Mechanistic Studies on a New Catalyst System (CuI–$NaHSO_4$·SiO_2) Leading to the One-Pot Synthesis of Imidazo[1,2-*a*]pyridines from Reactions of 2-Aminopyridines, Aldehydes, and Terminal Alkynes

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Abstract: One-pot reactions of aldehydes, 2-aminopyridines, and terminal alkynes, in the presence of the copper(I) iodide–$NaHSO_4$·SiO_2 combination catalyst in refluxing toluene, generate the corresponding imidazo[1,2-*a*]pyridines in high to excellent yields; the mechanism has been studied.

Key words: CuI–$NaHSO_4$·SiO_2, one-pot synthesis, imidazo[1,2-*a*]pyridine, 2-aminopyridine, cascade reaction

Due to its advantages over multistep synthesis, one-pot multicomponent synthesis has gained prime importance[1] over the last decade in the synthesis of medicinally important pharmacophores and also in drug development. The pyridine ring is a common fragment among many naturally occurring bioactive molecules,[2] of these the imidazo[1,2-*a*]pyridine framework is present in established drugs like Zolpidem,[3a] Necopidem,[3b] Saripidem,[3c] Zolimidine,[3d] Olprinone,[4] and Minodronic acid[4] (Figure 1), and also in other biologically active compounds.[2,4] Reports have been made of several multistep syntheses[5] of the imidazo[1,2-*a*]pyridine fragment that are not devoid of limitations. Although, various one-pot multicomponent syntheses of imidazo[1,2-*a*]pyridines have been reported, these are limited to the synthesis of 3-aminoimidazo[1,2-*a*]pyridine derivatives only.[6] Thus, an efficient general one-pot cascade synthesis of clinically potent compounds containing this backbone is highly desirable. In continuation of our research on one-pot multicomponent reactions,[7] we report herein, an efficient, and versatile one-pot synthesis of imidazo[1,2-*a*]pyridine scaffolds from cascade reactions of aldehydes, 2-aminopyridines, and terminal alkynes in the presence of the copper(I) iodide–$NaHSO_4$·SiO_2 combination catalyst (Tables 1 and 2).

Since copper,[8] iron,[9] and other metal salts[10] are known to form propargylamine in a one-pot reaction from an aldehyde, amine, and phenylacetylene, we initially screened copper(I) iodide, copper(II) acetate, iron(III) chloride, and ruthenium(III) chloride to check whether these also could effect the in situ generation of a propargylamine in a model reaction using 2-aminopyridine (**3a**), benzaldehyde (**1a**), and phenylacetylene (**2a**), with a view to cyclization to give a heterocyclic system. Although, copper(I) iodide (50 mol%) afforded the corresponding imidazo[1,2-*a*]pyridine **4a** in 45% yield (Table 1, entry 2), the remaining reagents did not generate **4a** (entries 3–5). It may be mentioned here that two reports have been made very recently, of the one-pot, three component synthesis of imidazo[1,2-*a*]pyridines from cascade reactions of 2-aminopyridines, aldehydes, and phenylacetylenes. A one-pot reaction was

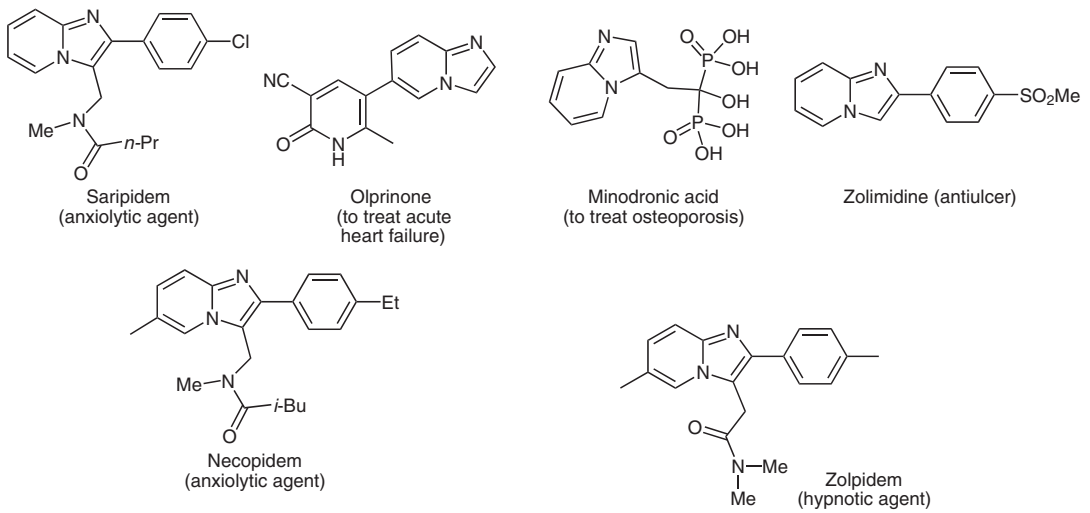

Figure 1 Drugs containing the imidazo[1,2-*a*]pyridine framework

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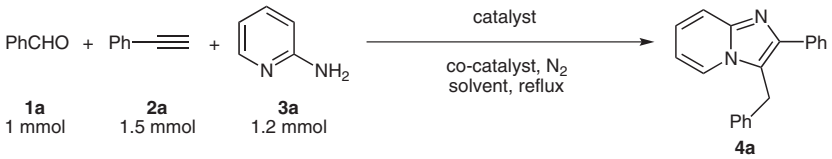
first developed by Gevorgyan's group, who used the CuCl–$Cu(OTf)_2$[11] [Cu(I)–Cu(II)] co-catalyst system, this was followed by the report of a similar one-pot synthesis by Liu et al. based on the $CuSO_4$–TsOH[12] system.

Recently silica-supported Brønsted acids[13] have gained much interest in organic synthesis. The use of Brønsted acids such as $HClO_4{\cdot}SiO_2$, $H_2SO_4{\cdot}SiO_2$, $HBF_4{\cdot}SiO_2$, $NaHSO_4{\cdot}SiO_2$, or K-10[14] or resins like Dowex 50W (H^+)[15a,b] or Amberlite IR 120 (H^+),[15c] (Table 1) together with copper(I) iodide (entries 6–16), copper sulfate (entry 18), or copper(I) chloride (entry 19) in different solvents improved the yields of the corresponding imidazopyridine **4a** to different extents. The best result was obtained using the copper(I) iodide (5 mol%)–$NaHSO_4{\cdot}SiO_2$ combination catalyst system in refluxing toluene (entry 12). Thus, under optimized reaction conditions, 2-aminopyridine (**3a**, 1.2 mmol), benzaldehyde (**1a**, 1 mmol), and phenylacetylene (**2a**, 1.5 mmol) reacted in the presence of copper(I) iodide (0.05 mmol) and $NaHSO_4{\cdot}SiO_2$[16] (0.27 mmol with respect to $NaHSO_4$) in refluxing toluene to furnish the corresponding imidazo[1,2-*a*]pyridine **4a** in excellent yield (91%, Table 1, entry 12, Table 2, entry 1).

To check the generality and scope of the present protocol (Table 2), benzaldehyde (**1a**, entries 14–18) or a variety of aromatic aldehydes containing electron-donating (entries 2–7, 11–13, 19, and 20) or electron-withdrawing substituents (entries 8–10, 21–23) were reacted under these conditions with 2-aminopyridine or its derivatives **3** (4- or 5-methyl or 5-bromo) and arylacetylene **2**, which afforded the corresponding imidazo[1,2-*a*]pyridine scaffolds within 12–14 hours in generally high yields (70–91%). Thus, this one-pot synthesis is not affected by electronic factors within these substrates. Even *ortho*-substituted aldehydes (entries 12 and 13) give good yields of the desired products. Unlike the reported $CuSO_4$–TsOH-based reactions,[12] where 4-(dimethylamino)benzaldehyde was found to intervene the reaction conditions, reaction of this substrate with 2-aminopyridine and phenylacetylene following the

Table 1 Screening of Solvent and Catalyst for the Three-Component Coupling Reaction



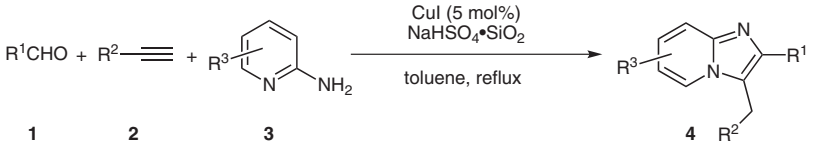
1a 1 mmol **2a** 1.5 mmol **3a** 1.2 mmol **4a**

Entry	Catalyst (mol%)	Co-catalyst[a]	Solvent	Time (h)	Yield (%) of **4a**
1	CuI (10)	–	toluene	24	35
2	CuI (50)	–	toluene	24	45
3	$FeCl_3$ (20)	–	toluene	24	–
4	$Cu(OAc)_2$ (50)	–	toluene	24	–
5	$RuCl_3$ (10)	–	toluene	24	–
6	CuI (5)	$H_2SO_4{\cdot}SiO_2$	toluene	14	50
7	CuI (5)	$HClO_4{\cdot}SiO_2$	toluene	14	60
8	CuI (5)	$HBF_4{\cdot}SiO_2$	toluene	14	65
9	CuI (5)	Amberlite	toluene	16	56
10	CuI (5)	Dowex-50	toluene	16	62
11	CuI (5)	K-10	toluene	14	75
12	CuI (5)	$NaHSO_4{\cdot}SiO_2$	toluene	12	91
13	CuI (5)	$NaHSO_4{\cdot}SiO_2$	THF	18	45
14	CuI (5)	$NaHSO_4{\cdot}SiO_2$	MeCN	18	60
15	CuI (5)	$NaHSO_4{\cdot}SiO_2$	DCE	18	30
16	CuI (5)	$NaHSO_4{\cdot}SiO_2$	xylene	10	75
17	–	$NaHSO_4{\cdot}SiO_2$	toluene	16	–
18	$CuSO_4$ (10)	$NaHSO_4{\cdot}SiO_2$	toluene	16	65
19	CuCl (5)	$NaHSO_4{\cdot}SiO_2$	toluene	16	70

[a] Catalytic load of each co-catalyst is 123 mg/mmol of aldehyde.

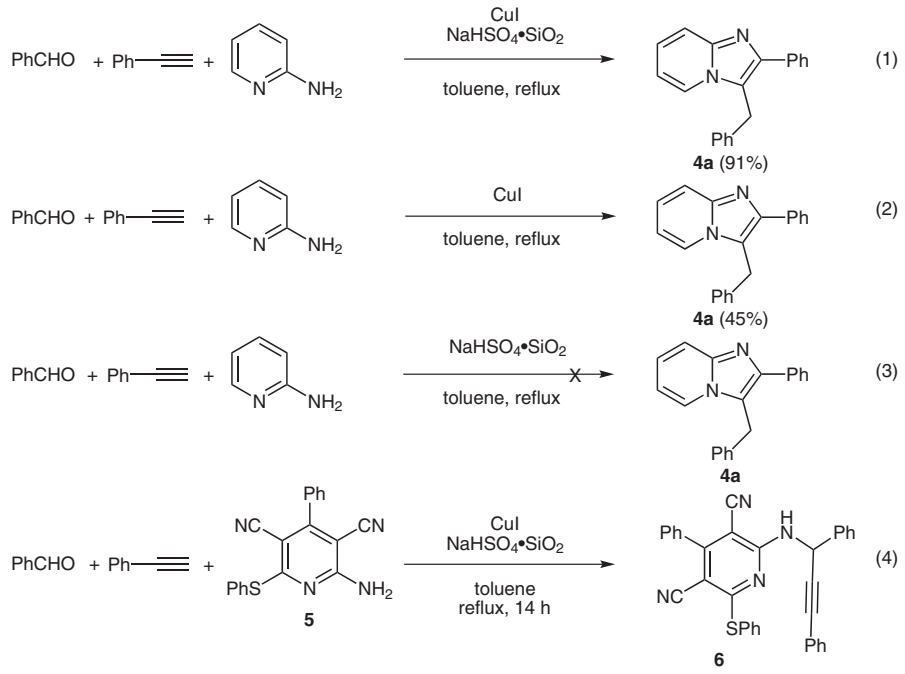
present methodology furnished the corresponding product **4k** in 73% yield (entry 11), thus once more establishing the generality of the present procedure. Heteroaromatic aldehydes such as thiophene-2-carbaldehyde (entries 24 and 25) also reacted with 2-aminopyridine or its 5-methyl analogue and phenylacetylene or its 4-methyl derivative under the standard protocol affording the corresponding imidazopyridines **4x** and **4y** in high yields. An alkyl-substituted acetylene, hex-1-yne, was also a good substrate and reacted with benzaldehyde and 2-aminopyridine re-

Table 2 Synthesis of Imidazo[1,2-*a*]pyridines



Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)	Mp (°C)
1	Ph	Ph	H	12	**4a**[11,12]	91	121
2	4-MeC_6H_4	Ph	H	12	**4b**[12]	88	160
3	4-$MeOC_6H_4$	Ph	H	12	**4c**[12]	86	127
4	3,4-$(MeO)_2C_6H_3$	Ph	H	12	**4d**	89	124
5	4-ClC_6H_4	Ph	H	14	**4e**[12]	75	142
6	4-FC_6H_4	Ph	H	13	**4f**[11,12]	88	80
7	4-BrC_6H_4	Ph	H	13	**4g**[11]	87	162 (dec)
8	4-NCC_6H_4	Ph	H	13	**4h**[11]	84	132
9	3-$O_2NC_6H_4$	Ph	H	14	**4i**[12]	71	165
10	4-$O_2NC_6H_4$	Ph	H	14	**4j**	70	158
11	4-$Me_2NC_6H_4$	Ph	H	14	**4k**	73	255–256
12	2-MeC_6H_4	Ph	H	14	**4l**	80	semisolid
13	2-ClC_6H_4	Ph	H	14	**4m**[12]	72	125–126
14	Ph	4-FC_6H_4	H	14	**4n**[12]	80	90
15	Ph	4-MeC_6H_4	H	13	**4o**[12]	72	syrup
16	Ph	Ph	4-Me	13	**4p**[11]	72	146
17	Ph	Ph	5-Br	13	**4q**	82	209–210
18	Ph	Ph	5-Me	14	**4r**[12]	80	80
19	4-MeC_6H_4	4-MeC_6H_4	4-Me	13	**4s**[11]	89	152
20	4-MeC_6H_4	Ph	5-Br	13	**4t**	80	208–209
21	4-NCC_6H_4	Ph	5-Br	14	**4u**	81	198
22	4-NCC_6H_4	Ph	5-Me	13	**4v**	83	205–206
23	4-NCC_6H_4	4-MeC_6H_4	4-Me	13	**4w**[11]	88	136
24	2-thienyl	4-MeC_6H_4	H	13	**4x**	70	126
25	2-thienyl	Ph	5-Me	14	**4y**	76	185
26	Ph	Bu	Ph	14	**4z**[11]	60[a]	syrup
27	Cy	Ph	Ph	14	**4aa**[12]	70	syrup
28	*i*-Pr	Ph	Ph	14	**4ab**[11]	66[b]	86

[a] Hex-1-yne (2.5 mmol) was added in 2 portions (initially 1.5 mmol and then after 4 h, 1 mmol).
[b] *i*-PrCHO (1.5 mmol) was used.

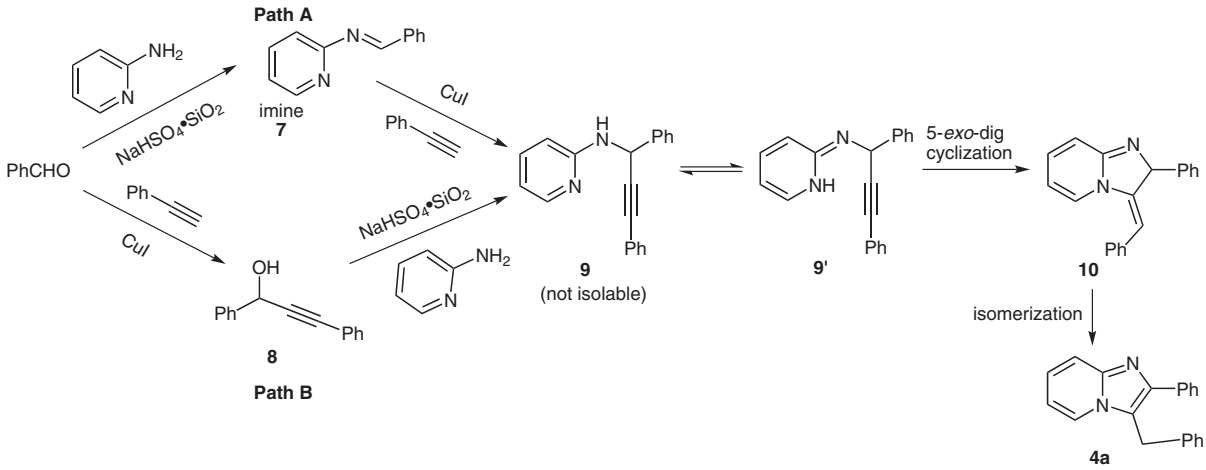


Scheme 1 Examination of various factors in the one-pot reaction to give imidazo[1,2-*a*]pyridine

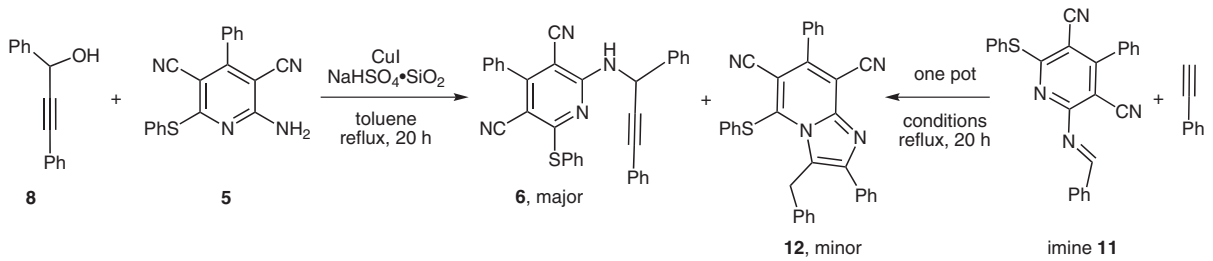
sulting in the desired product **4z** in good yield. Aliphatic aldehydes such as cyclohexanecarbaldehyde and 3-methylbutanal (entries 27 and 28) reacted under similar conditions with 2-aminopyridine and phenylacetylene affording the corresponding products **4aa** and **4ab** in high yields.

The mechanistic pathway for this one-pot synthesis was established from various reactions (Schemes 1– 3). Imidazopyridine **4a** was synthesized from the one-pot reaction of benzaldehyde, 2-aminopyridine, and phenylacetylene in the presence of a combination catalyst copper(I) iodide and $NaHSO_4{\cdot}SiO_2$ [Scheme 1, (1)]; the reaction performed with copper(I) iodide alone also gives **4a** in moderate yield [Scheme 1, (2)], but $NaHSO_4{\cdot}SiO_2$ alone is unable to carry out this transformation [Scheme 1, (3)]. It is interesting to note that refluxing a mixture of benzaldehyde, phenylacetylene, and a densely functionalized 2-aminopyridine **5** in the presence of copper(I) iodide and $NaHSO_4{\cdot}SiO_2$ in toluene for 14 hours generated the corresponding propargylamine **6** [Scheme 1, (4)]. Thus, propargylamines are intermediates for such one-pot reactions. An attempt to isolate such an intermediate **9** from an incomplete one-pot reaction, failed, indicating **9** to be highly reactive under the reaction condition, and, thus, instantaneously converted into the product **4a**.

To establish the roles of copper(I) iodide and $NaHSO_4{\cdot}SiO_2$ in this one-pot reaction, and also the reaction mechanism, two sets (Scheme 2, path A and path B) of multistep reactions were performed. In path A, benzaldehyde was first reacted with 2-aminopyridine in the presence of $NaHSO_4{\cdot}SiO_2$, and the resulting product was isolated and purified to give imine **7**, which was then re-



Scheme 2 Multistep reactions to study the reaction mechanism for copper(I) iodide–$NaHSO_4{\cdot}SiO_2$ catalyzed one-pot synthesis of imidazo[1,2-*a*]pyridine



Scheme 3 Reaction of propargyl alcohol **8** with hindered 2-aminopyridine **5** under the one-pot reaction conditions

fluxed in toluene with phenylacetylene catalyzed by copper(I) iodide to generate imidazopyridine **4a** via initial formation of the propargylamine **9**. Tautomerization of **9** to **9′** followed by 5-*exo-dig* cyclization formed **10**, which finally isomerized to product **4a**. In path B, the reaction of benzaldehyde and phenylacetylene catalyzed by copper(I) iodide furnished propargyl alcohol **8**. Isolated pure **8** was then reacted with 2-aminopyridine in the presence of $NaHSO_4{\cdot}SiO_2$ to afford imidazopyridine **4a**. It is noteworthy that the reaction of propargyl alcohol **8** with 2-aminopyridine in the presence of copper(I) iodide–$NaHSO_4{\cdot}SiO_2$ (not shown) proceeds at a faster rate than the above reaction.

To show whether both paths A and path B operate simultaneously, propargyl alcohol **8** was also reacted with the hindered 2-aminopyridine **5** under the one-pot reaction condition (Scheme 3), but for a prolonged time (20 h), which generated the propargyl amine **6** as the major product together with the corresponding imidazopyridine **12** as a minor product. A similar product composition (of **6** and **12**) was also obtained from the reaction of a mixture of imine **11** with phenylacetylene under the above reaction conditions. Thus, both path A and path B (Scheme 2) take place simultaneously in the one-pot formation of imidazopyridine. From the foregoing experiments it is clear that in the one-pot reaction, the presence of copper(I) iodide is mandatory for the C–H activation steps (for the formation of **9** from **7**, and also **8** from benzaldehyde). Copper(I) iodide also catalyzes the isomerization of **9** to **9′** as the final cyclization step. $NaHSO_4{\cdot}SiO_2$ enhances imine formation; it protonates the propargyl alcohol **8** thus activating it to nucleophilic attack by 2-aminopyridine giving propargylamine **9**, and it also promotes nucleophilic attack by the C–H activated phenylacetylene on the intermediate imine **7**. Cyclization of **9** to **4a** is also catalyzed by $NaHSO_4{\cdot}SiO_2$ via protonation of the alkyne group in **9**. $NaHSO_4{\cdot}SiO_2$ thus plays a synergistic rate enhancing role in various steps except the C–H activation step. It also appears that path A proceeds at a faster rate than path B, but both are operating simultaneously.

In conclusion, we have developed an efficient one-pot method for the synthesis of diverse imidazo[1,2-*a*]pyridines through copper(I) iodide or $NaHSO_4{\cdot}SiO_2$ combination catalyst based reactions of aldehydes, 2-aminopyridines, and terminal alkynes in refluxing toluene, and also have established the corresponding mechanistic pathways.

All commercial reagents were used as obtained without further purification. All reactions were carried out under a N_2 atmosphere and monitored by TLC. Toluene was dried by a standard method prior to use. TLC was performed on glass plates precoated with silica gel or on Merck silica gel plates (60-F_{254}). Column chromatography was carried out on silica gel 60–120 mesh (SRL, India). Mixtures of EtOAc, petroleum ether (PE), and Et_3N were used as eluents. Melting points were determined on a Toshniwal melting point apparatus and are uncorrected. IR spectra were measured on a Perkin Elmer spectrum BX-II FT-IR spectrophotometer. ^1H NMR spectra were recorded on a Bruker DPX-300 at r.t. in $CDCl_3$ at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker DPX-300 at r.t. in $CDCl_3$ at 75 MHz. HRMS (ESI) measurements were made with a Q-tof-Micro (YA-263) mass spectrometer.

All known compounds (see Table 2) had physical spectroscopic data (IR, ^1H NMR) corresponding to the literature; all new compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy, and HRMS spectrometry.

Imidazo[1,2-*a*]pyridines 4a–ab; General Procedure

To a mixture of 2-aminopyridine **3** (1.2 mmol) and CuI (0.05 mmol) in toluene (5 mL) under N_2 atmosphere were added aldehyde **1** (1 mmol), $NaHSO_4{\cdot}SiO_2$ (123 mg, 0.27 mmol with respect to $NaHSO_4$), and terminal alkyne **2** (1.5 mmol) successively. The resulting mixture was stirred under reflux until completion of the reaction (TLC monitoring, 12–14 h, Table 2). Then the mixture was filtered through a short plug of alumina, and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated under vacuum to give the crude product, which was purified by column chromatography (silica gel, EtOAc–PE–Et_3N).

3-Benzyl-2-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridine (4d)

White crystals (EtOAc–PE); yield: 0.305 g (89%); mp 124 °C.

IR (KBr): 3069, 3024, 2361, 1503, 1495, 1450, 1440, 1359, 1272, 1257 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 3.77 (s, 3 H), 4.36 (s, 2 H), 6.57–6.61 (t, *J* = 6.0 Hz, 1 H), 6.77–6.79 (d, *J* = 6.0 Hz, 1 H), 7.00–7.26 (m, 8 H), 7.54–7.61 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 55.75, 55.8, 111.1, 111.5, 112.1, 117.3, 120.2, 123.1, 124.0, 126.8, 127.6, 129.0, 136.9, 144.0, 144.7, 148.8, 149.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_2$: 345.1603; found: 345.1606.

3-Benzyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (4j)

Yellow crystals (EtOAc–PE); yield: 0.231 g (70%); mp 158 °C.

IR (KBr): 3079, 3052, 2352, 1519, 1492, 1350, 1280, 1250, 1091 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.53 (s, 2 H), 6.77–6.81 (t, *J* = 6.6 Hz, 1 H), 7.13 (d, *J* = 6.7 Hz, 2 H), 7.23 (s, 1 H), 7.26–7.37 (m, 3 H), 7.71 (d, *J* = 9.1 Hz, 1 H), 7.76 (d, *J* = 6.9 Hz, 1 H), 7.96 (d, *J* = 8.8 Hz, 2 H), 8.29 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0, 113.1, 118.0, 119.6, 123.7, 124.1, 125.3, 127.4, 127.7, 128.7, 128.9, 136.1, 141.2, 141.8, 145.4, 147.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}N_3O_2$: 330.1243; found: 330.1248.

3-Benzyl-2-[4-(dimethylamino)phenyl]imidazo[1,2-*a*]pyridine (4k)

Pale-yellow crystals (EtOAc–PE); yield: 0.238 g (73%); mp 255–256 °C.

IR (KBr): 2917, 2849, 1617, 1515, 1492, 1450, 1359, 1198, 1062 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (s, 6 H), 4.48 (s, 2 H), 6.66 (t, *J* = 6.7 Hz, 1 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 7.11–7.17 (m, 3 H), 7.24–7.32 (m, 3 H), 7.68 (t, *J* = 8.8 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1, 40.6, 111.9, 112.6, 116.5, 117.2, 122.7, 123.2, 123.8, 126.9, 127.9, 129.1, 137.3, 144.7, 144.8, 150.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_3$: 328.1814; found: 328.1808.

3-Benzyl-2-(2-methylphenyl)imidazo[1,2-*a*]pyridine (4l)

Semisolid; yield: 0.238 g (80%).

IR (KBr): 3021, 1643, 1602, 1505, 1491, 1449, 1358, 1258, 1172, 1028 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 4.30 (s, 2 H), 6.68 (t, *J* = 6.8 Hz, 1 H), 7.05 (d, *J* = 6.9 Hz, 2 H), 7.16–7.34 (m, 8 H), 7.64–7.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 29.8, 112.0, 117.6, 118.9, 123.9, 125.5, 126.8, 127.9, 128.7, 130.5, 130.6, 133.9, 136.9, 138.6, 144.6, 145.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}N_2$: 299.1548; found: 299.1551.

3-Benzyl-6-bromo-2-phenylimidazo[1,2-*a*]pyridine (4q)

White crystals (EtOAc–PE); yield: 0.298 g (82%);mp 209–210 °C.

IR (KBr): 3081, 2908, 2362, 1519, 1493, 1450, 1388, 1324, 1253, 1081 cm^{-1}.

^{1} H NMR (300 MHz, $CDCl_3$): δ = 4.47 (s, 2 H), 7.14 (d, *J* = 7.1 Hz, 2 H), 7.23–7.46 (m, 7 H), 7.58 (d, *J* = 9.5 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.84 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 107.0, 118.2, 118.3, 123.4, 127.2, 127.6, 128.0, 128.2, 128.7, 129.2, 134.0, 136.2, 143.3, 145.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}BrN_2$: 363.0497; found: 363.0500.

3-Benzyl-6-bromo-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine (4t)

White crystals (EtOAc–PE); yield: 0.303 g (80%); mp 208–209 °C.

IR (KBr): 3081, 2908, 2362, 1519, 1493, 1450, 1388, 1324, 1253, 1082 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 4.40 (s, 2 H), 7.06 (d, *J* = 6.9 Hz, 2 H), 7.14–7.30 (m, 6 H), 7.50 (d, *J* = 9.3 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 2 H), 7.75 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 29.9, 106.8, 118.1, 123.3, 127.1, 127.4, 127.7, 128.0, 129.2, 129.5, 131.1, 136.3, 137.9, 143.3, 145.1, 162.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}BrN_2$: 377.0653; found: 377.0657.

3-Benzyl-6-bromo-2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine (4u)

White crystals (EtOAc–PE); yield: 0.315 g (81%); mp 198 °C.

IR (KBr): 3066, 2360, 2220, 1608, 1518, 1495, 1409, 1242, 1068 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.48 (s, 2 H), 7.11 (d, *J* = 6.8 Hz, 2 H), 7.27 (d, *J* = 4.6 Hz, 1 H), 7.33–7.35 (m, 3 H), 7.59 (d, *J* = 9.5 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 2 H), 7.86–7.88 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 107.7, 111.4, 118.5, 118.9, 119.5, 123.5, 127.46, 127.50, 128.5, 129.4, 132.5, 135.5, 138.6, 142.8, 143.6, 152.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}BrN_3$: 388.0449; found: 388.0451.

3-Benzyl-6-methyl-2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine (4v)

White crystals (EtOAc–PE); yield: 0.268 g (83%); mp 205–206 °C.

IR (KBr): 3024, 2358, 2223, 1605, 1551, 1494, 1454, 1418, 1346, 1182 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 4.46 (s, 2 H), 7.06–7.12 (m, 3 H), 7.27–7.35 (m, 3 H), 7.51 (s, 1 H), 7.58 (d, *J* = 9.2 Hz, 1 H), 7.7 (d, *J* = 8.2 Hz, 2 H), 7.87 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 29.8, 110.8, 117.1, 118.7, 119.1, 121.0, 122.6, 127.2, 127.6, 128.2, 128.3, 129.2, 132.4, 136.3, 139.4, 141.8, 144.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{18}N_3$: 324.1501; found: 324.1504.

3-(4-Methylbenzyl)-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (4x)

White crystals (EtOAc–PE); yield: 0.214 g (70%); mp 126 °C.

IR (KBr): 3104, 1573, 1538, 1492, 1382, 1338, 1271, 1192, 1178, 1032 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.50 (s, 2 H), 6.70 (t, *J* = 4.2 Hz, 4.5 Hz, 1 H), 7.04 (d, *J* = 4.8 Hz, 2 H), 7.08–7.10 (m, 3 H), 7.14–7.18 (m, 1 H), 7.34 (d, *J* = 3.0 Hz, 1 H), 7.41 (d, *J* = 2.7 Hz, 1 H), 7.65 (d, *J* = 5.4 Hz, 1 H), 7.73 (d, *J* = 4.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 29.6, 112.4, 117.4, 117.7, 123.3, 124.5, 124.7, 125.6, 127.75, 127.8, 129.8, 133.3, 136.7, 137.7, 138.5, 144.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$: 305.1112; found: 305.1107.

3-Benzyl-6-methyl-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (4y)

Pale-yellow crystals (EtOAc–PE); yield: 0.231 g (76%); mp 185 °C.

IR (KBr): 3104, 3065, 2920, 1573, 1538, 1492, 1430, 1382, 1338, 1271, 1192, 1032 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 4.52 (s, 2 H), 7.01–7.09 (m, 2 H), 7.15–7.18 (d, *J* = 7.3 Hz, 2 H), 7.24–7.36 (m, 5 H), 7.51–7.57 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 30.6, 111.9, 117.4, 117.9, 121.5, 122.9, 125.1, 126.1, 127.6, 128.46, 128.5, 128.9, 129.8, 130.9, 137.3, 138.3, 140.0, 144.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$: 305.1112; found: 305.1116.

2-(1,3-Diphenylprop-2-ynylamino)-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (6)

White solid (EtOAc–PE); mp 183 °C.

IR (KBr): 3390, 3227, 3223, 1649, 1544, 1421, 1263, 1022 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (d, *J* = 8.2 Hz, 1 H), 6.06 (d, *J* = 8.1 Hz, 1 H), 7.16–7.19 (m, 2 H), 7.30–7.36 (m, 6 H), 7.45–7.47 (m, 5 H), 7.50–7.57 (m, 5 H), 7.64–7.67 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.2, 85.5, 86.3, 88.2, 95.4, 115.0, 115.2, 122.2, 127.2, 127.4, 128.5, 128.6, 128.9, 129.2, 129.4, 130.3, 131.1, 131.9, 133.4, 136.4, 138.0, 156.1, 158.5, 169.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{23}N_4S$: 519.1643; found: 519.1645.

3-Benzyl-2,7-diphenyl-5-(phenylthio)imidazo[1,2-*a*]pyridine-6,8-dicarbonitrile (12)

Yellow crystal (EtOAc–PE); mp 220–222 °C.

IR (KBr): 3480, 3323, 3157, 3028, 2903, 2368, 2208, 1607, 1498, 1363, 1260 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.58 (s, 1 H), 5.19 (s, 1 H), 7.01–7.03 (m, 2 H), 7.12 (m, 2 H), 7.32–7.34 (m, 6 H), 7.41–7.43 (m, 4 H), 7.57–7.59 (m, 4 H), 7.65–7.66 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9, 53.4, 59.6, 103.9, 114.3, 115.0, 122.0, 126.2, 126.9, 127.5, 128.66, 128.74, 128.9, 129.0, 129.4, 129.5, 129.6, 131.2, 131.6, 132.9, 133.2, 137.9, 141.1, 146.1, 153.2, 154.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{23}N_4S$: 519.1643; found: 519.1639.

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