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# Electrocatalytic assisted one pot three component reaction for construction of highly substituted pyridine

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An electrochemically environmentally benign synthetic strategy has been developed for preparation of substituted pyridine by condensation of structurally diverse aldehydes with various thiols and malononitrile.

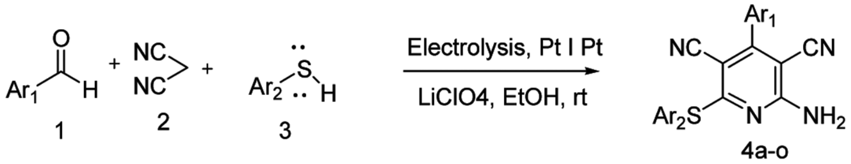
**Keywords**: Three component reaction, Substituted pyridine, Malononitrile, Condensation reaction, Electrocatalytic assisted

Heterocycles compounds are important essential material having multiple use in our daily life. The most commonly used heterocyclic have five or six membered ring containing hetero atoms like Nitrogen (N), Oxygen (O), Sulphur (S). Among all the available heterocyclics, N heterocyclic compounds have wide range of applications in pharmaceuticals, natural products and functional materials[2]. Some of N substituted heterocyclic compound play a vital role in genetic material information as they are linked with DNA and RNA. Genetic material DNA and RNA have privileged structural motifs composed by heterocyclics nitrogenous bases like pyrimidine and purines (Scheme 1).

The pyridine moiety got significant attention in the recent years as it has been found in a wide variety of both naturally occurring and synthetic bioactive compounds[1].

Biological properties of pyridine containing heterocyclics may be enhanced by incorporation of substituting organosulfur group[2]. Numerous patents have been filed on the specific medicinal utility of various substituted pyridine moiety. As, some of these compounds acts as potassium channel openers used to treat urinary incontinence as they exhibit anti-bacterial, anti-biofilm properties[3]. Beside these pyridine derivatives are extensively investigated to treat various disease[4] such as, Alzheimer, asthma, epilepsy, hypoxia, Parkinson's disease, kidney disease and cancer.

In the last decades, several new innovative methods have been developed which includes Vilsmeier reactions[5], Diels–Alder[6], Ni/Ru-catalysed cycloadditions of alkynes and nitriles[7], cycloadditions of oximinosulfonates[8], reaction of imines with enamines or carbonyl compounds[9], condensation of α,β-unsaturated esters or nitriles with thiols[10], and transformation of ketene dithioacetals to pyridine derivatives[11], Ionic liquid containing[12] nanocrystalline magnesium oxide[13]. These reactions are catalyzed by acid, base, ionic liquid, microwave irradiation and nano crystalline metal oxides in their experimental conditions. In addition to these reactions several MCR methods are also reported for synthesis of diverse substituted pyridines, using condensations of aldehyde, malononitrile, thiol and suitable base.



Scheme 1 — Electrocatalytic pathway for synthesis of highly substituted pyridine

Thus, during the development of novel synthetic methods consideration of efficiency, mild condition is fundamental need for sustainable and progressive research. Keeping the view of sustainable development electrochemically catalyzed multi component reactions may play significant role in synthesizing wide range of both naturally and synthetic bioactive substituted pyridine compounds. Therefore, searching mild efficient sustainable method for the synthesis of highly substituted sulphur containing pyridine compounds is aim of organic synthesis.

The electrochemical method allows to offer rapid and direct construction of complex molecules without isolation and purification of intermediates, minimizing waste, labour cost, effort, and time from available starting materials using greener and sustainable technologies[14].

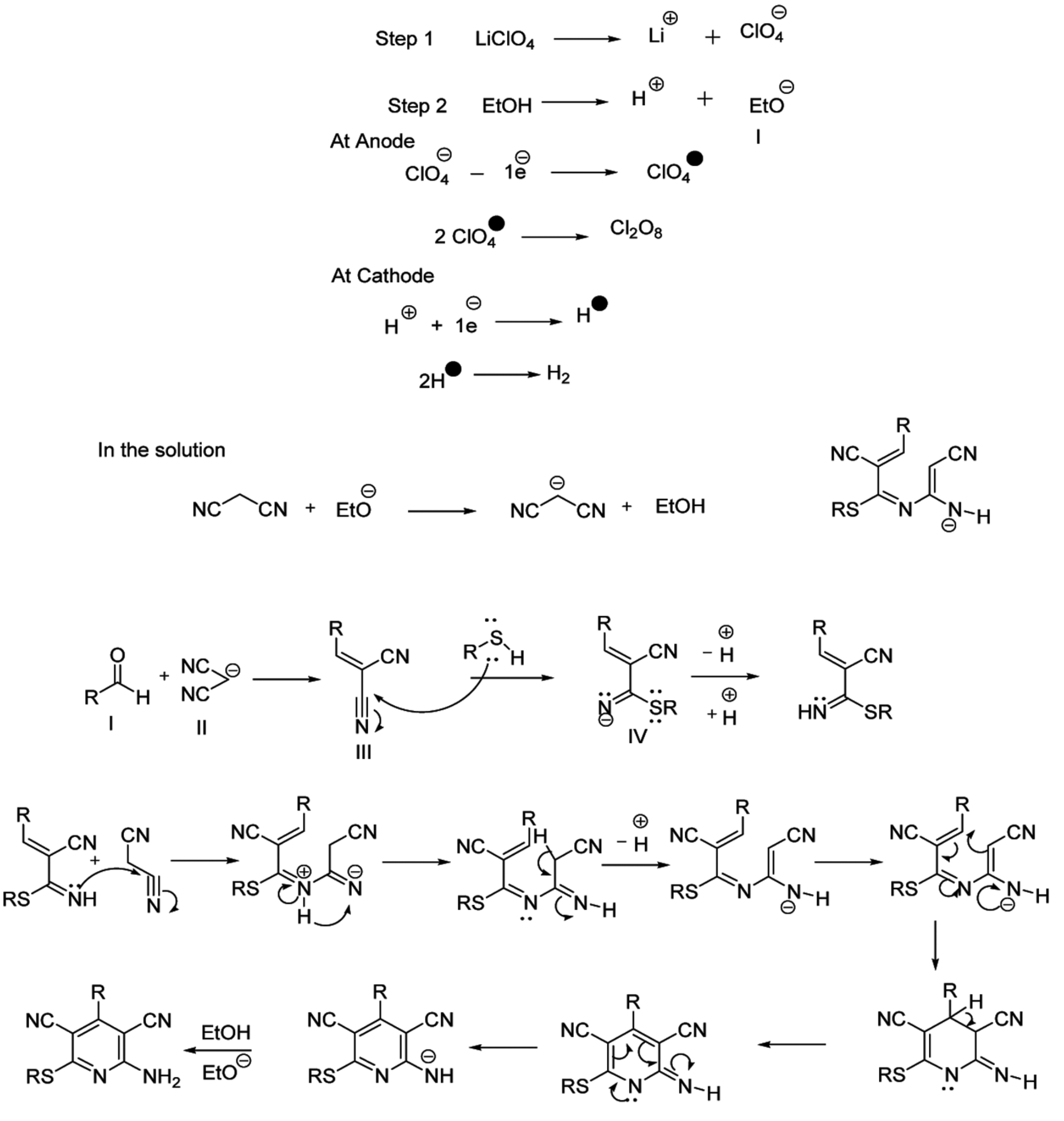
As part of the ongoing studies on the development of efficient and straightforward methods to prepare bioactive compounds, using electrochemical methods[15], it was found that pyridines could be efficiently prepared using electrochemical-mediated synthesis under mild reaction conditions. Herein, is reported an efficient and simple synthetic pathway to synthesise polysubstituted pyridines under mild conditions.

We began our studies by investigating benzaldehyde (1a, 1.1 mmol), malononitrile (2a, 2.2 mmol) and thiophenol (3a, 1 mmol) as the model substrates to optimize the reaction conditions. The suspension of benzaldehyde and malononitrile were electrolysed at constant potential (2.0 volt), reaction mixture stirred until benzaldehyde was completely consumed (30 minutes) in an undivided cell using $LiClO_4$ (0.1 M) electrolyte, EtOH (20.0 mL), as solvent and platinum as the working and counter electrodes. Thiophenol was added, in the stirred reaction mixture of benzaldehyde, malononitrile and $LiClO_4$ for a period of time until completion of the reaction (TLC). No conversion occurs in the absence of electricity (Table 1, entry 1). In the presence of electricity 40% of expected result was obtained (Table 1, entry 2). Subsequently, various solvents were extensively examined, and it was found that solvent (Table 1, entries 1-5) played a crucial role in the reactivity. Among them EtOH proved to be a suitable solvent in view of excellent yield. Pleasingly, when the reaction duration was 6h (Table 1, entry 6) product yields was increased to 90%, no further change in yield was observed by increasing the reaction time (Table 1, entry 7). No variation in either conversion or product yield were observed by changing the concentration of electrolyte $LiClO_4$ while other electrolyte $nBu_4NClO_4$, $Bu_4NBF_4$, NaBr, LiBr, $NH_4I$ exhibited lower reactivity (Table 1, entries 8-12). We observed negative effects for the reaction when cell voltage or current were changed (entries 13-16). It is necessary to mention that reaction works well in absence of nitrogen atmosphere also. while increasing the amount of benzaldehyde product 4a afforded no further change in yield. With the aforementioned optimal reaction conditions, transformation was investigated by exposing wide range of substituted aromatic as well as heteroaromatic aldehydes, with several substituted thiophenols and malononitrile to produce 2-amino-3,5-dicyano-6-sulfanyl pyridines as summarized in Scheme 2. However, when thiophenol was replaced by heptane thiol we observed slightly poor yield (Table 2 entry 4m). Notably, the reaction of aliphatic aldehyde malononitrile and thiophenol resulted to formation undefined product. However, in our finding the reaction conditions are compatible for aromatic aldehyde with good yields. Aromatic aldehyde having electron withdrawing groups ($-NO_2$, -Cl, - Br) generally gave expected product (Table 2, entries 2, 4, 5) formed in shorter time with higher current at

Table 1 — Optimization of the synthesis of 2-amino-3,5-dicyano-6-sulfanyl pyridines, **4a**

| Entry | Solvent | Potential (V) | Time (h) | Current (mA) | Electrolyte | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | MeOH | 0.0 | 4 | 0.0 | $LiClO_4$ | No Rxn. |
| 2 | MeOH | 2.0 | 4 | 10.0 | $LiClO_4$ | 40 |
| 3 | $CH_3CN$ | 2.0 | 4 | 10.0 | $LiClO_4$ | 65 |
| 4 | $^i$PrOH | 2.0 | 4 | 10.0 | $LiClO_4$ | 50 |
| 5 | EtOH | 2.0 | 4 | 10.0 | $LiClO_4$ | 80 |
| 6 | EtOH | 2.0 | 6 | 10.0 | $LiClO_4$ | 90 |
| 7 | EtOH | 2.0 | 10 | 10.0 | $LiClO_4$ | 90 |
| 8 | EtOH | 2.0 | 10 | 10.0 | $nBu_4NClO_4$ | 70 |
| 9 | EtOH | 2.0 | 10 | 10.0 | $nBu_4NBF_4$ | 70 |
| 10 | EtOH | 2.0 | 6 | 10.0 | NaBr | 61 |
| 11 | EtOH | 2.0 | 6 | 10.0 | LiBr | 65 |
| 12 | EtOH | 2.0 | 6 | 10.0 | $NH_4I$ | 50 |
| 13 | EtOH | 2.0 | 6 | 10.0 | $LiClO_4$ | 70 |
| 14 | EtOH | 2.0 | 6 | 10.0 | $LiClO_4$ | 65 |
| 15 | EtOH | 1.5 | 6 | 5.0 | $LiClO_4$ | 60 |
| 16 | EtOH | 1.5 | 6 | 15.0 | $LiClO_4$ | 55 |

[a] Optimized conditions: Benzaldehyde 1 (1.1 mmol), malononitrile 2 (2.2 mmol), thiophenol 3 (1 mmol), LiClO4 (0.1 M), EtOH solvent (20 mL), Pt electrode at RT. [b] Isolated yield of product **4a**



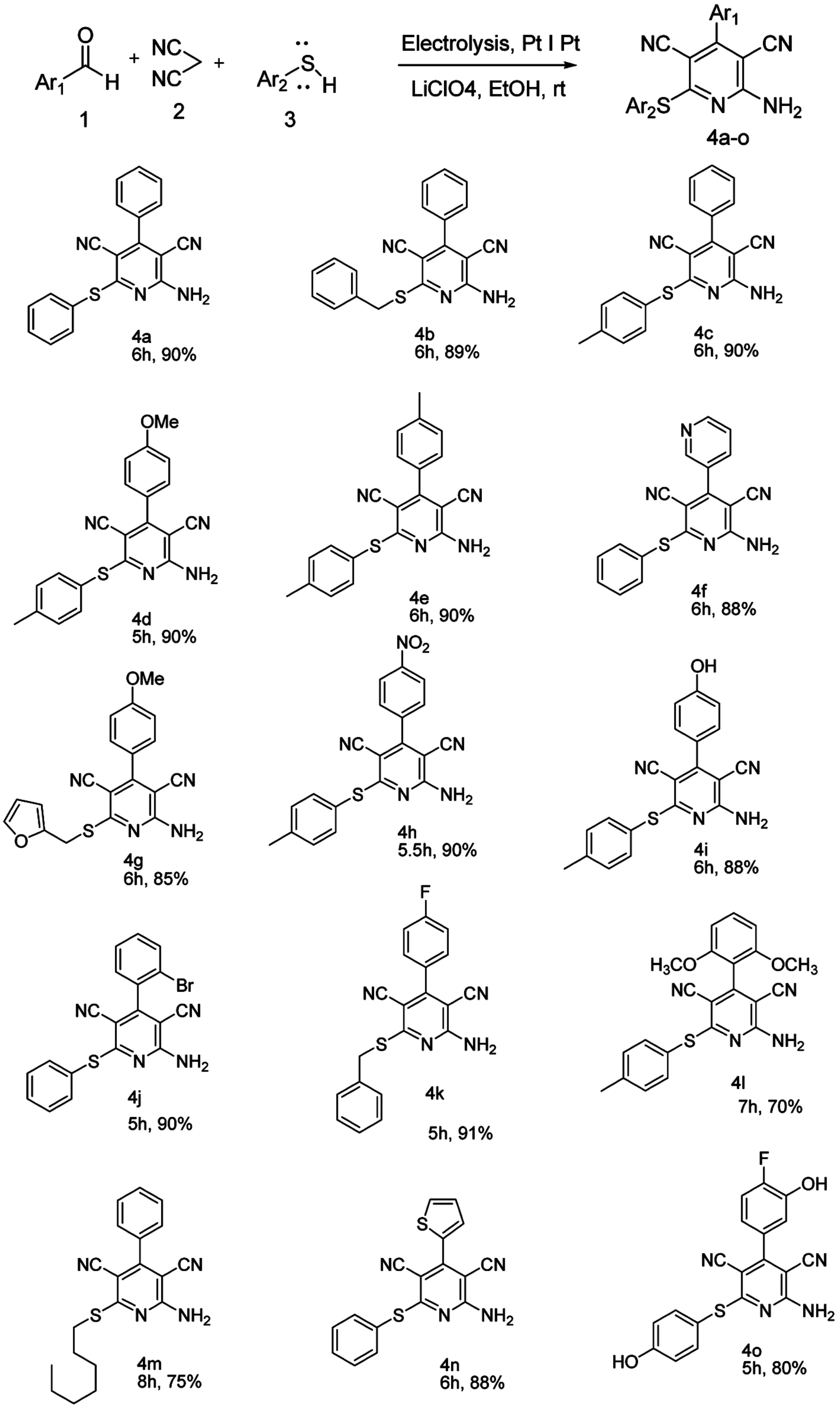
Scheme 2 — Plausible electro-catalyzed pathway for the synthesis of substituted pyridine derivatives

constant potential than electron-donating groups (-$OCH_3$, -$CH_3$) (Table 2, entries 6, 7). Therefore, we concluded that the electronic nature of the substituents on the aryl ring has no effect in the yield of the final products.

A plausible reaction scenario for the reaction is presented in Scheme 2. The first step is believed to be Knoevenagel condensation between an aldehyde I and malononitrile II to generate corresponding Knoevenagel product (III). Thiolate addition to CN of the Knoevenagel product (III), intermediate (IV) was obtained. After proton absorption the intermediate adduct (IV) undergoes Michael addition to the second molecule of malononitrile, which leads to substituted pyridine *via* N-cyclization followed by aromatization.

In summary, we have developed a simple and efficient, electrocatalyst, one pot three component, green method for the preparation of substituted pyridine. The method has several advantages including green reaction, atom economy, eco-friendly, mild reaction condition and environmentally friendly catalyst. The strategy may offer green approach for

Table 2 — Electro-catalyzed synthesis of substituted pyridine derivatives under optimized conditions[a]



synthesizing N-heterocyclic compound containing pyridine nucleus which is proceeded without using base or ligand, the developed procedure provides new route in modern synthetic organic chemistry for target and diversity oriented highly substituted pyridine derivatives.

## Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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