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Iodine-catalyzed three component reaction; A novel synthesis of 2-aryl-imidazo[1,2-*a*]pyridine scaffolds

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A facile and efficient protocol for the synthesis of novel imidazo[1,2-*a*]pyridines has been developed by one-pot reaction of aromatic aldehydes with 2-amino-5-chloropyridine and *tert*-butylisocyanide in the presence of I_2 in toluene at 70 °C. The present approach offers the advantages of simple methodology, clean, high atom-economy, mild condition, short reaction time, wide substrate scope, low environmental impact and high yield.

Key Words

Iodine, Imidazopyridines, Imidazo[1,2-a]pyridine, 2-aminopyridine, *tert*-butylisocyanide.

Introduction

Multi-component synthesis have received considerable attention of organic chemists and emerged as a powerful tool for the construction of novel and complex molecular structures due to their advantages over conventional multistep synthesis. The major advantages of MCR's include low cost, shorter reaction times, high atom economy, energy saving and avoidance of time consuming and expensive protection, deprotection, isolation and purification process[1].

The synthesis of fused bicyclic imidazo[1,2-*a*]pyridines is an important synthetic reaction as these scaffolds are found to form a very important core in numerous synthetic, pharmaceuticals and a wide variety of biologically active compounds[2]. A large number of compounds bearing imidazo[1,2-*a*]pyridines scaffolds have entered preclinical and clinical trials

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over the last few years. Many commercially available drugs **(Figure 1)** including, alpidem (anxiolytic), minodronic acid (to treat anxiety, heart failure and osteoporosis), olprinone (cardiotonic agent), optically active GSK 812397 candidate (HIV infection), saripidem (sedative and anxiolytic), zolimidine (an antiulcer drug) and zolpidem (a hypnotic drug) are derived from imidazo[1,2-*a*]pyridine core entities. Imidazo[1,2-*a*]pyridine structure moieties are also important as antimicrobial[3], antiviral[4], anticancer[5], antinflammatory[6], antioxidant[7] and Alzheimer diseases[8]. Hence, the synthesis of fused bicyclic imidazo[1,2-*a*]pyridines has evoked much attention as a result of which a variety of synthetic methodologies have been reported. The most important approaches are: (i) condensation of 2-aminopyridine with α-halocarbonyl compounds[9], (ii) one pot condensations of aldehydes, isonitriles and 2-aminopyridines[10], (iii) copper-catalyzed three-component reactions of 2-aminopyridines, aldehydes and alkynes[11]. Other methods have also been developed within the last three decades[12]. In recent time, very few methods have been describing the one pot multicomponent synthesis of fused bicyclic imidazo[1,2-*a*]pyridines based on catalysts such as $Sc(OTf)_3$[13], TMSCl[14], Montmorillonite clay[15], $InCl_3$[16], BDMS[17], $ZrCl_2$[18], glyoxalic acid[19], ionic liquid[20] and $H_3PMo_{12}O_{40}$[21] from the reaction of isocyanide, aromatic aldehydes and 2-aminopyridine. However, these methods have limitations in terms of the use of expensive and excess amount of catalysts, product diversity and yields. Hence, the development of a simple and high yielding environmentally benign protocol for the one pot multicomponent synthesis of fused bicyclic imidazo[1,2-*a*]pyridine scaffolds is still needed.

In recent years, Iodine has proved to be a very useful catalyst in carrying out synthesis of variety of heterocycles such as coumarins[22], quinolines[23], benzoxazoles[24], benzimidazoles[25] and lactones[26]. Iodine has received increasing attention as an inexpensive, non-toxic and readily available catalyst for organic synthesis. Iodine has high tolerance to moisture as well as air making it ideal catalyst. It can be easily removed from the reaction mixture by washing with reducing agents[27]. The use of iodine as a catalyst is not only the cost effective and

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environmentally benign, but also experimentally simple, easy to handle, clean, efficient and safe[28].

Result and discussion

First the optimization of the reaction was studied for which the reaction of 2-chloro-pyridine-3-carbaldehyde, 5-chloro-pyridin-2-ylamine and *tert*-butylisocyanide was selected as a model **(Scheme 1)**. It was hypothesized that a critical choice of iodine might efficiently catalyse the one step fusion of imidazo[1,2-*a*]pyridines by forming a better activated intermediate. A preliminary examination showed that I_2 in ethanol among several solvents effectively catalyzed the model reaction. Upon varying the temperature of the reaction from 30 to 70 $^{\circ}$C, the best yield of **2a** (table 1, entry 1) was obtained at 70 $^{\circ}$C. Further increase in the temperature (70 $^{\circ}$C), neither increased the yield nor shortened the reaction time. The time taken for complete conversion (monitored by TLC) and the isolated yields are recorded **(Table 1)**. Of the reactions using different quantities of reactant, the best results were obtained using 1.0: 1.0: 1.2 ratios of 2-chloro-pyridine-3-carbaldehyde, 5-chloro-pyridin-2-ylamine and *tert*-butylisocyanide respectively. When a mixture of 2-chloro-pyridine-3-carbaldehyde, 5-chloro-pyridin-2-ylamine and *tert*-butylisocyanide in ethanol was refluxed in the presence of iodine (10 mol%) at 70 $^{\circ}$C for 30 min, the fused heterocyclic products, *N*-tert-butyl-6-chloro-2-(2-chloropyridin-3-yl)*H*-imidazo[1,2-*a*]pyridin-3-amine **(2a)** was obtained in excellent yield (96%). At the same time, decreasing the amount of catalyst from 10 mol% to 5 mol% lowered the imidazo[1,2-*a*]pyridine yield (65%) while increasing the amount of catalyst from 10 mol% to 20 mol% did not shown any significant impact on the imidazo[1,2-*a*]pyridine yield indicating that the above reaction condition was suitable for the one pot assembly.

The role of solvents on the synthesis of imidazo[1,2-*a*]pyridine was then studied and the results are depicted **(Table 2)**. Replacing the ethanol by chloroform produced the model in an

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appreciable yield (entry 7) albeit lesser than that of the one produced by the former (entry 5). Other solvents such as acetonitrile, THF, dioxane and DMSO accomplished the model in moderate yields (80-86 %, entries 1, 3, 8 and 9), while DCM, DMF and toluene produced still lower yields (63-79 %, entries 2, 4 and 6) respectively.

Optimized condition was established in ethanol as a solvent system using a reaction temperature of 70 $^{\circ}$C and a time of 30 min. This remarkable activation in reaction rate prompted us to explore the potential of this protocol for the synthesis of a variety of imidazo[1,2-*a*]pyridines and the results are summarized **(Table 1)**. All the aforementioned reactions proceeded expeditiously and delivered better to excellent product yields accommodating a wide range of hetero aromatic aldehydes. The overall yield ranged from 96 % of *N*-tert-butyl-6-chloro-2-(2-chloropyridin-3-yl)*H*-imidazo[1,2-*a*]pyridin-3-amine **(2a)** (entry 1) to 81% of *N*-tert-butyl-6-chloro-2-(*1H*-imidazol-4-yl)*H*-imidazo[1,2-*a*]pyridin-3-amine **(2g)** (entry 7).

A probable mechanistic pathway for the formation of imidazo[1,2-*a*]pyridine is outlined, **(Figure 2)**, which is in analogy to the established mechanism as reported in the literature[29]. Iodine can serve as a catalyst for the reaction of 2-aminopyridine and aromatic aldehyde to give the corresponding imine. The subsequent attack of *tert*-butylisocyanide on the activated imine, followed by intramolecular Groebke-Blackburn-Bienayme type reaction under the reaction conditions, would eventually afford the final imidazo[1,2-*a*]pyridine. Iodine is likely to enhance the rate of this multicomponent reaction.

Conclusion

In conclusion, a straightforward and efficient protocol for the one pot synthesis of imidazo[1,2-*a*]pyridine scaffold has been developed in the presence of iodine as a catalyst via three component reaction of aromatic aldehydes, 2-aminopyridine and *tert*-butylisocyanide with excellent yields. Mild reaction conditions, absence of tedious separation procedures, operational

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simplicity, clean reaction profiles, high atom economy and environmentally benign catalyst are the key advantages of the present MCR's protocol.

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General information

The melting points were determined by open capillary method using electric melting point apparatus and are uncorrected. The IR spectra (KBr disc) were recorded on a Shimadzu-8400S FT-IR Spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 300 MHz spectrometer and ^{13}C NMR was recorded on Bruker 400 MHz spectrometer by using $CDCl_3$ as a solvent and TMS as an internal standard. The chemical shifts are expressed in δ ppm. The mass spectra were recorded on an Agilent-Single Quartz LC-MS. The purity of the compounds was checked by TLC. The elemental analyses were carried out using Elemental Vario Micro Cube CHNS Rapid Analyzer. All the compounds gave satisfactory elemental analysis.

Typical procedure for the synthesis of *N*-tert-butyl-(6-chloro-imidazo[1,2-*a*]pyridin-3-yl)-amine (2a).

To a stirring solution of 2-amino-5-chloropyridine (200 mg, 1.56 mmol), 2-chloro-pyridine-3-carbaldehyde (200 mg, 1.56 mmol) and *tert*-butylisocyanide (144 mg, 1.87 mmol) in ethanol (15 mL) was added iodine (20 mg, 10 mol %). The reaction flask was heated at 70 $^{\circ}$C in an oil bath for 30 min. After completion of the reaction, ethanol was removed under reduced pressure. The residue left out was dissolved with ethyl acetate and added aqueous $Na_2S_2O_3$ solution. The organic layer was separated and aqueous layer was extracted with ethyl acetate (15 ml X 3). The combined organic phase were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product which was purified on silica gel using hexane and ethyl acetate (7:3).

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_N_-tert-butyl-6-chloro-2-(2-chloropyridin-3-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2a)

Light yellow solid; mp 145-147 °C; IR (KBr, cm^{-1}): 3190 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9H of tert-butyl), 4.31 (s, 1H, N-H), 7.28 (dd, 1H, *J* = 9.6, 2.1 Hz, Ar-H), 7.51 (t, 1H, *J* = 4.8 Hz, Ar-H), 7.58 (d, 1H, *J* = 9.6 Hz, Ar-H), 8.07 (dd, 1H, *J* = 7.8, 2.1 Hz, Ar-H), 8.57 (d, 1H, *J* = 1.2 Hz, Ar-H), 8.69 (s, 1H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 30.0, 56.9, 104.5, 110.8, 117.3, 120.7, 121.3, 121.8, 123.2, 124.5, 126.0, 127.0, 128.6, 154.5 ppm; LC-MS: [M+H] 335; Anal. Calcd for $C_{16}H_{16}Cl_2N_4$: C, 57.33: H, 4.81: N, 16.71. Found: C, 57.21: H, 4.67: N, 16.57.

_N_-tert-butyl-6-chloro-2-(thiophen-3-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2b)

Light yellow solid; mp 197-199 °C; IR (KBr, cm^{-1}): 3214 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9H of tert-butyl), 3.20 (s, 1H, N-H), 7.16 (dd, 1H, *J* = 9.6, 2.0 Hz, Ar-H), 7.39 (dd, 1H, *J* = 7.5, 4.76 Hz, Ar-H), 7.5 (d, 1H, *J* = 9.24 Hz, Ar-H), 8.08 (dd, 1H, *J* = 7.7, 2.0 Hz, Ar-H), 8.36 (m, 1H, Ar-H), 8.44 (m, 1H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 29.9, 55.9, 117.8, 120.5, 121.7, 122.7, 125.7, 126.4, 131.1, 136.6, 140.7, 148.8, 149.2 ppm; Anal. Calcd for $C_{15}H_{16}ClN_3S$: C, 58.91: H, 5.27: N, 13.74: S, 10.48. Found: C, 58.72: H, 5.12: N, 13.53: S, 10.18.

_N_-tert-butyl-6-chloro-2-(5-methylthiophen-2-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2c)

Pale yellow solid; mp 196-197 °C; IR (KBr, cm^{-1}): 3203 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9H of tert-butyl), 2.52 (s, 3H, CH_3), 3.09 (s, 1H, N-H), 6.74 (m, 1H, Ar-H), 7.06 (dd, 1H, *J* = 7.4, 2.0 Hz, Ar-H), 7.36 (d, 1H, *J* = 4.0 Hz, Ar-H), 7.44 (d, 1H, *J* = 8 Hz, Ar-H), 8.20 (d, 1H, *J* = 1.6 Hz, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 15.3, 30.5, 56.8, 117.3, 119.9, 121.4, 122.8, 125.3, 125.6, 126.5, 132.3, 140.0, 140.1 ppm; Anal. Calcd for $C_{16}H_{18}ClN_3S$: C, 60.08: H, 5.67: N, 13.14: S, 10.02. Found: C, 59.91: H, 5.54: N, 13.01: S, 9.97.

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_N_-tert-butyl-2-(5-bromothiophen-2-yl)-6-chloro_H_-imidazo[1,2-_a_]pyridin-3-amine (2d)

Pale yellow solid; mp 223-225 °C; IR (KBr, cm^{-1}): 3231 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9H of tert-butyl), 2.96 (s, 1H, N-H, D_2O exchangeable), 7.03 (d, 1H, *J* = 3.88 Hz, Ar-H), 7.03 (dd, 1H, *J* = 1.96, 2.0 Hz, Ar-H), 7.33 (d, 1H, *J* = 3.92 Hz, Ar-H), 7.43 (d, 1H, *J* = 8 Hz, Ar-H), 8.18 (m, 1H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 30.0, 56.7, 109.8, 113.3, 117.5, 120.0, 120.7, 121.6, 124.7, 126.0, 130.8, 140.6, 151.8 ppm; Anal. Calcd for $C_{15}H_{15}BrClN_3S$: C, 46.83: H, 3.93: N, 10.92: S, 8.33. Found: C, 46.74: H, 3.80: N, 10.80: S, 8.21.

_N_-tert-butyl-2-(5-bromofuran-2-yl)-6-chloro_H_-imidazo[1,2-_a_]pyridin-3-amine (2e)

Pale yellow solid; mp 187-189 °C; IR (KBr, cm^{-1}): 3239 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9H of tert-butyl), 3.45 (s, 1H, N-H), 6.43 (d, 1H, *J* = 4.0 Hz, Ar-H), 6.84 (d, 1H, *J* = 3.4 Hz, Ar-H), 7.08 (dd, 1H, *J* = 9.3, 1.9 Hz, Ar-H), 7.40 (d, 1H, *J* = 9.9 Hz, Ar-H), 8.25 (m, 1H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 30.0, 56.7, 109.8, 113.3, 117.5, 120.0, 120.7, 121.6, 124.7, 126.0, 130.8, 140.6, 151.8 ppm; Anal. Calcd for $C_{15}H_{15}BrClN_3O$: C, 48.87: H, 4.10: N, 11.40. Found: 48.74: H, 4.01: N, 11.29.

_N_-tert-butyl-2-(benzofuran-2-yl)-6-chloro_H_-imidazo[1,2-_a_]pyridin-3-amine (2f)

Pale yellow solid; mp 217-220 °C; IR (KBr, cm^{-1}): 3234 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 9H of tert-butyl), 4.74 (s, 1H, N-H), 7.23-8.53 (m, 8H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 29.55, 57.31, 105.08, 114.07, 114.11, 117.26, 117.92, 121.14, 131.17, 140.89, 140.93, 145.86, 149.71, 150.56, 152.50 ppm; Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16: H, 5.34: N, 12.37. Found: C, 66.93: H, 5.06: N, 12.30.

_N_-tert-butyl-6-chloro-2-(1H-imidazol-4-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2g)

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Yellow solid; mp 218-220 °C; IR (KBr, cm^{-1}): 3182 cm^{-1} (N-H of tert-butyl), 3216 cm^{-1} (N-H of imidazole); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9H of tert-butyl), 4.15 (s, 1H, N-H of tert-butyl), 7.05 (dd, 1H, *J* = 9.5, 1.9 Hz, Ar-H), 7.37 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.59 (s, 1H, Ar-H), 7.68 (s, 1H, Ar-H), 8.27 (d, 1H, *J* = 1.60, Ar-H), 11.68 (s, 1H, N-H of imidazole) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): 30.2, 57.0, 116.8, 119.7, 121.6, 125.2, 128.2, 133.1, 134.8, 140.3 ppm; Anal. Calcd for $C_{14}H_{16}ClN_5$: C, 58.03: H, 5.57: N, 24.17. Found: C, 57.87: H, 5.42: N, 24.03.

_N_-tert-butyl-6-chloro-2-(4-chloro-2-ethyl-1H-imidazol-5-yl)_H_-imidazo[1,2-a]pyridin-3-amine (2h)

Yellow solid; mp 203-205 °C; IR (KBr, cm^{-1}): 3062 cm^{-1} (N-H of tert-butyl), 3235 cm^{-1} (N-H of imidazole); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9H of tert-butyl), 1.2 (t, 3H, *J* = 7.5 Hz, CH_3 of C_2H_5), 2.58 (q, 2H, *J* = 7.5 Hz, CH_2 of C_2H_5), 5.3 (s, 1H, N-H of tert-butyl), 7.11 (d, 1H, *J* = 9.3 Hz, Ar-H), 7.44 (d, 1H, *J* = 9.3 Hz, Ar-H), 8.36 (s, 1H, Ar-H), 11.63 (s, 1H, N-H of imidazole) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.02, 26.86, 30.22, 57.06, 115.76, 119.61, 121.33, 125.25, 128.23, 133.16, 134.86, 141.31, 144.31 ppm; Anal. Calcd for $C_{16}H_{19}Cl_2N_5$: C, 54.55: H, 5.44: N, 19.88. Found: C, 54.41: H, 5.35: N, 19.72.

_N_-tert-butyl-6-chloro-2-(2-phenyl-1H-imidazol-5-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2i)

Yellow solid; mp 232-235 °C; IR (KBr, cm^{-1}): 3242 cm^{-1} (N-H of tert-butyl), 3301 cm^{-1} (N-H of imidazole); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 9H of tert-butyl), 4.3 (s, 1H, N-H of tert-butyl), 7.16-8.49 (m, 9H, Ar-H), 12.74 (s, 1H, N-H of imidazole) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ =29.84, 57.14, 115.54, 117.14, 121.11, 124.61, 126.64, 127.24, 128.11, 128.82, 135.24, 136.44, 138.82, 157.80 ppm; Anal. Calcd for $C_{20}H_{20}ClN_5$: C, 65.66: H, 5.51: N, 19.14. Found: C, 65.53: H, 5.40: N, 19.02.

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_N_-tert-butyl-6-chloro-2-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2j)

Yellow solid; mp 209-211 °C; IR (KBr, cm^{-1}): 3182 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 9H of tert-butyl), 2.29 (s, 1H, CH_3 of pyrozole), 2.92 (s, 1H, N-H), 3.78 (s, 1H, N-CH_3), 7.04 (dd, 1H, J = 9.4, 1.88 Hz, Ar-H), 7.42 (d, 1H, J = 9.2 Hz, Ar-H), 8.26 (d, 1H, J = 1.4, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 12.2, 28.8, 35.2, 54.8, 110.5, 116.5, 119.0, 120.3, 124.4, 124.4, 124.6, 131.1, 139.5, 146.9 ppm; Anal. Calcd for $C_{16}H_{19}Cl_2N_5$: C, 54.55: H, 5.44: N, 19.88. Found: C, 54.49: H, 5.28: N, 19.75.

_N_-tert-butyl-6-chloro-2-(quinolin-4-yl)_H_-imidazo[1,2-a]pyridin-3-amine (2k)

Yellow solid; mp 191-193 °C; IR (KBr, cm^{-1}): 3260 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 9H of tert-butyl), 3.74 (s, 1H, N-H), 7.16-8.33 (m, 9H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 30.09, 56.85, 103.78, 110.87, 117.75, 121.17, 121.74, 123.16, 124.30, 126.13, 128.74, 138.10, 140.30, 140.15, 143.74, 150.07, 152.00, 153.13; Anal. Calcd for $C_{20}H_{19}ClN_4$: C, 68.47: H, 5.46: N, 15.97. Found: C, 68.24: H, 5.28: N, 15.78.

_N_-tert-butyl-6-chloro-2-(1H-indol-3-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2l)

Colorless solid; mp 206-208 °C; IR (KBr, cm^{-1}): 3153 cm^{-1} (N-H of tert-butyl), 3406 cm^{-1} (N-H of indole); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 9H of tert-butyl), 3.46 (s, 1H, N-H of tert-butyl), 7.1-8.33 (m, 8H, Ar-H), 9.40 (s, 1H, N-H of indole) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 30.1, 56.5, 111.6, 115.9, 120.3, 120.4, 120.8, 121.4, 122.3, 123.8, 124.9, 125.3, 125.8, 126.5, 128.2, 129.0, 136.0 ppm; Anal. Calcd for $C_{19}H_{19}ClN_4$: C, 67.35: H, 5.65: N, 16.53. Found: C, 67.03: H, 5.52: N, 16.40.

_N_-tert-butyl-6-chloro-2-(1-methyl-1H-indol-2-yl)_H_-imidazo[1,2-_a_]pyridin-3-amine (2m)

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Colorless solid; mp 209-211°C; IR (KBr, cm^{-1}): 3273 cm^{-1} (N-H); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 9H of tert-butyl), 3.94 (s, 3H, N-CH_3), 5.19 (s, 1H, N-H), 6.65-8.36 (m, 8H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 29.9, 31.2, 56.2, 103.3, 109.6, 117.1, 119.7, 120.7, 121.8, 122.1, 127.7, 138.1 ppm; Anal. Calcd for $C_{20}H_{21}ClN_4$: C, 68.0: H, 6.0: N, 15.88. Found: C, 67.82: H, 5.85: N, 15.72.

***N*-tert-butyl-6-chloro-2-(4-ethoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-amine (2n)**

Colorless solid; mp 180-182 °C; IR (KBr, cm^{-1}): 3210 cm^{-1} (N-H); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (s, 9H of tert-butyl), 1.44 (t, 3H, *J* = 7.12 Hz, CH_3 of ethoxy), 4.44 (q, 2H, *J* = 7.12 Hz, 7.12 Hz, CH_2 of ethoxy), 4.80 (s, 1H, N-H), 7.53-8.91 (m, 7H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): 14.2, 29.3, 56.4, 62.6, 122.5, 124.5, 126.0, 126.4, 127.3, 129.0, 131.9, 136.6, 141.7, 145.0, 148.9, 149.7, 158.6 ppm; Anal. Calcd for $C_{19}H_{22}ClN_3O$: C, 66.37: H, 6.45: N, 12.22. Found: C, 66.22: H, 6.31: N, 12.01.

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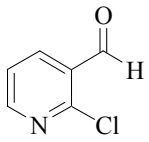
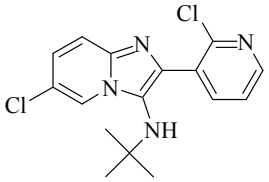
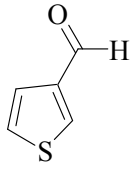
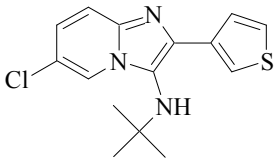
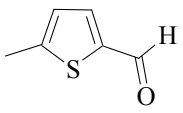
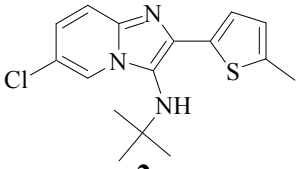
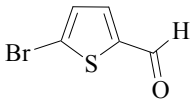
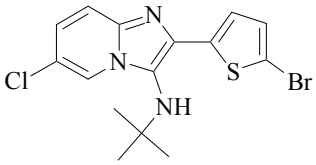
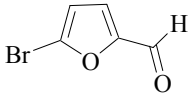
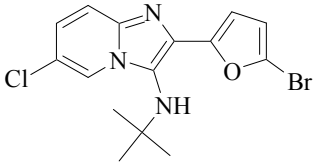
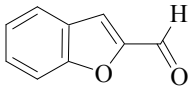
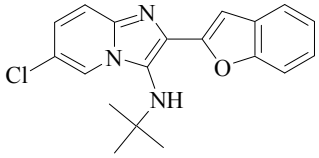
Table 1

Synthesis of 2-aryl-imidazo[1,2-*a*]pyridine products (2a-n)

Entry	Reagents (1a-n)	Products (2a-n)	Time (min)	Yield (%)
1	 **1a**	 **2a**	30	96
2	 **1b**	 **2b**	45	95
3	 **1c**	 **2c**	50	91
4	 **1d**	 **2d**	40	92
5	 **1e**	 **2e**	50	90
6	 **1f**	 **2f**	65	91

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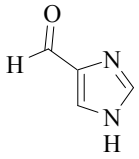
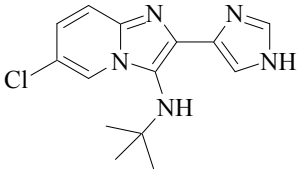
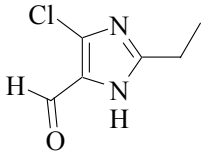
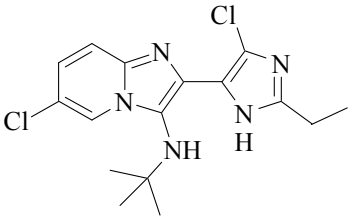
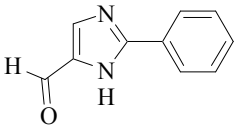
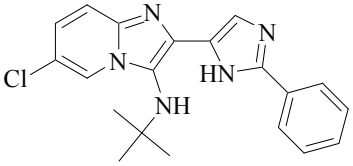
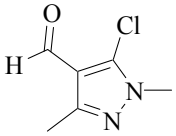
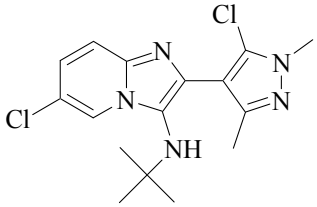
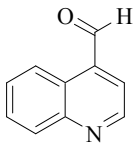
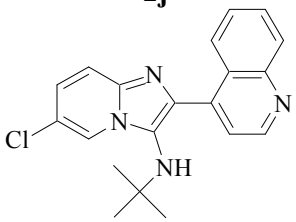
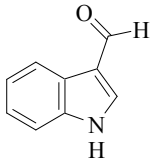
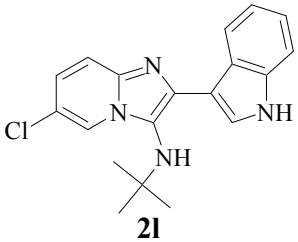
7	 **1g**	 **2g**	70	81
8	 **1h**	 **2h**	60	89
9	 **1i**	 **2i**	75	90
10	 **1j**	 **2j**	65	84
11	 **1k**	 **2k**	60	85
12	 **1l**	 **2l**	60	90

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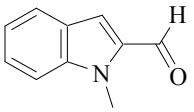
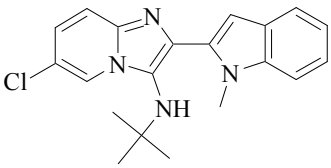
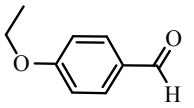
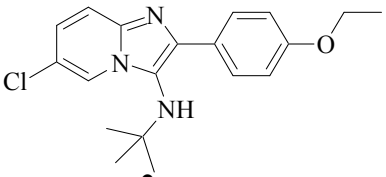
13	 **1m**	 **2m**	55	92
14	 **1n**	 **2n**	80	87

Table 2

Optimization of solvents at 70 °C for the synthesis **2a**

Entry	Solvents	Time (min)	Yield (%)
1	Acetonitrile	45	82
2	DCM	70	79
3	THF	40	84
4	DMF	65	63
5	**Ethanol**	**30**	**96**
6	Toluene	50	73
7	Chloroform	60	87
8	DMSO	40	85
9	Dioxane	45	80

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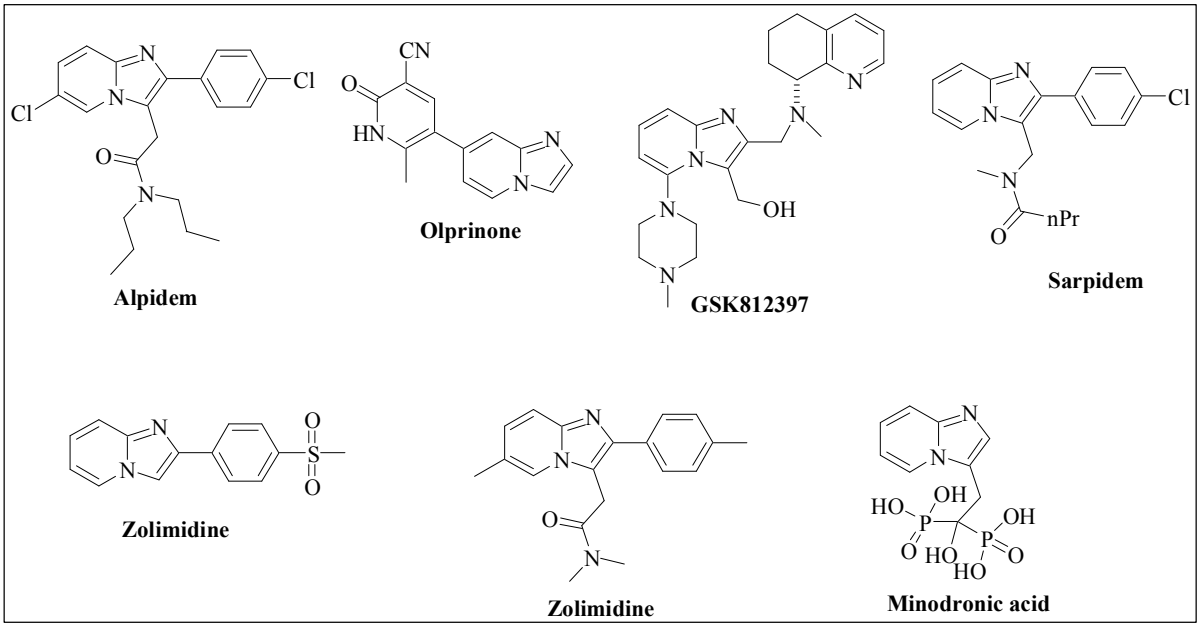
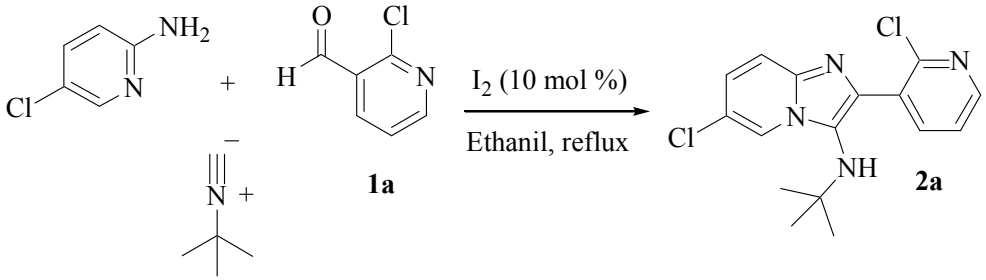


Figure 1. Imidazo[1,2-*a*]pyridine derived scaffolds.



Scheme 1. Iodine-catalysed synthesis of *N*-tert-butyl-6-chloro-2-(2-chloropyridin-3-yl)*H*-imidazo[1,2-*a*]pyridin-3-amine **(2a)**

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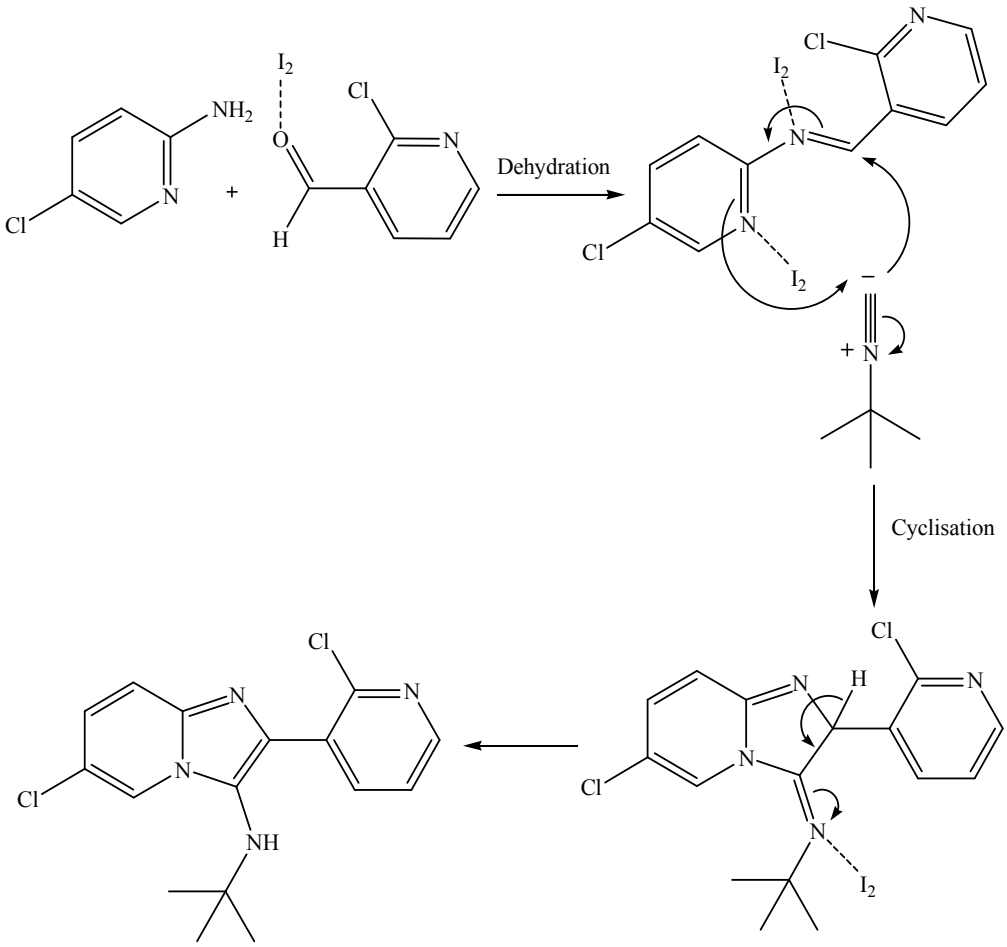

Figure 2. A Plausible reaction mechanism for the iodine catalysed one step fusion of 2-aryl-imidazo[1,2-*a*]pyridine heterocycles.

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A facile and efficient protocol for the synthesis of novel imidazo[1,2-*a*]pyridines has been developed by one-pot reaction of aromatic aldehydes with 2-amino-5-chloropyridine and *tert*-butylisocyanide in the presence of I_2 in toluene at 70 °C. The present approach offers the advantages of simple methodology, clean, high atom-economy, mild condition, short reaction time, wide substrate scope, low environmental impact and high yield.