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Title Key: Green Synthesis of 1-Pyridylimidazo-[1,5-A] …

Green Synthesis of 1-Pyridylimidazo-[1,5-A] Pyridine :A Bioactive Molecule

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Abstract

Potassium Ferro-cyanide complex catalyzed three component improved procedure for the synthesis of various 1-pyridylimidazo-[1,5-a]pyridines from 1,2-dipyridyl ketone, aromatic aldehydes and ammonium acetate at room temperature in excellent isolated yield has been reported. The 1-pyridylimidazo-[1,5-a]pyridines were synthesized and tested for antibacterial effects against *Bacillus Subtilis, Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa*. The antibacterial screening of the synthesized compounds was performed in vitro by the filter paper disc diffusion method and it is found that the 2, 4, 5-triaryl imidazoles show good antimicrobial activity. This is a simple and straightforward, high yielding, does not involve any hazardous or expensive catalyst. The synthesis is purely solvent free (Mechanostic).

1. Introduction

From several years, chemists have made efforts to developed environmental friendly methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. The use of potassium Ferro cyanide in organic synthesis has been known for a long time. Recently, coordinated complex has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with it enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, complex has been explored as a powerful catalyst for various organic transformations.[1, 2]

Fused imidazopyridine ring systems represent an important class of compounds not only for their theoretical interest but also from a pharmacological point of view. In particular, 1-pyridylimidazo[1,5-*a*]pyridines possess a bidentate structural feature with a pyridyl unit directly next to a fused imidazole heterocycles are a desirable class of compounds in the pursuit of structural diversity for property performance and have emerged as a new class of ligands for numerous organic transformations. Moreover, these heterocyclic structures are the part of the skeleton of natural alkaloids, [3] neuromuscular blocking agents, [4] of reversible inhibitors of the H^+, K^+-ATPase enzyme [5] with a potent anti-secretory activity [6] and of sedative hypnotics of the nervous system. [7] Imidazo [1,5-a]pyridine skeleton is also a basic structure of synthetic drug Pirmogrel, with human clinical applications as effective platelet aggregation

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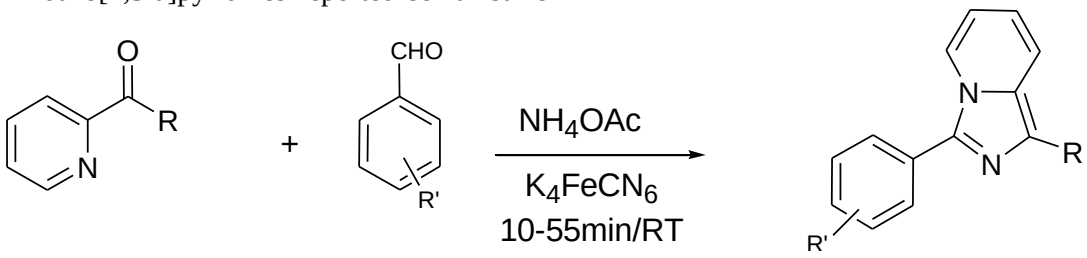
and thromboxane synthase inhibitors. [8] Due to its utility in medicinal chemistry, catalyst as well in material chemistry, very few methods are available for the synthesis of [1,5-a]pyridines in the literature. Most of the routes involve reaction of a 2-aminomethylpyridine with acylation followed by cyclization with phosphorus oxychloride or polyphosphoric acid[9] or thioacylatio mercuric salts.[10] by the Vilsmeier reaction,[11] or by reaction with dipyridyl ketone.[12–16] Very Siddiqui S.A et. al..

Many of the synthesis protocols for 1- reported the synthesis of 1-substituted imidazo[1,5-a]pyridines using ionic liquid[17]substituted imidazo[1,5-a]pyridines reported so far suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, longer reaction time periods, and the use of hazardous and often expensive catalysts. In continuation of our on going programme on synthesis of biologically potent heterocycles using non-conventional energy source e.g. Micro-wave and environmentally benign catalyst such as molecular iodine, we report here first time the synthesis of 1-pyridylimidazo [1, 5-a] pyridines by condensation of 1,2-dipyridyl ketone (1), aromatic aldehydes (2) and ammonium acetate in presence of catalytic amount of potassium ferro cyanide complex. (Scheme 1)



Scheme 1

Table:-1 Effect of catalytic amount of $K_4[Fe(CN)_6]\cdot 3H_2O$ [b]

[a]Entry	Catalyst	Amount (mol%)	Time(min)	Yield(%)[d] 1a	1b
1	NO	-	250	ND[c]	ND[c]
2	$K_4[Fe(CN)_6]\cdot 3H_2O$	5	130	90	91
3	$K_4[Fe(CN)_6]\cdot 3H_2O$	10	15	75	78
4	$K_4[Fe(CN)_6]\cdot 3H_2O$	20	65	73	70
5	$K_4[Fe(CN)_6]\cdot 3H_2O$	25	100	85	87
6	CeSO4	10	150	60	58

[a] Entry 1-6

$K_4[Fe(CN)_6]\cdot 3H_2O$ ND[c] No product formation, [d] isolated yield

1a(benzil) 1b(benzoin) obtained by column chromatography.

To examine the catalytic activity of $K_4[Fe(CN)_6]\cdot 3H_2O$, we explored a modification of the reaction of (1a) and (1b) aromatic aldehydes in acetonitrile first without $K_4[Fe(CN)_6]\cdot 3H_2O$ then ,5mol%, 10mol%, 20mol%, 25mol% amount of $K_4[Fe(CN)_6]$

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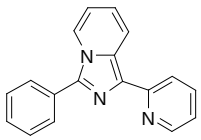
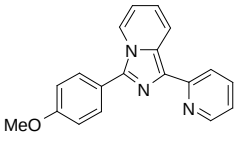
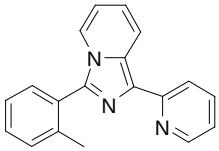
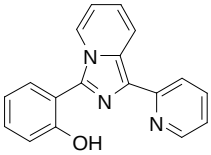
$\cdot 3H_2O$. The results are shown in **(Table.1).**According to observations in **Table.1** (10mol%) of $K_4[Fe(CN)_6] \cdot 3H_2O$ was enough and efficient , as 90 % .91% yield **(entry 2)** for both respectively an excessive amount of the catalyst was check for the same

reaction condition it is found that at the same reaction time, % yield did not increase . **(Table.1 entry 3-5)** .In the absence of $K_4[Fe(CN)_6] \cdot 3H_2O$, no reaction was found (Table.1, entry 1) . To investigate the real catalyst species, $K_4[Fe(CN)_6] \cdot 3H_2O$, $CeSO_4$, the experiment using $CeSO_4$ 20mol% in place of $K_4[Fe(CN)_6] \cdot 3H_2O$ has been tried. The product was obtained in 1a, with yield of 60%, 58% at 75°C (Table.1 entry 6) hence $K_4[Fe(CN)_6] \cdot 3H_2O$ should be the real catalyst species because its Lewis acidity.

Table:2 synthesis of 1-pyrimidazol[1,5-a]pyridines 3-11

Entry	*Product*	*Time(min)*	*Yield[a,b] (%)*
1	 **3**	**20**	*93*
2	 **4**	**22**	*92*
3	 **5**	**18**	*95*
4	 **6**	**20**	*92*

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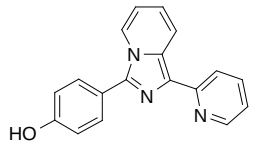
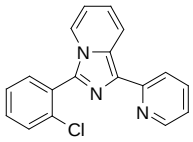
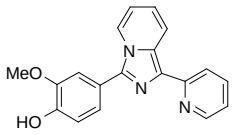
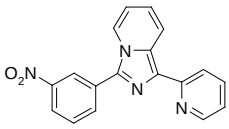
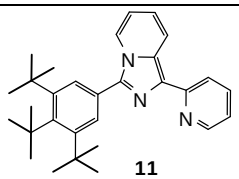
5	 **7**	**14**	*95*
6	 **8**	**15**	*93*
7	 **9**	**17**	*89*
8	 **10**	**12**	*91*
9	 **11**	**15**	*90*

[a]: Reaction Condition; 1,2-dipyridyl ketone (1 mmol),benzaldehyde (1 mmol), ammonium acetate (2 mmol) $K_4[Fe(CN)_6]\cdot 3H_2O$ (10mmol%) , EtOH (2 drops), 30 ^{0}C

[b]: Isolated yield after column chromatography.

Potassium Ferro cyanide due to it lewis acidic nature is capable of binding with the carbonyl oxygen increasing the reactivity of the parent carbonyl compound. Fe ion facilitates the formation of the imine intermediate, which under mild acid catalysis of it condenses further with the carbonyl carbon of the 1,2-dipyridylketone followed by dehydration to afford the intermediate (III), which rearranges to the required 1-pyridylimidazo[1,5-a]pyridines 3.

Antimicrobial Activity:

The antibacterial activities of the synthesized compounds (8) and (10) were studied against four bacteria, viz. ***Bacillus subtilis*** **(G+),** ***Escherichia coli*** **(G–),*Staphylococcus aureus*** **(G+)** and ***Pseudomonas aeruginosa*** **(G–).** For the detection of antibacterial activities, the

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filter paper discs diffusion method was used[18]. Streptomycin sulphate was used as positive control. Nutrient agar (NA) was used as basal medium for test bacteria. The discs were prepared by impregnating them in methanol solution of each sample (1 mg/1 mL). Each culture was prepared to a turbidity equivalent to McFarland and spread on the test tube. The paper disc containing the compound was placed on the agar surface previously inoculated with suspension of each microbe to be tested. All determinations were made in duplicate. Inhibition diameter was determined after incubation at 37°C ± 1 for 24 h. The antimicrobial activity was indicated by the presence of the clear inhibition zones around each disc.

Minimum inhibition concentration:

The determinations of the minimum inhibitory concentration (MIC), the serial dilution technique were followed using nutrient broth medium. The MIC was defined as the lowest concentration of samples that had restricted the growth of microbial. The MIC value of compound (g) was determined against *Escherichia coli* (G–)

2. Experimental Section:

General Experimental Method

The ^{1}H-NMR spectra were recorded on a 200 MHz instrument; chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. ^{1}H-NMR Spectra are reported in order: multiplicity, approximate coupling constant (*J* value) in hertz (Hz) and number of protons; signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad signal). The ^{13}C-NMR spectra were recorded at 50 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). The crude products were purified by column chromatography using silica gel (60–120 mesh size).

General Procedure for the Synthesis of 1-pyridylimidazo [1, 5-a]pyridines 3:

A mixture of 1,2-dipyridyl ketone (1, 10 mmol), aromatic aldehyde (2, 10 mmol), ammonium acetate (20 mmol) and $K_4[Fe(CN)_6]\cdot 3H_2O$ (10mol%) in ethanol (2 drops) was mixed well in mortor for the time specified in **Table 1.** The completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with H_2O (containing 15% $Na_2S_2O_3$). The solid products, which separated, were filtered off, washed with H_2O, and dried. The crude products thus obtained were pure and subjected to further purification by column chromatography on silica gel (60–120 mesh size) using 25% ethyl acetate in petroleum ether as eluent to yield **3-11.**

Antimicrobial Screening:

The antibacterial activity of compounds (g) and (h) has been assayed at the concentration 1000 μg/mL against four human pathogenic bacteria. Among them two were gram-positive and the other two were gram negative. The inhibitory effect of compounds (g) and (h) against these organisms are given in Table 3.The screening results indicate that only compound (h) was active against a gram-negative bacteria, Escherichia coli with a mean zone of inhibition 12·5 ± 0·3 mm (Table 3).

Determination of the minimum inhibitory concentration (MIC) :

The active sample in the disc diffusion method was then tested for its activity by the serial dilution method to determine the minimum inhibition concentration (MIC-value). The MIC value obtained for flavanone (f) was 1000 μg/mL against Escherichia coli.

Table 3. Antibacterial screening for the compounds (8) and (10)

Organism	**1-pyridylimidazo [1, 5 a]pyridines**	Streptomycin sulphate
Bacillus subtilis	–	22·0 ± 0·3
Staphylococcus aureus	–	22·5 ± 0·7
Escherichia coli	12·5 ± 0·3	22·0 ± 0·0
Pseudomonas aeruginosa	–	22·0 ± 0·0

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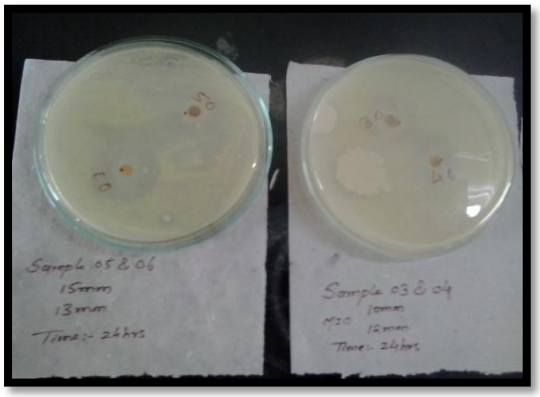

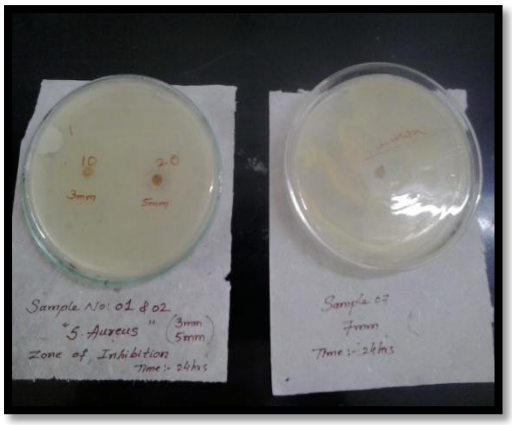

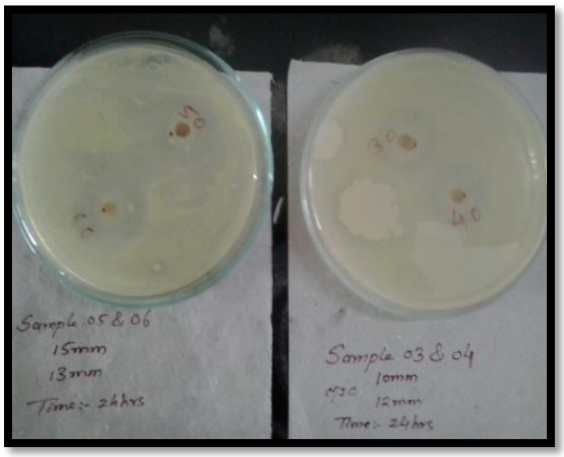

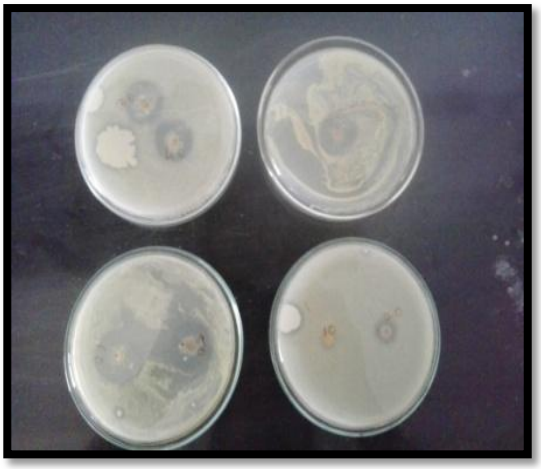

Fig:- Diameter of the zone of inhibition of Sample 8 and10

2.**Conclusion:-**

In conclusion, we describe a mild and efficient route for the synthesis of 1-pyridylimidazo[1,5-a]pyridines utilizing $K_4Fe(CN)_6$ as a novel Lewis acid catalyst. This method not only provides an excellent complement to 1-pyridylimidazo[1,5-a]pyridines synthesis but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents and catalyst under mild conditions, and experimental operational ease. Reactions employing $K_4Fe(CN)_6$ as a novel Lewis acid catalyst for other organic transformations are currently under investigation in our research group, and will be reported in due course.

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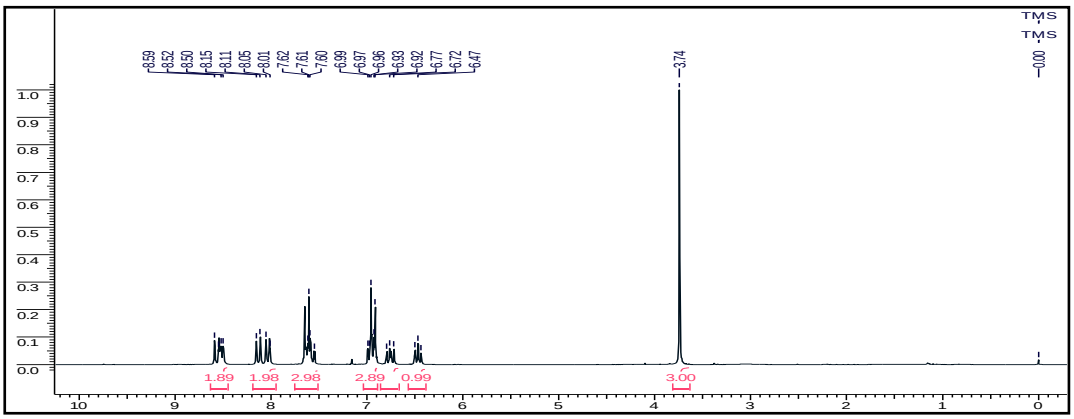
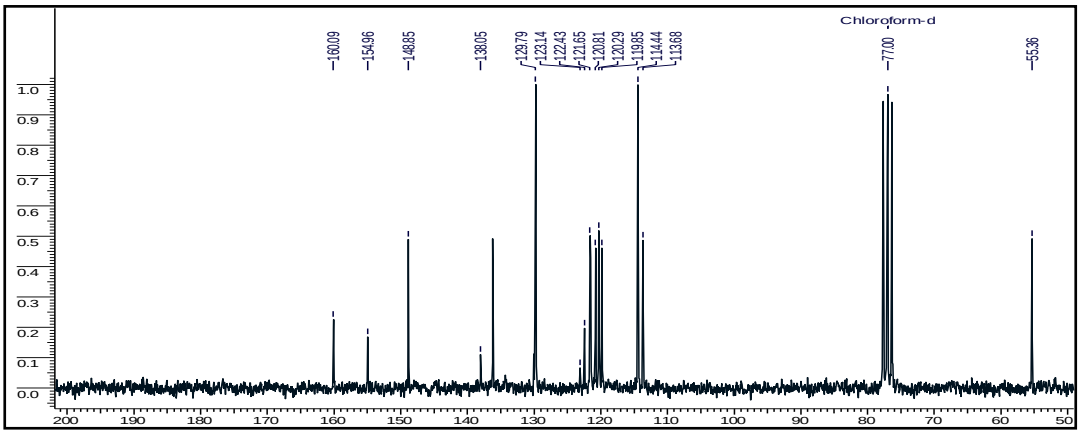
Spectra's of 3 compound:-

[1] ^{1}H NMR and ^{13}C NMR spectra of **3:-**



[2] ^{13}C NMR spectra of 3:-



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