Chapter 4

Persulfate Mediated C-3 Formylation of Imidazopyridines Using Glyoxylic Acid

4. Persulfate Mediated C-3 Formylation of Imidazopyridines Using Glyoxylic Acid

4.1 Introduction

Imidazo[1,2-a]pyridine has gained significant attention among heterocycles due to its versatile reactivity and diverse biological activities.[1–3] Numerous therapeutically relevant compounds containing the imidazo[1,2-a]pyridine pharmacophore, such as alpidem, zolpidem[4], necopidem[5], GSK 812397 (anti-HIV)[6], etc. underscore the importance of functionalization of this chemical entity (figure 4.1). The pharmacological activities of imidazo[1,2-a]pyridine can be attributed to the chemical nature of the functionality at its C-3 position. Hence, synthetic methodologies for incorporating formyl at the C-3 position of imidazo[1,2-a]pyridines have lured organic chemists, owing to its ability to undergo various tranasformation reactions. In 2011, Zhu's group performed Cu-catalyzed intramolecular dehydrogenative aminooxygenation of *N*-allyl-2-aminopyridines to produce imidazo[1,2-a]pyridine-3-carbaldehydes.[7] In 2012, Adimurthy's group performed aqueous synthesis of imidazo[1,2-a]pyridine-3-carbaldehydes via silver-catalyzed aminooxygenation of *N*-(prop-2-yn-1-yl)pyridin-2-amines.[8] In 2017, Rao *et al.* performed Cu-catalyzed synthesis of imidazo[1,2-a]pyridine-3-carbaldehydes by employing ethyl tertiary amines as carbon sources.[9] The direct C-3 formylation of imidazopyridines using dimethylsulfoxide, acting as both the solvent and carbonyl source was reported by Cao[10] and Liu group[11] using of copper and iron as a catalyst, respectively (scheme 4.1a). In 2018, Kibriya *et al.* synthesized C-3 formylated imidazo[1,2-a]pyridines using rose bengal as a photocatalyst and tetramethylethylenediamine (TMEDA) as the one-carbon source (scheme 4.1b).[12] Very recently, Tang *et al.* have reported the synthesis of C-3 formylated imidazo[1,2-a]pyridines by electrochemical oxidation of triethylamine using platinum plate electrodes and $LiClO_4$ as electrolyte (scheme 4.1c).[13] Despite the significant advancements, the use of complicated photocatalysts, transition metals under harsh

reaction conditions, or expensive electrodes limit the application of these methods. Therefore, generating an economical and sustainable direct C-3 formylation method for imidazopyridines would be highly desired.

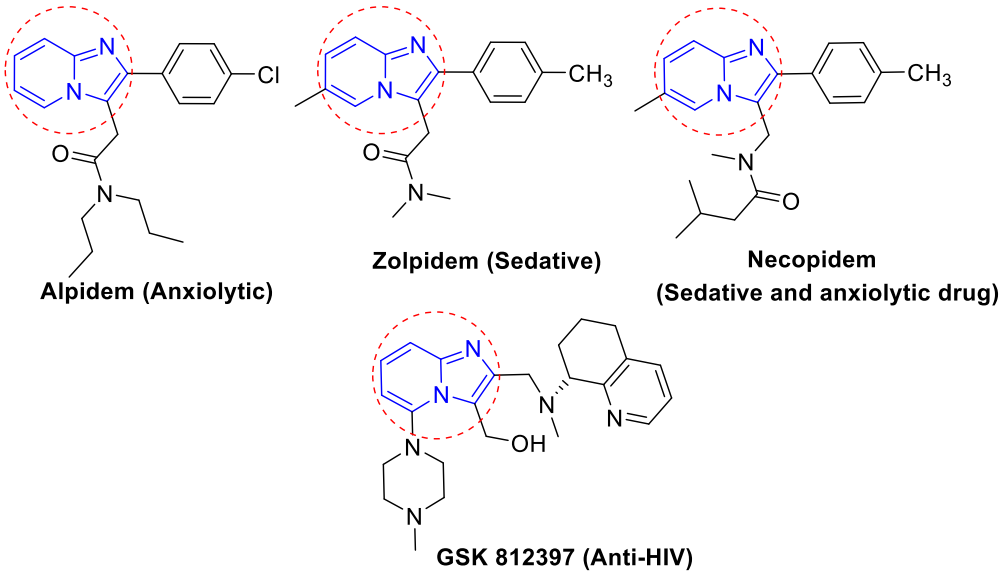
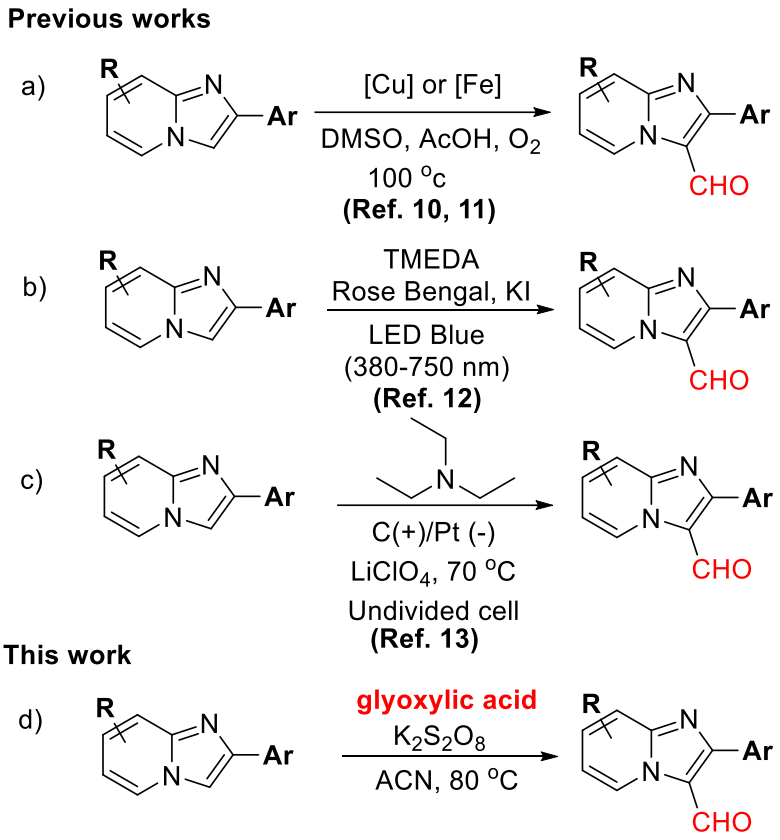


Figure 4.1: Pharmacologically active molecules containing imidazopyridine moiety.

Recently, glyoxylic acid used as a source of formyl radical synthons for Minisci type formylation.[14,15] Wu and co-workers reported synthesis of 3-formylindoles using Ni-catalyzed decarboxylative cross-coupling of indoles with glyoxylic acid.[16] Huang's group also reported 3-formylindoles employing glyoxylic via an electrochemical process.[17] Nagrajan *et al.* performed formylation β-carbolines with ammonium persulfate via direct decarboxylative cross-coupling of glyoxylic acid.[18] Later, Laha *et al.* reported formylation of various heterocycles (azaindoles, indoles, and pyrrole) using glyoxylic with potassium persulfate.[19] Although several reports are on the formylation of indoles and small heterocyclics, there is no such report on the use of glyoxylic acid for formylation of imidazopyridines. In continuation of our interest in the functionalization of imidazo[1,2-a]pyridines[5] and persulfate-based

method developments,[20,21] herein, we report a highly efficient C-3 formylation of imidazo[1,2-a]pyridines by using glyoxylic acid and persulfate.

Scheme 4.1: C-3 formylation of imidazo[1,2-a]pyridines.



4.2 Results and Discussion

To prove the feasibility of our proposed C-3 formylation strategy on imidazo[1,2-a]pyridines, we initiated our study with 2-phenylimidazo[1,2-a]pyridine (**1a**, 1 mmol) and glyoxylic acid (**2**, 1.2 mmol) as model substrates in the presence of 3 equiv. of $K_2S_2O_8$ in acetonitrile (ACN) and stirred at 80 °C for 12 h (Table 4.1). To our delight, we found the formation of desired 2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (**3a**) with a yield of 75 % (entry 1). The amount of the oxidant was then reduced to 2 equiv., and as a result, the yield of **3a** was improved to 85% (entry 2). However, a further decrease to 1 equiv. led to a significant deterioration in the yield of **3a** (entry 3). Once the reagent proportions were optimized, the effect of solvents and

temperature on the synthetic protocol were tested. The reaction was carried out in several solvents, like 1,2-dichloroethane (DCE, entry 4), dimethyl sulfoxide (DMSO, entry 5), dimethyl formamide (DMF, entry 6), ethanol (entry 7), toluene (entry 8), and water (entry 9), resulted yield of **3a** ranged between 13-75%. Among these, ACN was the most suitable for this reaction, affording an 85% yield of **3a**. After the screening of solvents, the reaction was carried out at room temperature (entry 10), but to our dismay, the desired product was not formed. When reaction was performed at 50 ^{o}C, the product formed, but its yield was as low as 48% (entry 11). When $K_2S_2O_8$ was replaced by $(NH_4)_2S_2O_8$, the yield of **3a** was found to be less (entry 12). There was no product formation in absence of $K_2S_2O_8$, thereby implicating the importance of persulfate in the reaction (entry 13).

Table 4.1: Optimization of reaction conditions.[a]

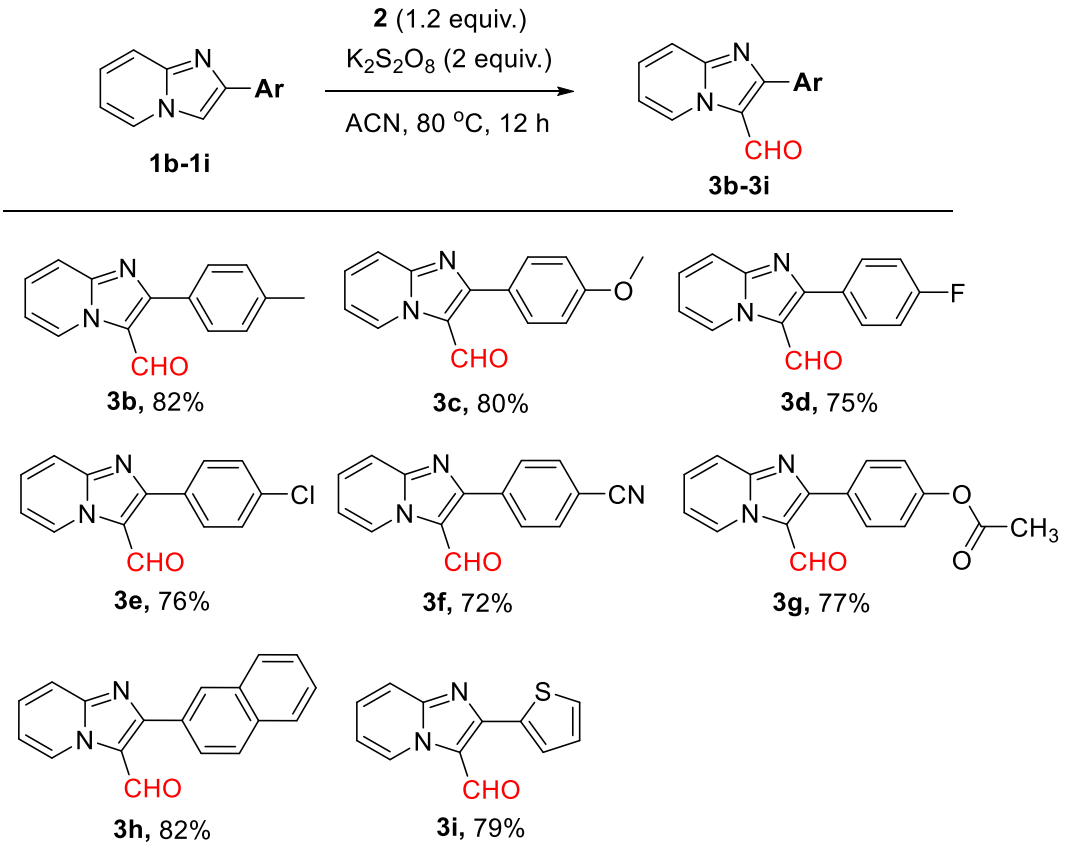
Entry	Oxidant	Solvent	Temp/Time	Yield (%)[b]
1.	$K_2S_2O_8$ (3 equiv.)	ACN	80 ^{o}C/12 h	75
2.	$K_2S_2O_8$ (2 equiv.)	ACN	80 ^{o}C/12 h	85
3	$K_2S_2O_8$ (1 equiv.)	ACN	80 ^{o}C/12 h	53
4.	$K_2S_2O_8$ (2 equiv.)	DCE	80 ^{o}C/12 h	75
5.	$K_2S_2O_8$ (2 equiv.)	DMSO	80 ^{o}C/12 h	13

6.	$K_2S_2O_8$ (2 equiv.)	DMF	80 °C/12 h	20
7.	$K_2S_2O_8$ (2 equiv.)	EtOH	80 °C/12 h	45
8.	$K_2S_2O_8$ (2 equiv.)	Toluene	80 °C/12 h	15
9.	$K_2S_2O_8$ (2 equiv.)	Water	80 °C/12 h	50
10.	$K_2S_2O_8$ (2 equiv.)	ACN	rt/12 h	N.R [c]
11.	$K_2S_2O_8$ (2 equiv.)	ACN	50 °C/12 h	48
12.	$(NH_4)_2S_2O_8$ (2 equiv.)	ACN	80 °C/12 h	68
13.	-	ACN	80 °C/12 h	N.R [c]

Reaction conditions: **1a** (1 mmol), **2** (1.2 equiv.), oxidant, solvent (3 mL), temp., 12 h, [b]isolated yield, [c]N.R. no reaction.

After optimization of the reaction conditions (entry 2, Table 4.1), the reaction scope has been investigated as shown in scheme 4.2. First, we explored the effects of various electron donating (**3b** and **3c**) and electron withdrawing (**3d** and **3e**) groups on the phenyl ring at the C-2 position of imidazo[1,2-a]pyridines. The corresponding formylated products was obtained between 75-82% yield. To our delight, the naphthyl (**3f**) and thiophene (**3g**) substituted imidazo[1,2-a]pyridines afforded the corresponding formylated products with good yields.

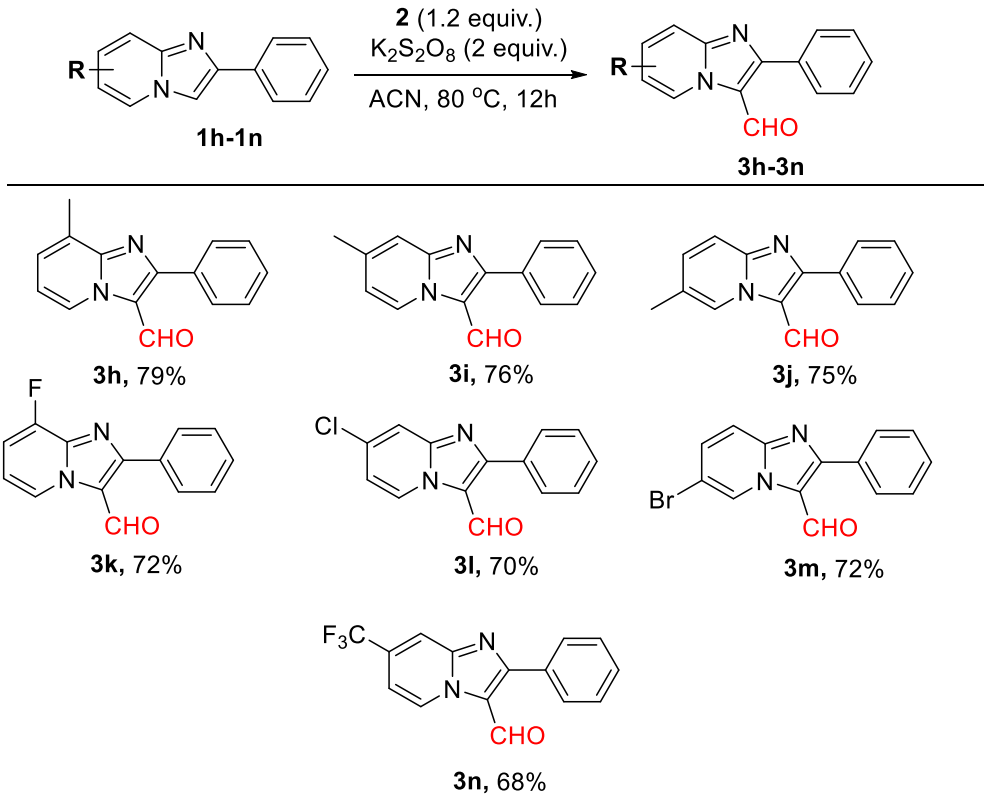
Scheme 4.2: Scope of substrates having various substitutions on the phenyl ring at the C-2 position of imidazopyridine.[a]



[a]Reaction was carried out using **1** (1 mmol), **2** (1.2 equiv.), $K_2S_2O_8$ (2 equiv.) in ACN at 80 °C for 12 h.

Further, the effect of substitution on the pyridine counterpart of the imidazo[1,2-a]pyridines was checked for substrate scope (scheme 4.3). Imidazo[1,2-a]pyridines bearing a methyl substituent on the pyridine ring at different positions efficiently reacted under optimized condition to afford the desired products with good yields (**3j-3l**). This clearly indicated that the position of substituents on the pyridine rings has no considerable effect on C-3 formylation reaction. Also, withdrawing groups like -F, -Cl, -Br, and -CF_3 produced good yields (**3m-3p**, 68-72%).

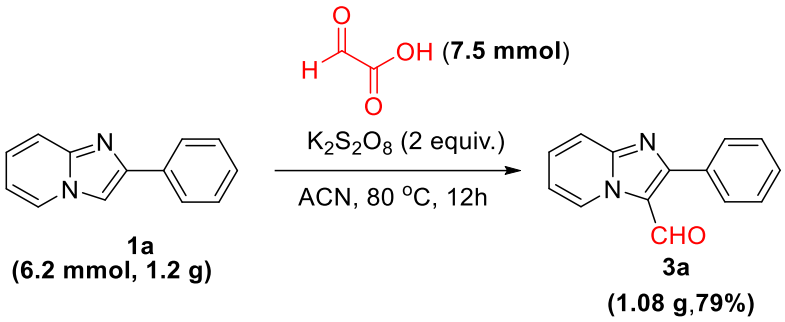
Scheme 4.3: Scope of substrates having various substitutions on the pyridine ring of imidazopyridines.



[a]Reaction was carried out using **1** (1 mmol), **2** (1.2 equiv.), $K_2S_2O_8$ (2 equiv.) in ACN at 80 °C for 12 h.

A gram-scale reaction (scheme 4.4) was carried out under the idealized reaction conditions for the synthesis of **3a** to check the adaptability of our established methodology. To our delight, we obtained 79% yield of **3a**.

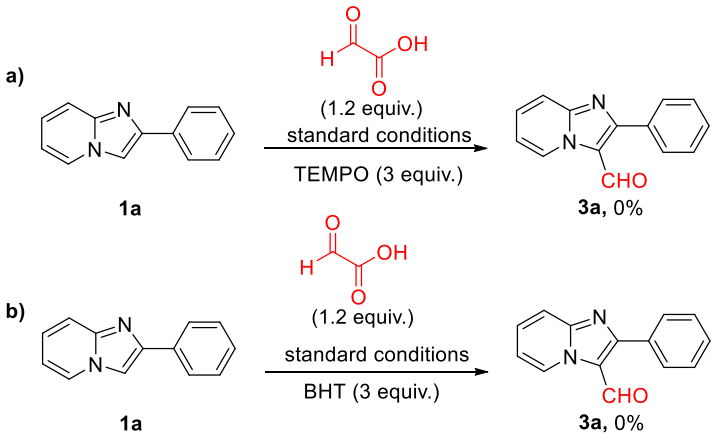
Scheme 4.4: Gram-scale synthesis of **3a**.[a]



[a]Reaction conditions: **1** (6.2 mmol), **2** (7.5 mmol), $K_2S_2O_8$ (2 equiv.) in ACN at 80 °C for 12 h.

A few control experiments were carried out to comprehend the mechanistic pathway for the formylation of imidazopyridines using glyoxylic acid. In the presence of the radical scavenger, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) [scheme 4.5(a)], the reaction did not proceed, implicating the progression of the reaction via a radical pathway. Additionally, when 2,6-di-tert-butyl-4-methylphenol (BHT) was included during the reaction, the formation of **3a** ceased [scheme 4.5(b)].

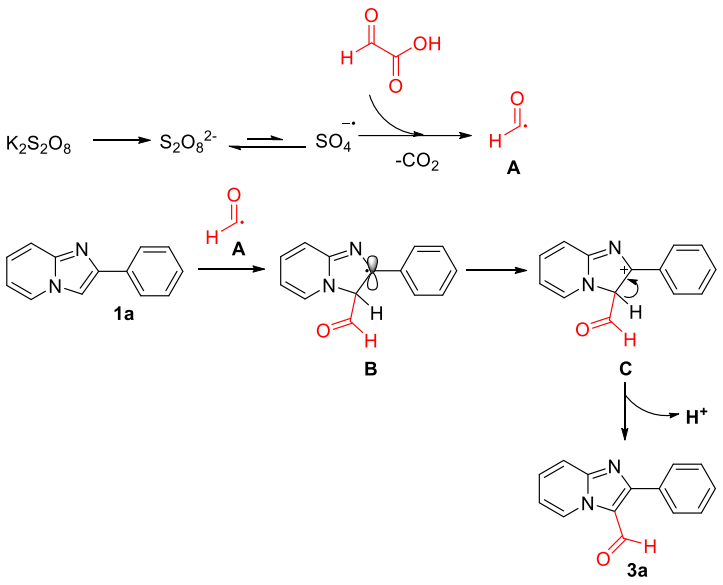
Scheme 4.5: Control experiments.



Reaction conditions: (a) **1a** (1 mmol), **2** (1.2 equiv.), $K_2S_2O_8$ (2 equiv.), TEMPO (3 equiv.), ACN, 80 °C, 12 h, (b) **1a** (1 mmol), **2** (1.2 equiv.), $K_2S_2O_8$ (2 equiv.), BHT (3 equiv.), ACN, 80 °C, 12 h.

Following the inferences of control experiments (scheme 4.5) and prior literature reports,[5,19-22] we tried to establish a plausible reaction mechanism of our developed methodology (scheme 4.6). The sulfate radical anion formed from $K_2S_2O_8$ abstracts a hydrogen radical from glyoxylic acid to form the formyl radical (**A**) with the elimination of CO_2. This generated formyl radical (**A**) interacts with the imidazopyridine **1a** to produce an intermediate alkyl radical **B**, which could be stabilized by the nearby nitrogen atom and phenyl group of the scaffold. $K_2S_2O_8$ then oxidizes the radical intermediate **B** to the carbocation **C** which then loses a proton to form the desired products (**3a**).

Scheme 4.6: Plausible reaction mechanism pathway.



4.3 Conclusion

In conclusion, we have developed the first example of regioselective C-3 formylation of imidazo[1,2-a]pyridines using glyoxylic acid as a key formylating agent. The method is easily scalable and is well tolerated by various substituted imidazopyridines, ensuring practical feasibility in late-stage modifications. Control experiments suggested that formylation reaction would likely proceed via a radical pathway.

4.4 Experimental section

4.4.1 General procedure for the synthesis of imidazopyridines (1a-1p): 2-aminopyridines (5.3 mmol), acetophenones (10 mmol), CuI (5 mol %,), $BF_3{\cdot}Et_2O$ (10 mol %), and H_2O (2 mL) were placed in a 25 mL double-necked, round-bottomed flask. The mixture was heated in an oil bath at 60–65 °C for 24 h under air atmosphere. After completion of the reaction, it was allowed to attain room temperature, then the mixture was extracted with dichloromethane (30 mL×3) and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel using 25% EtOAc:hexane to obtain **1a-1p** in the range of 80-90% yield.

4.4.2 General procedure for the synthesis of 3-formylated imidazopyridines 3a-3n: Imidazo[1,2-a]pyridines (1 mmol), glyoxylic acid (2, 1.2 equiv.), $K_2S_2O_8$ (2 equiv.), and acetonitrile (3 mL) were added to an oven-dried reaction vessel equipped with a magnetic stirrer bar, and the reaction vessel was carried out at 80 °C for 12 h. TLC monitored the progress of the reaction. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude residue, which was then purified by column chromatography on silica gel (60-120 mesh) using hexane/ethyl acetate as an eluent to afford the pure formylated products.

4.4.3 Gram-scale procedure for the synthesis of compound 3a: A round bottom flask was charged with imidazo[1,2-a]pyridines (1.2 g, 6.2 mmol), glyoxylic acid (0.68 g, 7.5 mmol), $K_2S_2O_8$ (3.34 g, 2 equiv.) in ACN (20 mL). The resulting solution was stirred at 80 °C for 12 h. The reaction mixture was diluted with water (20 mL), then extracted with ethyl acetate (40 mL × 3). After drying with anhydrous Na_2SO_4, the organic phase was evaporated to dryness

and purified by column chromatography using 20% ethyl acetate: hexane. Compound **3a** was obtained as a white solid (1.08 g, 79% yield).

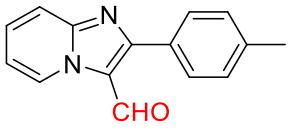
4.4.4 Control experiments

4.4.4.5 TEMPO addition in the general procedure: An oven-dried screw cap vial was charged with imidazo[1,2-a]pyridines (1 mmol), glyoxylic acid (1.2 equiv.), $K_2S_2O_8$ (2 equiv.), TEMPO (3 equiv.) in ACN (5 mL). The resulting solution was stirred at 80 °C for 12 h. We have not observed formation of product **3a**.

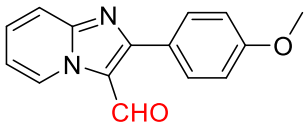
4.4.4.6 BHT addition in the general procedure: An oven-dried screw cap vial was charged with imidazo[1,2-a]pyridines (1 mmol), glyoxylic acid (1.2 equiv.), $K_2S_2O_8$ (2 equiv.), BHT (3 equiv.) in ACN (5 mL). The resulting solution was stirred at 80 °C for 12 h. We have not observed formation of product **3a**.

4.5 Analytical Data of synthesized compounds (3a-3p)

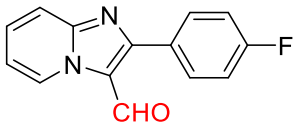
2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3a): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3a** was obtained as a white solid, yield 85%, m.p. 126-128 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 9.67 (d, *J* =7 Hz, 1H), 7.85-7.81 (m, 3H), 7.61-7.52 (m, 4H), 7.15-7.12 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 158.3, 147.7, 130.4, 129.8, 129.7, 128.9, 128.8, 120.7, 117.4, 115.3. FTIR (ATR): ν_{max} 3036, 2833, 1629, 1489, 1476, 1438, 1400, 1374, 1323, 1247, 1187, 1145, 1074, 928, 857 cm^{-1}. HRMS (ESI-TOF) m/z $[M + H]^+$ calculated for $C_{14}H_{11}N_2O$ 223.0871, found 223.0875.



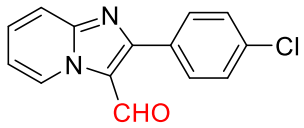
2-(*p*-tolyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3b): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3b** was obtained as a white solid, yield 82%, m.p. 167-169 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) 9.91 (s, 1H), 9.40 (d, *J* =6 Hz, 1H),7.72 (d, *J* = 6 Hz, 1H), 7.46-7.41 (m, 4H), 6.84 (d, *J* =6 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.1, 157.4, 147.1, 141.1, 131.4, 128.7, 128.7, 127.8, 126.9, 119.5, 116.6, 115.1, 20.7. FTIR (ATR): ν_{max} 2920, 1628, 1430, 1380, 1326, 1251, 1170 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_{13}N_2O$ 237.1028; found 237.1029.



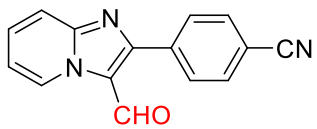
2-(4-methoxyphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3c): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3c** was obtained as a white solid**,** yield 80%, m.p. 147-149 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (s, 1H), 9.65 (d, *J* =6.6 Hz, 1H),7.80-7.79 (m, 3H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J*= 6.6 Hz, 1H) 7.06 (d, *J* =6.6 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 161.1, 158.05, 147.6, 131.2, 130.5, 128.8, 124.6, 120.4, 117.1, 115.1, 114.4, 55.4. FTIR (ATR): ν_{max} 2912, 1633, 1380, 1321, 1257, 1074 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_{13}N_2O_2$ 253.0977; found 253.0978.



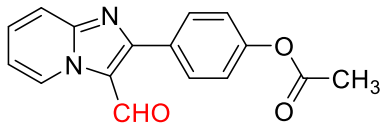
2-(4-fluorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3d): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3d** was obtained as a white solid**,** yield 75%, m.p. 143-145 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.58 (d, *J* = 6 Hz, 1H),7.76-7.72 (m, 3H), 7.53-7.51 (m, 1H), 7.17-7.14 (m, 2H), 7.08-7.06 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.1, 162.9 (d, J_{F-C}= 249 Hz), 156.21, 146.7, 130.63 (d, J_{F-C} = 9 Hz), 129.5, 127.8, 127.5 (d, J_{F-C}= 3 Hz), 119.6, 115.0 (d, J_{F-C}= 21 Hz), 114.4. FTIR (ATR): ν_{max} 3032, 2916, 2847, 2795, 1640, 1606, 1494, 1476, 1407, 1371, 1326, 1250, 1224, 1148 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_{10}FN_2O$ 241.0777; found 241.0779.



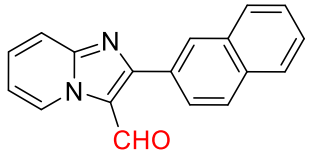
2-(4-chlorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3e): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3e** was obtained as a white solid, yield 76%, m.p. 186-188 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.64 (d, *J* = 6.6 Hz, 1H), 7.61-7.59 (m, 1H), 7.81-7.77 (m, 3H), 7.52-7.50 (m, 2H), 7.16-7.14 (m, 1H). 13C NMR (150 MHz, CDCl3) δ 179.1, 156.8, 147.7, 136.2, 130.9, 130.8, 130.6, 129.1, 128.8, 120.7, 117.4, 115.4. FTIR (ATR): ν_{max} 3056, 3011, 2862, 1630, 1489, 1410, 1371, 1326, 1244, 1084, 929 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_9ClN_2O$ 256.0403; found 256.0406.



4-(3-formylimidazo[1,2-a]pyridin-2-yl)benzonitrile (3f) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3f** was obtained as a white solid, yield 72 %. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.0 (s, 1H), 9.59 (d, *J* =5.5 Hz, 1H), 7.89 (d, *J* =6.5 Hz, 2H), 7.76-7.75 (m, 3H), 7.58-7.55 (m, 1H), 7.12 (t, *J* =5.5 Hz, 1H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.7, 154.5, 146.7, 135.8, 131.6, 129.9, 129.3, 127.8, 120.0, 117.3, 116.6, 114.9, 112.4. FTIR (ATR): ν_{max} 2940, 1634, 1435, 1380, 1257, 1140 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_9N_3O$ 248.0818; found 248.0824.

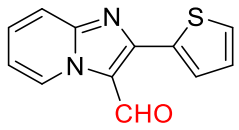


4-(3-formylimidazo[1,2-a]pyridin-2-yl)phenyl acetate (3g) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3g** was obtained as a white solid, yield 77 %, m.p. 141-143 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.66 (d, *J* =5.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.80 (d, *J* =7.5 Hz, 1H), 7.61-7.58 (m, 1H), 7.29-7.26 (m, 2H), 7.15-7.13 (m, 1H), 2.35 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.3, 169.2, 157.2, 152.0, 147.7, 130.9, 130.5, 130.0, 128.8, 122.2, 120.7, 117.4, 115.4, 21.1. FTIR (ATR): ν_{max} 2856, 1634, 1470, 1337, 1241, 1085 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{12}N_2O_3$ 281.0921; found 281.0926.

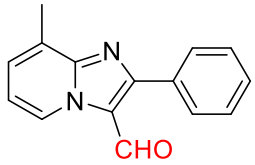


2-(naphthalen-2-yl)imidazo[1,2-a]pyridine-3-carbaldehyde (3h): The representative general procedure mentioned above was followed. The compound was purified by column

chromatography using 20% ethyl acetate:hexane Compound **3h** was obtained as a white solid, yield 82 %, m.p. 108-110 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.09 (s, 1H), 9.62-9.61 (m, 1H), 8.22 (s, 1H), 7.93-7.83 (m, 4H), 7.76 (d, *J* = 9 Hz), 7.53-7.48 (m, 3H), 7.08-7.06 (m, 1H), 3.89(s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.7, 158.2, 147.8, 133.8, 113.1, 130.5, 129.9, 129.7, 128.9, 128.7, 128.6, 127.8, 127.2, 126.8, 126.7, 120.9, 117.4, 115.3. FTIR (ATR): ν_{max} 3056, 1634, 1487, 1408, 1338, 1328, 1241, 1172, 1121, 1058, 928, 894 cm^{-1}. HRMS (EI-TOF) m/z $[M+H]^+$ calculated for $C_{18}H_{12}N_2O$ 272.0950; found 272.0948.

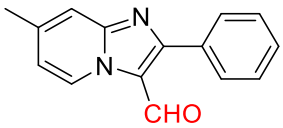


2-(Thiophen-2-yl)imidazo[1,2-a]pyridine-3-carbaldehyde (3i): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3i** was obtained as a white solid, yield 79%, m.p. 121-123 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.18 (s, 1H), 9.48 (d, *J* = 6 Hz, 1H), 7.63 (d, *J* = 9 Hz, 1H) 7.52 (s, 1H), 7.43-7.42 (m, 2H), 7.08-7.07 (m, 1H), 6.98-6.96 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.3, 150.2, 146.7, 133.8, 129.6, 128.0, 127.8, 127.7, 127.2, 118.9, 116.0, 114.2. FTIR (ATR): ν_{max} 3060, 2921, 2845, 1628, 1487, 1487, 1403, 1369, 1330, 1244, 1116, 1084, 928 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$calculated for $C_{12}H_8N_2OS$ 229.0430; found 229.0431.

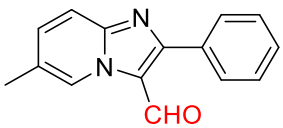


8-methyl-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3j): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3j** was obtained as a white solid,

yield 79%, m.p. 119-121 °C ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.42 (d, *J* = 6 Hz, 1H),7.74 (d, *J* = 6.6 Hz, 2H), 7.45-7.42 (m, 3H), 7.28 (d, *J* = 6.6 Hz, 1H), 6.94 (t, *J* = 6.6 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.5, 156.8, 146.8, 131.5, 128.8, 128.6, 128.3, 127.7, 126.5, 125.4, 120.09, 114.2, 15.9. FTIR (ATR): ν_{max} 2924, 1628, 1489, 1436, 1380, 1321, 1257, 1174 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_{13}N_2O$ 237.1028; found 237.1027.

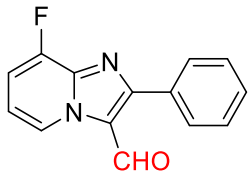


7-methyl-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3k): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3k** was obtained as a white solid, yield 76 %, m.p. 156-158 °C. ^{1}H NMR (600 MHz, $CDCl_3$). δ 9.93 (s, 1H), 9.43 (d, *J* = 6.6 Hz, 1H), 7.74 (d, *J* = 6.0 Hz, 2H), 7.48-7.42 (m, 4H), 6.88-6.87 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.1, 157.5, 147.1, 141.2, 131.4, 128.7, 127.9, 127.8 126.9, 119.5, 116.7, 115.1, 20.7. FTIR (ATR): ν_{max} 2914, 2845, 1628, 1489, 1401, 1367, 1243, 905 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_{13}N_2O$ 237.1028; found 237.1027.

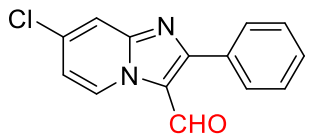


6-methyl-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3l): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3l** was obtained as a white solid, yield 75 %, m.p. 120-122 °C**.** ^{1}H NMR (600 MHz, $CDCl_3$). δ 9.93 (s, 1H), 9.43 (d, *J* = 6.6 Hz, 1H),7.74 (d, *J* = 6 Hz, 2H), 7.48-7.42 (m, 4H), 7.28 (d, *J* = 6.6 Hz, 1H), 6.88-6.87 (m, 1H),

2.43 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4, 157.1, 145.6, 132.7, 132.2, 131.4, 128.7, 128.6, 127.8, 125.7, 124.4, 119.5, 17.3. FTIR (ATR): ν_{max} 2832, 1619, 1428, 1446, 1403, 1367, 1325, 1241, 1224, 1064, 1025, 956, 864 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_{13}N_2O$ 237.1028; found 237.1027.

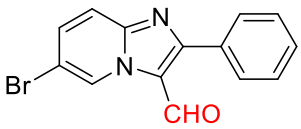


8-fluoro-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3m) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3m** was obtained as a white solid, yield 72 %, m.p. 167-169 ^oC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.28 (d, J = 6.6 Hz, 1H), 7.71-7.70 (m, 2H), 7.37 (s, 2H), 7.16-7.13 (m, 1H), 6.91-6.90 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.8, 156.7, 149.8 (d, J_{F-C} = 253.5 Hz), 138.9 (d, J_{F-C} = 25.5 Hz), 130.7, 128.9, 128.8, 127.8, 123.8 (d, J_{F-C} = 6 Hz), 120.6, 113.5 (d, J_{F-C} = 6 Hz), 112.3 (d, J_{F-C} = 15 Hz). FTIR (ATR): ν_{max} 3022, 1630, 1558, 1492, 1407, 1373, 1323, 1259, 1249, 1172, 1133, 1052 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_{10}FN_2O$ 257.0482; found 257.0481.

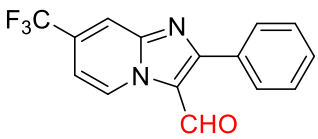


7-chloro-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3n) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3n** was obtained as a white solid, yield 70 %, m.p. 151-153 ^oC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.46 (d, J =6.6 Hz, 1H), 7.71-7.67 (m, 3H), 7.42 (s, 3H), 6.99-6.98 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ

178.5, 157.7, 146.7, 135.9, 130.8, 129.0, 128.8, 128.7, 127.9, 119.6, 115.6, 115.5. FTIR (ATR): ν_{max} 3054, 3017, 1638, 1474, 1408, 1369, 1332, 1239, 1172, 1123, 1058, 894 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_9ClN_2O$ 256.0403; found 256.0406.



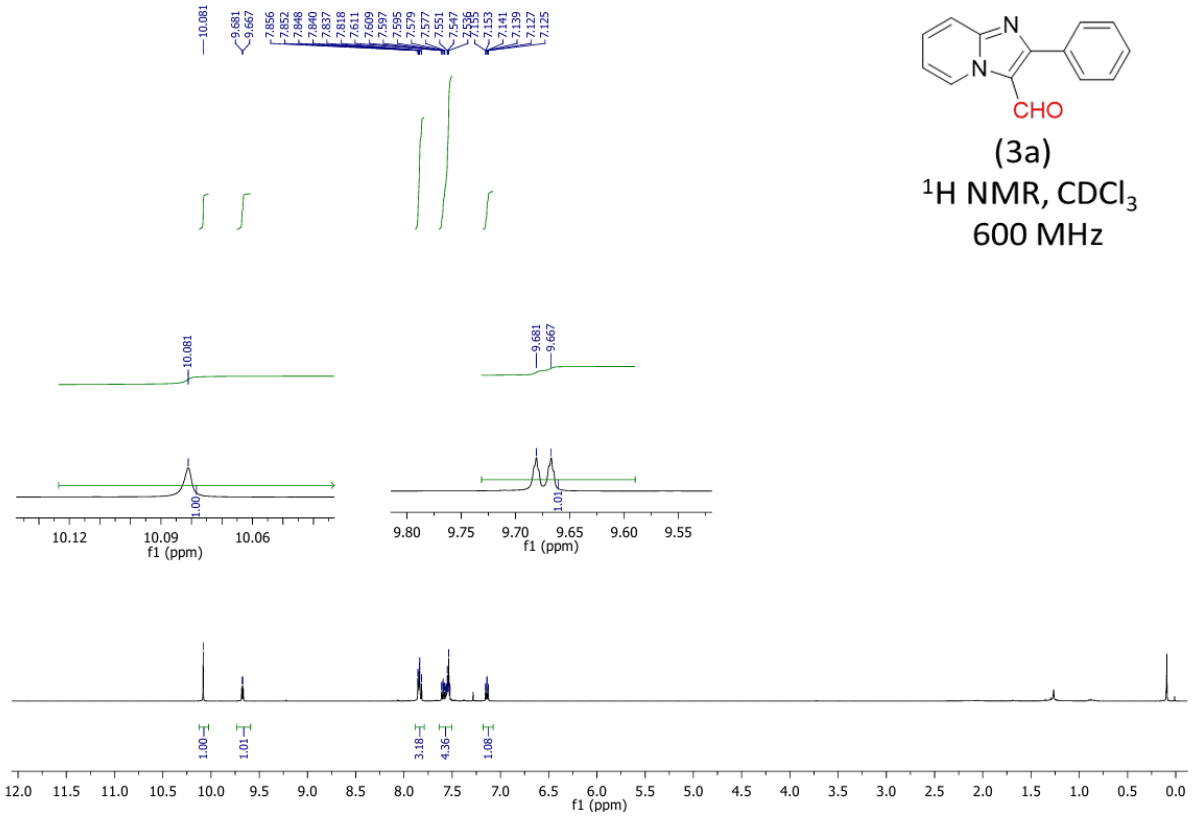
6-bromo-2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (3o): The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3o** was obtained as a yellow solid, yield 72%, m.p. 162-164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.84 (d, *J* =1.2 Hz, 1H), 7.82-7.81 (m, 2H), 7.70-7.68 (m, 1H), 7.65-7.63 (m, 1H), 7.55-7.52 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.7, 162.7, 158.0, 146.0, 133.8, 131.7, 130.1, 129.7, 129.0, 128.8, 117.9, 110.1. FTIR (ATR): ν_{max} 3048, 3011, 1634, 1477, 1405, 1332, 1241, 1099, 1052, 929, 818 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_9BrN_2O$ 299.9898; found 299.9895.

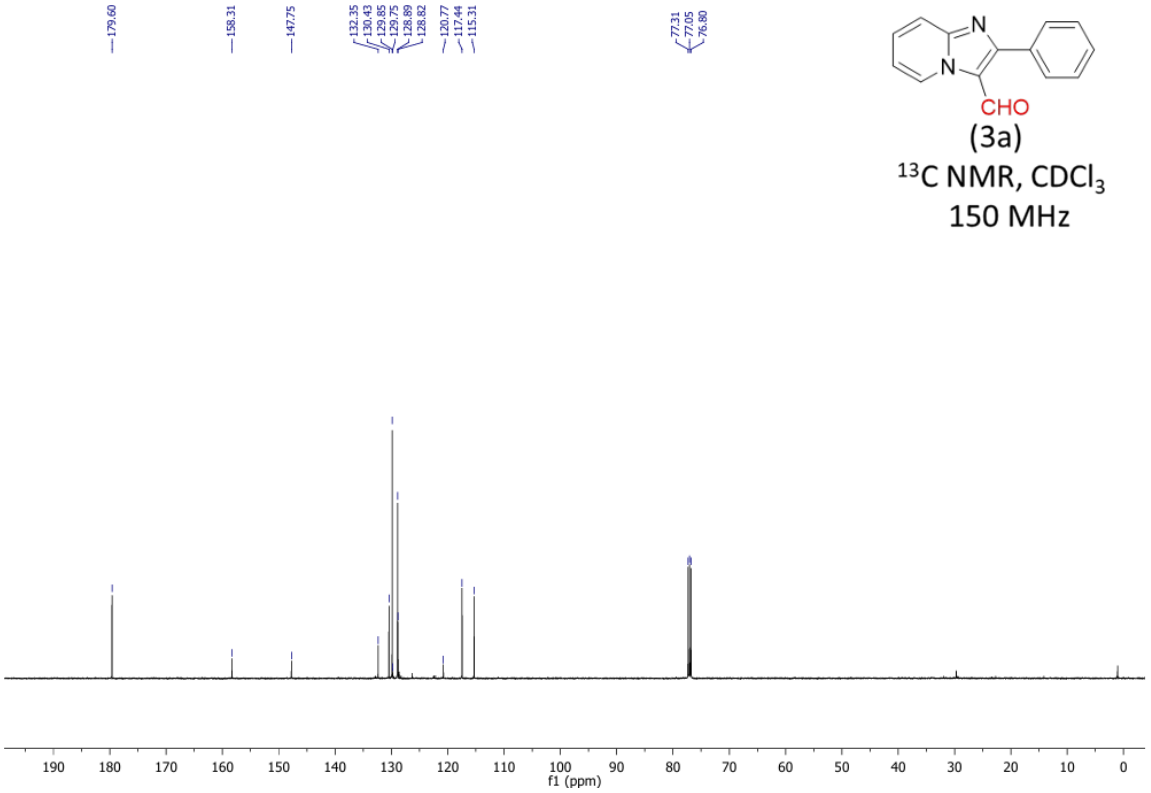


2-phenyl-7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carbaldehyde (3p) : The representative general procedure mentioned above was followed. The compound was purified by column chromatography using 20% ethyl acetate:hexane Compound **3p** was obtained as a white solid, yield 68 %, m.p. 147-149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.0 (s, 1H), 9.65 (d, *J* =5.4 Hz, 1H), 7.98 (s, 1H), 7.74-7.73 (m, 2H), 7.44 (s, 3H), 7.19-7.18 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.1, 157.8, 145.0, 130.7 (q, *J* = 34.5 Hz), 130.6, 129.2, 128.7, 128.4, 128.0, 121.6 (q, *J* = 270 Hz), 120.15, 114.1 (q, *J* = 4.5 Hz), 110.0, 109.9. FTIR (ATR): ν_{max}

3058, 2857, 1634, 1492, 1408, 1326, 1243, 1174, 1120 cm^{-1}. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{15}H_9F_3N_2O$ 290.0667; found 290.0671.

4.6 Spectral Data of Synthesized Products

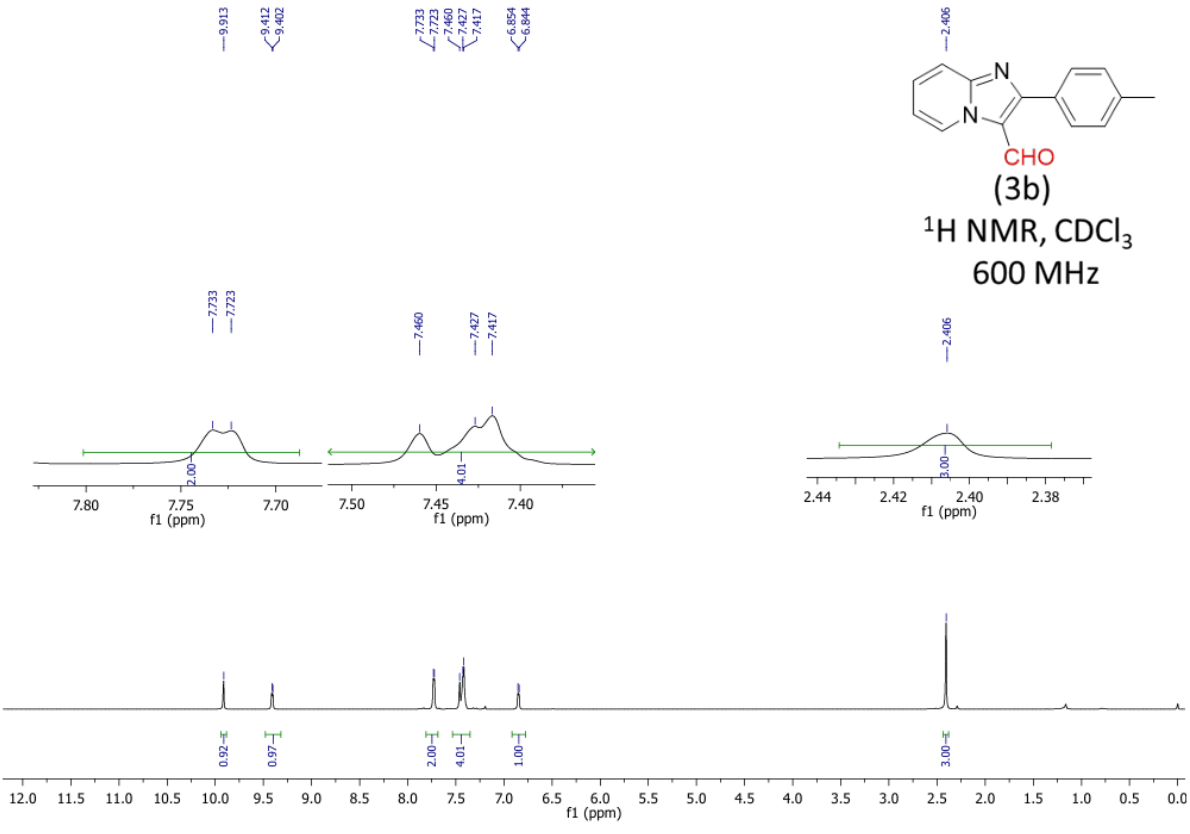




(3a)

^{13}C NMR, $CDCl_3$

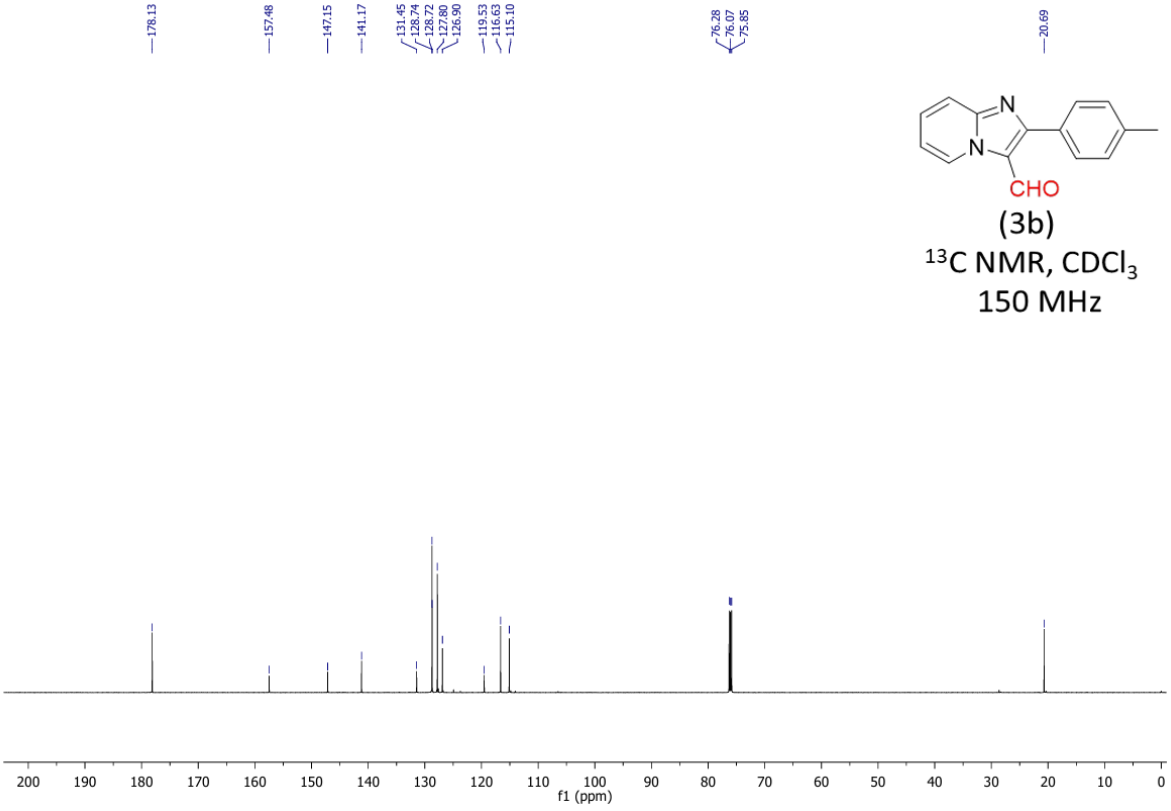
150 MHz



(3b)

^{1}H NMR, $CDCl_3$

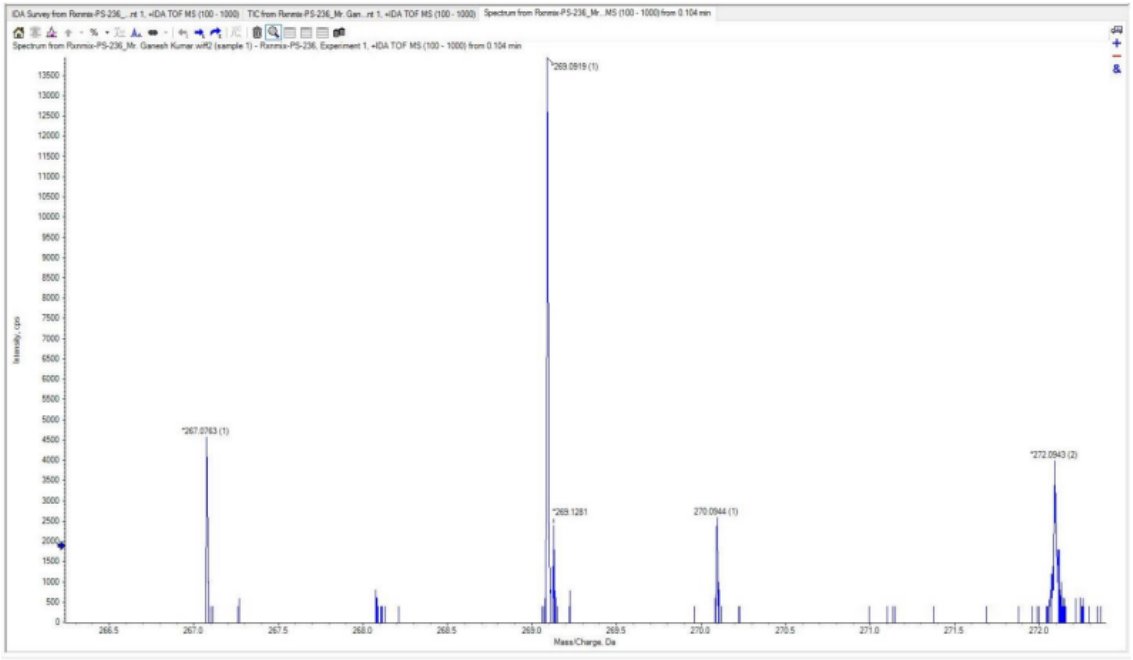
600 MHz



(3b)

^{13}C NMR, $CDCl_3$

150 MHz



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