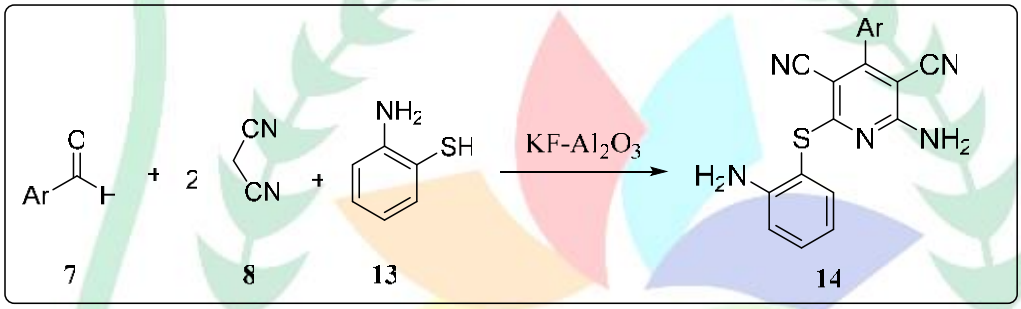
Aromatic Aldehydes, β-Ketoesters and ammonium chloride in presence Iron(III)chloride (Scheme 2).



Scheme 2: Synthesis of 2-amino, 3-cyano -1,4-dihydropyridine derivatives catalysed by Iron(III)chloride.

Das et al., Approach. [51]

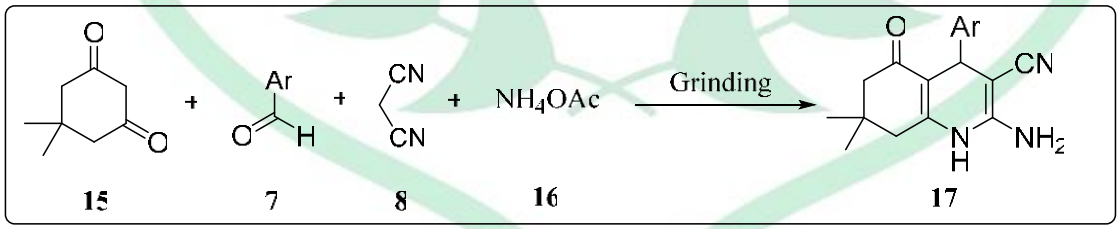
Das and co- authors were reported synthesis the below compounds by replacing the catalyst boric acid by potassium fluoride coated with alumina (KF-Al_2O_3) as green catalyst (Scheme 3).



Scheme 3: Synthesis of 2-amino, 3-cyano pyridine derivatives catalysed by potassium fluoride coated with alumina (KF-Al_2O_3).

Kumar et al,. Approach. [52]

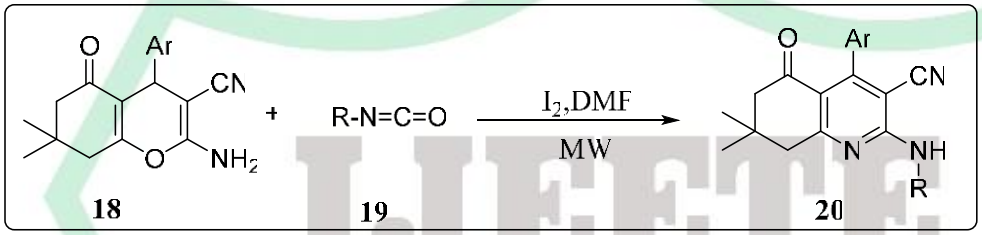
Kumar and co-authors developed an efficient methodology for the synthesize of substituted 2-amino, 3- cyano di dhyro pyridine derivatives via a four component reaction by mixing of of dimedone, aldehydes, ammonium acetate and malononitrile at room temperature without any solvent by means of on grinding (Scheme 4).



Scheme 4: Synthesis of substituted 2-amino, 3- cyano di dhyro pyridine derivatives via grinding

Jiang, Bo et al., Approach. [53]

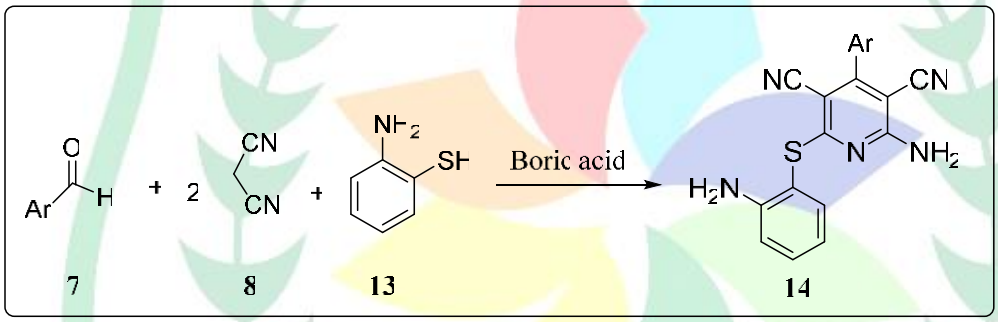
Jiang, Bo and co- authors were prepared the substituted 2-amino,3-cyano pyridine derivatives by reacting 2-amino chromone 3- carbonitrile with aryl/ cyclo alkyl isocyanate in presence of Iodine and by means of microwave irradiation in an DMF solvent at 150 ^{o}C (Scheme 5).



Scheme 5: Iodine catalysed synthesis of subtituted 2-amino,3-cyano pyridine derivatives

Shinde et al., Approach.[54]

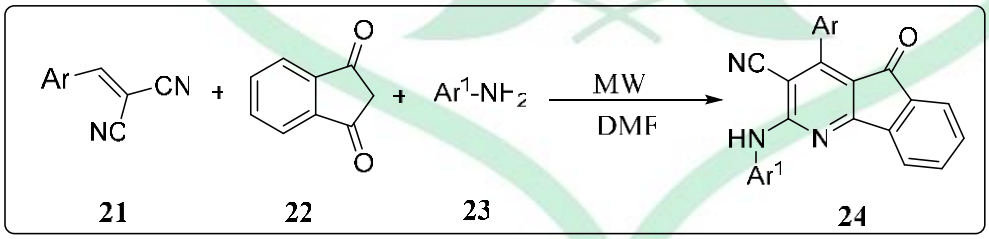
Shinde and co- workers were prepared the 2-amino-3,5- dicyano, 6- thioxy pyridine derivatives by means of multicomponent coupling of 2-amino- thio phenol, malononitrile and wide variety of aldehydes in presence of boric acid as catalyst (Scheme 6).



Scheme 6: Boric acid catalysed synthesis of 2-amino,3-cyano pyridine derivatives

Tu, Shujiang et al., Approach.[55]

Tu, Shujiang and co -authors were reported the preparation of substituted 2-amino,3cyano pyridine derivatives by means of three component reaction by reacting arylidene malononitrile, aromatic amine and 1,3-indenodione under microwave irradiation in DMF at 120 ^{0}C (Scheme 7).



Scheme 7: Micro wave assisted synthesis of substituted 2-amino,3-cyano pyridine derivatives

We have reviewed above various methodologies for the synthesis of 2-amino, 3- cyano pyridine derivatives. All these compounds show an interesting and wide variety of biological activities besides other functions. In view of their importance and the fact that reported methodologies have their own merits and demerits, therefore we have decided to expediate the broad spectrum and novel route for their synthesis.

The main objective of the present work was to development the ultrasound assisted organic reactions [56] have attracted enormous attention due to the efficiency (e.g. shorter reaction time, milder conditions, higher yields etc.) and greenness (in terms of energy conservation and waste minimization) of these processes over the conventional heating methods. On the other hand, because of its non-hazardous nature polyethylene glycol 400 (PEG-400) is considered as an environmental friendly solvent in various organic reactions.[57] Thus, in search of a more convenient and straight forward method for the synthesis of N-substituted 2-aminopyridines we decided to explore the use of ultrasound and PEG-400 for our purpose. Indeed, we were successful in our effort. Herein, we report a FeF_3 mediated four component reactions under ultrasound irradiation leading to the target pyridine derivatives from readily available starting materials. Though as a catalyst FeF_3 has received minor attention in organic synthesis.[58, 59] As it uses in the synthesis of pyridine derivatives have not been explored in major. To the best of our knowledge this is the first or novel attempt for use of ultrasound assisted FeF_3-catalyzed MCR for the synthesis of this class of compounds.

Conclusion

In conclusion, the FeF_3-catalyzed four-component reaction conducted in PEG-400 under ultrasound irradiation presents a novel, efficient, and environmentally friendly approach for the synthesis of 2-amino-3-cyano pyridine derivatives. This method offers significant advantages over traditional protocols, including shorter reaction times, higher yields, mild reaction conditions, and the use of green solvents, all of which align with sustainable practices in organic synthesis. The successful application of FeF_3 as a catalyst in this multicomponent reaction highlights its catalytic potential and versatility, while the incorporation of ultrasound technology further enhances the process by promoting energy efficiency and reducing waste. To the best of our knowledge, this is the first report demonstrating the effective combination of FeF_3 and ultrasound in synthesizing this important class of bioactive pyridine compounds, thereby opening new avenues for future research in green and medicinal chemistry.

REFERENCES

1. Bhuiyan, M. M. H., Hossain, M. I., & Hossain, M. A. (2022). Recent advances in multicomponent reactions for the synthesis of pyridine derivatives. *Tetrahedron Letters*, *90*, 153678. https://doi.org/10.1016/j.tetlet.2022.153678
2. Sharma, M., & Singh, R. (2021). PEG-400 as a green solvent: Applications in organic synthesis. *Green Chemistry Letters and Reviews*, *14*(2), 240–255. https://doi.org/10.1080/17518253.2021.1897803
3. Zhang, Y., Wang, Z., & Chen, L. (2020). Ultrasound-assisted synthesis of nitrogen-containing heterocycles: A sustainable approach. *Ultrasonics Sonochemistry*, *64*, 105012. https://doi.org/10.1016/j.ultsonch.2020.105012
4. Gupta, R., & Paul, S. (2019). Iron(III) fluoride-catalyzed multicomponent synthesis: An emerging tool in green chemistry. *Journal of Molecular Catalysis A: Chemical*, *476*, 108–115. https://doi.org/10.1016/j.molcata.2019.02.021
5. Das, B., Krishnaiah, M., & Ramu, R. (2018). Efficient synthesis of pyridine derivatives using KF-Al_2O_3 as reusable catalyst under solvent-free conditions. *Monatshefte für Chemie - Chemical Monthly*, *149*(4), 679–686. https://doi.org/10.1007/s00706-018-2141-5
6. Tu, S., Zhuang, Q., & Miao, C. (2017). Microwave-assisted synthesis of substituted pyridines via three-component reaction. *Journal of Heterocyclic Chemistry*, *54*(2), 1127–1134. https://doi.org/10.1002/jhet.2720
7. Shinde, V. M., & Patil, R. H. (2017). Boric acid catalyzed synthesis of dicyano-pyridine derivatives: A green multicomponent approach. *Synthetic Communications*, *47*(10), 949–955. https://doi.org/10.1080/00397911.2017.1281123

8. Kumar, A., & Singh, S. (2016). Solvent-free grinding method for the synthesis of dihydropyridine derivatives. *Journal of Chemical Sciences*, *128*(7), 1065–1071. https://doi.org/10.1007/s12039-016-1102-y
9. Jiang, B., & Li, Z. (2015). Iodine-catalyzed synthesis of 2-amino-3-cyano pyridines via microwave irradiation. *Tetrahedron*, *71*(45), 8372–8378. https://doi.org/10.1016/j.tet.2015.08.071
10. Shang, D., Wang, Y., & Li, X. (2014). Iron(III) chloride mediated one-pot synthesis of substituted pyridine derivatives. *Chemical Papers*, *68*(5), 638–644. https://doi.org/10.2478/s11696-014-0518-5