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GREEN SYNTHESIS OF 1-PYRIDYLIMIDAZO-[1,5-A]PYRIDINES

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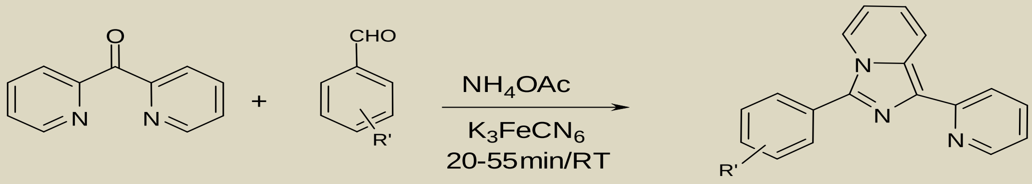
Introduction

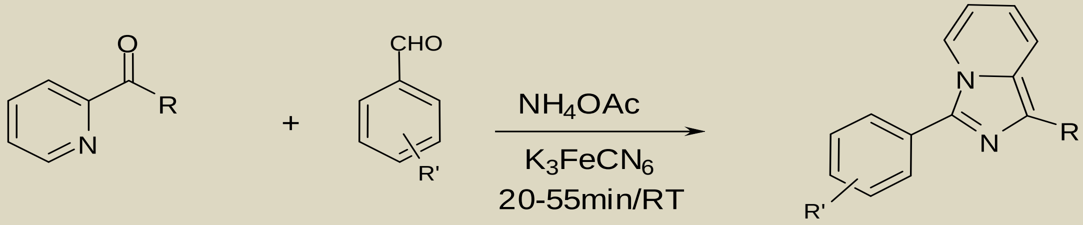
From several years, chemists have made efforts to developed environmental friendly methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. The use of potassium Ferro cyanide in organic synthesis has been known for a long time. Recently, coordinated complex 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 (Phukan *et al*. **2004,** Ko *et al*,**2005**).

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(Biachi,*et al* ,**1989**) neuromuscular blocking agents(Zito,*et al* ,**1980**) of reversible inhibitors of the H^+, K^+-ATPase enzyme(Arbilla *et al* **1986**) with a potent anti-secretory activity (Bolger *et al* **1972)** and of sedative hypnotics of the nervous system(Jansonius *et al* **1985**). Imidazo [1,5-a]pyridine skeleton is also a basic structure of synthetic drug Pirmogrel, with human clinical applications as effective platelet aggregation and thromboxane synthase inhibitors(Ford *et al* **1985**). 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(El Khadem *et al* **1989**) or thioacylation followed by ring closure using DCC or mercuric salts(Winterfeld *et al* **1963**). Imidazo[1,5-*a*]pyridines were also obtained from 2-cyanopyridine by the Vilsmeier reaction(Palacios *et al* **1995**) or by reaction with, or oxidization of, Schiff bases in the presence of molecular sieves or metal ions requiring two to three steps from the dipyridyl ketone(Kartritzky *et al* **2001**, Sasaki *et al* **1998**). Very recently Srinivasan et. al. reported the synthesis of 1-substituted imidazo[1,5-a]pyridines using ionic liquid. These ionic liquids are so expensive and one step is added in the syntheses process for their recovery(Siddiqui *et al* **2006**).

Many of the synthesis protocols for 1-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. Moreover, the syntheses of these heterocycles have been carried out in DMF, DMSO, and acetic acid leading to complex isolation and recovery procedures.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 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



Scheme 2 Initially, a systematic study was carried out for catalytic evaluation of complex for 1,2-dipyridyl ketone, benzaldehyde and ammonium acetate (Table 1). The enhancement of mol% of iodine, enhance the yield of the product and reduce the reaction time (entry 1-5). The reaction went to completion in 3 h at reflux temperature with 10 mol% $K_2[Fe(CN)_6]$. Accordingly, 10 mol% was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher molar ratios of complex were used. However, no product formation was observed in absence of $K_2[Fe(CN)_6]$.

Table 1: Catalytic evaluation of iodine for the synthesis of 3

Entry	Catalyst () ($K_2[Fe(CN)_6]$. mol %)	Time (min)	Yield [a,b] (%)
1	0	20	00
2	2	20	65
3	5	17	90
4	10	12	96
5	15	10	94

[a]: Reaction Condition; 1,2-dipyridyl ketone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2 mmol), EtOH (2 drops), RT Room temperature

[b]: Isolated yield after column chromatography.

To check the efficiency of potassium ferrocyanide complex we also tried several conventional acid catalysts or acid under identical conditions, results are showed in table2.

When conventional Lewis acids such as $AlCl_3$, $TiCl_4$, $ZnCl_2$ used under identical condition it gave product 20, 10 and 40 % isolated yield, where as *p*TSA gave traces of product. AcOH gave 70% of product after 6 h, which was replaced by strong acids such as H_2SO_4 and PPA (poly phosphoric acid) there is progressive increase in yield of product and drop out of reaction time, but problem with using these acid catalyst is the critical isolation method and generation hazardous waste material.Toluene, acetonitrile, methanol and ethanol were found to be suitable solvent, where as solvents such as DMF, DMSO, DCM does not gave products in satisfactory amount. As we found that ethanol is best solvent, we proceeded with ethanol, which is considered as a relatively benign organic solvent. We used ethanol of two drops which is necessary for the well mixing of the reaction mixtures. It is important to note that in case of ethanol, 1-pyridylimidazo [1,5-a]pyridines **3** precipitated on dilution of the reaction mixture with an aqueous solution of $Na_2S_2O_3$ and were isolated by simple filtration whereas in other hazardous solvents for the extraction of the products were required. At room temperature, there is no product formation was observed even after 12 h, however, with increase in temperature, product 3 was obtained within a few hours (Table3).

Table 2: Study of different acid catalyst for the synthesis of 3

Entry	Acid catalyst/acid (mol%)	Solvent/Temp. (^{0}C)	Time (h)	Yield ^{a} (%)
1	$AlCl_3$ (20 mol%)	EtOH/reflux	12	20
2	$TiCl_4$ (20 mol%)	EtOH/reflux	12	10
3	*p*TSA (20 mol%)	EtOH/reflux	12	Traces
4	$ZnCl_2$ (30 mol%)	CH_3CN/reflux	12	40
5	AcOH	AcOH/110	6	70
6	H_2SO_4	H_2SO_4/80	4	90
7	PPA	PPA/80	3	90

^{a}: Isolated yield after column chromatography

Table 3: Study of temperature effect for the synthesis of 3

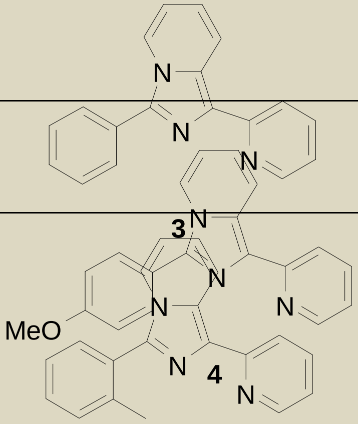
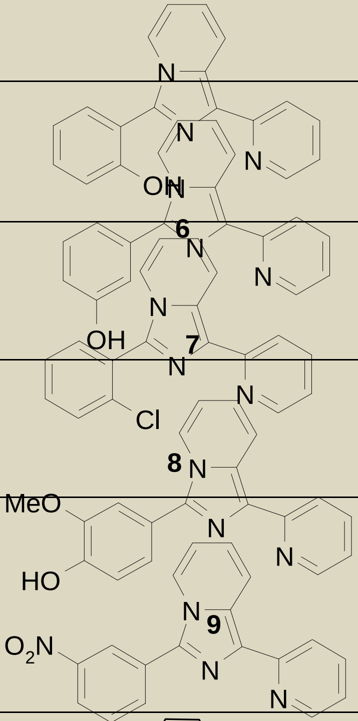
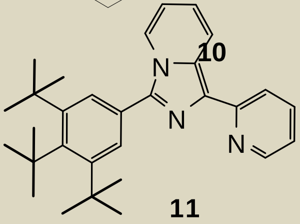
Entry	Temp. (^{0}C)	Time (min)	Yield ^{a} (%)
1	00	20	00
2	30	12	94
3	50	25	75
4	60	35	80
5	75	30	90

^{a}:

Isolated yield after column chromatography.

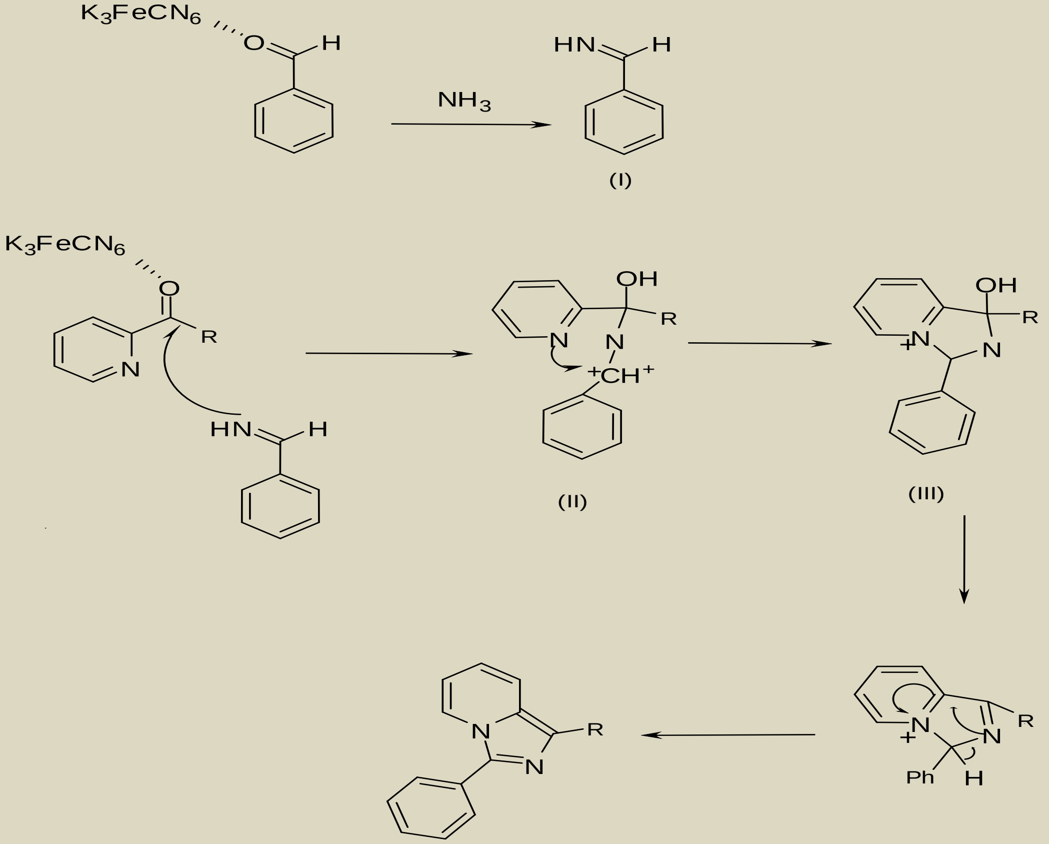
After getting these encouraged results, we have extended the methodology to a variety of aromatic aldehydes, which are summarized in Table 4. This method is effective for the preparation of 1-pyridylimidazo [1,5-a]pyridines **3** from both electron efficient as well as electron deficient aromatic aldehydes . The aryl groups substituted with different groups and also the same groups located at different positions of the aromatic ring did not show any marginal effect on the formation of 1-pyridylimidazo [1,5-a]pyridines **3.** Anotheradvantage of this methodology is a nearly stoichiometric amount of ammonium acetate was used in the course of the reaction, whereas previously a many-fold of ammonium acetate was required. This is an additional advantage of the novel methodology.

Table:4 synthesis of 1-pyrimidazol[1,5-a]pyridines 3-11

Entry	Product	Time(min)	Yield^{a,b} (%)
1	 3	10	93
2	4	12	92
3	5	14	91
4	 6	18	90
5	7	12	93
6	8	15	92
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) $K_2Fe(CN_6)$ (10mmol%) , EtOH (2 drops), 30 ^{0}C
[b]: Isolated yield after column chromatography.

Scheme 2: Plausible mechanism for the formation of [1,5a]pyridines



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.

In conclusion, we describe a mild and efficient route for the synthesis of 1-pyridylimidazo[1,5-a]pyridines utilizing $K_2Fe(CN_6)$ 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 iodine as a catalyst for other organic transformations are currently under investigation in our research group, and will be reported in due course.

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 $K_2Fe(CN_6)$ (10mol%) in ethanol (2 drops) was mixed well in mortor for the time specified in Table 4. 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..

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Spectral Data:

1-(2-Pyridyl)-3-phenylimidazo [1,5-a]pyridine(3): Yellow solid, mp 91-92 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.60 (t, *J* = 6.5, 1H), 6.88 (dd, *J* = 9, 1H) 7.05 (t, *J* = 6.5**,** 1H), 7.42 (t, *J* = 7.5, 1H), 7.50 (t, *J* = 7.5, 2H), 7.67 (t, *J* = 7.5, 1H), 7.80 (d, *J* = 7.5, 2H), 8.21 (d, *J* = 7.5, 2H), 8.58 (d, *J* = 4.5, 1H), 8.66 (d, *J* = 9, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) : δ 113.8, 119.8, 120.3, 120.9, 121.5, 121.6, 128.2, 128.8, 128.9, 129.9, 130.1, 130.4, 136.1, 137.9, 148.8, 154.8. Anal. Calcd. for $C_{18}H_{13}N_3$**:** C, 79.68; H, 4.83; N, 15.49. Found C, 79.25; H, 4.19; N, 15.07.

1-(2-Pyridyl)-3-(4-methoxy-phenyl) imidazo [1,5-*a*] pyridine (4): yellow solid, mp 120-121 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H), 6.57 (t, *J* = 7.7, 1H), 6.85 (dd, *J* = 9, 6.4, 1H), 6.96-7.04 (m, 3H), 7.69-7.59 (m, 3H), 8.17 (dd, *J* = 8.19, 7, 2H), 8.56 (d, *J* = 5.85, 1H), 8.61 (d, *J* = 9.34, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.3, 113.6, 114.4, 119.8, 120.2, 120.8, 121.5, 122.4, 122.6, 129.7, 129.8, 130, 136.2, 138, 148.8, 154.9, 160. Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found C, 75.21; H, 4.59; N, 13.41.

1-(2-Pyridyl)-3-(2-methyl-phenyl) imidazo [1,5-*a*] pyridine (5): yellow solid, mp 114-115 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 2.21 (s, 3H), 6.54 (t, *J* = 6.5, 1H), 6.86 (dd, *J* = 9, 6.3, 3H), 7.03 (t, *J* =6.5, 3H), 7.21-7.38 (m, 3H), 7.45 (d, *J* = 7.5, 1H), 7.57 (d, *J* = 7.5, 1H), 7.65 (t, *J* = 8, 1H), 8.19 (d, *J* = 8, 1H), 8.58 (d, *J* = 4.5, 1H), 8.66 (d, *J* = 9, 1H). ^{13}C NMR (50 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 19.8, 113.6, 119.9, 120.4, 121, 121.6, 121.7, 126.2, 129, 129.7, 129.9, 130.6, 130.9, 136.3, 137.8, 138.6, 139.1, 149, 152.5. Anal. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73. Found C, 79.6; H, 5.09; N, 14.42.

1-(2-Pyridyl)-3-(2-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (6): pale yellow solid, mp 195-196 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 7.18 (t, *J* = 6.8, 1H), 7.34-7.54 (m, 4H), 7.76 (t, *J* = 8,1H), 8.16 (d, *J* = 7.91, 1H), 8.52 (d, *J* = 7.78, 1H), 8.66 (d**,** *J* = 6.77, 1H), 9 (d, *J* = 4.5, 1H), 9.12 (d, *J* = 9.26, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 112.5, 113.8, 114.8, 117.3, 118, 118.9, 119.9, 120.6, 128.2, 128.6, 129.4, 134.8, 136.4, 147.3, 153.3, 156.5. Anal. Calcd. for $C_{18}H_{13}N_3O$**:** C, 75.25; H, 4.56; N, 14.63. Found C, 74.71; H, 4.07; N, 14.28.

1-(2-Pyridyl)-3-(3-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (7): yellow solid, mp 200-201 ^{0}C, ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 6.72-7.01 (m, 5 H), 7.09-7.15 (m, 1H), 7.31-7.35 (d, *J* = 8.04, 1H), 7.70-7.79 (m, 1H), 8.11-8.15 (d, *J* = 8.08, 1H), 8.37-8.40 (d, *J* = 7.08, 1H), 8.55-8.58 (d, *J* = 5.6, 1H), 8.60-8.62 (d, *J* = 9.25, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$/DMSO-*d*$_6$): δ 112.5, 113.8, 114.8, 117.3, 118, 118.9, 119.9, 120.6, 128.2, 128.6, 129.4, 134.8, 136.4, 147.3, 153.3, 156.5. Anal. Calcd. for $C_{18}H_{12}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found C, 74.82; H, 4.42;

N, 14.48.

1-(2-Pyridyl)-3-(2-chloro-phenyl) imidazo [1,5-*a*] pyridine (8): bright yellow solid, mp 178-179 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.60-6.67 (m, 1H), 6.90-6.98 (m, 1H), 7.1-7.16 (m, 1H), 7.37-7.72(m, 6H), 8.19-8.24 (m, 1H), 8.6-8.63 (m, 1H), 8.69-8.74 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 113.4, 119.7, 120.3, 121.1, 121.4, 122.2, 127.2, 129.1, 129.7, 129.8, 130.8, 133.2, 134.3, 135.5, 136.1, 148.9, 154.8. Anal. Calcd. for $C_{18}H_{12}N_3Cl$: C, 70.47; H, 3.91; N, 13.70.Found: C, 70.09; H, 3.41; N, 13.29.

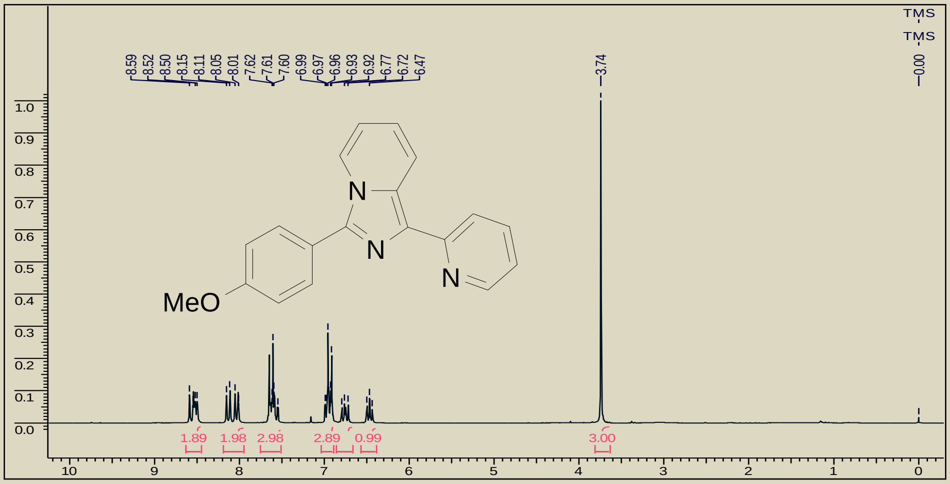
1-(2-Pyridyl)-3-(3-methoxy-4hydroxyphenyl) imidazo [1,5-*a*] pyridine (9): yellow solid, mp 132-133 ^{0}C, ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-d_6): δ 8.44-8.39 (d, *J* = 8.4, 2H), 8.03-7.99 (d, *J* =9.6, 2H), 7.56-7.46 (m, 1H), 7.14-7.12 (m, 1H), 7.05-7.01 (m, 1H), 6.90 (m, 2H), 6.73-6.63 (m, 1H), 6.45-6.41 (t, *J =9.1* 1H), 5.11(br s ,1H), 3.70 (s, 3H).^{13}C-NMR (50 MHz, $CDCl_3$/DMSO-d_6): δ 153.8, 147.8, 147.5, 146.7, 137.6, 135.6, 129.0, 128.7, 127.6, 121.9, 120.6, 120.4, 120.3, 120.2, 119.5, 119.0, 114.8, 113.0,111.5,55.3. Anal Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.54; H, 4.38; N, 13.12

1-(2-Pyridyl)-3-(3-nitro-phenyl) imidazo [1,5-*a*] pyridine (10): yellow solid, mp 187-188 ^{0}C, ^{1}H NMR (200 MHz, $CDCl_3$/DMSO-d_6): δ 6.81 (t, *J* = 7, 1H), 7.09 (t, *J* =7, 1H), 7.14 (t, *J* = 7, 1H), 7.79-7.8 (m, 2H), 8.10 (d, *J* = 8, 1H), 8.26 (d, *J* = 7.5, 1H), 8.34 (d, *J* = 7, 1H), 8.57-8.6 (m, 4H). ^{13}C-NMR (50 MHz, $CDCl_3$/DMSO-d_6): δ 115.8, 120, 121.5, 121.8, 123.2, 123.3, 123.7, 124, 130, 131, 131.3, 131.8, 134.1, 136, 138.1, 149, 149.5, 155. Anal Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 67.83; H, 3.39; N, 17.32.

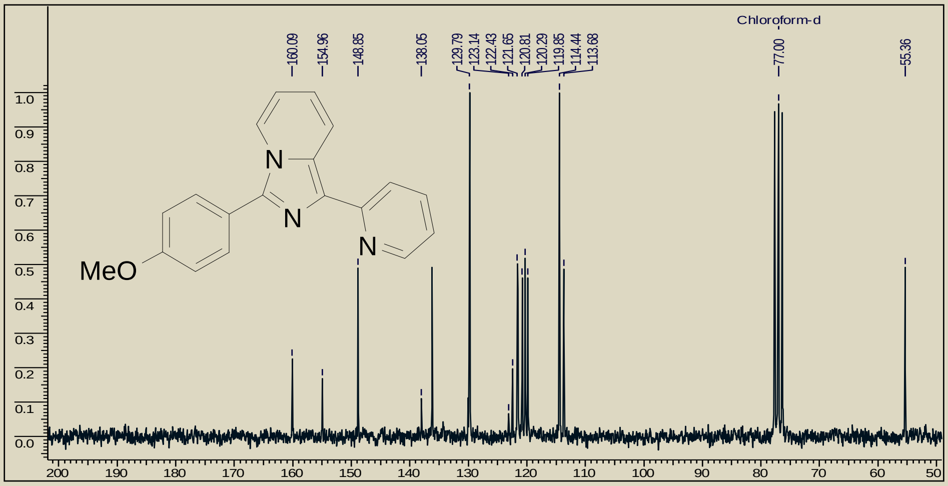
1-(2-Pyridyl)-3-(3, 5-di-*tert*-butyl-4-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (11): yellow solid, mp 212-213 ^{0}C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 18H), 5.45 (brs, 1H), 6.84-6.92 (m, 1H), 7.03-7.1 (m, 1H), 7.58 (s, 2H), 7.66-7.74 (m, 1H), 8.12-8.16 (d, *J* = 7.28, 1H), 8.24-8.28 (d, *J* = 8.48, 1H), 8.60-8.71 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.2, 113.5, 119.9, 120.2, 120.7, 121.7, 125.6, 136.2. Anal Calcd. for $C_{26}H_{29}N_3O$: C, 78.16; H, 7.32; N, 10.52. Found C, 77.89; H, 6.89; N, 9.92.

Spectra's of some representative compounds

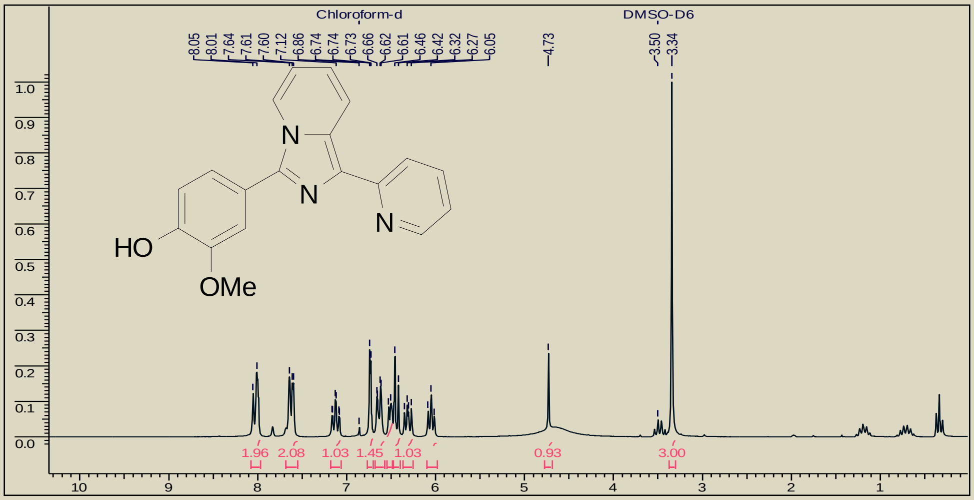
[1] ^{1}H NMR spectra:



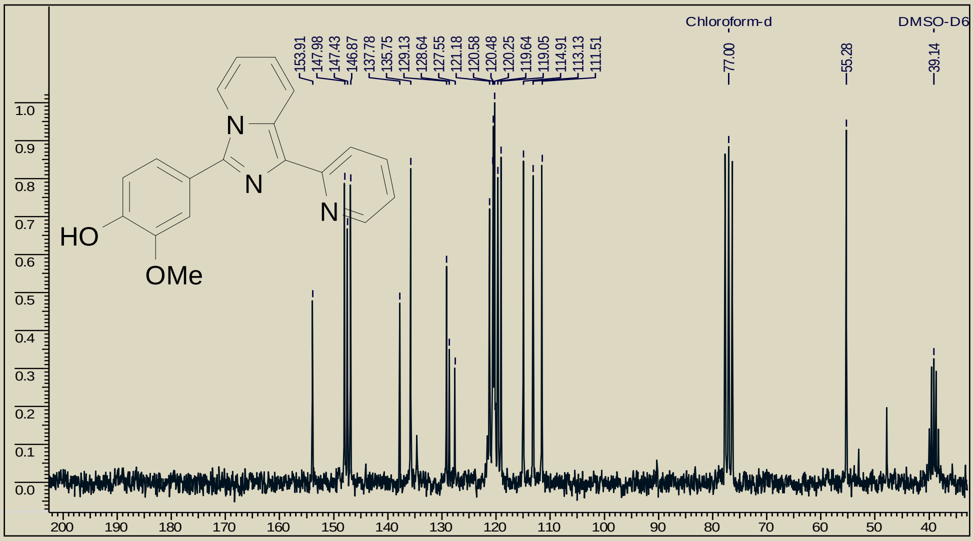
[2] ^{13}C NMR spectra of 3b



[3] ^{1}H NMR spectra of 3g



[4] ^{13}C NMR spectra of 3g



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