

## Synthesis of some nuclear substitution derivatives of 4-acetyl pyridine

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**ABSTRACT**

Five nuclear substitution derivatives of 4- acetyl pyridine (**2a** to **6a**) were prepared via N-oxidation followed by either nitration or arylation in the yield of 60-80%. Substitution at 2- position is promoted due to the electron withdrawing and meta-directing ability of acetyl group at 4- position making the pyridine N-oxide vulnerable to attack at C-2.

**Keywords:** 4- acetyl pyridine, N-oxidation, nitration, arylation, nuclear substitution.

**INTRODUCTION**

Substituted N-heterocycles are important structural motifs of bio-active compounds and advanced materials.<sup>1</sup> Hence, methods that allow for regioselective construction of C–C bonds to N-heterocycles have attracted continuous attention.<sup>2</sup> In particular, introduction of substituents in the C-2 position of pyridines, quinolines and related six-membered nitrogenous heterocycles is an important strategy in heterocyclic synthesis that represents a significant synthetic challenge.<sup>3</sup> One of the most commonly used strategies is based on transition metal-catalyzed coupling reactions of organometallic reagents with 2-haloazines,<sup>4</sup> which are prepared from the corresponding N-oxides<sup>5</sup>. In recent years, direct arylation has emerged as an attractive alternative to typical cross-coupling reactions.<sup>6</sup> In direct arylation, one of the preactivated cross-coupling partners (typically the organometallic species) is replaced by an un functionalized arene. Consistent with an electrophilic aromatic substitution (SEAr) pathway, electron-rich heterocyclic arenes have been featured prominently in recent developments.<sup>7</sup> While some simple arenes can now be used,<sup>8,9</sup> direct arylation reactions with  $\pi$ -electron deficient heteroarenes, such as pyridine, remain a challenging goal.<sup>10</sup> Bakke and coworkers were the first to report a remarkable reaction of pyridines with dinitrogen pentoxide in sulfur dioxide solution, to give N-nitropyridinium ion intermediates which, on treatment with water, gave 3-nitropyridines in good yield. They proposed that this reaction proceeds by a [1,5] sigma tropic shift of the nitro group from the 1- to the 3- position in the pyridine ring rather than an electrophilic aromatic substitution. A mixture of 3-nitropyridine and 3, 5-dinitropyridine was obtained in low yield by Suzuki and coworkers from the reaction of pyridine with dinitrogen pentoxide generated in situ from nitrogen dioxide and ozone.<sup>11,12</sup> A similar attempt was made

recently to generate dinitrogen pentoxide, the anhydride of nitric acid, from nitric acid itself using phosphorus pentoxide,<sup>13</sup> for the in situ reaction with pyridine. Some 3-nitropyridine was obtained, but in low yield. Katritzky *et al.* have reported the preparation of nitropyridines by nitration of pyridines with nitric acid using nitric acid– TFAA system.<sup>14</sup>

**RESULTS AND DISCUSSION**

As per our plan to synthesize some new pyridine containing compounds, we have prepared a set of 4- acetyl pyridine derivatives (table 1) as described in scheme 1. Many electrophilic substitutions on pyridine either do not proceed or proceed only partially; however, the heteroaromatic character can be activated by electron-donating functionalization. Common alkylations and acylations, such as Friedel–Crafts alkylation or acylation, usually fail for pyridine because they lead only to the addition at the nitrogen atom. Substitutions usually occur at the 3-position, which is the most electron-rich carbon atom in the ring and is, therefore, more susceptible to an electrophilic addition. Substitutions to pyridine at the 2- or 4- position result in an energetically unfavorable  $\sigma$  complex. They can be promoted, however, using clever experimental techniques, such as conducting electrophilic substitution on the pyridine-N-oxide followed by deoxygenation of the nitrogen atom. Addition of oxygen reduces electron density on the nitrogen atom and promotes substitution at the 2- and 4-carbons. The oxygen atom can then be removed via several routes, most commonly with compounds of trivalent phosphorus or divalent sulfur, which are easily oxidized.<sup>15</sup> As the nuclear substitution on pyridine ring itself is relatively difficult, we attempted to perform substitutions on pyridine N-oxide which is more nucleophilic and electrophilic, having higher dipole moment (4.37D for pyridine N-

oxide vs. 2.03D for pyridine), much weaker base (pKa 0.79 for pyridine N-oxide vs. pKa 5.2 for

The N-O moiety of pyridine N-oxides possesses a unique functionality which can act effectively as a push electron donor and as a pull electron acceptor group. This strong push-pull property has an essential chemical consequence; it accounts for the equally easy synthesis of 4-substituted derivatives of pyridine N-oxides with donor as well as acceptor groups. The contribution of

Further, we were interested in the production of nitro pyridines using nitric acid, which is readily available, cheap and overcomes the problem of handling the unstable and difficult-to-obtain reagent, dinitrogen pentoxide. We sought to generate dinitrogen pentoxide easily in situ, under conditions in which it would react with pyridines immediately. These requirements led us to select the nitric acid–TFAA system as reported in the literature.<sup>14</sup> As a result of nitration of 4-acetylpyridine-N-oxide (**1**) we got 2-nitro-4-acetylpyridine N-oxide which was reduced by Pd/C to the base, 2-nitro-4-acetylpyridine (**2a**). The nitro group of compound **2a** was then reduced to amino group through Sn/HCl system to get 2-amino-4-acetylpyridine (**3a**) which through Sandmeyer reaction produced corresponding chloro compound

pyridine). It exists as many mesomeric forms (fig. 1)<sup>16</sup>.

the resonance forms I and II depends on the nature of the substituent at position 4. The moderate electron-acceptor acetyl group favors the charge transfer form II. Thus, acetyl group being electron withdrawing and meta directing group removes electron density from a  $\pi$  system, making the  $\pi$  system more electrophilic, as well as directs the substitution on the ring, meta to it, i.e. at position 2 (fig. 2).<sup>17,18</sup>

(**4a**). As a parallel path to some more 2-substituted derivatives, Arylation of N-oxide was carried out as per the reported procedure of Fagnou *et al.*<sup>19</sup> Reaction development was carried out with pyridine N-oxide and 4-bromotoluene. From these studies, palladium acetate in combination with tri-tert-butylphosphine (added to the reaction mixture as the commercially available and air-stable HBF<sub>4</sub> salt) emerged as the optimal metal-ligand combination. Potassium carbonate was deemed the optimal base, and toluene the optimal solvent. While the reaction with bromobenzene under these conditions lead us **5a**, the combination with 4-bromotoluene gave compound **6a**. The structures of all the compounds were confirmed through IR and proton NMR spectroscopy (table 2) and elemental analysis carried out (table 3).

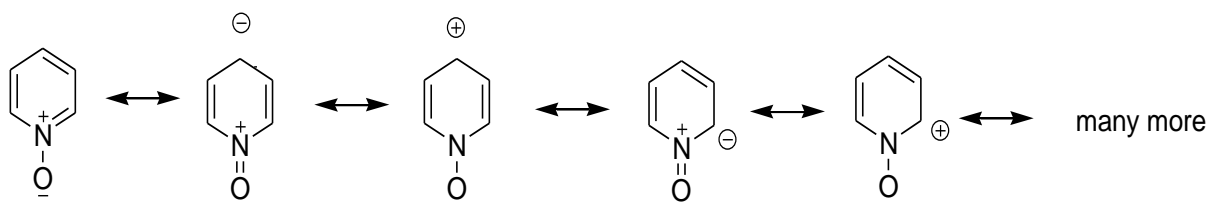


Fig. 1: Mesomeric forms of pyridine N-oxide.

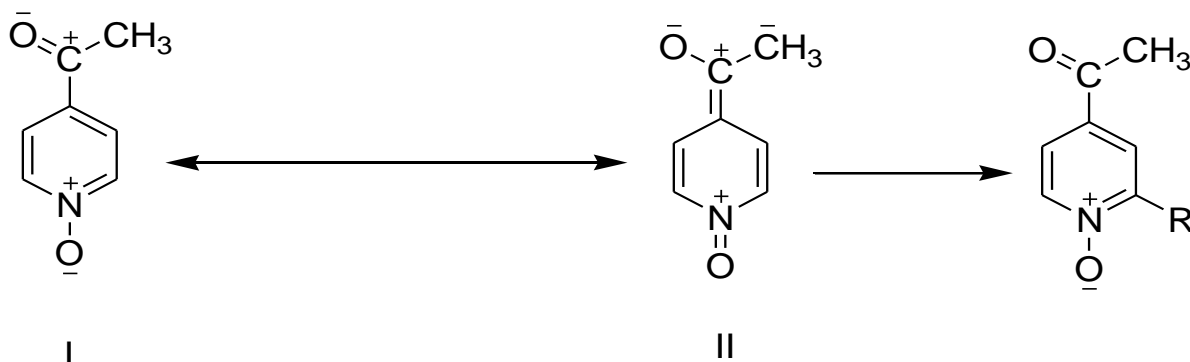


Fig. 2: Substitution at 2- position on 4- acetyl pyridine.

## CONCLUSION

As a part of our synthetic strategy to get new series of heterocyclic compounds, we have prepared five new derivatives of 4-acetylpyridine either via nitration or N-oxidation which were confirmed through IR, NMR and Mass spectroscopy.

## Experimental

All the chemicals and reagents used were of Synthetic grade and purchased from Alfa Aesar or Sigma Aldrich and used as such without purification. Melting point was determined on Veego digital melting point apparatus and was uncorrected. IR spectra were recorded using Bruker Alpha FTIR Spectrometer equipped with ZnSe ATR crystal. <sup>1</sup>H NMR spectra were recorded on Bruker Spectrometer (400 MHz) in CDCl<sub>3</sub> using TMS as an internal standard. Mass spectra were recorded on LC-MSD Trap-SL 2010A-Shimadzu. Micro analysis was performed on a Perkin Elmer-240 CHN elemental analyzer.

**Preparation of 4-acetylpyridine-N-oxide (i<sub>1</sub>):** For N-oxidation, 4-acetylpyridine (1 equivalent) was taken in a round bottom flask, and added to it, from a dropping funnel, 1.2 equivalent 30% w/v solution of hydrogen peroxide at a temperature of 0-5°C with constant stirring. The stirring of reaction mixture at the same temperature for 15 min yielded N-oxide almost quantitatively as a white hygroscopic solid (M.P 140-142°C). The N-oxide was filtered and dried under vacuum and stored in vacuum desiccators for future use.

**2-Nitro-4-acetylpyridine[1-(2-Nitro-4-pyridinyl)ethanone(2a)].** 4-Acetylpyridine (2.0 g, 18.2 mmol) N-oxide was added slowly to TFAA (10.6 mL, 76.4 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. conc. HNO<sub>3</sub> (2.4 mL, 38.2 mmol) was added to the mixture dropwise and the mixture stirred at 0 °C for 8 h. The reaction mixture was added dropwise to a stirred solution of Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (2.54 g, 18.2 mmol) in water (20 mL) at 0 °C and the mixture stirred at 0 °C for 16 h. The pH of the solution was adjusted to 6-7 with 1 M NaOH solution and the mixture was extracted with DCM (3 x 50 mL). The combined organic fraction was washed with water (50 mL), washed with brine (50 mL), dried and the solvent evaporated. The residue on reduction with Pd/Cu in ethyl formate and MeOH gave ketone (1.66 g, 55%) as oil.

**2-Amino-4-acetylpyridine [1-(2-aminopyridin-4-yl) ethanone (3a)].** 2-Nitro-4-acetylpyridine (1g, 6.01 m mol) was added to 2.5g tin (16.84 m mol) and then 20 ml. conc. HCl was added under reflux. The reaction mixture was cooled and added to it, 10-15 ml. of water. 20% NaOH was then added to dissolve

the tin hydroxide completely and make the solution sufficiently alkaline so as to be extracted with ether thrice. The combined ether extract was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and solvent was removed by distillation and the residue was recrystallized to give 0.64g (78%) of pale yellow product (M.P. 138°C).

## 2-Chloro-4-acetylpyridine[1-(2-chloropyridin-4-yl)ethanone(4a)]

**a. Preparation of copper (I) Chloride solution:** 3.5g (0.014 mol) of Copper Sulphate pentahydrate and 0.92 g (0.0157 mol) of pure Sodium Chloride was dissolved in 12.5 ml. of water with warming. A solution of 0.84g (0.0044 mol) of sodium metabisulphite in 9 ml. water was added to the hot solution during about 5 min. by constant shaking. The reaction mixture was cooled to room temperature and the supernatant liquid was decanted from the colorless copper (I) chloride. The precipitated Copper (I) chloride was washed twice with SO<sub>2</sub> dissolved water (to prevent oxidation), dissolved in 6 ml. conc. HCl and used within 24 hrs of its preparation.

**b. Preparation of Chloro- compound via Sandmeyer reaction:** The freshly prepared Cu(I)Cl solution in HCl was cooled in an ice-salt mixture whilst the diazotization is being carried out. 1g (7.3m mol) of 2-amino-4-acetylpyridine was dissolved in 2.5 ml. of conc. HCl and 2.5 ml water in a flask. The mixture was cooled to 0°C in an ice-salt bath with vigorous stirring and the addition of little crushed ice. The hydrochloride salt was separated as finely divided crystalline precipitate. Added during 10-15 min, a solution of 0.5 g (0.0075mol) of Sodium Nitrite in 5 ml of water (1); at a temperature of 0-5°C by the addition of little crushed ice from time to time. When all the Nitrate solution had been introduced, the solution contained a trace of free nitrous acid which was tested with potassium iodide-starch paper.

The cold diazonium chloride solution was poured slowly by shaking into the cold Cu(I)Cl solution (2). The mixture became very thick owing to the separation of an addition product between the diazonium salt and Cu(I)Cl (MeCOC<sub>5</sub>H<sub>4</sub>N. N<sub>2</sub><sup>+</sup> Cl<sup>-</sup>.CuCl). Without external heating, the mixture was allowed to warm up to room temperature with occasional shaking (3).

When the temperature reached to about 15°C, the solid addition complex broke down with the liberation of Nitrogen. The mixture was warmed on a water bath to about 60°C to complete the decomposition of the double salt, with occasional shaking. When the evolution of Nitrogen has ceased, the reaction mixture was transferred to 1M NaOH and extracted with three equal portions of EtoAc. The combined organic layer was washed with brine solution, then with water, dried over Na<sub>2</sub>SO<sub>4</sub> and

evaporated under *vacuo* to yield after recrystallization with 2-propanol afforded 0.78g (68.4%) pale white powder (155.58) with M.P. 85-86°C.

### 2-Phenyl-4-acetylpyridine [1-(2-phenylpyridin-4-yl)ethanone (5a)]

**a. Preparation of 2-Phenyl-4-acetylpyridine N-oxide:**  $K_2CO_3$  (2 equiv.),  $PtBu_3 - HBF_4$  (0.15 equiv.),  $Pd(OAc)_2$  (0.05 equiv.) and 4-acetylpyridine N-oxide (4 equiv.) are weighed to air and placed in a round bottom flask with a magnetic stir bar. The reflux condenser was capped with rubber septa. The reaction is evacuated and backfilled with Nitrogen. Bromobenzene (1 equiv.) is then added via syringe as a stock solution in toluene (0.3M). The mixture is then heated to 110°C for 6 hours. The reaction mixture is filtered, (wash with  $Me_2CO$  and DCM) then evaporated under reduced pressure and purified by silica gel column chromatography using DCM/Acetone (1:1) mixture as mobile phase. The N-oxide so obtained was then reduced to the base by following procedure:

**b. Reduction of N-oxide to the base 2-Phenyl-4-acetylpyridine (5a):** Ammonium formate (~10 equiv.) is added to a stirring solution of 2-Phenyl-4-acetylpyridine N-oxide (1 equiv.), Pd/C (0.1 equiv.)

in MeOH (0.3M) in a round bottom flask. The flask is then capped with rubber septa and purged with Nitrogen. The mixture is then stirred under an atmosphere of Nitrogen at room temperature. When the reaction is deemed complete by TLC analysis, the reaction is filtered and evaporated under reduced pressure. The residue is then purified via silica gel chromatography using DCM/Acetone mixtures. 2-Phenyl-4-acetylpyridine was obtained as yellow amorphous solid (yield 69%) with melting point 150 °C.

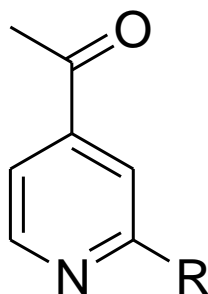
### 2-Toluoyl-4-acetylpyridine [1-(2-p-tolylpyridin-4-yl)ethanone; 6a]

4-acetylpyridine N-oxide on reaction with *p*-Bromotoluene (described in 7.2.4 b) and heating to 110 °C for 8 hrs afforded 2-Toluoyl-4-acetylpyridine N-oxide, which on subsequent Reduction by Pd/C in MeOH (by the procedure described in 7.2.4 c) yielded 2-Toluoyl-4-acetylpyridine as pale yellow solid (72%, M.P.170 °C) after recrystallization with hot ethanol.

### ACKNOWLEDGEMENT

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Table 1: Nuclear substitution derivatives of 4-acetyl pyridine



Compound	R	% yield
1a	H	Purchased
2a	NO <sub>2</sub>	55
3a	NH <sub>2</sub>	78
4a	Cl	68.4
5a	C <sub>6</sub> H <sub>5</sub>	69
6a	C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	72

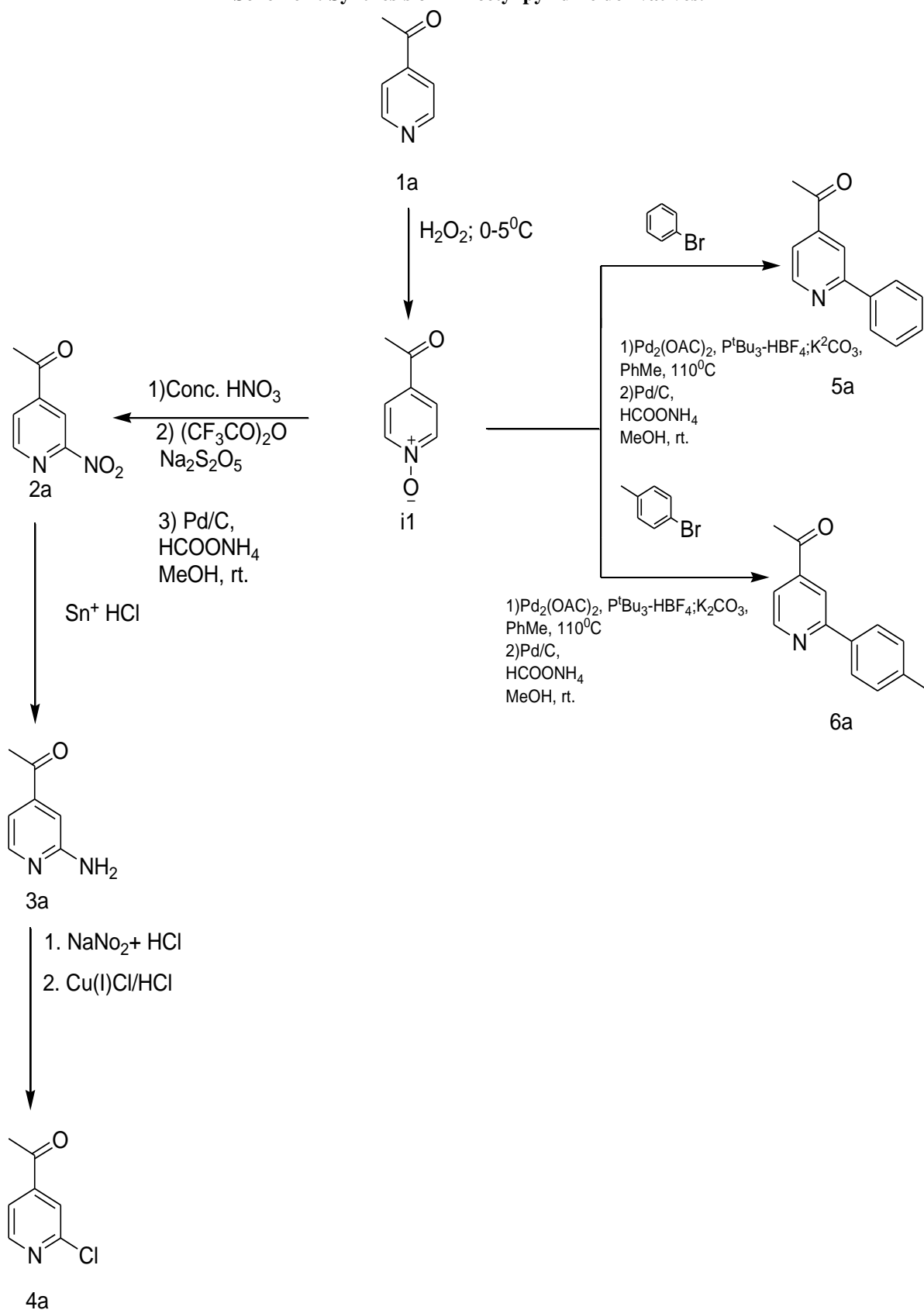
**Table 2: Physical constants and spectral data for 4-acetyl pyridine derivatives**

Compound	M.P. (uncorrected) or B.P./mmHg	<sup>1</sup> H-NMR δ (ppm) (CDCl <sub>3</sub> )
<b>1a</b>	212.8°C at 760 mmHg.	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.46-8.44 (d, 2H, Ar-H), 7.38-7.36 (d, 2H, Ar-H), 2.19 (s, 3H, CH <sub>3</sub> ). IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 2923, 1692, 1596, 1556, 1492, 1407. LCMS m/z [M] <sup>+</sup> 122.1 Commercially available - CAS # 1122-54-9
<b>2a</b>	oil	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.72-8.71 (d, 1H, Ar-H), 8.37 (d, 1H, Ar-H), 8.09-8.07 (d, 1H, Ar-H), 2.23 (s, 3H, CH <sub>3</sub> ). IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 1696, 1540, 1335, 855, 759, 695. LCMS m/z [M] <sup>+</sup> 167.2
<b>3a</b>	142-144°C	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.44-8.42 (d, 1H, Ar-H), 7.19-7.15 (m, 2H, Ar-H), 2.61 (s, 3H, CH <sub>3</sub> ), 1.58 (s, 2H, NH <sub>2</sub> ); IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 3381, 3405, 3036, 1697, 1590, 688, 759, 855. LCMS m/z [M] <sup>+</sup> 136.1
<b>4a</b>	35-40 °C	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.80-8.79 (d, 1H, Ar-H), 8.02-7.89 (m, 2H, Ar-H), 2.43 (s, 3H, CH <sub>3</sub> ). IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 2913, 1698, 1615, 1698, 1475, 696, 760. LCMS m/z [M] <sup>+</sup> 157.1
<b>5a</b>	128-132 °C	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.78-8.76 (d, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.91-7.93 (d, 1H, Ar-H), 7.47-7.30 (m, 5H, Ar-H), 2.49 (s, 3H, CH <sub>3</sub> ); IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 3047, 1698, 1615, 760. LCMS m/z [M] <sup>+</sup> 197.1
<b>6a</b>	179-182 °C	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> , 400 MHz): δ= 8.59 (d, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.71-7.69 (d, 2H, Ar-H), 7.29-7.27 (d, 1H, Ar-H), 7.10-7.09 (d, 2H, Ar-H), 2.31 (s, 3H, CH <sub>3</sub> ), 2.13 (s, 3H, CH <sub>3</sub> ). IR (ν <sub>max</sub> /cm <sup>-1</sup> ): 3049, 2353, 1697, 759. LCMS m/z [M] <sup>+</sup> 212.1

**Table 3: Analytical data for Acetyl pyridines**

Compound	Formulae	Analyses (%)					
		Calculated			Found		
		C	H	N	C	H	N
<b>1a</b>	C <sub>7</sub> H <sub>7</sub> NO	69.41	5.82	11.56	69.68	5.36	11.26
<b>2a</b>	C <sub>7</sub> H <sub>6</sub> N <sub>2</sub> O <sub>3</sub>	50.61	3.64	16.86	50.85	3.47	16.56
<b>3a</b>	C <sub>7</sub> H <sub>8</sub> N <sub>2</sub> O	61.75	5.92	20.58	61.58	5.68	20.18
<b>4a</b>	C <sub>7</sub> H <sub>6</sub> ClNO	54.04	3.89	9.00	54.12	3.74	9.08
<b>5a</b>	C <sub>13</sub> H <sub>11</sub> NO	79.16	5.62	7.10	79.28	5.76	7.18
<b>6a</b>	C <sub>14</sub> H <sub>13</sub> NO	79.59	6.20	6.63	79.65	6.29	6.55

Scheme 1: Synthesis of 4- Acetyl pyridine derivatives.



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