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# 2-AMINO-3-CYANOPYRIDINE: A BIOACTIVE SCAFFOLD

Kuntal Manna, Partha Sakha Ghosh*, Manik Das, Udayan Banik and Ashish Das

Department of Pharmacy, Tripura University (A Central University), Suryamaninagar, Agartala, Tripura (West), India

**Keywords:**

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**Correspondence to Author:**

**Partha Sakha Ghosh**

M.Pharm Candidate, Department of Pharmacy, Tripura University (A Central University), Suryamaninagar, Pin - 799022 Tripura, India.

**E-mail:** ghoshpartha.tu@gmail.com

**ABSTRACT:** One of the most fascinating branches of pharmaceutical field is the chemistry of heterocyclic molecules. Heterocyclic compounds are widely distributed in nature and have biological and industrial significance. Already most of the drugs available in the market are heterocyclic in nature. Cyanopyridine, a structural motif is a cause of concern for biologist and chemist in last twenty years. Specifically 2-amino-3-cyanopyridine scaffolds demand importance due to their diverse biological activity like antiviral, antibacterial, and fungicidal activities, novel IKK-β inhibitors, $A_{2A}$ adenosine receptor antagonists, potent inhibitor of HIV-1 integrase. Due to high reactivity of this scaffold, it has been found as reactive chemical intermediates in organic synthesis like, commercial production of nicotinamide, and pharmaceuticals such as Ridogrel and Pirenzepine. In this short review we have focused on the recent development in synthesis of 2-amino-3-cyanopyridine derivatives and all possible pharmacology reported for this compound. This review may helpful for medicinal chemist in research regarding 2-amino-3-cyanopyridine in future.

**INTRODUCTION:** Molecules containing pyridine always have grave importance in chemistry as well as in biology. The pyridine substructure is one of the most prevalent heterocyclic molecular frameworks found in natural products, pharmaceuticals, vitamins and functional materials [1–4].

The pyridine ring systems have emerged as integral backbones of over 7000 existing drugs [5, 6].

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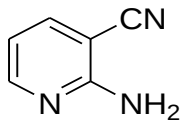
Cyanopyridines a pyridine derivative attract attention as its many derivative having different pharmacological activities, used in the industrial production of nicotinamide, nicotinic acid and isonicotinic acid, intermediates to pharmaceuticals such as Ridogrel and Pirenzepine, also serves as the intermediate in many organic synthesis. Fused cyanopyridines also have wide range of pharmacological activity. Among these compounds, 2-amino-3-cyanopyridine derivatives have been reported to possess antiviral, antibacterial, and fungicidal activities [7, 8]. 2-Amino-3-cyanopyridine derivatives were also reported as novel IKK-β inhibitors [9], $A_{2A}$ adenosine receptor antagonists[10], potent inhibitor of HIV-1 integrase[11], and so on. 2-Amino-3-cyanopyridines are important and useful intermediates in preparing variety of heterocyclic compounds [12, 13].

A complete review on this compound is hard to find, that's why we have tried to accumulate all the synthetic work, and biological evaluation regarding this compound up to present time which will be useful to find a new lead compound in the pharmaceutical arena and may also useful to the chemist.

**Structure of 2-amino-3-cyanopyridine:**




2-aminopyridine-3-carbonitrile

**FIGURE 1:**

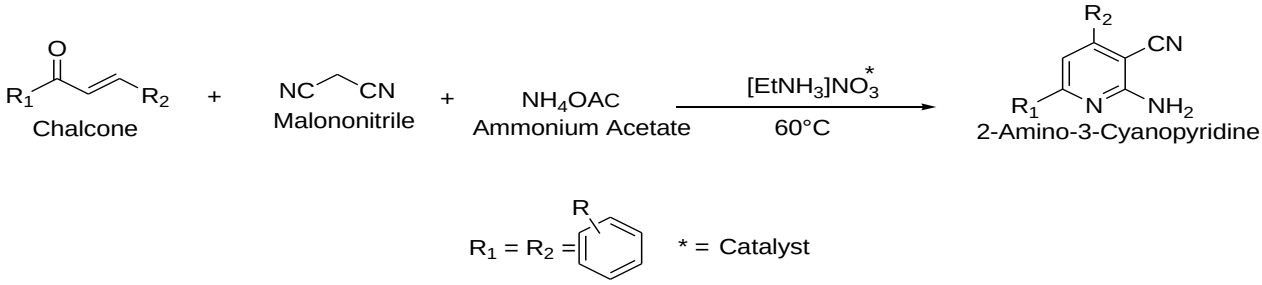
White to tan crystals or lumps having characteristic odour, and easily soluble in water and gives a clear solution at around 40°C. Melting range is 48-50°C. Due to the presence of lone pair, it has the ability to form significant additive complexes. X-Ray crystallographic studies have shown that it has two isomers. Both isomers are planar in nature, with the characteristic deformation of the aromatic ring due to the presence of lone pair and the ideal symmetrical hexagon form, especially around the pyridine nitrogen atom. The internal angles C – N – C are significantly smaller than 120° and two angles N – C – C within the rings are greater than 120° [32].

**Synthesis of 2-amino-3-cyanopyridine:** Various preparation methods of 2-amino-3-carbonitrile have been reported. The common method used in the preparation of 2-amino-3-cyanopyridine is the condensation of chalcone or carbonyl compound with malononitrile and ammonium acetate by conventional heating up-to 5 to 6 hours in the presence of ethyl alcohol as a solvent. The same method was repeated by using microwave irradiation [14], ultrasound irradiation [15, 16]. To enhance the yield, lowering the reaction time, hexadecyldimethyl benzyl ammonium bromide [17], triethylamine [17, 18], DMF [19] and acetic acid [20] are also used as Catalyst or solvent. These reported methods suffered from several drawbacks like prolonged reaction times, low yields, harsh reaction conditions, critical isolation procedures, and expensive catalysts.

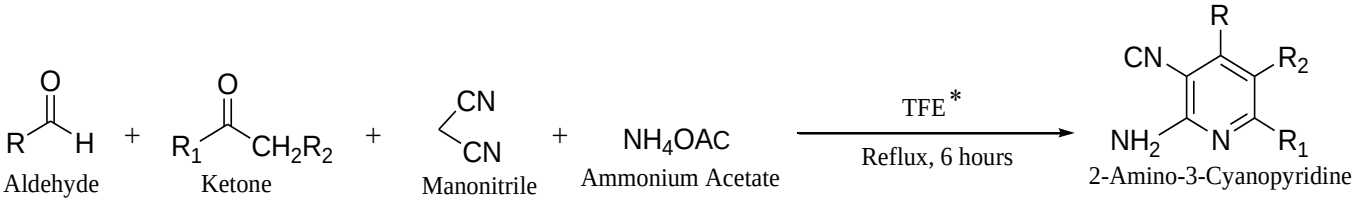
In recent years few synthetic methods were published which overcomes the drawbacks of the conventional methods.

**Method (A) [21]:** Reaction of Chalcone with Malononitrile and Ammonium acetate in presence of ethylammoniumnitrate at 60°C gave corresponding 2-amino-3-cyanopyridine. Material used, the ionic liquid EAN (2mL), chalcones (1 mmol), malononitrile, (1 mmol, 0.066 g), and ammonium acetate (8 mmol, 0.601 g). This process gives a good yield.

**Method (B) [22]:** Four-component condensation of benzaldehyde, acetophenone, malononitrile, and ammonium acetate in trifluoroethanol at refluxing temperature for 6 h results in the formation of 2-amino-3-cyanopyridine.

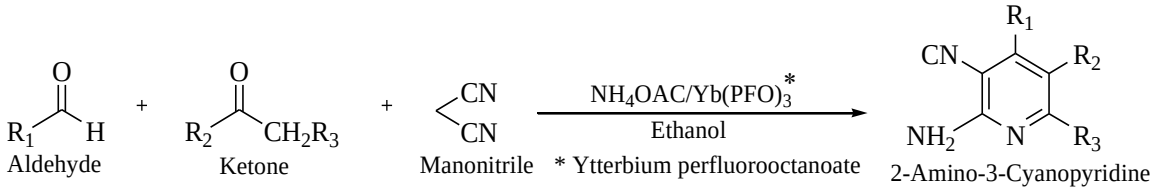



**SCHEME 1: SYNTHESIS OF 2-AMINO-3-CYANOPYRIDINE FROM CHALCONES**



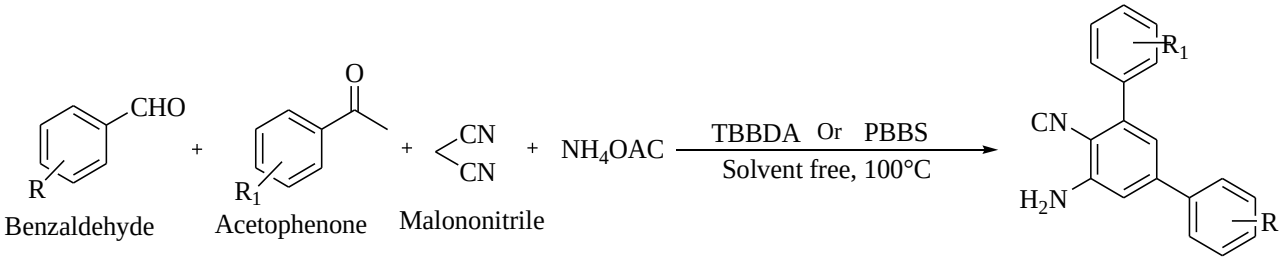

**SCHEME 2: SYNTHESIS OF 2-AMINO-3-CYANOPYRIDINE FROM ALDEHYDE & KETONE USING TRIFLUORO ETHANOL AS CATALYST**

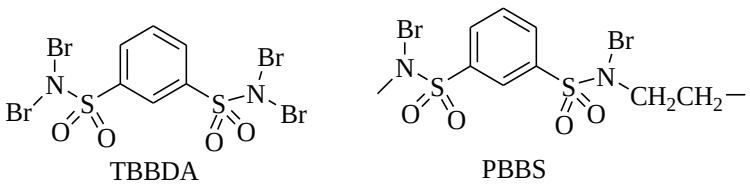
**Method (C) [23]:** The one-pot reaction of synthesis of 2-amino-3-carbonitrile was done by taking a mixture of benzaldehyde, acetophenone, malononitrile, ammonium acetate, and of $Yb(PFO)_3$, in ethanol at refluxing temperature for 12 h yielded the crude product in 92%.




**SCHEME 3: ONE POT SYNTHESIS OF 2-AMINO-3-CYANOPYRIDINE FROM ALDEHYDE & KETONE USING YTTERBIUM PERFIUOROOCTANOATE**

**Method (D) [24]:** A mixture of aldehyde, substituted acetophenone, malononitrile, ammonium acetate and TBBDA (Tetra-bromobenzene-1, 3-disulfonamide) or PBBS (Poly(N-bromo-N-ethylbenzene-1,3-dis-ulfonamide)) was heated under stirring at 100°C for appropriate times yielded the final product.



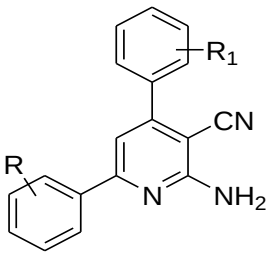




**SCHEME 4: SOLVENT FREE SYNTHESIS OF 2-AMINO-3-CYANOPYRIDINE USING TBBDA OR PBBS**

**Pharmacology of 2-amino-3-cyanopyridine:** Heteroaromatic rings containing nitrogen atoms often play important roles as the scaffolds of bioactive substances. The pyridine ring system is one of the most popular N-heteroaromatics incorporated into the structure of many pharmaceuticals.

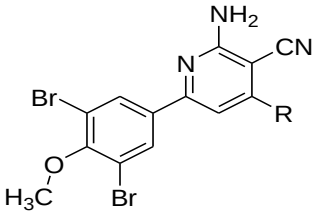
**Anti-inflammatory activity [25]:** Kumar *et al* has reported eight derivatives of 2- amino-4,6-diphenylpyridine-3-carbonitrile and carried out anti-inflammatory screening in healthy rats using indomethacin as standard. Among them, three derivatives have shown potential anti-inflammatory activity.

**Antimicrobial activity [26]:** Vyas *et al* reported the synthesis of some new cyanopyridine derivatives and their screening against *M. tuberculosis* and other microorganism. Anti-tubercular data was compared to the rifampin. Antimicrobial activities of the compounds were compared with norfloxacin, griseofulvin, benzyl penicillin, amoxicillin and ampicillin against various bacterial strain, *Bacillus subtillis, Bacillus megaterium, E. coli, Proteus Vulgaris*, and *Aspergillus niger*.



2-amino-4,6-diphenylpyridine-3-carbonitrile

Few derivatives have shown promising Antimicrobial and Antitubercular activity.

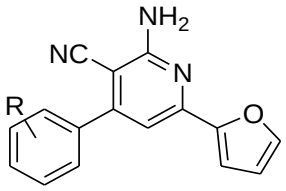


2-amino-6-(3,5-dibromo-4-methoxyphenyl)pyridine-3-carbonitrile

**FIGURE 2:**

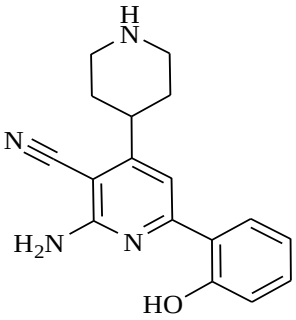
**$A_{2A}$ Adenosin receptor antagonist [10]:** Mantri *et al* reported the synthesis of 2-Amino-6-furan-2-yl-4-substituted Nicotinonitriles as $A_{2A}$ Adenosine Receptor Antagonists. A molecular super-imposition model was constructed using previously published antagonist ligands having high affinity and selectivity for the $A_{2A}$ adenosine receptor. All these molecules were selected with the criteria of having diverse scaffolds based on the heterocyclic aromatic core of each molecule. The actual ligand taken from a specific scaffold class was the one that had a combination of high affinity and selectivity for the $A_{2A}$ adenosine receptor.

**IKK-β inhibitory activity:** Murata *et al* reported the novel IKK-β inhibitory activity of 2-amino-3-cyanopyridine derivative. IKK-β inhibition helps the brain cell to stay alive in harsh condition.



2-amino-6-(furan-2-yl)-4-phenylpyridine-3-carbonitrile [9]

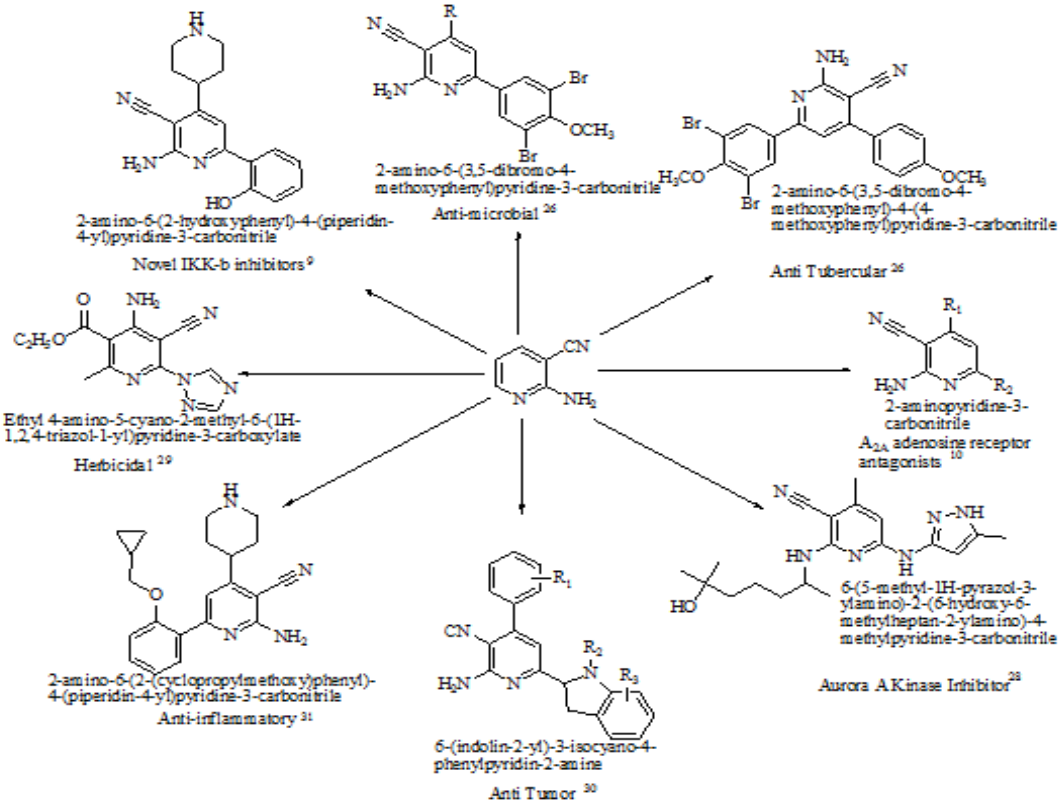
**FIGURE 3:**



2-amino-6-(2-hydroxyphenyl)-4-(piperidin-4-yl)pyridine-3-carbonitrile

**FIGURE 4:**

**Other activity:** 2-amino-3- cyanopyridine derivatives are known to have multiple biological activities, such cardiotonic [27], antiparkinsonism [10], aurora a kinase inhibitor [28], Herbicidal [29] and anti-tumor properties [30] and potent inhibitor of HIV-1 integrase [11].



**CONCLUSION:** It is found that 2-amino-3-cyanopyridine is an important bioactive scaffold having diverse biological activities. Unfortunately there are no marketed drugs at present having 2-amino-3-cyanopyridine in there structure. For further research it can be proposed that 2-amino-3-cyanopyridine molecular skeleton can be conjugated with drugs, like antibiotics, antitumor, to suppress their adverse effect or to alter the physiochemical property.

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