Regioselective synthesis of 2- and 3-substituted imidazo[1,2-*a*]pyridines

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A range of 2- or 3-substituted imidazo[1,2-*a*]pyridines were prepared from 2-aminopyridine derivatives and *gem*-dibromovinyl compounds by the tandem nucleophilic substitution (or nucleophilic addition)/cyclisation reaction.

Keywords: imidazo[1,2-*a*]pyridine, 2-aminopyridine, *gem*-dibromovinylbenzene, regioselectivity, nucleophilic substitution

Imidazo[1,2-*a*]pyridines are a class of compounds that possess a wide range of pharmacological properties including antibacterial, antifungal, antiviral, anti-inflammatory activities.[1,2] They can also be used for prophylactic and therapeutic treatment of anxiety, diabetes, hyperglycaemia, hypertension, and arteriosclerosis.[3] Several drugs based on imidazo[1,2-*a*]pyridine are already on the market including alpidem, necopidem, saripidem, zolimidine and zolpidem.[4–6] The common approach for preparation of imidazo[1,2-*a*]pyridine ring system mainly involves: (i) construction of the five-membered imidazole ring by the two- or three-component coupling of pyridine derivatives with a diversity of coupling partners or intramolecular condensation of *N*-substituted-2-aminopyridines prepared in advance;[7–17] or (ii) construction of the six-membered pyridine ring using substituted imidazoles as starting materials.[18,19]

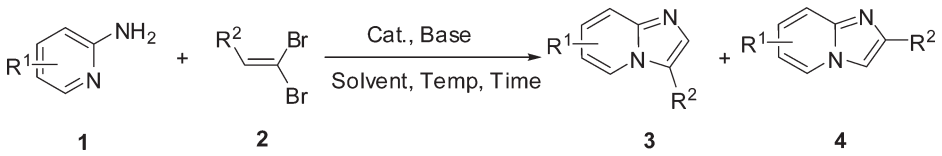
The pharmaceutical activity of imidazo[1,2-*a*]pyridines is closely related to the substituted position and electronic properties of C-2 or C-3 substituents on the imidazole ring.[20–22] Various 2-substituted and/or 3-substituted imidazo[1,2-*a*]pyridines were prepared relying on the condensation or functionalisation reactions of the skeleton of imidazo[1,2-*a*]pyridine.[7–19,23] However, there is no general methodology for the selectively synthesis of 2- and 3-substituted imidazo[1,2-*a*]pyridines. Recently, our laboratory reported the use of *gem*-dihalovinyl substrates to achieve diverse heteroaromatics via the tandem C-heteroatom coupling/C-H activation.[24] In continuation of our interest in the cyclisation reaction of heteroaromatics, we now present the synthesis of 2- and 3-substituted imidazo[1,2-*a*]pyridines using various *gem*-dibromovinyl substrates as starting materials (Scheme 1).

Result and discussion

As shown in Table 1, optimisation of the reaction conditions was carried out first. According to our experience,[24] the initial investigation started with the coupling of *gem*-dibromovinylbenzene **1a** and 2-aminopyridine **2a** in the presence of CuI using Cs_2CO_3 as the base in DMF for 24 h at 110 °C. 2-Phenylimidazo[1,2-*a*]pyridine (**3a**) was obtained in 20% yield (Table 1, entry 1). When TBAF·$3H_2O$ (tetrabutylammonium fluoride, 4.0 equiv.) was employed as the base, **3a** was obtained in 40% and 50% yield in DMF and DMSO, respectively (Table 1, entries 2, 3). In controlled experiments, it was found that CuI was not necessary for this reaction (Table 1, entries 4–6). Subsequently, the amount of TBAF·$3H_2O$ necessary was investigated. Increasing TBAF·$3H_2O$ loading resulted in a negative effect (Table 1, entry 4), and reducing the amount of TBAF·$3H_2O$ could improve the reaction efficiency (Table 1, entries 5 and 6). Note that 3-substituted imidazo[1,2-*a*]pyridine (**3a**) was obtained in 67% isolated yield together with 2-substituted imidazo[1,2-*a*]pyridine (**4a**) in 8% isolated yield while 3.0 equiv. of TBAF·$3H_2O$ was employed (Table 1, entry 5). The two compounds **3a** and **4a** can be easily separated by column chromatography due to their very different molecular polarity. After screening other bases (*e.g.*, KF, K_2CO_3, and K_3PO_4), we found that KF gave the best result with 76% yield of **3a** together with 6% yield of **4a** in DMF (Table 1, entry 8). In addition, decreasing the reaction temperature could significantly diminish yields (Table 1, entries 11 and 12). Thus, the optimal reaction condition was obtained when KF (3.0 equiv.) was employed as the base in DMF at 130 °C for 12 h under nitrogen atmosphere.

Under optimised conditions, the generality of the reaction was examined (Table 2). It was found that the reaction of a variety of *gem*-dibromovinyl substrates bearing electron-neutral or electron-rich aryls (*e.g.*, phenyl, *p*-methylphenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl and naphthyl), *p*-halophenyls (*e.g.*, *p*-fluorophenyl, *p*-chlorophenyl and *p*-bromophenyl), heteroaryls (*e.g.*, 2-thienyl and 2-pyridyl), vinyl and alkyl with 2-aminopyridine mainly obtained 3-substituted imidazo[1,2-*a*]pyridines (**3**), together with trace to small amounts of 2-substituted imidazo[1,2-*a*]pyridines (**4**). Note that 1,1-dibromodec-1-ene was able to react with 2-aminopyridine, when CuI (10 mol%) was employed as a catalyst, and 3-octylimidazo[1,2-*a*]pyridine in 75% yield (Table 2, entry **3l**). The reaction condition was also suitable for various substituted 2-aminopyridine substrates. 3-methyl-2-aminopyridine, 5-methyl-2-aminopyridine, 5-phenyl-2-aminopyridine and 3-benzyloxy-2-aminopyridine could be efficiently converted into the corresponding 3-substituted imidazo[1,2-*a*]pyridines in synthetically useful yields (Table 2, entries **3m**–**p**).

Further studies showed that the reaction of *gem*-dibromovinyl substrates bearing strongly electron-deficient aryls (e.g., *p*-nitrophenyl, *m*-nitrophenyl, *o*-nitrophenyl, and *p*-cyanophenyl) and *o*-halophenyls (e.g., *o*-chlorophenyl, and *o*-bromophenyl) with 2-aminopyridine under the same reaction condition mainly obtained 2-substituted imidazo[1,2-*a*]pyridines (**4**), together with trace to a moderate amount of 3-substituted imidazo[1,2-*a*]pyridines (**3**).



Scheme 1 Synthesis of 2-substituted and 3-substituted imidazo[1,2-*a*]pyridines.

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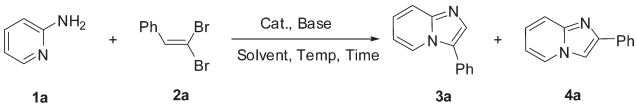
Table 1 Optimisation of the reaction of *gem*-dibromovinylbenzene with 2-aminopyridine[a]



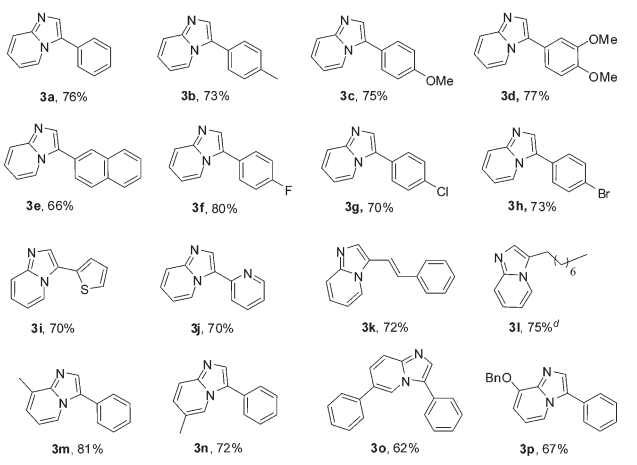
1a **2a** **3a** **4a**

Entry	Cat.	Base (n equiv.)	Solvent	Temp /°C	Time /h	Yield[b] (**3a**:**4a**)
1	CuI	Cs_2CO_3 (4)	DMF	110	24	20% (**3a**)
2	CuI	TBAF·$3H_2O$ (4)	DMF	110	24	40% (**3a**)
3	CuI	TBAF·$3H_2O$ (4)	DMSO	110	24	54% (**3a**)
4	-	TBAF·$3H_2O$ (5)	DMSO	130	12	23% (**3a**)
5	-	TBAF·$3H_2O$ (3)	DMSO	130	12	67% (**3a**) 8% (**4a**)
6	-	TBAF·$3H_2O$ (2)	DMSO	130	12	61% (**3a**) 8% (**4a**)
7	-	KF (3)	DMSO	130	12	75% (**3a**) 6% (**4a**)
8	-	KF (3)	DMF	130	12	76% (**3a**) 6% (**4a**)
9	-	K_2CO_3 (3)	DMF	130	12	50% (**3a**)
10	-	K_3PO_4 (3)	DMF	130	12	52% (**3a**)
11	-	KF (3)	DMF	100	12	54% (**3a**)
12	-	KF (3)	DMF	80	12	17% (**3a**)

[a]Reaction conditions: CuI (10 mol%), base (2–5 equiv.), *gem*-dibromovinylbenzene (0.5 mmol), 2-aminopyridine (0.6 mmol) and solvent (1.0 mL) under nitrogen atmosphere.
[b]Yield of isolated product.
DMF, dimethyl formamide; DMSO, dimethyl sulfoxide; TBAF, tetrabutylammonium fluoride.

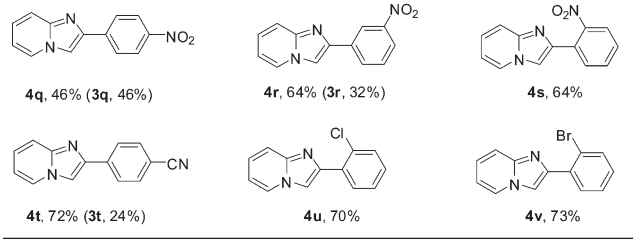
A proposed mechanism for regioselective synthesis of 2- and 3-substituted imidazo[1,2-*a*]pyridines is shown in Scheme 2. The reaction probably involves 1-bromoalkyne *in situ* generated from dehydrohalogenation of *gem*-dibromovinyl substrates. Subsequently, the nucleophilic substitution and nucleophilic addition of 1-bromoalkyne would take place simultaneously and competitively. The nucleophilic substitution of 1-bromoalkyne bearing electron-rich, electron-neutral and weakly electron-deficient aryls may be more prone to occur, followed by isomerisation and intramolecular hydroamination, and thus mainly give 3-substituted imidazo[1,2-*a*] pyridines. When the alkynyl is adjacent to the strongly electron-deficient functional groups, it may be more likely to be attacked by the nucleophile (amino group), and then undergo the nucleophile addition reaction of π-bond to give 2-substituted imidazo[1,2-*a*]pyridines. It is well known that the electron-withdrawing characteristics of *o*-halophenyls are stronger than *p*-halophenyls because of the inductive effect of the *ortho*-substituent. Therefore, *gem*-dibromovinyl substrates bearing *o*-halophenyls would mainly undergo the nucleophilic addition pathway (Path B) to provide 2-substituted imidazo [1,2-*a*]pyridines, while *gem*-dibromovinyl-4-halobenzenes would mainly undergo the nucleophilic substitution pathway (Path A) to give 3-substituted imidazo[1,2-*a*]pyridines.

Table 2 Synthesis of 3-substituted imidazo[1,2-*a*]pyridines[a,b,c]



[a]Reaction conditions: KF (3 equiv.), *gem*-dibromovinyl substrate (0.5 mmol), 2-aminopyridine or substituted 2-aminopyridine (0.6 mmol) and DMF (1.0 mL) under nitrogen atmosphere.
[b]Isolated yield of **3**.
[c]Together with trace to small amounts of **4**.
[d]CuI (10 mol%) was added.

Table 3 Synthesis of 2-substituted imidazo[1,2-*a*]pyridines[a,b,c]



[a]Reaction conditions: KF (3 equiv.), *gem*-dibromovinyl substrate (0.5 mmol), 2-aminopyridine (0.6 mmol) and DMF (1.0 mL) under nitrogen atmosphere.
[b]Isolated yield of **4**.
[c]Together with trace to moderate amounts of **3**.

Experimental

NMR spectra were obtained on a Bruker AMX-400 or a Bruker AMX-600. The ^{1}H NMR (400 MHz or 600 MHz) chemical shifts were measured relative to $CDCl_3$ as the internal reference ($CDCl_3$: δ 7.26 ppm). The ^{13}C NMR (100 MHz or 150 MHz) chemical shifts were given using $CDCl_3$ as the internal standard ($CDCl_3$: δ 77.16 ppm). The following abbreviations were used to designate the multiplicities: s, singlet; d, doublet; t, triplet; bs, broad signal; m, multiplet. High-resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI). IR spectra were obtained on NEXUS 670 FTIR using KBr disks. Melting points were determined with XRC-1 and are uncorrected.

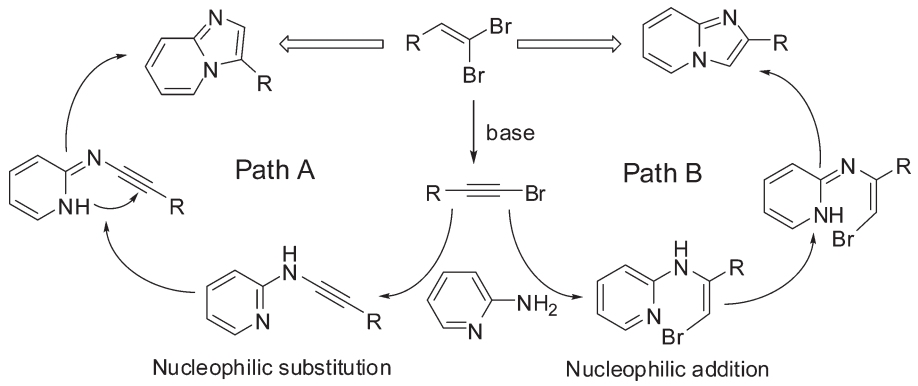
Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. *gem*-Dibromovinyl substrates were prepared according to the literature procedures.[25–27] Solvents were dried over CaH_2 (DMF or DMSO), and freshly distilled prior to use. Unless otherwise indicated, all syntheses and manipulations were carried out under N_2 atmosphere.

Synthesis of 2-substituted and 3-substituted imidazo[1,2-a]pyridines; general procedure

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with 1,1-dibromovinyl substrate (0.5 mmol), 2-aminopyridine (0.6 mmol), KF (90 mg, 1.5 mmol), and DMF (1.0 mL) under N_2. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with N_2. The reaction mixture was stirred for 10 min at room temperature, and then heated at 130 ºC for 12 h. The reaction mixture was then cooled to ambient temperature, DMF was removed under the reduce pressure, the residue was dissolved with 5–10 mL of CH_2Cl_2, filtered through a plug of silica gel, and washed with 10–20 mL of CH_2Cl_2. The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

3-Phenylimidazo[1,2-a]pyridine (**3a**)[28]: Colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (t, J = 6.8 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.49–7.56 (m, 4H), 7.65–7.69 (m, 2H), δ 8.32 (d, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.6, 118.3, 123.4, 124.3, 125.8, 128.1, 128.2, 129.3, 129.3, 132.5, 146.1 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_2$ $[M+H]^+$ 195.0922, found 195.0924.

2-Phenylimidazo[1,2-a]pyridine (**4a**)[29]: Grey solid, m.p. 131–133 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (t, J = 6.8 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.62 (d,



Scheme 2 Proposed mechanism for synthesis of 2-substituted and 3-substituted imidazo[1,2-*a*]pyridines.

J = 9.2 Hz, 1H), 7.86 (s, 1H), 7.95 (d, *J* = 6.8 Hz, 2H), 8.10 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 108.1, 112.6, 117.5, 124.8, 125.6, 126.1, 128.0, 128.8, 133.6, 145.6, 145.7 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_2$ $[M+H]^+$ 195.0922, found 195.0924.

3-p-Tolylimidazo[1,2-a]pyridine (**3b**): White solid, m.p. 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 6.77 (t, *J* = 6.8 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.65–7.67 (m, 2H), 8.29 (d, *J* = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.4, 112.4, 118.2, 123.4, 124.1, 125.8, 126.3, 128.1, 129.9, 132.2, 138.2, 146.0 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079, found 209.1079. IR (ATR): ν (cm^{-1}): 3112, 2920, 2857, 1633, 1544, 1491, 1353, 759.

3-(4-Methoxyphenyl)imidazo[1,2-a]pyridine (**3c**): Yellow solid, m. p. 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.74 (t, *J* = 6.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.61–7.64 (m, 2H), 8.22 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 55.4, 112.4, 114.7, 118.1, 121.5, 123.3, 124.0, 125.5, 129.6, 131.9, 145.8, 159.6 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225.1028, found 225.1026. IR (ATR): ν (cm^{-1}): 3082, 2929, 2843, 1609, 1571, 1548, 1357, 1242, 751.

3-(3,4-Dimethoxyphenyl)imidazo[1,2-a]pyridine (**3d**): Yellow solid, m.p. 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90–3.95 (m, 6H), 6.76 (t, *J* = 6.6 Hz, 1H), 6.98–7.00 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.62–7.65 (m, 2H), 8.25 (d, *J* = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 56.04, 56.09, 108.6, 111.9, 112.4, 113.9, 118.2, 120.9, 121.9, 123.3, 123.9, 125.6, 132.1, 145.8, 147.9, 149.3, 149.6 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_2O_2$ $[M+H]^+$ 255.1134, found 255.1135. IR (ATR): ν (cm^{-1}): 3080, 2924, 2851, 1634, 1501, 1252, 1225, 758.

3-(Naphthalen-2-yl)imidazo[1,2-a]pyridine (**3e**): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (t, *J* = 6.8 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.52–7.54 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 9.2Hz, 1H), 7.80 (s, 1H), 7.87–7.89 (m, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 8.41 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.7, 118.3, 123.4, 124.4, 125.8, 126.5, 126.7, 126.7, 126.8, 127.9, 128.0, 129.0, 132.9, 133.0, 133.6, 146.3 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{12}N_2$ $[M+H]^+$ 245.1079, found 245.1077. IR (ATR): ν (cm^{-1}): 3053, 2921, 1630, 1499, 1356, 753.

3-(4-fluorophenyl)imidazo[1,2-a]pyridine (**3f**): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (t, *J* = 6.8 Hz, 1H), 7.18–7.22 (m, 3H), 7.49–7.52 (m, 2H), 7.65–7.67 (m, 2H), 8.22 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.7, 116.3, 116.5, 118.3, 123.1, 124.3, 124.7, 125.3, 125.4, 130.0, 130.1, 132.4, 146.1, 161.3, 163.8 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9FN_2$ $[M+H]^+$ 213.0828, found 213.0827. IR (ATR): ν (cm^{-1}): 3155, 3049, 1716, 1553, 1449, 1409, 1140.

3-(4-Chlorophenyl)imidazo[1,2-a]pyridine (**3g**): White solid, m.p. 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (t, *J* = 6.8 Hz, 1H), 7.18 (t, *J* = 6.8 Hz, 1H), 7.48 (s, 4H), 7.66–7.68 (m, 2H), 8.26 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.8, 118.4, 123.2, 124.5, 124.6, 127.8, 129.2, 129.6, 132.7, 134.1, 146.3 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9ClN_2$ $[M+H]^+$ 229.0533, found 229.0531. IR (ATR): ν (cm^{-1}): 3092, 3021, 2923, 1537, 1482, 1090, 730.

3-(4-Bromophenyl)imidazo[1,2-a]pyridine (**3h**): White solid, m.p. 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (t, *J* = 6.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.63–7.68 (m, 4H), 8.26 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.9, 118.4, 122.1, 123.2, 124.5, 124.6, 128.2, 129.5, 132.5, 132.8, 146.3 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9BrN_2$ $[M+H]^+$ 273.0027, found 273.0021. IR (ATR): ν (cm^{-1}): 3106, 2922, 1537, 1472, 1069, 838, 754.

3-(Thiophen-2-yl)imidazo[1,2-a]pyridine (**3i**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (t, *J* = 6.8 Hz, 1H), 7.18–7.21 (m, 2H), 7.27 (d, *J* = 3.6 Hz, 1H), 7.42 (d, *J* = 5.2 Hz, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.76 (s, 1H), 8.38 (d, *J* = 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.9, 118.1, 119.2, 123.8, 124.5, 126.0, 127.9, 129.9, 133.6, 146.3 ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_8N_2S$ $[M+H]^+$ 201.0486, found 201.0484. IR (ATR): ν (cm^{-1}): 3103, 2924, 1499, 1301, 844, 700.

3-(Pyridin-2-yl)imidazo[1,2-a]pyridine (**3j**): White solid, m.p. 68–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (t, *J* = 6.8 Hz, 1H), 7.14–7.16 (m, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.67–7.72 (m, 3H), 8.14 (s, 1H), 8.65 (d, *J* = 4.8 Hz, 1H), 9.93 (d, *J* = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.9, 117.6, 120.4, 120.9, 123.6, 125.5, 128.1, 134.6, 136.6, 147.5, 148.7, 150.6 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_9N_3$ $[M+H]^+$ 196.0875, found 196.0876. IR (ATR): ν (cm^{-1}): 3047, 2924, 1677, 1591, 1494, 1321, 748.

(E)-3-Styrylimidazo[1,2-a]pyridine (**3k**): Yellow solid, m.p. 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (t, *J* = 6.8 Hz, 1H), 7.13 (d, *J* = 6.8 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.90 (s, 1H), 8.21 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.9, 113.1, 118.3, 123.3, 124.0, 124.2, 126.2, 127.8, 128.4, 128.8, 132.1, 137.0, 146.2 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N_2$ $[M+H]^+$ 221.1079, found 221.1076. IR (ATR): ν (cm^{-1}): 3103, 3034, 2928, 1629, 1493, 1350, 954, 753.

3-Octylimidazo[1,2-a]pyridine (**3l**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87–0.90 (m, 3H), 1.26–1.47 (m, 10H), 1.73–1.81 (m, 2H), 2.80–2.84 (m, 2H), 6.79 (t, *J* = 6.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.2, 22.8, 24.0, 27.1, 29.4, 29.5, 29.6, 29.8, 32.0, 112.0, 118.1, 123.0, 123.2, 124.7, 130.8, 145.4 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}N_2$ $[M+H]^+$ 231.1861, found 231.1863. IR (ATR): ν (cm^{-1}): 3080, 2926, 2854, 1635, 1502, 1310, 752.

8-Methyl-3-phenylimidazo[1,2-a]pyridine (**3m**): White solid, m.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.69 (s, 1H), 8.20 (d, *J* = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 17.1, 112.6, 121.3, 123.1, 126.2, 128.0, 128.1, 129.2, 129.6, 131.8, 146.5 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079, found 209.1076. IR (ATR): ν (cm^{-1}): 2955, 2922, 2852, 1604, 1492, 749.

6-Methyl-3-phenylimidazo[1,2-a]pyridine (**3n**): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 7.02 (d, *J* = 9.2 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.48–7.57 (m, 5H), 7.63 (s, 1H), 8.09 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 117.5, 120.9, 122.2, 125.4, 127.5, 128.1, 129.2, 129.5, 132.3, 145.2 ppm, HRMS (ESI): *m/z* calcd for $C_{14}H_{12}N_2$ $[M+H]^+$ 209.1079, found 209.1082. IR (ATR): ν (cm^{-1}): 3071, 2924, 2854, 1603, 1507, 760.

3,6-Diphenylimidazo[1,2-a]pyridine (**3o**): White solid, m.p. 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.48 (m, 5H), 7.52–7.61

(m, 6H), 7.72–7.76 (m, 2H), 8.49 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.1, 120.7, 125.1, 126.2, 127.1, 127.2, 127.9, 128.1, 128.3, 129.1, 129.4, 133.1, 137.6, 145.5 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{14}N_2$ $[M+H]^+$ 271.1235, found 271.1234. IR (ATR): ν (cm^{-1}): 3056, 2919, 1602, 1483, 1306, 760.

8-Benzyloxy-3-phenylimidazo[1,2-a]pyridine (**3p**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (s, 2H), 6.49 (d, J = 7.6 Hz, 1H), 6.62 (t, J = 6.8 Hz, 1H), 7.30–7.42 (m, 4H), 7.48–7.56 (m, 6H), 7.66 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.7, 102.6, 112.4, 116.6, 126.8, 127.4, 128.1, 128.2, 128.2, 128.6, 129.2, 129.4, 131.6, 136.2, 140.7, 148.3 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}N_2O$ $[M+H]^+$ 301.1341, found 301.1342. IR (ATR): ν (cm^{-1}): 3058, 2924, 2854, 1604, 1545, 1272, 698.

2-(4-Nitrophenyl)imidazo[1,2-a]pyridine (**4q**): Red solid, m.p. 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (t, J = 6.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.48 (m, 4H), 7.66–7.68 (m, 2H), 8.25 (d, J = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.1, 113.3, 118.1, 124.4, 125.8, 126.0, 126.6, 140.4, 143.5, 146.2, 147.4 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773, found 240.0776. IR (ATR): ν (cm^{-1}): 3133, 2924, 1595, 1507, 1341, 748.

3-(4-Nitrophenyl)imidazo[1,2-a]pyridine (**3q**): Grey solid, m.p. > 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (t, J = 6.8 Hz, 1H), 7.28–7.33 (m, 1H), 7.69–7.78 (m, 2H), 7.86 (s, 1H), 8.37–8.44 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.6, 118.7, 123.2, 123.7, 124.7, 125.5, 127.5, 134.7, 135.9, 146.8, 147.3 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773, found 240.0772. IR (ATR): ν (cm^{-1}): 3137, 3081, 2925, 1598, 1510, 1336, 754.

2-(3-Nitrophenyl)imidazo[1,2-a]pyridine (**4r**): Grey solid, m.p. 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (t, J = 6.4 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.70–7.74 (m, 2H), 7.82 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 8.0 Hz, 2H), 8.32 (d, J = 7.6 Hz, 1H), 8.45 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.1, 113.0, 117.8, 120.8, 122.5, 125.5, 125.8, 129.7, 131.8, 135.7, 143.5 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773, found 240.0770. IR (ATR): ν (cm^{-1}): 3136, 2923, 1634, 1521, 1342, 719.

3-(3-Nitrophenyl)imidazo[1,2-a]pyridine (**3r**): Yellow solid, m.p. 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (t, J = 6.8 Hz, 1H), 7.22 (t, J = 8.4 Hz, 2H), 7.70–7.74 (m, 2H), 7.99 (s, 1H), 8.16 (d, J = 6.8 Hz, 2H), 8.32 (d, J = 7.6 Hz, 1H), 8.76 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.4, 118.6, 122.1, 122.7, 122.9, 123.4, 125.2, 130.4, 131.1, 133.5, 133.8, 146.8, 148.9 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773, found 240.0776. IR (ATR): ν (cm^{-1}): 3095, 2923, 1635, 1545, 1348, 735.

2-(2-Nitrophenyl)imidazo[1,2-a]pyridine (**4s**): Grey solid, m.p. 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (t, J = 6.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.60–7.64 (m, 2H), 7.70 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.6, 112.8, 117.9, 123.5, 125.2, 125.8, 127.7, 128.5, 131.4, 131.8, 140.2, 145.3, 149.3 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9N_3O_2$ $[M+H]^+$ 240.0773, found 240.0772. IR (ATR): ν (cm^{-1}): 3149, 2921, 1525, 1362, 1279, 785, 753.

2-(4-Cyanophenyl)imidazo[1,2-a]pyridine (**4t**): Yellow solid, m.p. 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (t, J = 6.8 Hz, 1H), 7.20 (t, J = 8.8 Hz, 1H), 7.62 (d, J =9.2 Hz, 1H), 7.69 (d, J =8.0 Hz, 2H), 7.94 (s, 1H), 8.03 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 6.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.3, 113.4, 118.5, 118.6, 123.2, 124.0, 125.3, 127.7, 133.1, 134.0, 134.1, 147.1 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_9N_3$ $[M+H]^+$ 220.0875, found 220.0871. IR (ATR): ν (cm^{-1}): 3136, 3040, 2222, 1635, 1608, 1373, 757.

3-(4-Cyanophenyl)imidazo[1,2-a]pyridine (**3t**): Yellow solid, m.p. 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (t, J = 6.8 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.70 (t, J = 6.0 Hz, 3H), 7.80–7.82 (m, 3H), 8.38 (d, J = 7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.5, 111.1, 113.1, 117.8, 119.0, 120.2, 125.5, 125.8, 126.4, 130.2, 132.6, 138.3, 138.6, 143.7, 146.0 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_9N_3$ $[M+H]^+$ 220.0875, found 220.0873. IR (ATR): ν (cm^{-1}): 3202, 3026, 2222, 1635, 1606, 1299, 732.

2-(2-Chlorophenyl)imidazo[1,2-a]pyridine (**4u**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (t, J = 6.8 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.24 (t, J = 8.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 6.8 Hz, 1H), 8.28–8.31 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.6, 112.6, 117.8, 125.0, 125.9, 127.2, 128.7, 130.5, 131.1, 131.8, 132.4, 142.0, 144.6 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9ClN_2$ $[M+H]^+$ 229.0533, found 229.0532. IR (ATR): ν (cm^{-1}): 3068, 2927, 1634, 1498, 1300, 1059, 755.

2-(2-Bromophenyl)imidazo[1,2-a]pyridine (**4v**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (t, J = 5.2 Hz, 1H), 7.15–7.19 (m, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.62–7.68 (m, 2H), 8.12–8.16 (m, 2H), 8.28 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.0, 112.5, 117.6, 121.5, 124.9, 125.8, 127.6, 128.9, 131.7, 133.7, 134.4, 143.2, 144.5 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_9BrN_2$ $[M+H]^+$ 273.0027, found 273.0022. IR (ATR): ν (cm^{-1}): 3168, 2922, 1676, 1585, 1310, 1028, 755.

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References

1 F. Couty, G. Evano in *Comprehensive heterocyclic chemistry III*, Vol. 11, eds A.R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor, Elsevier, Oxford, 2008, pp. 409–499.
2 K.S. Gudmundsson, J.D. Williams, J.C. Drach and L.B. Townsend, *J. Med. Chem.*, 2003, **46**, 1449.
3 S.C. Goodacre, L.J. Street, D.J. Hallett, J.M. Crawforth, S. Kelly, A.P. Owens, W.P. Blackaby, R.T. Lewis, J. Stanley, A.J. Smith, P. Ferris, B. Sohal, S.M. Cook, A. Pike, N. Brown, K.A. Wafford, G. Marshall, J.L. Castro and J.R. Atack, *J. Med. Chem.*, 2006, **49**, 35.
4 N. Hsua, S.K. Jha, T. Coleman and M.G. Frank, *Behav. Brain Res.*, 2009, **201**, 233.
5 T. Okubo, R. Yoshikawa, S. Chaki, S. Okuyamac and A. Nakazato, *Bioorg. Med. Chem.*, 2004, **12**, 423.
6 S.Z. Langer, S. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol.*, 1990, **46**, 61.
7 H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang and Q. Zhu, *Angew. Chem. Int. Ed.*, 2011, **50**, 5678.
8 T. Han, Z. Shi, Y. Peng and Z. Zhao, *J. Chem. Res.*, 2011, **35**, 243.
9 Z. Wu, Y. Pan and X. Zhou, *Synthesis*, 2011, 2255.
10 N. Chernyak and V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2010, **49**, 2743.
11 E. Kianmehr, M. Ghanbari, M.N. Niri and R. Faramarzi, *J. Comb. Chem.*, 2010, **12**, 41.
12 S.K. Guchhait and C. Madaan, *Org. Biomol. Chem.*, 2010, **8**, 3631.
13 J. Koubachi, S.E. Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *J. Org. Chem.*, 2007, **72**, 7650.
14 A.L. Rousseau, P. Matlaba and C.J. Parkinson, *Tetrahedron Lett.*, 2007, **48**, 4079.
15 S. Carballares, M.M. Cifuentes and G.A. Stephenson, *Tetrahedron Lett.*, 2007, **48**, 2041.
16 A.R. Katritzky, Y.-J. Xu and H. Tu, *J. Org. Chem.*, 2003, **68**, 4935.
17 M.P. Groziak, S.R. Wilson, G.L. Clauson and N.J. Leonard, *J. Am. Chem. Soc.*, 1986, **108**, 8002.
18 H.-J. Knölker, R. Boese and R. Hitzemann, *Chem. Ber.*, 1990, **123**, 327.
19 H. Galons, I. Bergerat, C. Combet Farnoux and M. Miocque, *Synthesis*, 1982, 1103.
20 K.S. Gudmundsson, J.C. Drach, L.B. Townsend, *Tetrahedron Lett.*, 1996, **37**, 6275.
21 P.A. Bonnet, A.Michel, F. Laurent, C. Sablayrolles, E. Rechencq, J.C. Mani, M. Boucard and J.P. Chapat, *J. Med. Chem.*, 1992, **35**, 3353.
22 M. Yamanaka, K. Miyake, S. Suda, H. Ohhara and T. Ogawa, *Chem. Pharm. Bull.*, 1991, **39**, 1556.
23 D.S. Ermolat'ev, V.N. Giménez, E.V. Babaev and E. Van der Eycken, *J. Comb. Chem.*, 2006, **8**, 659.
24 X. Qin, X. Cong, D. Zhao, J. You and J. Lan, *Chem. Commun.*, 2011, **47**, 5611.
25 M.L.N. Rao, D.N. Jadhav and P. Dasgupta, *Org. Lett.*, 2010, **12**, 2048.
26 A. Coste, F. Couty and G. Evano, *Org. Lett.*, 2009, **11**, 4454.
27 G. Chelucci, F. Capitta and S. Baldino, *Tetrahedron*, 2008, **64**, 10250.
28 B.B. Touré, B.S. Lane, D. Sames, *Org. Lett.*, 2006, **8**, 1979.
29 M. Aginagalde, Y. Vara, A. Arrieta, R. Zangi, V.L. Cebolla, A.D. Camón, F.P. Cossío, *J. Org. Chem.*, 2010, **75**, 2776.