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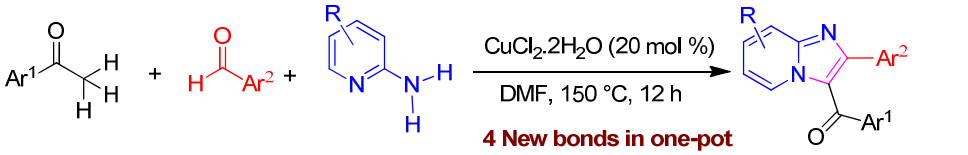
Table of Contents/Abstract Graphic



16 examples, Yield 26-82%

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PAPER

One-pot, Three Component Tandem Reaction of 2-Aminopyridines, Acetophenones and Aldehydes: Synthesis of 3-Aroylimidazo[1,2-*a*]pyridines

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A facile synthesis of 3-aroylimidazo[1,2-*a*]pyridine derivatives has been achieved through the one-pot, three-component tandem reaction of acetophenones, arylaldehydes and 2-aminopyridines in the presence of catalytic amount of copper(II) chloride and air as a sole oxidant. The developed one-pot method is atom-economical and utilizes readily available precursors to offer highly functionalized *N*-fused imidazoles in moderate to good yields (26-82%). The presented tandem process is expected to proceed *via* crossed aldol condensation, Michael addition, copper catalyzed oxidative cyclization and subsequent aromatization.

Introduction

Construction of bioactive fused heterocycles by exploiting transition metal catalyzed coupling reactions is highly challenging and attractive task in organic synthesis.[1] Multicomponent reactions (MCRs) together with tandem sequences have been recognized as a powerful tool in modern organic chemistry for the synthesis of fused heterocycles with diverse substitutions.[2] The basic concepts of disconnections are generally overruled for the synthesis of molecules following the combination of MCRs and tandem processes. Several innovative strategies have been witnessed in last decade where coupling reactions have been amalgamated with MCRs/tandem reactions.[3]

In recent years, synthesis of imidazo[1,2-*a*]pyridines have gained great interest because of their significance in medicinal chemistry, material science and organometallics.[4] Several drugs such as alpidem, zolpidem, zolimidine, saripidem, and necopidem (Figure 1) contain imidazo[1,2-*a*]pyridine skeleton as a core with slight variations in substitutions. In addition, several novel molecules with imidazo[1,2-*a*]pyridine as a key structure have been synthesized and studied for their activity against various biological targets.[5] Among them, 3-aroylimidazo[1,2-*a*]pyridines are the interesting structures with anticancer activities (Figure 1).[6] It has been reported that direct C-3 aroylation of imidazo[1,2-*a*]pyridine nucleus is unsuccessful and desired 3-aroylimidazo[1,2-*a*]pyridines were obtained in four-steps from 2-aminopyridine.[6a] Aroyl functionality has also been reported to be highly responsible for the elevated biological applications of various other heterocycles.[7] In this context, direct methods toward the synthesis of 3-aroylimidazo[1,2-*a*]pyridines is highly desirable.

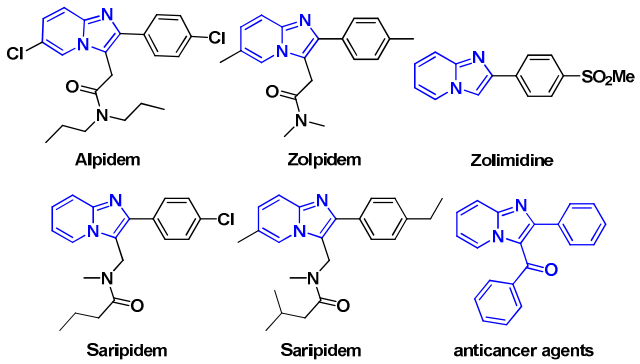
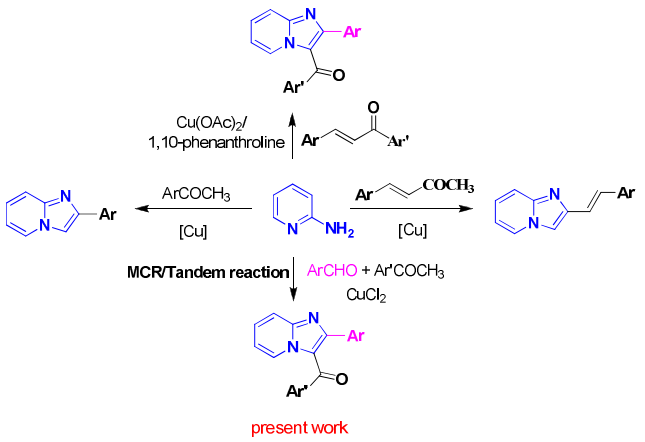


Fig. 1 Bio-active molecules containing imidazo[1,2-*a*]pyridine skeleton

2-Aminopyridine is the most common precursor for the syntheses of imidazo[1,2-*a*]pyridines. Recently, some interesting results have been obtained when 2-aminopyridine was reacted with carbonyl compounds in the presence of copper catalysts (Scheme 1).[8] Several groups including ours have independently shown that 2-arylimidazo[1,2-*a*]pyridines are obtained by the reaction of 2-aminopyridine with methyl ketones in presence of catalytic amount of copper *via* imine formation followed by intramolecular oxidative cyclization (Scheme 1)[9] and Su group reported that 2-alkenylimidazo[1,2-*a*]pyridines were obtained when 2-aminopyridine was reacted with methyl vinyl ketones in the presence of copper (Scheme 1).[10]

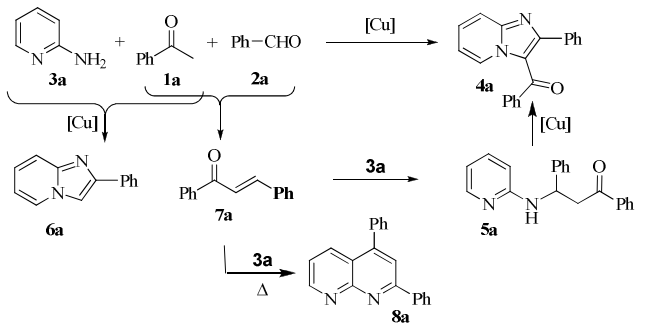
Very recently, Hajra and our group[11] independently reported the copper catalyzed oxidative cyclization of chalcones and 2-aminopyridines for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines. However, to the best of our knowledge there is no report available for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines *via* one-pot, three-component tandem approach. With our continuous interest in synthesis and functionalizations of imidazo[1,2-*a*]pyridines,[9b, 12] herein we wish to report an efficient synthesis of 3-aroylimidazo[1,2-*a*]pyridines *via* one-pot three-component copper catalyzed tandem reaction of acetophenones, arylaldehydes and 2-aminopyridines with air as a sole oxidant (Scheme 1).



Scheme 1 Reaction of 2-aminopyridines with various carbonyl partners in the presence of copper

Results and Discussion

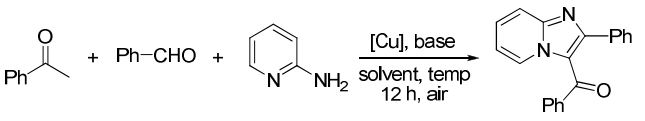
In our initial study, acetophenone (**1a**), benzaldehyde (**2a**) and 2-aminopyridine (**3a**) were chosen as model substrates for the screening of reaction conditions. Based on literature survey, several competing reactions could be expected with the present set of substrates and other parameters which includes 1,3-diphenyl-3-(pyridin-2-ylamino)propan-1-one (**5a**),[11] 2-phenylimidazo[1,2-*a*]pyridine (**6a**),[9b] chalcone (**7a**), 2,4-diphenyl-1,8-naphthyridine (**8a**)[13] (Scheme 2). With these concerns in mind, **1a** (1.0 mmol) was treated with **2a** (1.0 mmol) and **3a** (1.0 mmol) in presence of $CuCl_2.2H_2O$ in toluene for 12 h at reflux. As envisaged, moderate yields of expected product, phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (**4a**) was obtained along with other by-products such as **6a** and **7a** in minor quantities (entry 1, Table 1). However, Michael adduct (**5a**) and naphthyridine (**8a**) were not detected in the reaction mass. The structure of **4a** was characterized by spectral data (IR, MS, and NMR). In the IR spectrum of **4a**, a strong peak appeared at 1597 cm^{-1} for C=O stretching. In the ^1H NMR spectrum of **4a**, a doublet appeared at δ 9.60 ppm for highly deshielded C_5-H along with other protons at their respective positions. The ketonic carbon of **4a** appeared at δ 187.34 along with all other expected carbons in the ^{13}C NMR spectrum. The peak at 299.1162 for $[M+H]^+$ ion in the HRMS mass spectrum of **4a** further confirmed its structure.



Scheme 2 Competing reactions with selected set of precursors

To enhance the yields of tandem product, we turned our focus on minimization of unwanted products by varying the molar ratios of precursors. It was observed that the formation of by-product **6a** could be reduced if rate of reaction between **1a** and **2a** to give **7a** is faster than the rate of reaction between **1a** and **3a**. We succeeded in eliminating formation of **6a** in the reaction by keeping **1a** as a limiting agent with other substrates (**2a** and **3a**) in 1.2 equivalents. Addition of K_2CO_3 to the reaction keeping other parameters same resulted in slight improvement in the yield of **4a** (entry 2, Table 1). A smooth enhancement in yield of **4a** was observed with DMF as solvent (entry 3, Table 1). With the encouraging result in hand, we next increased the reaction temperature to 150 °C keeping other parameters constant. Gratifyingly, excellent yield of **4a** was observed at 150 °C (entry 4, Table 1). Among other solvents, good yields of **4a** were obtained in polar solvents like DMA and DMSO (entries 6-7, Table 1) while moderate yields of **4a** was obtained in water (entry 5, Table 1). Desired product **4a** was not obtained when 1,4-dioxane and ethanol were used as solvents (entries 9-10, Table 1). Simultaneously, various bases were screened for the model reaction and the use of K_2CO_3 gave the optimum result for the tandem process among other bases like Cs_2CO_3, K_3PO_4 and KOH which also offered good yields of tandem products (entries 10 and 12-13, Table 1). However, no product was noticed in case of $NaHCO_3$ (entry 11, Table 1). Attempts were failed to replace the copper catalyst to facilitate higher yields of tandem products (entries 14-17, Table 1).

Table 1 Optimization of reaction conditions[a]



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

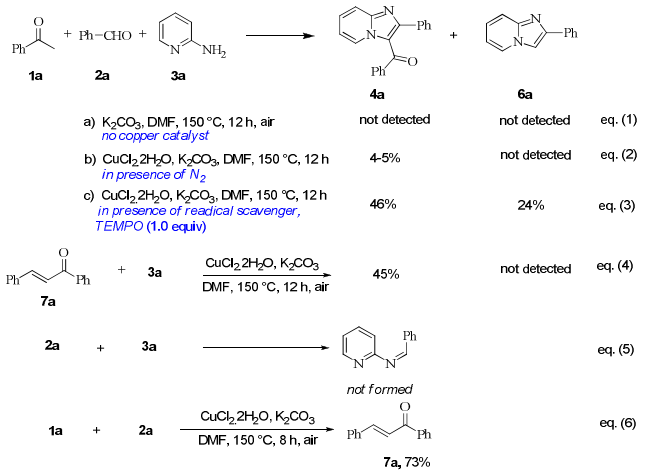
entry	catalyst	base	solvent	temp (°C)	yield (%)[b]
1	$CuCl_2.2H_2O$	-[c]	toluene	120	35
2	$CuCl_2.2H_2O$	K_2CO_3	toluene	120	38
3	$CuCl_2.2H_2O$	K_2CO_3	DMF	120	45
4	**$CuCl_2.2H_2O$**	**K_2CO_3**	**DMF**	**150**	**81**
5	$CuCl_2.2H_2O$	K_2CO_3	water	reflux	55
6	$CuCl_2.2H_2O$	K_2CO_3	DMA	150	72
7	$CuCl_2.2H_2O$	K_2CO_3	DMSO	150	63
8	$CuCl_2.2H_2O$	K_2CO_3	1,4-dioxane	reflux	-[d,e]
9	$CuCl_2.2H_2O$	K_2CO_3	EtOH	reflux	-[d,e]
10	$CuCl_2.2H_2O$	Cs_2CO_3	DMF	150	52
11	$CuCl_2.2H_2O$	$NaHCO_3$	DMF	150	-[d,e]
12	$CuCl_2.2H_2O$	KOH	DMF	150	46
13	$CuCl_2.2H_2O$	K_3PO_4	DMF	150	64
14	$Cu(OAc)_2.H_2O$	K_2CO_3	DMF	150	38
15	$Cu(OTf)_2$	K_2CO_3	DMF	150	66
16	CuBr	K_2CO_3	DMF	150	-[d,e]
17	CuI	K_2CO_3	DMF	150	48

[a]Reagents and conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), **3a** (1.2 mmol), catalyst (20 mol %), base (2.0 mmol), solvent (4 mL), 12 h, air. [b]Isolated yields. [c]No base was present in the reaction and **1a**, **2a**, and **3a** were used 1 mmol each. [d]Starting materials were recovered. [e]**4a** not detected.

With the optimized conditions in hand (entry 4, Table 1), substrate scope for cascade process was evaluated and the results are summarized in Table 2. In early experiments, diversely substituted 2-aminopyridines were tested which offered moderate to good yields of 3-aroylimidazo[1,2-*a*]pyridines (entries 2-4 and 15, Table 2). It is worth to mention that highly sensitive bromo substitution, towards transition metal catalyzed transformations was well tolerated under the optimized conditions and afforded

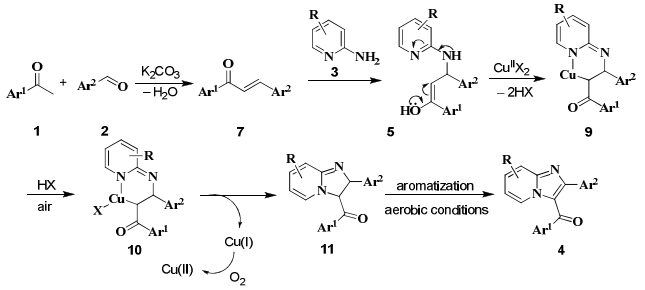
good yields of tandem product (entry 15, Table 1). Aryl aldehydes substituted with electron-withdrawing groups such as 4-Cl, 2-F and 4-NO_2 offered high yields of tandem products (entries 7-8 and 10-16, Table 2). On the other hand, reactions involving aryl aldehydes with electron rich substituents produced 2-arylimidazo[1,2-*a*]pyridines instead of tandem product (entry 17, Table 2). This may be due to the fact that under these reaction conditions, reaction of acetophenones and 2-aminopyridines is faster as compared to the tandem reaction to give corresponding 2-arylimidazo[1,2-*a*]pyridines.[9] To our delight, heterocyclic ketones and aldehydes such as 2-acetylthiophene and thiophene-2-carbaldehyde reacted smoothly under the optimized conditions to give the corresponding tandem products in moderate yields (entries 6 and 9, Table 2).

Next, we performed some control experiments to understand the synthetic sequence and plausible mechanism of the reported protocol (Scheme 3). In the absence of copper catalyst, no product formation was observed (eq. 1, Scheme 3) which confirmed the crucial role of copper catalyst for the successful formation of **4**. When the model reaction was performed under nitrogen atmosphere, only catalytic amount of product was formed which confirms the necessity of aerobic conditions for the current transformation (eq. 2, Scheme 3). Reaction performed in the presence of radical scavenger, (2,2,6,6-tetramethylpiperdin-1-yl)oxy (TEMPO), produced both tandem product **4a** and **6a** in 46% and 24% isolated yields, respectively (eq. 3, Scheme 3). It was concluded that both **4a** and **6a** are formed *via* a non-radical pathway as reported earlier for **6a**.[9] Two synthetic routes could be possible to attain the tandem product **4** from corresponding substrates *via* chalcone intermediate and b) *via* imine intermediate. However, formation of imine was not observed from the reaction of **2a** with **3a** in the absence of **1a** under these conditions (eq. 5, Scheme 3). This excludes the possibility of imine as intermediate in this tandem process. In other experiment **1a** and **2a** were reacted under the same standard reaction condition to result chalcone (**7a**) which confirm the given reaction path (eq. 6, Scheme 3). Thus, it is believed that the probable pathway for this transformation is *via* chalcone intermediate which is formed through the crossed aldol condensation between **1a** and **2a.** This was further supported by the fact that reaction of pre-synthesized chalcone **7a** with **3a** under similar conditions afforded good yield of tandem product **4a** (eq. 4, Scheme 3). It is important to mention that the yield of **4a** was higher from tandem reaction than that of step-wise approach under these conditions.



Scheme 3 Control experiments

Based on literature reports[3a, 11a] and findings from the control experiments, the mechanism of the tandem process for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines is proposed as shown in Scheme 4. It is believed that initially chalcone (**7**) is generated by the crossed aldol condensation of **1** and **2** which then undergoes Michael addition with **3** to afford intermediate **5**. Interaction of **5** with copper salt through pyridinium nitrogen and enolic carbon simultaneously affords intermediate **9**.[11a] Oxidation of copper (II) to copper (III)[9a, 14] gives intermediate **10,** which on reductive elimination may result in the formation dihydro imidazopyridine **11**. Rapid aromatization of intermediate **11** under aerobic conditions affords the desired product **4**. Oxidation of Cu(I) to Cu(II) in the presence of air completes the catalytic cycle.[15] Reaction of 2-aminopyridine (**3**) with methylketones (**1**) in presence of copper results in the formation of 2-arylimidazo[1,2-*a*]pyridines (**6**).[9]



Scheme 4 Plausible mechanism for the synthesis of 3-aroylimdazo[1,2-*a*]pyridines

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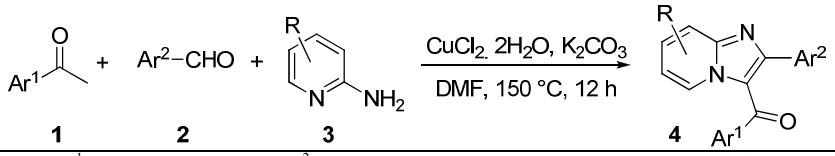
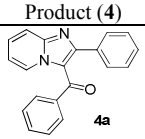
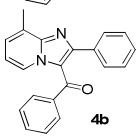
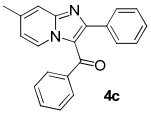
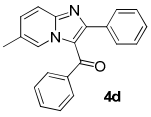
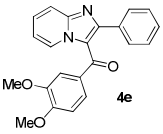
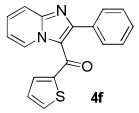
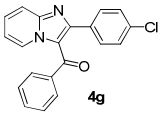
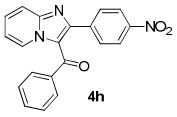
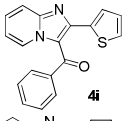
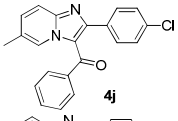
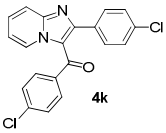
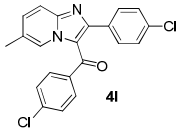
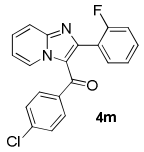
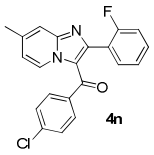
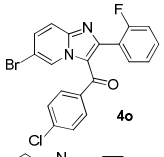
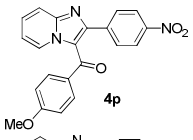
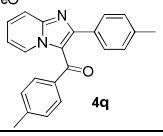
Table 2 Substrate scope for one-pot, three-component tandem reaction for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines[a]



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

Entry	Ar^1	Ar^2	R	Product (**4**)	Yield (%)[b]
1.	C_6H_5	C_6H_5	H	 **4a**	81
2.	C_6H_5	C_6H_5	3-Me	 **4b**	62
3.	C_6H_5	C_6H_5	4-Me	 **4c**	46
4.	C_6H_5	C_6H_5	5-Me	 **4d**	63
5.	3,4-$(OMe)_2C_6H_3$	C_6H_5	H	 **4e**	47
6.	2-thienyl	C_6H_5	H	 **4f**	36
7.	C_6H_5	4-ClC_6H_4	H	 **4g**	52
8.	C_6H_5	4-$NO_2C_6H_4$	H	 **4h**	76
9.	C_6H_5	2-thienyl	H	 **4i**	46
10.	C_6H_5	4-ClC_6H_4	5-Me	 **4j**	82
11.	4-ClC_6H_4	4-ClC_6H_4	H	 **4k**	63

12.	4-ClC_6H_4	4-ClC_6H_4	5-Me	 4l	75
13.	4-ClC_6H_4	2-FC_6H_4	H	 4m	45
14.	4-ClC_6H_4	2-FC_6H_4	4-Me	 4n	42
15.	4-ClC_6H_4	2-FC_6H_4	5-Br	 4o	51
16.	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	H	 4p	44
17.	4-MeC_6H_4	4-MeC_6H_4	H	 4q	-[c,d]

[a]Reagents and conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), **3a** (1.2 mmol), $CuCl_2.2H_2O$ (20 mol %), K_2CO_3 (2.0 mmol), DMF (4 mL), 150 °C, 12 h, air. [b]Isolated yields. [c]**4q** was not formed. [d]2-(*p*-Tolyl)imidazo[1,2-*a*]pyridine was isolated in 56% yield.

Experimental Section

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 F_{254} plates (Merck). The chemical structures of final products were determined by their NMR spectra (^1H and ^{13}C NMR). Chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. The HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. IR spectra were recorded on a FTIR spectrophotometer and the ν_{max} is expressed in cm^{-1}. All chemicals were obtained from the commercial suppliers and used without further purification.

General procedure for synthesis of 4a:

An oven-dried 10 mL RB flask was charged with acetophenone (120 mg, 1.0 mmol), benzaldehyde (122 mg, 1.2 mmol), 2-aminopyridine (113 mg, 1.2 mmol), K_2CO_3 (276 mg, 2.0 mmol), $CuCl_2.2H_2O$ (34 mg, 20 mol %) and DMF (4 mL). The resulting solution was stirred at 150 °C for 12 h. On completion of the reaction, the reaction mass was allowed to cool to ambient temperature and then diluted with water (10 mL). The mixture was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc: Hexanes) to afford **4a** in 81% (241 mg) yield.

Phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (4a): Yield 81%; Colorless solid; mp 124-127 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.37 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.22 – 7.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 155.0, 147.4, 138.7, 134.0, 131.7, 130.2, 129.5, 129.2, 128.3, 128.2, 127.7, 120.0, 117.5, 114.6; IR (KBr): 3070, 1597, 1388, 1326, 1218 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{15}N_2O$ 299.1179 found 299.1162 $[M+H]^+$.

(8-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl) methanone (4b): Yield 62%; Colorless solid; mp 140-143 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, *J* = 4.9 Hz, 1H), 7.51 (d, *J* = 6.5 Hz, 2H), 7.38 – 7.32 (m, 3H), 7.30 – 7.22 (m, 1H), 7.15 – 7.06 (m, 5H), 7.04 – 6.98 (m, 1H), 2.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.5, 154.6, 147.7, 138.9, 134.4, 131.7, 130.4, 129.6, 128.2, 127.8, 127.8, 127.6, 126.1, 120.6, 114.7, 17.2; IR (KBr): 3063, 1606, 1466, 1388, 1250, 910, 702 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ 313.1335 found 313.1352 $[M + H]^+$.

(7-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl) methanone (4c): Yield 26%; Off-white solid; mp 137-140 °C;^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 3.0 Hz, 1H), 7.63 (s, 1H), 7.56 (d, *J* = 6.2 Hz, 2H), 7.41 – 7.28 (m, 3H), 7.20 – 7.11 (m, 5H), 7.01 (d, *J* = 0.9 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1, 155.4, 147.9, 140.9, 138.8, 134.2, 131.6, 130.2, 129.1, 128.2, 127.7, 127.7, 127.5, 117.1, 116.1, 21.6; IR (KBr):

3060, 1605, 1466, 1396, 918, 694 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ 313.1335 found 313.1321 $[M + H]^+$.

(6-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)(phenyl) methanone (4d): Yield 63%; Colorless solid; mp 156-158 °C ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 6.7 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.14 – 7.04 (m, 5H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.4, 154.9, 146.5, 138.8, 134.2, 132.2, 131.7, 130.2, 129.6, 128.2, 127.8, 127.8, 126.2, 124.6, 119.9, 116.7, 18.6; IR (KBr): 3063, 1605, 1466, 1389, 903, 733 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{17}N_2O$ 313.1335 found 313.1348 $[M + H]^+$.

(3,4-Dimethoxyphenyl)(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (4e): Yield 47%; Gummy mass; ^1H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 7.0 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.34 (dd, *J* = 7.5, 1.7 Hz, 2H), 7.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.11 – 7.06 (m, 3H), 7.05 (d, *J* = 1.8 Hz, 1H), 6.98 (t, *J* = 6.9 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0, 153.4, 152.5, 148.3, 147.3, 134.2, 131.1, 130.1, 128.7, 128.4, 128.0, 127.9, 124.5, 119.9, 117.4, 114.3, 112.4, 110.0, 56.0, 55.7; IR (KBr): 3073, 2947, 1605, 1466, 1389, 1227, 913, 733 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}N_2O_3$ 359.1390 found 359.1385 $[M + H]^+$.

Phenyl(2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-yl) methanone (4f): Yield 36%; pale yellow solid; mp 122-124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.45 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.18 – 7.12 (m, 3H), 7.02 (dd, *J* = 3.7, 0.7 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.63 – 6.55 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 153.2, 147.2, 143.6, 134.5, 134.2, 133.1, 130.0, 128.8, 128.5, 128.1, 127.8, 127.4, 119.8, 117.5, 114.3; IR (KBr): 3078, 2947, 1589, 1466, 1389, 1227, 795, 756, 733 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{13}N_2OS$ 305.0743 found 305.0749 $[M + H]^+$.

(2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (4g): Yield 52%; Off-white solid; mp 132-134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.82 (d, *J* = 9.0, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.52 (m, 1H), 7.51 (d, *J* = 1.3 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.28 (t, *J* = 1.5 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.18 – 7.12 (m, 3H), 7.10 – 7.08 (m, 1H), 7.07 – 7.05 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2, 153.5, 147.4, 138.5, 134.5, 132.5, 132.0, 131.4, 129.4, 129.4, 128.3, 182.0, 120.1, 117.5, 114.8; IR (KBr): 3070, 1605, 1489, 1466, 1389, 1327, 1227, 933, 748 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{14}ClN_2O$ 333.0789 found 333.0795 $[M + H]^+$.

(2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)(phenyl) methanone (4h): Yield 76%; pale yellow solid; mp 241-243 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, *J* = 6.9 Hz, 1H), 7.98 – 7.89 (m, 3H), 7.78 – 7.69 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.28 (m, 2H), 7.19 – 7.16 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 186.7, 151.7, 147.2, 147.1, 141.2, 138.9, 132.5, 131.6, 130.7, 130.6, 129.9, 128.4, 128.4, 123.0, 117.9, 116.1; IR (KBr): 3078, 1605, 1512, 1466, 1389, 1250, 1227, 856, 748 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{14}N_3O_3$ 344.1030 found 344.1025 $[M + H]^+$.

(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)(thiophen-2-yl) methanone (4i): Yield 46%; Off-white solid; mp 118-120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.46 – 7.40 (m, 1H), 7.37 – 7.28 (m, 1H), 7.21 – 7.19 (m, 1H), 7.18 – 7.16 (s, 1H), 7.17 – 7.15 (m, 1H), 6.98 (td, *J* = 6.9, 1.2 Hz, 1H), 6.63 – 6.58 (m, 1H), 6.56 – 6.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1, 147.5, 147.2, 138.6, 135.8, 132.3, 130.1, 129.5, 129.3, 128.2, 128.0, 127.7, 127.2, 117.3, 114.6, 100.0; IR (KBr): 3078, 2947, 1603, 1466, 1389, 1227, 748, 756 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{13}N_2OS$ 305.0743 found 305.0746 $[M + H]^+$.

(2-(4-Chlorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)(phenyl)methanone (4j): Yield 82%; Off-white solid; mp 148-150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.39 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1, 153.4, 146.4, 138.7, 134.3, 132.7, 132.3, 131.9, 131.3, 129.6, 127.9, 126.1, 124.8, 119.9, 116.7, 18.5; IR (KBr): 3089, 2947, 1612, 1458, 1389, 1227, 1088, 795, 733 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{16}ClN_2O$ 347.0946 found 347.0956 $[M + H]^+$.

(4-Chlorophenyl)(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (4k): Yield 63%; Off-white solid; mp 192-194 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.61 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 7.30 – 7.24 (m, 2H), 7.17 – 7.09 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7, 153.6, 147.5, 138.5, 136.9, 134.9, 132.4, 131.4, 130.9, 129.6, 128.2, 128.2, 119.9, 117.6, 115.0; IR (KBr): 3086, 1612, 1496, 1404, 1335, 1227, 795, 756 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{13}Cl_2N_2O$ 367.0399 found 367.0387 $[M + H]^+$.

(4-Chlorophenyl)(2-(4-chlorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (4l): Yield 75%; Off-white solid; mp 154-156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 1.8, Hz, 1H), 7.71 (dd, *J* = 9.1, 0.5 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.45 – 7.39 (m, 2H), 7.28 – 7.23 (m, 2H), 7.15 – 7.10 (m, 4H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6, 153.5, 146.5, 138.3, 137.2, 134.7, 132.6, 132.5, 131.3, 130.9, 128.2, 128.1, 126.1, 125.0, 119.7, 116.8, 18.5; IR (KBr): 3063, 2955, 1605, 1466, 1381, 1335, 1242, 957, 764 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{15}Cl_2N_2O$ 381.0556 found 381.0551 $[M + H]^+$.

(4-Chlorophenyl)(2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (4m): Yield 45%; Off-white solid; mp 144-146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 6.6 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 5.4 Hz, 1H), 7.21 – 7.05 (m, 4H), 6.74 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.75, 159.11 (d, *J* = 248.7 Hz), 148.4, 147.7, 137.8, 136.9, 131.2 (d, *J* = 2.4 Hz), 130.9, 130.9 (d, *J* = 8.3 Hz), 129.3, 128.2, 127.7, 124.2 (d, *J* = 3.5 Hz), 122.8, 122.7, 120.9, 117.6, 115.2 (d, *J* = 22.0 Hz), 115.0; IR (KBr): 3055, 2924, 1612, 1481, 1389, 1227, 1080, 764 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{15}Cl_2N_2O$ 381.0556 found 381.0551 $[M+H]^+$. HRMS calcd for $C_{20}H_{13}ClFN_2O$ 351.0695 found 351.0698 $[M + H]^+$.

(4-Chlorophenyl)(2-(2-fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methanone (4n): Yield 42%; Off-white solid; mp

147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 7.1 Hz, 1H), 7.59 (s, 1H), 7.49 (td, *J* = 7.4, 1.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.26 – 7.19 (m, 1H), 7.12 – 7.04 (m, 3H), 7.00 – 6.96 (m, 1H), 6.75 – 6.65 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6, 159.2 (d, *J* = 248.7 Hz), 148.8, 148.2, 141.1, 137.6, 137.0, 131.2 (d, *J* = 2.5 Hz), 130.8 (d, *J* = 8.3 Hz), 130.5, 127.6, 127.5, 124.1 (d, *J* = 3.5 Hz), 123.0, 122.8, 120.6, 117.5, 116.2, 115.2 (d, *J* = 22.0 Hz), 21.6; IR(KBr): 3055, 2965, 1612, 1481, 1227, 1076, 764 cm^{-1}; HRMS calcd for $C_{21}H_{15}ClFN_2O$ 365.0851 found 365.0835 $[M + H]^+$.

(6-Bromo-2-(2-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)(4-chlorophenyl)-methanone (4o): Yield 51%; Off-white solid; mp 173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.73 (d, *J* = 9.3 Hz, 1H), 7.63 (d, *J* = 9.4 Hz, 1H), 7.53 (t, *J* = 6.9 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 5.4 Hz, 1H), 7.15 – 7.05 (m, 3H), 6.71 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7, 159.1 (d, *J* = 249.1 Hz), 148.3, 146.1, 138.2, 136.4, 136.4, 132.7, 131.2 (d, *J* = 6.4 Hz), 131.1, 130.4, 128.3, 127.8, 124.3 (d, *J* = 3.5 Hz), 122.3 (d, *J* = 14.0 Hz), 120.9, 118.1, 115.3 (d, *J* = 22.0 Hz), 109.9; IR (KBr): 3101, 3055, 2924, 1612, 1481, 1389, 1227, 1080, 764 cm^{-1}; HRMS calcd for $C_{20}H_{12}BrClFN_2O$ 428.9800 found 428.9822 $[M+H]^+$.

(4-Methoxyphenyl)(2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methanone (4p): Yield 44%; pale yellow solid; mp 199-201 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.07 (d, *J* = 6.9 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.67 – 7.57 (m, 5H), 7.18 – 7.16 (m, 1H), 6.70 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.6, 163.4, 150.3, 147.2, 147.2, 140.7, 132.0, 130.9, 130.8, 129.2, 127.9, 123.0, 120.6, 117.7, 114.9, 113.5, 55.5; IR (KBr): 3109, 3070, 2222, 1612, 1512, 1478, 1342, 1026, 756 cm^{-1}; HRMS calcd for $C_{21}H_{16}N_3O_4$ 374.1135 found 374.1123 $[M + H]^+$.

Conclusions

In summary, we have developed a straightforward method for the synthesis of 3-aroylimidazo[1,2-*a*]pyridines through one-pot, three-component tandem reaction. This protocol makes the use of simple and readily available precursors like acetophenones, aldehydes and 2-aminopyridines to deliver highly functionalized bio-active imidazo[1,2-*a*]pyridines in single step. Atom and step-economy, use of economically attractive and readily available precursors, simple isolation procedures, moderate to good yields of tandem products, air as a sole oxidant, and good functional group tolerance are the salient features of the method.

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Notes and references

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