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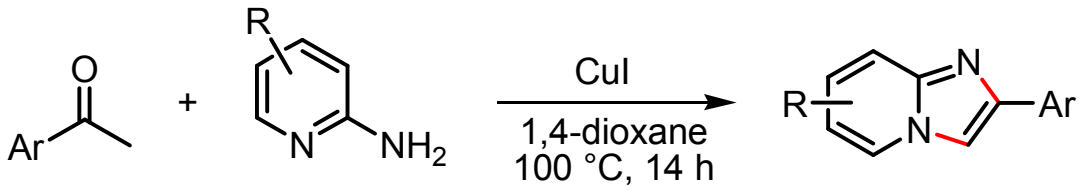
Graphical Abstract



31 examples

R = H, 3-CH_3, 4-CH_3, 5-CH_3
Ar = Ph, 4-OCH_3Ph, 2-BrPh, 4-BrPh, 4-FPh, 4-ClPh, Napth, 3-CH_3Ph, 4-CH_3Ph, 3-NO_2Ph, 4-NO_2Ph, 3,4-$(OCH_3)_2$Ph, 2-OCH_3Ph, 2-OHPh, Thienyl

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Paper

Copper catalyzed tandem oxidative C–H amination/cyclizations: Direct access to imidazo[1,2-a]pyridines†

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A simple and convenient strategy is described for the synthesis of imidazo[1,2-a]pyridines *via* inexpensive copper catalyzed tandem imine formation and intramolecular aerobic oxidative C–H bond amination/cyclizations. An array of imidazo[1,2-a]pyridines were prepared by the reaction of readily available acetophenones and 2-aminopyridines in good to excellent yields (48-92%). The scope of method was validated by single step synthesis of Zolimidine, drug used for peptic ulcers, in 61% yield.

Introduction

Transition metal-catalyzed C–H activation reactions have emerged as an active field of research in organic synthesis.[1-3] These reactions are most ideal for forming carbon-carbon (C–C) or carbon-heteroatom (C–heteroatom) bonds from the viewpoint of synthetic simplicity, atom-economy and efficiency. Moreover, this activation of C–H bond avoids pre-functionalization of the substrates prior to the coupling reactions and provides a more efficient and straightforward access to the target molecules. Over the last decade, excellent efforts have been made towards the synthesis of ample of bioactive heterocyclic molecules and natural products through direct C–C or C–heteroatom bond formations.[4-7] Efficiency of copper catalysts is well demonstrated in literature since last century where these salts are proved to catalyze plethora of cross-coupling reactions to form C–C as well as C–heteroatom bonds for the synthesis of natural products and bioactive molecules.[8-11] Because of their economical attractiveness, low toxicity and good functional group tolerance, copper salts have became potential alternative to their expensive counterparts such as palladium, rhodium and ruthenium catalysts.[12-14]In this context, copper salts also proved as an efficient catalyst for direct C–C as well as C–heteroatom bond formations *via* oxidative cyclizations, cross dehydrogenative couplings (CDC).[15-20]

Imidazo[1,2-a]pyridines are an important class of privileged structural motifs in bioactive compounds, pharmaceuticals and organic functional materials. Compounds with imidazo[1,2-a]pyridines motif have been studied for various biological properties such antiviral,[21, 22] antibacterial,[23]antifungal,[24, 25] K^+-stimulated ATPase inhibition,[26] bradykinin B2 receptor antagonists,[27] anti-rhinoviral,[28, 29] antiulcer,[30] and antihelminthics .[24] This structural motif have been found in several commercially available drugs such Alpidem, Zolpidem, Olprinone, Zolimidine, Saripidem, Necopidem, Miroprofen and recently developed anti-HIV drug, GSK812397 (Figure 1). Moreover, 2-(2-hydroxy phenyl)imidazo[1,2-a]pyridines have displayed excellent excited state intramolecular proton transfer (ESIPT).[31-33]Ubiquity of these skeletons in biologically active compounds continues to give an impetus to develop novel methods for their synthesis.

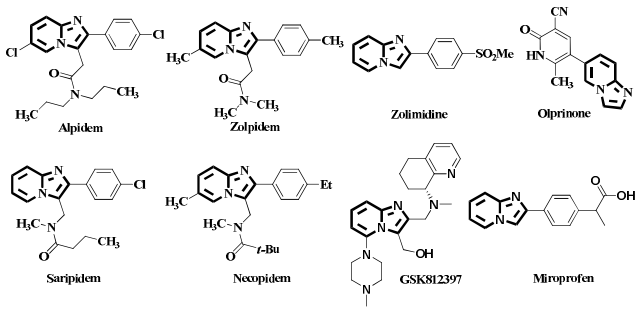

Fig. 1 Chemical structure of drugs containing imidazo[1,2-a]pyridine motif

The most convenient method to attain imidazo[1,2-a]pyridine nucleus is the reaction between 2-aminopyridines and α-halo carbonyl compounds.[34] However, use of lachrymatory phenacyl bromides makes this method less preferred in present era of green chemistry. Other methods, which result substituted imidazo[1,2-a]pyridines are (a) three component reaction of 2-aminopyridines, aldehydes and isonitriles also referred as Groebke-Blackburn-Bienayme reaction[35-37] (b) three component reaction of 2-aminopyridines, aldehydes and alkynes[38, 39] (c) *via* Ortolova-king type reaction[32] (d) using bielectrophilic nitro-alkene precursors[40-42] (e) oxidative cross-coupling reaction using alkynes[43, 44] as well as β-ketoesters or 1,3-diones[45]as electrophiles. Although, several synthetic methodologies have been exploited towards the synthesis of imidazo[1,2-a]pyridines,[46, 47]there have been no reports of a ligand free catalyst system that can effectively synthesize imidazo[1,2-a]pyridines from acetophenones and 2-aminopyridines.[48] Thus, there is an intrinsic need to develop a

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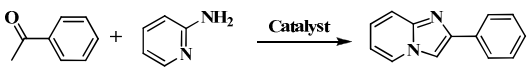
novel method to construct these significant bioactive motifs from commercially available precursors. To our continuous interest in the area of imidazo[1,2-a]pyridines,[49-51] we wish to report an efficient method for the synthesis of 2-arylimidazo[1,2-a] pyridines by the reaction of acetophenones and 2-aminopyridines *via* tandem oxidative C–H amination/cyclizations catalyzed by copper iodide (CuI) in the absence of external ligand.

Results and discussion

We envisioned that the use of lachrymatory phenacyl bromides in the synthesis of imidazo[1,2-a]pyridines can be replaced by simple acetophenones using copper catalysts as they can enable the C–N bonding by oxidative C–H aminations.[17, 18] Acetophenone (**1a**), and 2-aminopyridine (**2a**) were chosen as the model substrates for the initial investigations to optimize the reaction conditions, and the results are summarized in Table 1. A mixture of **1a** (1 mmol), **2a** (1.2 mmol), and $Cu(OTf)_2$ (0.1 mmol) in 1,4-dioxane was stirred at 100 °C for 14 h. Unfortunately, no reaction was occurred in presence of $Cu(OTf)_2$ (entry 1). However, to our delight, when the starting materials were treated with dual catalytic system, $Cu(OTf)_2$ (10 mol %) and CuI (10 mol %), the product was isolated in 45% yield, which was confirmed as the targeted 2-phenylimidazo[1,2-a]pyridine (**3aa**) (entry 2). We then attempted the same conversion with only 10 mol % of CuI, which resulted the product (**3aa**) in 48% isolated yield (entry 3). From these observations, CuI was found to be effective catalyst for this transformation. When the catalyst loading was increased to 20 mol %, the target molecule **3aa** was isolated in 71% yield (entry 4). Further increase in the catalyst loading did not influence the yields of tandem product. Other catalysts examined were either poorly effective (CuBr, CuCl, $Cu(OAc)_2.H_2O$, $CuBr_2$, $CuCl_2.2H_2O$, entries 5, 6, 7, 8, and 9 respectively) or entirely ineffective (Cu(OTf) and $CuSO_4.5H_2O$, entries 10 and 11).

Table 1 Optimization of reaction conditions for the synthesis of **4a**.[a]



1a **2a** **3aa**

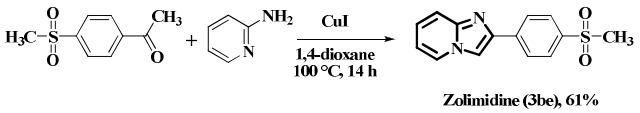
Entry	Catalyst	Solvent	Yield(%)[b]
1.	$Cu(OTf)_2$	1,4-Dioxane	NR[c,d]
2.	$Cu(OTf)_2$/ CuI	1,4-Dioxane	45[c]
3.	CuI	1,4-Dioxane	48[c]
4.	**CuI**	**1,4-Dioxane**	**71**
5.	CuBr	1,4-Dioxane	35
6.	CuCl	1,4-Dioxane	26
7.	$Cu(OAc)_2.H_2O$	1,4-Dioxane	22
8.	$CuBr_2$	1,4-Dioxane	16
9.	$CuCl_2.2H_2O$	1,4-Dioxane	31
10.	Cu(OTf)	1,4-Dioxane	NR[d]
11.	$CuSO_4.5H_2O$	1,4-Dioxane	NR[d]
12.	CuI	DMF[e]	48
13.	CuI	DMSO[f]	42
14.	CuI	Toluene	46
15.	CuI	DCE[g]	67
16.	CuI	ACN[h]	62
17.	CuI	EtOH	65
18.	CuI	H_2O	12

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), Catalyst (0.2 mmol), Solvent (3.0 mL), 100 °C, 14 h. [b]Isolated yields. [c]10 mol % of catalyst used. [d] NR= no reaction.[e]*N, N*-Dimethylformamide . [f] Dimethyl sulfoxide. [g]1,2-Dichloroethane. [h]Acetonitrile.

During the examination of the effect of solvent using 20 mol % of CuI, we found that solvents like *N, N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and toluene gave moderate yields of tandem product (entries 12, 13, and 14 respectively), while 1,2-dichloroethane (DCE), acetonitrile (ACN) and ethanol produced good yields of **3aa** (entries 15, 16, and 17 respectively). It is noteworthy that use of water as reaction medium was found less effective for this transformation (entry 18). Among the solvents screened, 1,4-dioxane was found to be best solvent for the synthesis of **3aa** (entry 4). The results showed that the reaction proceeded optimally with 20 mol % CuI in 1,4-dioxane.

With the optimized conditions in hand (entry 4, Table 1), we next explored the generality of the reaction, and the results are summarized in Table 2. Diversely substituted 2-aminopyridines reacted smoothly to give tandem products in good yields (60-79%, entries 1, 2, 4, and 6, Table 2). The results demonstrated that a wide range of acetophenones regardless of electron-rich and electron-deficient groups on *ortho*-, *meta*-, *para*- position of aryl ring were suitable substrates for the tandem cyclization reaction and gave corresponding imidazo[1,2-a]pyridines in moderate to excellent yields (Table 2). For example, acetophenones bearing electron rich groups such as methyl, methoxy, dimethoxy provided good yields of tandem products (48-79%, entries 5-14, Table 2). Acetophenones with halo substitutions like fluoro, chloro, and bromo were well tolerated under the reaction conditions and gave good yields of tandem products (56-87%, entries 15-22, Table 2). When 2'-bromo acetophenone was used as a substrate, reactions proceeded smoothly with the quantitative conversions but traces of de-halogenated product were observed during column purifications (entries 19 and 20, Table 2). Acetophenones bearing electron withdrawing groups, such as nitro gave good to excellent yield of corresponding imidazo[1,2-a]pyridines (52-92%, entries 23-28, Table 2). It is worth to mention that the synthesis of these 2-(4-nitrophenyl)imidazo[1,2-a]pyridines (entries 27 and 28, Table 2) is exceptional in the reported oxidative coupling methods.[41, 44] 2-(Imidazo[1,2-a]pyridin-2-yl)phenol, which displayed ESIPT could be successfully achieved using the optimized reaction conditions (61%, entry 29, Table 2). The optimized condition was smoothly extended towards heterocyclic compound like 2-acetyl thiophene and the corresponding tandem product, 2-(thiophen-2-yl) imidazo[1,2-a]pyridine was isolated in good yield (56%, entry 30, Table 2).

Finally, scope of the methodology was validated by synthesizing Zolimidine, drug used for peptic ulcers, in single step (Scheme 1). When 1-(4-(methylsulfonyl)phenyl)ethanone (1.0 mmol) was treated with 2-aminopyridine (1.2 mmol) in the presence of CuI (0.2 mmol) in 1,4-dioxane at 100 °C for 14 h, Zolimidine (**3be**) was isolated in 61% yield.



Scheme 1 One-step synthesis of Zolimidine (**3be**)

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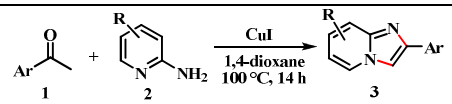
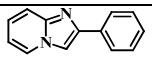
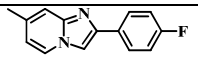
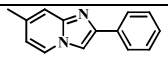
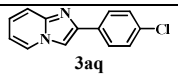
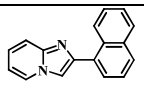
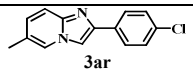
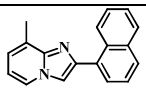
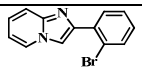
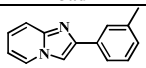
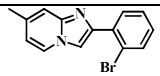
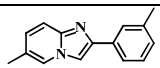
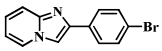
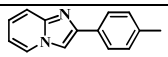
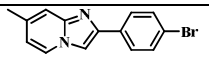
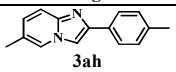
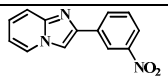
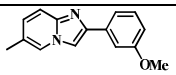
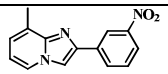
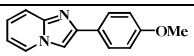
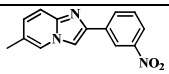
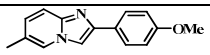
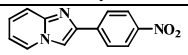
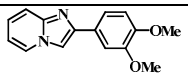
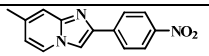
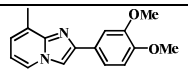
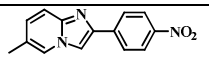
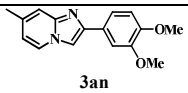
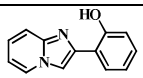
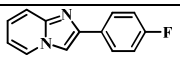
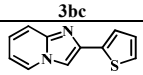
Paper

Table 2 CuI catalyzed tandem synthesis of substituted imidazo[1,2-a]pyridines[a]



Entry	1(Ar)	2(R)	Product	Yield%[b]		Entry	1(Ar)	2(R)	Product	Yield %[b]
1	Ph	H	 **3aa**	71		16	4-FC_6H_4	3-Me	 **3ap**	58
2	Ph	4-Me	 **3ab**	79		17	4-ClC_6H_4	H	 **3aq**	62
3	1-Naphthyl	H	 **3ac**	68		18	4-ClC_6H_4	5-Me	 **3ar**	56
4	1-Naphthyl	3-Me	 **3ad**	60		19	2-BrC_6H_4	H	 **3as**	60
5	3-MeC_6H_4	H	 **3ae**	79		20	2-BrC_6H_4	4-Me	 **3at**	87
6	3-MeC_6H_4	5-Me	 **3af**	73		21	4-BrC_6H_4	H	 **3au**	58
7	4-MeC_6H_4	H	 **3ag**	72		22	4-BrC_6H_4	4-Me	 **3av**	76
8	4-MeC_6H_4	5-Me	 **3ah**	76		23	3-$NO_2C_6H_4$	H	 **3aw**	52
9	3-$OMeC_6H_4$	5-Me	 **3ai**	49		24	3-$NO_2C_6H_4$	3-Me	 **3ax**	69
10	4-$OMeC_6H_4$	H	 **3aj**[c]	48		25	3-$NO_2C_6H_4$	5-Me	 **3ay**	60
11	4-$OMeC_6H_4$	5-Me	 **3ak**	62		26	4-$NO_2C_6H_4$	H	 **3az**	86
12	3,4-$(OMe)_2C_6H_3$	H	 **3al**	74		27	4-$NO_2C_6H_4$	4-Me	 **3ba**	92
13	3,4-$(OMe)_2C_6H_3$	3-Me	 **3am**	68		28	4-$NO_2C_6H_4$	5-Me	 **3bb**	91
14	3,4-$(OMe)_2C_6H_4$	4-Me	 **3an**	71		29	2-OHC_6H_4	H	 **3bc**	61
15	4-FC_6H_4	H	 **3ao**	63		30	2-Thienyl	H	 **3bd**	56

[a] Reaction conditions; 1 (1.0 mmol), 2 (1.2 mmol), CuI (0.2 mmol), 1,4-dioxane, 100 °C, 14 h. [b] Isolated yields. [c] Ethanol was used as solvent with reaction time 22 h

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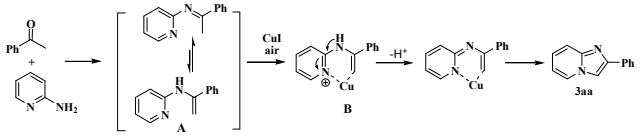
The mechanism of the reported reaction is uncertain at this stage. It is proposed that the formation of imidazo[1,2-a]pyridine **3** could be explained by initial formation of imine from the reaction of ketone and 2-aminopyridine which can equilibrate to enamine **A** (Scheme 2). Reaction of **A** with CuI generates adduct **B** that undergoes intramolecular aerobic oxidative cyclization to give **3aa**. The proposed mechanism is based on literature precedent[48, 52, 53] and further investigation is under progress in our laboratory.



Scheme 2 Plausible mechanism for the synthesis of **3aa**.

Experimental

General

Melting points were determined in open capillary tubes on a EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were characterized by nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) determined on a Bruker AV 300 spectrometer. ^{13}C NMR spectra are fully decoupled. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (internal) as the standard. All chemicals were obtained from commercial suppliers and used without further purification.

General procedure for the synthesis of 2-aryl imidazo[1,2-a]pyridines via tandem oxidative amination /cyclizations: A clean oven-dried 10 mL RB flask was charged with acetophenone **1a** (120 mg, 1.0 mmol), 2-amino pyridine **2a** (113 mg, 1.2 mmol), CuI (38 mg, 0.2 mmol) and 1,4-dioxane (3.0 mL). The resulting solution was stirred at 100 °C for 14 h under ambient air. On completion, the reaction mass was evaporated to dryness. The crude residue was purified by column chromatography (EtOAc: Hexanes, 1:2) to obtain tandem product, 2-phenylimidazo[1,2-a]pyridine **3aa** in 138 mg**.**

2-Phenylimidazo[1,2-a]pyridine (3aa): Yield 71%; off-white solid; mp 134-136 °C (lit. 136-137 °C,[54] 131-133 °C[47]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 6.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.85 (s, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.78 (t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.74, 137.95, 133.65, 128.69, 127.99, 126.11, 125.59, 124.76, 117.55, 112.51, 108.19.

7-Methyl-2-phenylimidazo[1,2-a]pyridine (3ab): yield 79%; off-white solid; mp 162-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.84 (m, 3H), 7.71 (s, 1H), 7.43 – 7.37 (m, 3H), 7.33 – 7.23 (m, 1H), 6.55 (dd, J = 6.9, 1.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.14, 145.50, 135.54, 133.97, 128.65, 127.76, 125.97, 124.77, 115.88, 115.00, 107.54, 21.37.

2-(Naphthalen-1-yl)imidazo[1,2-a]pyridine (3ac): yield 68%; yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 – 8.57 (m, 1H), 8.09 (dt, J = 6.8, 1.1 Hz, 1H), 7.92 – 7.79 (m, 3H), 7.78 (s, 1H), 7.68 (dd, J = 9.1, 0.7 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.20 – 7.11 (m, 1H), 6.75 (td, J = 6.8, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.38, 145.23, 133.99, 131.81, 131.52, 128.47, 128.37, 127.71, 126.46, 125.98, 125.80, 125.57, 125.42, 124.58, 117.70, 112.40, 111.23.

8-Methyl-2-(naphthalen-1-yl)imidazo[1,2-a]pyridine (3ad): yield 60%; brownish syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 – 8.55 (m, 1H), 8.00 (d, J = 6.4 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.80 (dd, J = 7.1, 1.2 Hz, 1H), 7.77 (s, 1H), 7.56 – 7.45 (m, 3H), 6.99 – 6.95 (m, 1H), 6.69 (t, J = 6.8 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.75, 144.72, 134.00, 132.08, 131.76, 128.35, 128.30, 127.76, 127.72, 126.33, 126.15, 125.75, 125.43, 123.40, 123.26, 112.39, 111.67, 17.27.

2-m-Tolylimidazo[1,2-a]pyridine (3ae): yield 79%; colorless solid; mp 97-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dt, J = 6.8, 1.1 Hz, 1H), 7.83 (s, 1H), 7.81 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.62 (dd, J = 9.1, 0.7 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.18 – 7.08 (m, 2H), 6.73 (td, J = 6.8, 1.1 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.89, 145.63, 138.39, 133.63, 128.75, 128.59, 126.74, 125.56, 124.57, 123.11, 117.48, 112.34, 108.12, 21.45.

6-Methyl-2-m-tolylimidazo[1,2-a]pyridine (3af): yield 73%; colorless solid; mp 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.98 (dd, J = 9.2, 1.4 Hz, 1H), 2.40 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.46, 144.63, 138.33, 133.69, 128.59, 128.54, 127.84, 126.62, 123.31, 123.00, 122.00, 116.70, 107.87, 21.44, 18.07.

2-p-Tolylimidazo[1,2-a]pyridine (3ag): yield 72%; colorless solid; mp 144-146 °C (lit.[46] 144-145 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dt, J = 6.8, 1.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.75 (s, 1H), 7.59 (dd, J = 9.1, 0.6 Hz, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.14 – 7.06 (m, 1H), 6.69 (td, J = 6.8, 1.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.89, 145.61, 137.76, 130.98, 129.43, 125.93, 125.52, 124.45, 117.38, 112.23, 107.78, 21.30.

6-Methyl-2-p-tolylimidazo[1,2-a]pyridine (3ah): yield 76%; colorless solid; mp 204-205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.67 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.02 (dd, J = 9.2, 1.5 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.10, 144.49, 137.74, 130.56, 129.37, 128.23, 125.73, 123.35, 122.27, 115.92, 107.70, 21.10, 17.85.

2-(3-Methoxyphenyl)-6-methylimidazo[1,2-a]pyridine (3ai): yield 49%; pale-yellow solid; mp 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.73 (s, 1H), 7.56 – 7.52 (m, 1H), 7.51 – 7.48 (m, 1H), 7.48 – 7.45 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 6.99 (dd, J = 9.2, 1.6 Hz, 1H), 6.87 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.88 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.04, 145.35, 144.67, 135.39, 129.65, 127.84, 123.31, 122.04, 118.40, 116.79, 114.02, 110.85, 108.12, 55.37, 18.08.

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2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine (3aj): yield 48%; colorless solid; mp 136-138 °C (lit.[46] 137-138 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dt, J = 6.8, 1.2 Hz, 1H), 7.87 (d, J = 8.9 Hz, 2H), 7.73 (s, 1H), 7.59 (dd, J = 9.1, 0.7 Hz, 1H), 7.16 – 7.08 (m, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.71 (td, J = 6.8, 1.1 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.58, 145.71, 145.61, 127.29, 126.50, 125.46, 124.42, 117.25, 114.14, 112.21, 107.24, 55.30.

2-(4-Methoxyphenyl)-6-methylimidazo[1,2-a]pyridine (3ak): yield 62%; pale-yellow solid; mp 179-180 °C (lit.[54] 179-181 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 1H), 7.80 (d, J = 8.9 Hz, 2H), 7.63 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 7.01 (dd, J = 9.2, 1.6 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.46, 144.94, 144.49, 128.13, 127.11, 126.18, 123.31, 122.18, 115.83, 114.10, 107.19, 55.20, 17.86.

2-(3,4-Dimethoxyphenyl)imidazo[1,2-a]pyridine (3al): yield 74%; yellow solid; mp 104-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 6.8 Hz, 1H), 7.76 (s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.43 (dd, J = 8.3, 2.0 Hz, 1H), 7.17 – 7.09 (m, 1H), 6.93 – 6.88 (m, 1H), 6.72 (td, J = 6.8, 0.9 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.23, 149.01, 145.77, 145.56, 126.90, 125.45, 124.46, 118.47, 117.24, 112.27, 111.31, 109.25, 107.49, 56.01, 55.92.

2-(3,4-Dimethoxyphenyl)-8-methylimidazo[1,2-a]pyridine (3am): yield 68%; off-white solid; mp 124-126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 6.7 Hz, 1H), 7.74 (s, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.45 (dd, J = 8.3, 2.0 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.63 (t, J = 6.8 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.17, 148.88, 146.09, 145.19, 127.31, 127.26, 123.29, 123.18, 118.58, 112.22, 111.30, 109.48, 107.96, 55.96, 55.92, 17.10.

2-(3,4-Dimethoxyphenyl)-7-methylimidazo[1,2-a]pyridine (3an): yield 71%; yellow solid; mp 135-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.68 (s, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 8.3, 1.8 Hz, 1H), 6.98 (dd, J = 9.2, 1.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.22, 148.88, 145.45, 144.62, 127.63, 127.09, 123.23, 121.87, 118.31, 116.52, 111.29, 109.15, 107.25, 56.01, 55.92, 18.07.

2-(4-Fluorophenyl)imidazo[1,2-a]pyridine (3ao): yield 63%; colorless solid; mp 161-163 °C (lit.[55] 164-165 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dt, J = 6.8, 1.1 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.75 (s, 1H), 7.60 (dd, J = 9.1, 0.6 Hz, 1H), 7.19 – 7.05 (m, 3H), 6.73 (td, J = 6.8, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.32, 161.05, 145.67, 144.90, 130.05, 130.00, 127.73, 127.62, 125.57, 124.75, 117.43, 115.76, 115.48, 112.44, 107.79.

2-(4-Fluorophenyl)-7-methylimidazo[1,2-a]pyridine (3ap): yield 58%; off-white solid; mp 138-139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 6.9 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.68 (s, 1H), 7.35 (d, J = 0.6 Hz, 1H), 7.15 – 7.04 (m, 2H), 6.58 (dd, J = 6.9, 1.6 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.22, 160.95, 146.16, 144.64, 135.71, 130.22, 130.18, 127.63, 127.53, 124.75, 115.81, 115.70, 115.41, 115.07, 107.18, 21.36.

2-(4-Chlorophenyl)imidazo[1,2-a]pyridine (3aq): yield 62%; colorless solid; mp 201-202 °C (lit.[55] 201-202 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 6.8 Hz, 1H), 7.86 – 7.78 (m, 3H), 7.58 (d, J = 9.1 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.26 – 7.15 (m, 1H), 6.79 (t, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.58, 144.20, 133.74, 131.87, 128.87, 127.18, 125.72, 125.43, 116.89, 112.83, 108.44.

2-(4-Chlorophenyl)-6-methylimidazo[1,2-a]pyridine (3ar): yield 56%; colorless solid; mp 210-212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.82 – 7.74 (m, 2H), 7.71 (s, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.05 (dd, J = 9.2, 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.59, 143.83, 133.55, 131.96, 128.81, 128.66, 127.04, 123.41, 122.62, 116.08, 108.17, 17.90.

2-(2-Bromophenyl)imidazo[1,2-a]pyridine (3as): yield 60%; pale yellow solid; mp 80-81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.17 – 8.13 (m, 2H), 7.68 – 7.62 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 2H), 6.78 (t, J = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.53, 143.27, 134.48, 133.64, 131.68, 128.85, 127.50, 125.73, 124.72, 121.50, 117.67, 112.43, 111.97.

2-(2-Bromophenyl)-7-methylimidazo[1,2-a]pyridine (3at): yield 87%; colorless solid; mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 6.9 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.49 – 7.36 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 6.63 (d, J = 6.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.28, 143.27, 136.09, 134.92, 133.96, 132.01, 129.02, 127.77, 125.25, 121.82, 116.27, 115.47, 111.73, 21.58.

2-(4-Bromophenyl)imidazo[1,2-a]pyridine (3au): yield 58%; off-white solid; mp 201-203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 6.8 Hz, 1H), 7.87 – 7.75 (m, 3H), 7.61 (d, J = 9.1 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.21 – 7.12 (m, 1H), 6.77 (td, J = 6.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.73, 144.68, 132.76, 131.83, 127.55, 125.62, 124.95, 121.87, 117.56, 112.62, 108.22.

2-(4-Bromophenyl)-7-methylimidazo[1,2-a]pyridine (3av): yield 76%; pale yellow solid; mp 210-212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 6.9 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.71 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.35 (s, 1H), 6.59 (dd, J = 6.9, 1.5 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.20, 144.40, 135.88, 132.98, 131.75, 127.46, 124.78, 121.61, 115.89, 115.22, 107.63, 21.40.

2-(3-Nitrophenyl)imidazo[1,2-a]pyridine (3aw): yield 52%; yellow solid; mp 201-203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.80 – 8.76 (m, 1H), 8.64 (d, J = 0.4 Hz, 1H), 8.56 (dt, J = 6.8, 1.2 Hz, 1H), 8.43 – 8.36 (m, 1H), 8.21 – 8.14 (m, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.64 (dd, J = 9.1, 0.7 Hz, 1H), 7.35 – 7.27 (m, 1H), 6.95 (td, J = 6.8, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.86, 145.49, 142.44, 136.20, 132.17, 130.83, 127.63, 126.17, 122.64, 120.18, 117.34, 113.24, 111.05.

8-Methyl-2-(3-nitrophenyl)imidazo[1,2-a]pyridine (3ax): yield 69%; yellow solid; mp 167-169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 – 8.74 (m, 1H), 8.59 (s, 1H), 8.42 – 8.35 (m, 2H), 8.19 – 8.12 (m, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.16 – 7.06 (m, 1H), 6.84 (t, J = 6.8 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.78, 145.97, 141.81, 136.31, 132.12, 130.70, 126.87, 125.28, 124.45, 122.45, 120.07, 113.14, 111.46, 17.10.

6-Methyl-2-(3-nitrophenyl)imidazo[1,2-a]pyridine (3ay): yield 60%; yellow solid; mp 159-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (t, J = 1.9 Hz, 1H), 8.32 – 8.26 (m, 1H), 8.17 – 8.10 (m, 1H), 7.91 (s, 1H), 7.87 (s, 1H), 7.64 – 7.46 (m, 2H), 7.06 (dd, J = 9.2, 1.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.69, 144.97, 143.08, 135.89, 131.65, 129.60, 128.65, 123.47, 122.70, 122.24, 120.57, 117.00, 108.77, 18.11.

2-(4-Nitrophenyl)imidazo[1,2-a]pyridine (3az): yield 86%; yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.58 (d, J = 6.8 Hz, 1H), 8.31 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.1 Hz, 1H), 7.37 – 7.27 (m, 1H), 6.96 (td, J = 6.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.94, 145.72, 142.45, 140.97, 127.72, 126.76, 126.40, 124.65, 117.45, 113.39, 112.15.

7-Methyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (3ba): yield 92%; yellow solid; mp 214-216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.45 (d, J = 7.0 Hz, 1H), 8.29 (d, J = 9.1 Hz, 2H), 8.20 (d, J = 9.1 Hz, 2H), 7.39 (s, 1H), 6.80 (dd, J = 6.9, 1.6

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Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.79, 146.14, 142.22, 141.17, 136.90, 126.86, 126.62, 124.59, 115.89, 115.58, 111.62, 21.33.

6-Methyl-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (3bb): yield 91%; yellow solid; mp 239-241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.36 (s, 1H), 8.29 (d, J = 9.0 Hz, 2H), 8.21 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.2 Hz, 1H), 7.18 (dd, J = 9.3, 1.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.80, 144.81, 142.27, 141.14, 129.39, 126.61, 124.96, 124.60, 122.67, 116.86, 111.83, 17.98.

2-(Imidazo[1,2-a]pyridin-2-yl)phenol (3bc): yield 61%; colorless solid; mp 140-141 °C (lit.[32] 142-143 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.16 (d, J = 6.7 Hz, 1H), 7.87 (s, 1H), 7.64 – 7.56 (m, 2H), 7.31 – 7.21 (m, 2H), 7.07 (d, J = 8.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.87 (t, J = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.34, 145.30, 143.44, 129.67, 125.75, 125.41, 125.18, 118.99, 117.70, 116.76, 116.21, 113.16, 106.73.

2-(Thiophen-2-yl)imidazo[1,2-a]pyridine (3bd): yield 56%; colorless solid; mp 137-139 °C (lit.[46] 137-138 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 6.8 Hz, 1H), 7.73 (s, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 7.29 (dd, J = 4.9, 0.9 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.10 – 7.05 (m, 1H), 6.73 (t, J = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.43, 140.85, 137.54, 127.74, 125.43, 125.03, 124.81, 123.68, 117.30, 112.53, 107.44.

2-(4-(Methylsulfonyl)phenyl)imidazo[1,2-a]pyridine (Zolimidine, 3be): yield 61%; white-crystalline solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.09 (m, 3H), 8.06 – 7.92 (m, 3H), 7.66 (d, J = 9.1 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 6.84 (t, J = 6.8 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.95, 143.54, 139.22, 139.20, 127.89, 126.57, 125.81, 125.54, 117.84, 113.08, 109.64, 44.59.

Conclusions

In summary, we have successfully developed a novel and efficient method for the synthesis of imidazo[1,2-a]pyridines, a key structural motif of several important pharmacological drug molecules, from commercially available acetophenones and 2-aminopyridines using CuI as catalyst without the use of any additional Lewis acid or external ligand. Since, the depicted methodology tolerates several reactive functionalities such as fluoro, chloro, bromo, hydroxyl, nitro, methoxy etc, these tandem products will allow access to complex molecules by post functionalization. The present methodology is smoothly extended to synthesize anti-ulcer drug, Zolimidine in single step.

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† Electronic Supplementary Information (ESI) available: copy of ^{1}H and ^{13}C NMR of the synthesized compounds **3aa-3bd** and **Zolimidine (3be)**]. See DOI: 10.1039/b000000x/

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