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Mechanistic Synthesis of 1-Pyridylimidazo [1, 5-*a*] Pyridines by Using $K_4[Fe(CN)_6]\cdot 3H_2O$

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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. This is a simple and straight forward, high yielding, does not involve any hazardous or expensive catalyst. The synthesis is purely solvent free (Mechanostic).

Keywords: 1-Pyridylimidazo [1, 5-*a*] pyridines, ammonium acetate aldehyde, $K_4[Fe(CN)_6]\cdot 3H_2O$

INTRODUCTION

Imidazoles are heterocycles with a wide range of applications and receive growing attention[1]. The imidazole ring system is of particular interest because it is a component of histidine and its decarboxylation metabolite histamine[2]. The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active site[3] (e.g. Zn, Fe, Mg). Also, improved pharmakinetics and bioavailability of peptide based protease inhibitors have been observed by replacing an amide bond with an imidazoles[4].

In addition, the substituted imidazole ring systems are substantially used in ionic liquids[5] that have been given a new approach to "Green Chemistry". Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazoles from 1, 2-dicarbonyl compound, various aldehydes and ammonia to obtain the imidazoles[6-7]. Also Siddiqui et al. proposed the synthesis of the 1-Pyridylimidazo [1, 5-*a*] pyridines using ionic liquids[8]. Recently, there are several methods reported in the literature for the synthesis of imidazoles using Zeolite HY/silica gel[9], $ZrCl_4$[10], $NiCl_2\cdot 6H_2O$[11], iodine[12], sodium bisulfite[13], Boric acid [14]; however these methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method for the synthesis of 1-Pyridylimidazo [1, 5-*a*] pyridines derivatives would be highly desirable.

In recent years, potassium ferro-cyanide has gained special attention as a catalyst in organic synthesis like synthesis of anti-Alzheimer drug(-) Galanthamine[15] due to its high stability, oxidizing power selectivity and a non toxic by product Fe(III)[16] ·It promoted oxidative cyclization of 5-S Cysteinyldopa [17]. X.Z.Yu et al studied

the liberation of cyanide into the environment which has terristerial importance for ecosystem[18]. M.A.Gaffar et al studied the kinetic of the potassium ferro cyanide[19]because of many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness, eco-friendly nature, readily available and high reactivity.

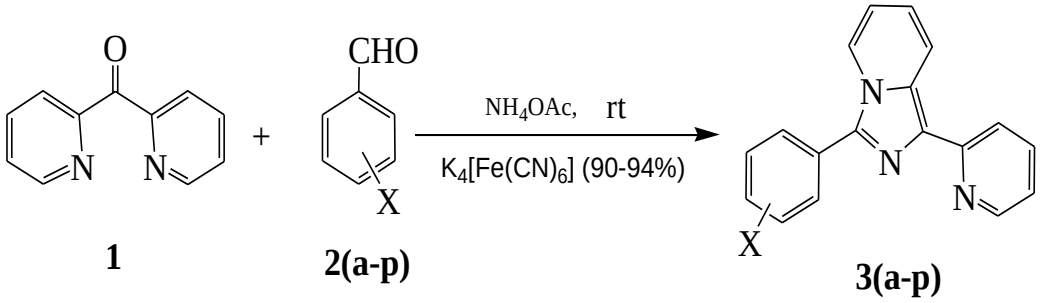
EXPERIMENTAL

General procedure for the synthesis of 1-pyridylimidazo [1, 5-*a*] pyridines 3(a-r)

A mixture of aldehyde (1 mmol), 1, 2-dipyridylketone (1 mmol) ammonium acetate (5 mmol), and $K_4[Fe(CN)_6].3H_2O$ (15 mol %) were ground together in a mortar with a pestle at room temperature for appropriate time (Table 1**).** After completion of reaction confirmed by TLC, the mixture was treated with water to furnish the crude products. The crude was further purified by column chromatography by using petroleum ether: ethyl acetate (9:1) eluent and get the corresponding 1-pyridylimidazo [1, 5-*a*] pyridines **3(a-r).** The products were confirmed by comparison with authentic sample, ^{1}H NMR, ^{13}C NMR, mass, elemental analysis and melting points[19].

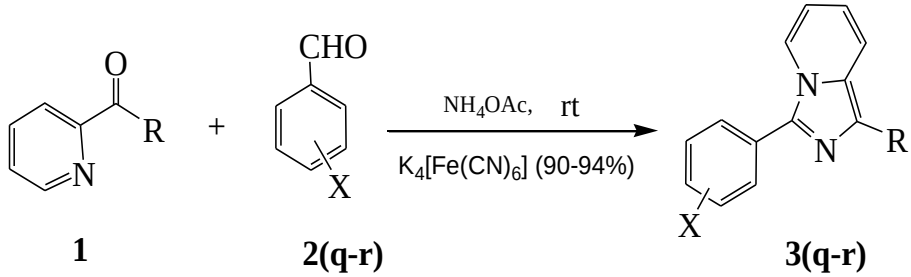
RESULTS AND DISCUSSION

As a part of our ongoing investigation in developing a versatile and efficient method for synthesis of heterocycles compounds[20-23] herein, we report efficient synthetic method for the synthesis of 1- pyridylimidazo [1, 5-*a*] pyridines from 1, 2-dipyridyl ketone, substituted aldehyde and ammonium acetate in the presence of potassium ferrocyanide (**Scheme1, 2).**



1 **2(a-p)** **3(a-p)**

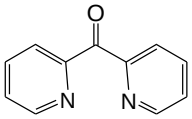
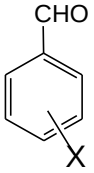
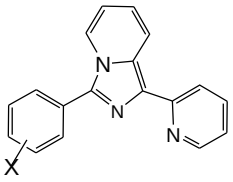
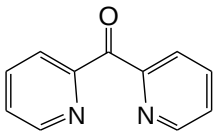
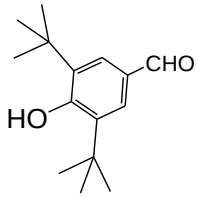
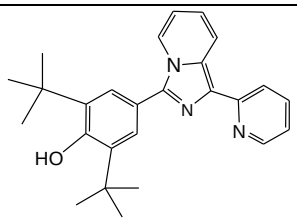
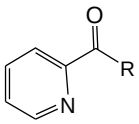
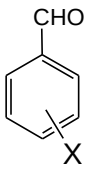
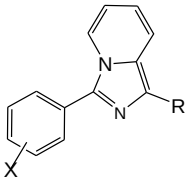
Scheme 1



1 **2(q-r)** **3(q-r)**

Scheme 2

Table 1 Synthesis of 1-Pyrimidazo [1, 5-*a*] Pyridines **3(a-r)**

Entry	Ketone **1**	Ar-CHO **2 (a-r)**	Products **3 (a-r)**	Yield [a, b] (%)	Time (min)
1.					
		a. X = H		93	10
		b. X = 4-OMe		92	12
		c. X = 2-Me		91	14
		d. X = 2-OH		90	18
		e. X = 3-OH		93	12
		f. X = 2-Cl		92	15
		g. X = 3-OMe,4- OH		90	17
		h. X = 3- NO_2		91	12
		i. X = 3- Me		93	12
		j. X = 4-OEt		93	13
		k. X = 3-OMe		90	12
		l. X = 4-OEt		90	14
		m. X = NMe_2		94	16
		n. X = 2-F		90	17
		o. X = 3-Cl		93	15
2.		 **p.**		90	15
3.	 R = Ph, Me				
		q. X = 2- NH_2		94	18
		r. X = 2-OH		90	18

[a]Products were characterized by [1]H NMR, [13]C NMR, Mass, elemental analysis and comparison with authentic sample, [b]Isolated yield after column chromatography.

Reaction was carried out simply by mixing 1, 2 dipyridylketone/2-acetyl pyridine with an aldehyde, ammonium acetate in the presence of a catalytic amount 15mol % of $K_4[Fe(CN)_6]\cdot 3H_2O$ under solvent free condition. The mixture was ground to gather in a mortar with a pestle at room temperature for short reaction time, and then purified by column chromatography, substituted imidazole derivatives were obtained in excellent yields. Accordingly, (15 mol %) of catalyst was sufficient to catalyze the reaction. A rate enhancement with high yield

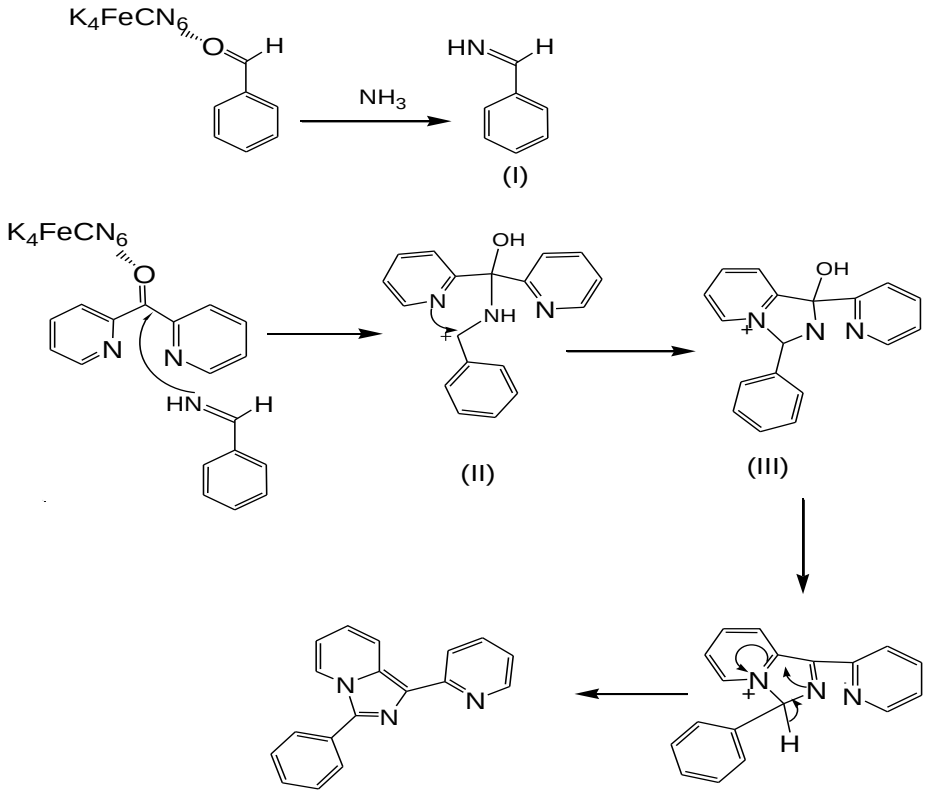
was observed when higher molar ratios of $K_4[Fe(CN)_6]\cdot 3H_2O$ were used. However no product formation was observed in absence of $K_4[Fe(CN)_6]\cdot 3H_2O$.

Table 2 Catalytic concentration for synthesis of **3a** X=H under solvent free conditions.

Entry	Time (min)	Yield [a] (%)	$K_4[Fe(CN)_6]\cdot 3H_2O$ (mol %)
1	20	00	No
2	10	traces	01
3	05	20	02
4	02	85	05
5	01	98	10
6	01	98	15

[a]*Isolated yield after column chromatography*

By getting this result, we have extended this protocol to a variety of aldehydes and ketones summarized in Table1. This protocol is rapid and efficient for the preparation of several substituted imidazoles from both electrons efficient as well as electron deficient aromatic aldehydes. There is no effect on electron-withdrawing group and electron-donating group on reaction yield time. When aliphatic aldehyde and ketones (e.g. acetaldehyde, acetone) were also used as starting carbonyl compounds for the same reaction, no products formation took place in this reaction by grinding the reagents after extensive time more than 30 minutes. Different *ortho* and *para* phenyl group substituent did not show any effect on the formation rate of imidazoles.



Scheme 3

However, *meta* substitution requires somewhat greater time as compared to the *o/p* substituents. Heteroaromatic ketones reacted fast and gave excellent yields of desired imidzoles. A nearly stoichiometric amount of ammonium acetate was used in the course of the reaction, where as previously a many-fold excess of ammonium acetate was required. This is an additional advantage of the novel methodology. The possible mechanism of this reaction is shown in Scheme 3.

The $K_4[Fe(CN)_6]\cdot 3H_2O$ increase the elctrophillic character of aldehyde towards the ammonia to give the imines as intermediate I. Further imine I react with acetyl carbonyl to give intermediate III which on further dehydration afford the corresponding desired products (**Scheme 3**).

1-(2-Pyridyl)-3-phenylimidazo[1,5-*a*]pyridine (3a): mp 92-93 °C. ^{1}H NMR ($CDCl_3$): δ 8.66 (1H, d, *J* = 9.0 Hz), 8.58 (1H, d, *J* = 4.5 Hz), 8.21 (2H, d, *J* =7.5 Hz), 7.80 (2H, d, *J* =7.5 Hz), 7.67 (1H, t, *J* = 7.5 Hz), 7.50 (2H, t, *J* =7.5 Hz), 7.42 (1H, t, *J*= 7.5 Hz), 7.05 (1H, t, *J*= 6.5 Hz), 6.88 (1H, dd, *J* =9.0 Hz), 6.60 (1H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$): δ 155.2, 149.2, 138.3, 136.5, 130.8, 130.5,130.4, 129.3, 129.2, 128.6, 122.1, 121.8, 121.3, 120.7, 120.2, 114.1; GC-MS *m*/*z* 271 (M+).

1-(2-Pyridyl)-3-(2-methylphenyl)imidazo[1,5-*a*]pyridine (3c): mp 112-113 °C. ^{1}H NMR ($CDCl_3$): δ 8.66 (1H, d, *J*= 9.0 Hz), 8.58 (1H, d, *J* =4.5 Hz), 8.19 (1H, d, *J* = 8.0 Hz), 7.65 (1H, t, *J*= 8.0 Hz), 7.57 (1H,d, *J* = 7.5 Hz), 7.45 (1H, d, *J* =7.5 Hz), 7.38-7.21 (3H, m), 7.03 (1H, t, *J* = 6.5 Hz), 6.86 (1H, dd, *J* = 9.0 Hz), 6.54 (1H, t, *J*= 6.5 Hz), 2.21 (3H, s); ^{13}C NMR ($CDCl_3$): δ 155.2, 149.0, 139.14, 138.6, 137.8, 136.3, 130.9, 130.6, 129.9, 129.7, 129.3, 126.2, 121.7, 121.6, 121.0, 120.4, 119.9, 113.6, 19.8; GC-MS *m*/*z* 285 (M+).

1-(2-Pyridyl)-3-(4-ethoxyphenyl) imidazo[1,5-*a*]pyridine (3l): mp 130-131 °C. ^{1}H NMR ($CDCl_3$): δ 8.63 (1H, d, *J* = 9.0 Hz), 8.57 (1H, d, *J* = 4.5 Hz), 8.19 (1H, d, *J* =8.0 Hz), 8.12 (1H, d, *J*= 7.0 Hz), 7.70-7.63 (3H, m), 7.04-6.99 (3H, m), 6.83 (1H, dd, *J* = 9.0 Hz), 6.56 (1H, t, *J* =7.0 Hz), 4.06 (2H, tetra, *J*= 7.0 Hz), 1.41 (4H, t, *J*= 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 159.5, 155.1, 149.0, 136.2, 130.2, 129.8, 123.0, 121.8, 121.6, 120.8, 120.3, 119.9, 115.0, 113.7, 63.6,14.8; GC-MS *m*/*z* 315 (M+).

1-(2-Pyridyl)-3-(4-dimethylaminophenyl) imidazo[1,5-*a*]-pyridine (3m): mp 180-182 °C. ^{1}H NMR ($CDCl_3$): δ 8.61 (1H, d, *J* = 9.0 Hz), 8.57 (1H, d, *J* = 4.5 Hz), 8.21 (1H, t, *J* = 6.5 Hz), 8.14 (1H, d, *J* = 7.0 Hz), 7.67-7.63 (3H, m), 7.01 (1H, t, *J* = 6.0 Hz), 6.82-6.78 (3H, m), 6.52 (1H, t, *J* = 7.0 Hz), 2.97 (6H, s); ^{13}C NMR ($CDCl_3$): δ 155.3, 150.7, 148.9, 139.0, 130.2, 129.9, 129.8, 129.4, 121.9, 121.7, 120.6, 120.2,119.9, 117.6, 113.3, 112.3, 40.4; GC-MS *m*/*z* 314 (M+). Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.22; H, 5.71; N, 17.70.

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