Novel Synthesis of 6-Substituted 2-Picolines from Aryl/heteroaryl β-Enaminones and Meldrum's Acid Using $CeCl_3.7H_2O$/NaI

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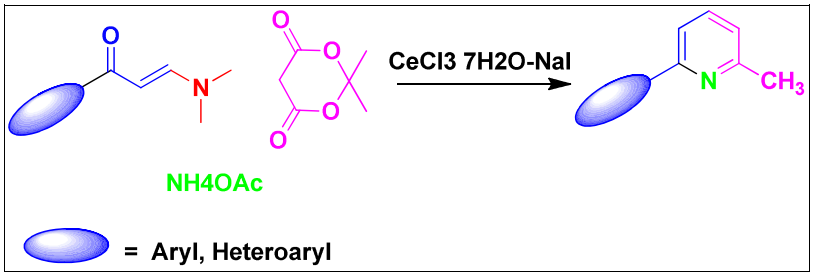

One-pot condensation of aryl/heteroaryl β-enaminones, Meldrum's acid, and ammonium acetate in the presence of $CeCl_3.7H_2O$/NaI via tandem Michael addition–cyclodehydration–elimination sequence led to the formation of novel regioselective 6-substituted 2-picolines.

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INTRODUCTION

Given the prevalence and diversity of nitrogen containing heterocyclic motifs in various complex bioactive molecules, the development of synthetic methods for direct C–C and C–N bond formation using safe, environmentally benign, and low-cost starting materials remain a challenge for modern synthetic organic chemists [1]. β-Enaminones [2], because of the presence of ambident nucleophilic character of enamine moiety and the ambident electrophilic character of enone moiety, turned out to be simple and reactive starting materials for the synthesis of diversely substituted heterocycles [3]. Taking advantage of their electronic properties, we explored aryl and heteroaryl embodied β-enaminones in our laboratory [4] as polarized variants in one-pot Bohlmann–Rahtz reaction. The Lewis acid catalyzed condensation β-enaminones with cyclic and acyclic 1,3-dicarbonyls and ammonium acetate resulted a series of 2,3,6-trisubstituted pyridines and dihydro-6*H*-quinoline-5-ones in good to excellent yields [4,5]. Encouraged by these results, we further examined the reaction of β-enaminone with Meldrum's acid and ammonium acetate under similar reaction conditions. Contrary to our expectation, Meldrum's acid on reaction with β-enaminone derived L-Rhamnose and ammonium acetate in the presence of $CeCl_3.7H_2O$/NaI gave 2-methyl-6-((4R,4′S,5S)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)pyridine (**1**) as the major product rather than 2,3,6-trisubstituted pyridine analogue [5]. The result prompted us to further investigate the Lewis acid catalyzed condensation of β-enaminone with Meldrum's acid.

In general, 6-substituted-2-picolines **2–4** (Fig. 1) play an important part in the development of potent bioactive derivatives for systematic exploration towards drug discovery [6]. For example, **2** and **3** are the first drugs developed to act as a selective antagonist for the metabotropic glutamate receptor subtype $mGluR_5$ with anticonvulsant and neuroprotective effects following acute brain injury and reduced glutamate release [7]. The substituted picolines are mostly prepared through metal catalyzed aromatic coupling reactions [8]. These methods use palladium and other metal catalysts, and each has limitations in applicability for library generation. In view of the importance of these derivatives in medicinal applications, we herein describe our efforts on exploration of a series of β-enaminones in the preparation of 6-substituted-2-picolines. Also discussed here is a plausible mechanism via Meldrum's acid degradation leading to the formation of 6-substituted-2-picolines.

RESULTS AND DISCUSSION

β-Enaminones **5a–l** required for the study (Fig. 2) are prepared by the condensation of respective aryl/heteroaryl methyl ketones with dimethylformamide dimethylacetal (DMF-DMA) refluxing in xylene according to the general protocol standardized in our laboratory [4,5]. All the new as well as literature described β-enaminones **5a–l** [4] are fully characterized by ^1H, ^{13}C NMR, and mass spectral analysis.

On the basis of our previous work, initially, dimethylamino-1-(2,4-dimethyl-2,3-dihydrobenzofuran-7-yl)propenone (**5e**) was selected to react with Meldrum's acid **6** and ammonium acetate in the presence of $CeCl_3.7H_2O$/NaI catalyst. The product 2-(2,4-dimethyl-2,3-dihydrobenzofuran-7-yl)-6-methylpyridine (**7e**) resulted in 68% yield. A study designed to optimize catalysts showed that $CeCl_3.7H_2O$/NaI

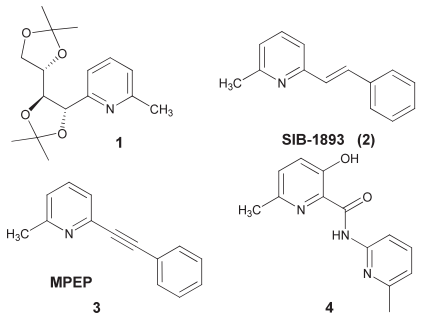
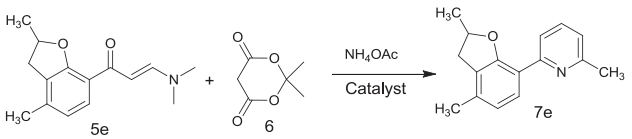


Figure 1. Bioactive analogues of 6-substituted-2-picolines.

is superior to $K_5CoW_{12}O_{40}.3H_2O$ and $SnCl_2.2H_2O$ (Table 1, entries 10 and11). After a series of experiments, the condensation of enaminone **5e** with Meldrum's acid **6** and ammonium acetate was successful, using $CeCl_3.7H_2O$/NaI (30.0 mol%) on refluxing in 2-propanol for 6 h (Table 1, entry 5) to afford optimum yield (77%) of 6-substituted 2-picoline **7e**. We have attempted a similar reaction in the presence of NaI without using $CeCl_3.7H_2O$; the reaction was not successful (Table 1, entry 9). Also notice that with the absence of NaI, the procedure with $CeCl_3.7H_2O$ requires 24 h to give products **7e** in low yields (Table 1, entry 12). Here, it is also noteworthy that yields of **7e** varied with the number of mole equivalents of Meldrum's acid, ammonium acetate, and $CeCl_3.7H_2O$/NaI.



After screening the reaction parameters, we turned to examining broader scope of the reaction with various aryl/heteroaryl β-enaminones **5a–l** and ammonium acetate under optimal conditions (30 mol% $CeCl_3.7H_2O$/NaI in 2-propanol at reflux temperature). All the aryl/heteroaryl

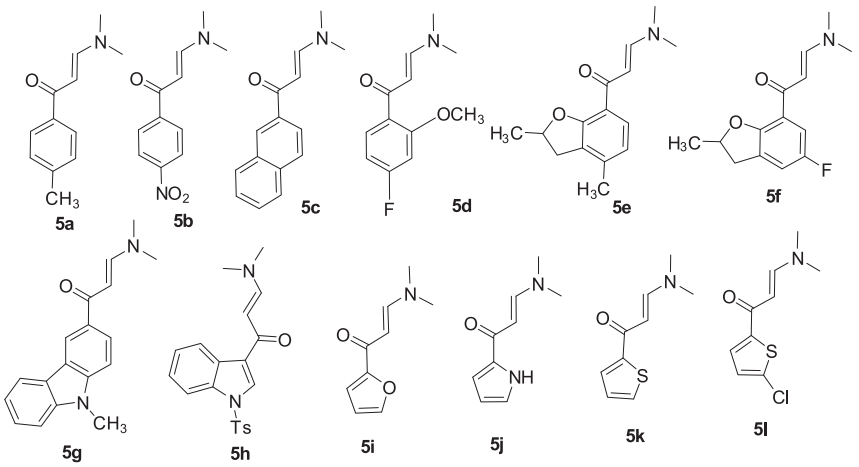


Figure 2. Enaminones used for the study.

Table 1

Optimization of reaction conditions.[a]

Entry	Catalyst	mol (%)	Time (h)	Equivalents of reactants			Products (% yield)[b]
				5e	**6**	NH_4OAc	**7e**
1	$CeCl_3.7H_2O$/NaI	20	8	1	2	2	53
2	$CeCl_3.7H_2O$/NaI	20	8	1	3	3	60
3	$CeCl_3.7H_2O$/NaI	20	12	1	4	3	65
4	$CeCl_3.7H_2O$/NaI	30	4	1	2.5	2	69
5	$CeCl_3.7H_2O$/NaI	30	6	1	2.5	2	77
6	$CeCl_3.7H_2O$/NaI	30	12	1	2.5	2	76
7	$CeCl_3.7H_2O$/NaI	30	24	1	2.5	2	75
8	$CeCl_3.7H_2O$/NaI	30	6	1	0	2	-
9	NaI	30	24	1	3	3	<10
10	$K_5CoW_{12}O_{40}.3H_2O$	30	24	1	2.5	2	18
11	$SnCl_2.2H_2O$	30	24	1	2.5	2	14
12	$CeCl_3.7H_2O$	30	24	1	3	3	16

[a]Compound **5e** (1 mmol), Meldrum's acid **6**, ammonium acetate, and the catalyst were refluxed in *i*-PrOH.
[b]Isolated yield based on **5e**.

β-enaminones **5a–l** reacted with Meldrum's acid, and the-corresponding 6-substituted 2-picolines **7a–l** were obtained in moderate to good yields (Table 2) The structures of 6-substituted 2-picolines **7a–l** were fully characterized and clearly assigned from their IR, ^{1}H NMR, ^{13}C NMR, and mass (ESI–MS and HRMS) spectral analysis. (Scheme 1, Table 2)

A cerium activated [9] plausible mechanism involving tandem Michael addition–cyclodehydration–elimination sequence leading to the formation of **7** is presented in Scheme 2. It is well established that the thermal instability of Meldrum's acid in the presence of Lewis acid allows access to the highly reactive ketene along with acetone and CO_2 [10]. Here, under the optimized reaction condition, Meldrum's acid **6** behaving as masked ketone generated acetone and then reacted with ammonium acetate to give respective amine. This amine further undergoes cerium assisted regioselective Michael addition on the cerium (III) activated β-enaminones **7a–l** followed by cyclodehydration and aromatization leading to the pyridine ring with the elimination of dimethyl amine completing the catalytic cycle. The use of ammonium formate instead of ammonium acetate did not alter the product or the yield.

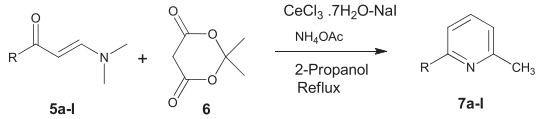
Table 2

Formation of 6-substituted 2-picolines **7a–l**.

Entry	Enaminone 5	Reaction time (h)	Product 7[a]	Yield (%)
1	**5a**	6	**7a**	75
2	**5b**	6	**7b**	70
3	**5c**	4	**7c**	72
4	**5d**	5	**7d**	75
5	**5e**	6	**7e**	77
6	**5f**	4	**7f**	73
7	**5g**	4	**7g**	76
8	**5h**	4	**7h**	74
9	**5i**	6	**7i**	77
10	**5j**	5	**7j**	72
11	**5k**	5	**7k**	75
12	**5l**	5	**7l**	73

[a]Isolated yield.

Scheme 1



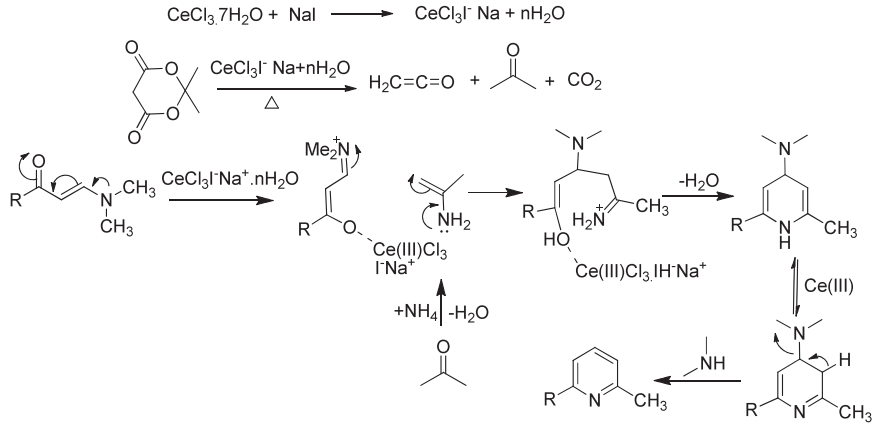
CONCLUSIONS

In summary, we have developed a cerium (III) catalyzed protocol for one-pot regioselective synthesis of novel 6-substituted 2-picolines **7a–l** from β-enaminones **5a–l**, Meldrum's acid **6**, and ammonium acetate. Mechanistically, the reaction proceeds through sequential Michael addition–cyclodehydration–elimination reactions. The method appears to be very general and reactive with respect to starting materials. It is likely that the novelty of this method combined with its operational simplicity will make it attractive for the construction of environmentally benign, low-cost, and biologically relevant compounds.

EXPERIMENTAL

All the reactions were monitored by TLC (precoated silica plates and visualized under UV light). Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator (Solvents (SD Fine, Mumbai) Agilent Technologies, USA). ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Bruker UXNMR FT-300 MHz (Avance) spectrometer and Varian FT-500 MHz (Inova). Chemical shifts reported are relative to an internal standard TMS (δ = 0.0 ppm). Mass spectra were recorded in EI conditions at 70 eV on LC–MSD (Agilent technologies) spectrometers. All high-resolution spectra were recorded on QSTAR XL hybrid MS/MS system (Applied Biosystems/ MDS SCIEX, Foster City, CA, USA), equipped with an ESI source

Scheme 2 Plausible mechanism for the formation of 6-substituted 2-picolines **7a–l**.



(IICT, Hyderabad). Column chromatography was performed on a silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Commercially available solvents CH_2Cl_2, THF, and EtOAc were used as such without further purification.

General experimental procedure for the synthesis of 7a–l. To a mixture of **5f** (0.30 g, 1.20 mmol), Meldrum's acid **6** (0.43 g, 3.0 mmol), and NH_4OAc (0.18 g, 2.40 mmol) in *i*-PrOH (5 mL), $CeCl_3.7H_2O$ (81.8 mg, 0.3 mmol) and NaI (44.9 mg, 0.3 mmol) were added, and the mixture was refluxed for 4 h (TLC monitoring). The mixture was cooled to RT, and the solid precipitate was filtered and washed (cold *i*-PrOH). The combined solvent was evaporated, and the crude residue was subjected to column chromatography (silica gel, hexane/EtOAc, 9:1) to give 2-(5-fluoro-2-methyl-2,3-dihydrobenzofuran-7-yl)-6-methyl pyridine **7f** brown syrup (0.22 g, 78%).

2-Methyl-6-p-tolylpyridine (7a). Light yellow syrup, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.02 (d, J = 7.6 Hz, 1H), 2.60 (s, 3H), 2.40 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 153.0, 140.2, 137.4, 128.1, 127.1, 123.4, 31.9, 29.7. IR (neat) 2926, 1639, 1582, 1381, 1238, 903, 781 cm^{-1}. MS (ESI) *m/z* 184 $[M+H]^+$; HRMS (ESI) Calcd for $C_{13}H_{14}N$ $[M+H]^+$: 184.1126. Found: 184.1127.

2-Methyl-6-(4-nitrophenyl) pyridine (7b). Brown syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 8.9 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.58 (d, J = 8.0 Hz,1H), 7.15 (d, J = 7.5 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 154.0, 147.6, 141.5, 134.0, 127.7, 123.9, 29.7. IR (neat) 2921, 2852, 1637, 1460, 1344, 1262, 1157, 771 cm^{-1}. MS (ESI) *m/z* 215 $[M+H]^+$; Calcd for $C_{12}H_{11}N_2O_2$.

2-Methyl-6-(naphthalen-2-yl)pyridine (7c). Yellow syrup,^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43(s, 1H), 8.12 (dd, J = 2.26 Hz, J = 6.79 Hz 1H), 7.79–7.91(m, 3H), 7.61–7.64 (m, 3H), 7.43–7.46 (m, 2H), 7.05–7.08 (m, 1H), 2.65 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 156.0, 136.8, 133.67, 133.60, 128.7, 128.3, 127.7, 126.3, 126.1, 124.8, 121.6, 117.8, 24.8. IR (neat) 2924, 2854, 1585, 1450, 1272, 1125, 1070, 791, 733 cm^{-1}. MS (ESI) *m/z* 220 $[M+H]^+$; HRMS (ESI) Calcd for $C_{16}H_{14}N$ $[M+H]^+$: 220.1126. Found: 220.1130.

N-[(2-2-(4-Fluoro-2-methoxyphenyl)-6-methylpyridine (7d). Light yellow syrup,^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.52–7.58 (m, 2H), 7.04 (d, J = 6.8 Hz, 1H), 6.95–6.99 (m, 1H), 6.86 (dd, J = 3.91 Hz, J = 4.8 Hz, 1H), 3.80 (s, 3H), 2.59 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.6, 155.7, 135.9, 122.0, 121.5, 117.9, 117.6, 115.7, 114.2, 112.5, 56.1, 29.7. IR (neat) 2924, 2852, 1580, 1495, 1460, 1255, 1183, 1028, 808, 746 cm^{-1}. MS (ESI) *m/z* 218 $[M+H]^+$; HRMS (ESI) Calcd for $C_{13}H_{13}NOF$ $[M+H]^+$;218.0981. Found: 218.0973.

2-(2,4-Dimethyl-2,3-dihydrobenzofuran-7-yl)-6-methyl pyridine (7e). Brown syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.30 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H),6.95 (d, J = 6.8 Hz, 1H), 6.71(d, J = 7.8 Hz, 1H), 5.01–5.06 (m, 1H), 3.25 (dd, J = 9.02 Hz, J = 6.09 Hz, 1H), 2.75 (dd, J = 7.36 Hz, J = 7.84 Hz, 1H), 2.58 (s, 3H), 2.22 (s, 3H), 1.52 (d, J = 6.34 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.9, 154.1, 136.3, 135.2, 127.8, 126.6, 121.8, 120.8, 120.5, 119.5, 79.6, 35.9, 24.6, 22.1, 18.9. IR (neat) 2923, 2852, 1721, 1621, 1451, 1381, 1241, 1193, 1189, 1032, 907, 773 cm^{-1}. MS (ESI) *m/z* 240 $[M+H]^+$; HRMS (ESI) Calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388. Found. 240.1388.

2-(5-Fluoro-2-methyl-2,3-dihydrobenzofuran-7-yl)-6-methyl pyridine (7f). Yellow syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.30 Hz, 1H), 7.79 (dd, J = 3.02 Hz, J = 8.30 Hz, 1H), 7.56 (t, J = 7.55 Hz, 1H), 7.01 (d, J = 7.55 Hz, 1H), 6.82 (dd, J = 3.02 Hz, J = 4.53 Hz, 1H), 4.97–5.05 (m, 1H), 3.33 (dd, J = 8.30 Hz, J = 9.06 Hz, 1H), 2.83 (dd, J = 7.55 Hz, J = 9.06 Hz, 1H), 2.59 (s, 3H), 1.52 (d, J = 6.79 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ.157.7, 153.3, 152.3, 137.2, 132.3, 130.0, 128.2, 121.6, 121.0, 113.7, 112.6, 80.4, 36.9, 29.6, 22.6. IR (neat) 2925, 2855, 1625, 1460, 1391, 1256, 1218, 1181, 761 cm^{-1}. MS (ESI) *m/z* 244$[M+H]^+$: HRMS (ESI) Calcd for $C_{15}H_{15}NOF$ $[M+H]^+$: 244.1137. Found: 244.1127.

3-(6-Methylpyridin-2-yl)-9H-carbazole (7g). Light yellow syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.07–8.12 (m, 2H), 8.01(t, J = 8.30 Hz, 2H), 7.29–7.43 (m, 3H), 7.16–7.22 (m, 1H), 6.99 (t, J = 4.53 Hz, 1H), 3.83 (s, 3H), 2.65 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 157.7, 141.4, 136.8, 130.7, 125.8, 125.0, 123.1, 120.66, 120.6, 119.17, 119.14, 117.3, 108.5, 108.4, 29.7, 24.7. IR (neat) 2924, 2852, 1587, 1480, 1328, 1254, 1154, 786, 743 cm^{-1}. MS (ESI) *m/z* 273 $[M+H]^+$; HRMS (ESI) Calcd for $C_{19}H_{17}N_2[M+H]^+$; 273.1391. Found: 273.1381.

***3-(6-Methylpyridin-2-yl)-1-tosyl-1H*-indole (7h).** Brown syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (dd, J = 1.51 Hz, J = 1.51 Hz, 1H), 7.96-7.99 (m, 2H), 7.77 (d, J = 8.30 Hz, 2H), 7.57 (t, J = 7.74 Hz, 1H), 7.45 (d, J = 7.74 Hz, 1H), 7.24–7.34 (m, 2H), 7.17(d, J = 7.93 Hz, 2H), 7.02 (d, J = 7.55 Hz, 1H), 2.61(s, 3H), 2.31 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 157.5, 145.0, 136.7, 135.6, 130.2, 129.8, 128.8, 126.9, 124.9, 123.8, 122.3, 121.2, 118.3, 113.4, 29.6, 21.5, IR (neat) 2923, 2854, 1586, 1448, 1360, 1173, 1133, 1088, 753, 668 cm^{-1}. MS (ESI) *m/z* 363 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{21}H_{19}N_2O_2S$ $[M+H]^+$: 363.1167. Found: 363.1177.

2-(Furan-2-yl)-6-methylpyridine (7i). Yellow syrup,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, J = 6.85 Hz, 1H), 7.49 (d, J = 9.36 Hz, 2H), 7.05 (s, 1H), 6.99 (d, J = 7.53 Hz, 1H), 6.49 (s, 1H), 2.58(s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 156.4, 154.8, 147.4, 143.2, 121.6, 115.8, 112.0, 109.1, 29.7. IR (neat) 2924, 1462, 1388, 1282, 1167, 1013, 764 cm^{-1}. MS (ESI) *m/z* 160 $[M+H]^+$.

***2-Methyl-6-(1H*-pyrrol-2-yl) pyridine (7j).** Light yellow syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (bs, 1H), 7.47 (t, J = 7.29 Hz, 1H); 7.31 (d, J = 7.30 Hz, 1H); 6.84 (d, J = 7.50 Hz, 2H), 6.60 (s, 1H), 6.20 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 142.4, 139.2, 130.2, 120.0, 19.4, 114.0, 110.0, 29.6. IR (neat) 2923, 2853, 1639, 1592, 1461, 1252, 786, 730 cm^{-1}. MS (ESI) *m/z* 159 $[M+H]^+$; HRMS (ESI) Calcd for $C_{10}H_{11}N_2$ $[M+H]^+$: 159.0922. Found: 159.0924.

2-Methyl-6-(thiophen-2-yl)pyridine (7k). Brown syrup,^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 3.02 Hz, 1H), 7.49 (d, J = 7.55 Hz, 1H), 7.40 (d, J = 7.55 Hz, 1H), 7.31 (d, J = 6.04 Hz, 1H), 7.04 (t, J = 5.28 Hz, 1H), 6.95 (d, J = 7.55 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$). δ 158.3, 151.9, 136.7, 127.8, 127.1, 124.3, 121.4, 115.8, 29.7. IR (neat) 2924, 2854, 1578, 1457, 1231, 786, 701 cm^{-1}. MS (ESI) *m/z* 176 $[M+H]^+$; HRMS (ESI) Calcd for $C_{10}H_{10}NS$ $[M+H]^+$: 176.0533. Found: 176.0531.

2-(5-Chlorothiophen-2-yl)-6-methylpyridine (7l). Light yellow syrup, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, J = 7.55 Hz, 1H), 7.30 (d, J = 7.55 Hz, 1H), 7.27 (d, J = 3.77 Hz, 2H), 6.95 (d, J = 7.55 Hz, 1H), 6.85 (d, J = 3.77 Hz, 1H), 2.53(s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 151.01, 143.8, 136.8, 126.9, 123.2, 121.6, 115.0, 21.7. IR (neat) 2923, 2853, 1579, 1457, 1215, 1038, 780 cm^{-1}. MS (ESI) *m/z* 210 $[M+H]^+$; HRMS(ESI) Calcd for $C_{10}H_{10}NSCl$ $[M+H]^+$; 210.0144. Found:210.0141.

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