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Synthesis of Di-Substituted 3-Phenylimidazo[1,2-*a*]pyridines via a 2-Aminopyridine/$CBrCl_3$ *α*-Bromination Shuttle

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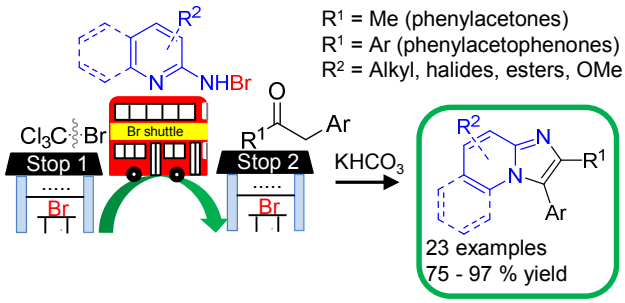
ABSTRACT

A versatile protocol for the synthesis of di-substituted 3-phenylimidazo[1,2-*a*]pyridines by coupling 2-aminopyridine with phenylacetophenones, phenylacetones or *β*-tetralone has been developed. Isolated yields of up to 97 % were obtained at 80 °C within 5 h. The 2-aminopyridine/$CBrCl_3$ system acts as an α-bromination shuttle by transferring Br from $CBrCl_3$ to the *α*-carbon of the carbonyl moiety. This triggers a series of steps with double C-N/C-N bond formation to the final product. The distinct advantages of this protocol include the use of commercially available inexpensive substrates, simplicity of a metal-free one-pot synthesis, and ease of scale-up to multi-gram quantities.



INTRODUCTION

The regioselective α-bromination of 1,3-dicarbonyls and related 1,3-diactivated derivatives, such as phenylacetones and phenylacetophenones is an important transformation in organic synthesis.[1] These α-brominated products serve as important synthetic intermediates to construct more complex molecules.[2–6] A large variety of brominating reagents have been utilized for α-bromination, including Br_2,[7,8] NBS,[9–15] bromodimethylsulfonium bromide,[16] tetraethylammonium bromide,[17] $CuBr_2$,[18] NaOBr[19] and $CBrCl_3$.[20,21] The reaction normally requires catalytic or stoichiometric amounts of reagents including Lewis and Brønsted acids, inorganic or organic bases, oxidants and transition metal complexes.[7–21] Recently, the *in-situ* α-halogenation of acetophenones or 1,3-dicarbonyls and their derivatives has been exploited for the construction of heteroaromatics, with an emphasis on step economy. In these transformations, α-halogenation of the 1,3-dicarbonyl is the first step of a cascade reaction that leads to the heteroaromatic structures. *In-situ* α-iodination and bromination has been utilized in constructing various heteroaromatic backbones including oxazoles,[22–24] thiazoles[25–27] and benzothiazoles,[28,29] quinoxalines,[30] pyrido[1,2-*a*] benzimidazoles[31] and imidazo[1,2-*a*]pyridines.[32–36] Most of these methods use highly energetic species like NBS and NIS as the halogenating reagent and/or require overstoichiometric amounts of peroxide oxidants such as TBHP or corrosive Brønsted acids like *p*-toluenesulfonic acid (PTSA). Therefore, these reactions face challenging safety concerns for scale-ups.

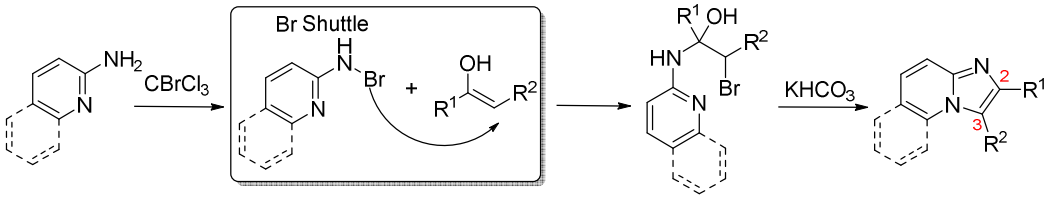
In a recent communication, we employed an *in-situ* α-bromination strategy to synthesize imidazo[1,2-*a*]pyridines in high yields from 2-aminopyridines and 1,3-dicarbonyls.[37] Bromotrichloromethane, $CBrCl_3$, was used as brominating reagent. The low toxicity and exothermicity of $CBrCl_3$ and its low boiling point which allows for easy removal via rotary

evaporation are distinct advantages. The reaction follows a unique α-Br shuttle mechanism where 2-aminopyridine is not only the substrate but also transfers the Br from $CBrCl_3$ to the *α*-carbon of the 1,3-dicarbonyl. This then initiates a cascade reaction that forms the imidazo[1,2-*a*]pyridine structure. The study draws inspiration on the synthesis of oxazoles via *in-situ α*-iodination by Zhu's group.[22] In contrast to the direct *α*-halogenation hypothesis, they proposed that the iodine atom is transferred to the *α*-carbon with the help of TBHP reagent. The concept of the *N*-brominated 2-aminopyridine as a shuttle was drawn from the work of Antonchick's group on pyrido[1,2-*a*]benzimidazole, where in the mechanism, an *N*-iodinated form of 2-aminopyridine was introduced.[38]

Particular advantages of our methodology are that it is a one-pot synthesis, does not require any oxidants or prefunctionalization of the substrates and employ commercially available and inexpensive substrates and reagents. The transition metal-free nature makes it suitable for applications in the pharmaceutical industry, for example, to synthesize libraries of physiologically active compounds. Hence, we investigated the feasibility of extending it to other 1,3-diactivated derivatives, including phenylacetones, phenylacetophenones and β-tetralones (Scheme 1). This would give ready access to a large diversity of disubstituted 3-phenylimidazo[1,2-*a*]pyridines, which are less reported in the literature. The reported reactions couple 2-aminopyridines with α-bromo phenylacetaldehyde,[39] α-bromoacetophenones,[40–44] alkynyl-iodonium salts and (bromoethynyl)benzene.[45,46] Shortcomings of these reactions include the need to prefunctionalize the substrate with a halide which requires additional steps, high reaction temperatures and low to moderate yields of up to 80 % only. Hence, an efficient one-pot synthesis of 3-phenylimidazo[1,2-*a*]pyridines with *in-situ* halogenation is highly desirable. In this work, substitutions at C-2 and C-3 position of the imidazo[1,2-*a*]pyridines backbone are

explored. This structural motif is prevalent in psychoactive drugs known as nonbenzodiazepines, which includes Zolpidem, Zolimidine, TP-003 and Miroprofen.[47]

Scheme 1. Coupling reaction with 2-aminopyridine as an α-bromination shuttle.

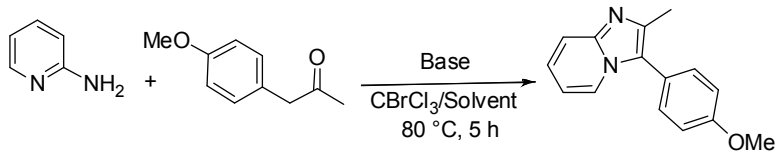


Previous work: R^1= Alkyl, Ar; R^2 = ester, ketone, amide
This work: R^1= Me, Ar; R^2 = Ar

RESULTS AND DISCUSSION

The reaction between 2-aminopyridine **1a** and 4-methoxyphenylacetone **2a** was tested at 80 °C using various solvents containing 10 % v/v of $CBrCl_3$ (Table 1). After 5 h, the yield of **3a** was 78 % in MeCN while slightly lower yields were obtained in DMAc, DMF, and NO_2Me (Table 1, entries 1-4). No conversion was observed with DMSO which could be due to its radical quenching ability (Table 1, entry 5).[48] Toluene, a non-polar solvent, was not suitable for the reaction (Table 1, entry 6). Without a base like $KHCO_3$, the yield of **3a** dropped significantly (Table 1, entry 7). Hence, several bases were screened for the reaction (Table 1, entries 8 - 11). No **3a** was formed with KO*t*Bu which may be due to the fact that its conjugate acid, *tert*-butanol, is a radical scavenger and could quench any radicals formed in the reaction.[49] Both $NaHCO_3$ and K_2CO_3 gave lower yields than $KHCO_3$, whereas with $CsHCO_3$, the yield of **3a** was slightly higher, 84 %. However, as $CsHCO_3$ is more expensive than $KHCO_3$, we used $KHCO_3$ for subsequent reactions.

Table 1. Reaction optimization.[a]



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

Entry	Solvent	Base	Yield **3a** (%)[b,c]
1	MeCN	$KHCO_3$	78 (72)
2	DMAc	$KHCO_3$	70 (57)
3	DMF	$KHCO_3$	69 (58)
4	NO_2Me	$KHCO_3$	55 (44)
5	DMSO	$KHCO_3$	0
6	Toluene	$KHCO_3$	0
7	MeCN	-	45 (29)
8	MeCN	KO*t*Bu	0
9	MeCN	K_2CO_3	49 (33)
10	MeCN	$NaHCO_3$	65 (60)
11	MeCN	$CsHCO_3$	84 (79)
12[d]	MeCN	$KHCO_3$	67 (54)
13[e]	MeCN	$KHCO_3$	93 (91)
14[f]	MeCN	$KHCO_3$	94 (91)
15[e,g]	MeCN	$KHCO_3$	80 (77)
16[h]	MeCN	$KHCO_3$	33

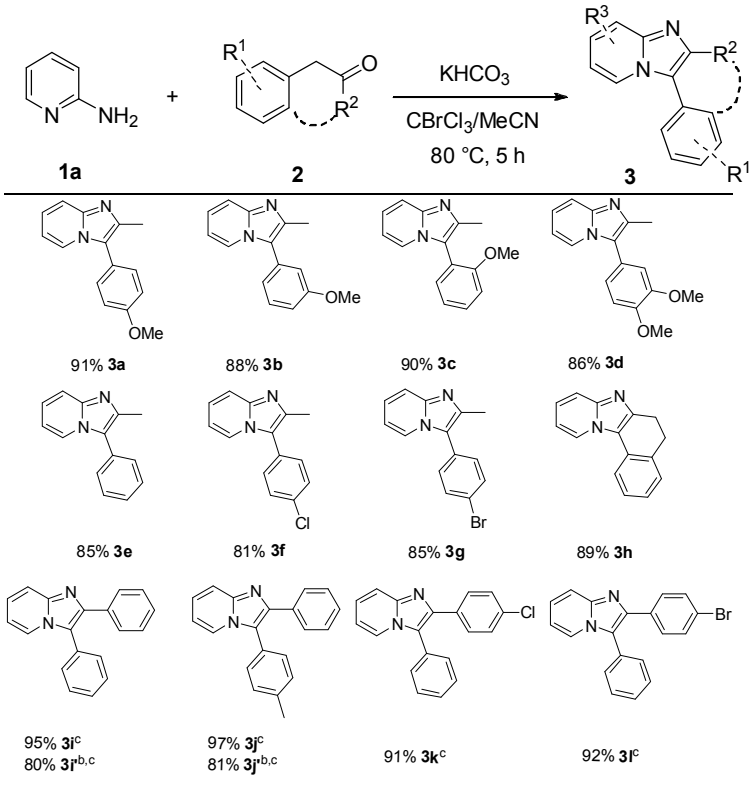
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) and base (1.0 mmol) in 2 mL of 1:9 (v/v) $CBrCl_3$/solvent mixture (2.0 equiv. wrt **1a**) at 80 °C for 5 h. [b]Yield from GC with respect to **2a**. [c]Isolated yields in parenthesis. [d]1.25 equiv. of **1a** was used [e]1.1 equiv. of **2a** was used. [f]1.25 equiv. of **2a** used. [g]Ratio of $CBrCl_3$/MeCN changed to 1:18 (v/v).[h]Reaction at 50 °C.

To further optimize the yield of **3a**, the amounts of **1a**, **2a** and $CBrCl_3$ were varied. Increasing 4-methoxyphenylacetone **2a** to 1.25 equivalents decreased the yield of **3a** to 67 % (Table 1, entry 12). On the other hand, 93 – 94 % of **3a** was obtained when **1a** was increased to over-stoichiometric 1.1 and 1.25 equivalents (Table 1, entries 13 and 14). Decreasing $CBrCl_3$ from 2 to 1 equivalent and reducing the reaction temperature to 50 °C caused significant drops in yield (Table 1, entries 15 and 16). Hence, the highest **3a** yield was obtained using 1 mmol of 4-

methoxyphenylacetone **2a** together with 1.1 equivalents of 2-aminopyridine **1a** and 1 equivalent of $KHCO_3$ in a solvent system of $CBrCl_3$/MeCN (1:9 v/v) at 80 °C for 5 h.

Using the optimized conditions, various phenylacetones were tested as substrates (Table 2). Methoxyphenylacetones with OMe substituents at the *para*, *meta*, or *ortho* position and even disubstituted derivatives were well tolerated (Table 2, **3a** – **3d**). Good yields were achieved with phenylacetone and its *p*-Cl and *p*-Br derivatives (Table 2, **3e** – **3g**). Interestingly, the cyclic phenylacetone derivative, *β*-tetralone, also reacted smoothly with 2-aminopyridine to form the multiply-fused ring product **3h** with 89 % isolated yield.

Table 2. Scope of reaction (1,3-diactivated compounds).[a]

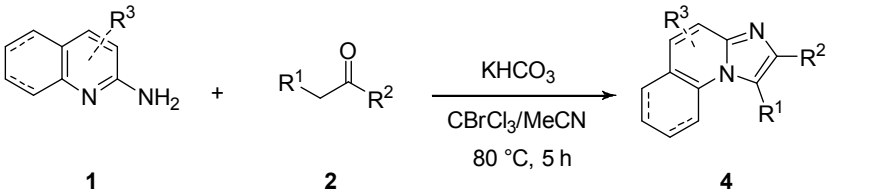


[a]Reaction conditions: **1a** (1.1 equiv), **2** (1.0 mmol), and $KHCO_3$ (1.0 equiv) in 2 mL of 1:9 (v/v) $CBrCl_3$/MeCN mixture (2.0 equiv. wrt **2**) at 80 °C for 5 h. Percentage isolated yields. [b]1 equiv. of phenylacetophenone derivative used. [c]Reaction time of 4 h.

Phenylacetophenones were more reactive substrates than phenylacetones and a shorter reaction time of 4 h was sufficient for adequate yields. Excellent yields of 95 % **3i** and 97 % **3j** were obtained with phenylacetophenone and 4-methylbenzyl phenyl ketone, respectively. However, as observed with **3a**, using a lower stoichiometric ratio of 1 equivalent of phenylacetophenone decreased the yields of **3i** and **3j** significantly. The reaction also proceeded well with substituents at the other phenyl ring. Hence, 4'-chloro-2-phenylacetophenones and 4'-bromo-2-phenylacetophenones formed **3k** and **3l** with yields of 91 % and 93 %, respectively.

Next, we investigated the scope of 2-aminopyridines and their heteroaromatic analogues for the reaction with derivatives of phenylacetone and phenylacetophenone (Table 3). 2-Aminopicolines with methyl or ethyl substituent at the C-3, C-4 and C-5 position reacted smoothly with both phenylacetone and phenylacetophenone derivatives to give excellent yields (Table 3, **4a - 4c** and **4f**). Interestingly, 2-amino-6-methylpyridine was unreactive with phenylacetone and phenylacetophenone derivatives. Even after extending the reaction time to 10 h, only traces of the product was formed (Table 3, **4d**). This did not improve when the stronger base $CsHCO_3$ was used. This surprising trend was also observed with 2-amino-4,6-dimethylpyridine which likewise has a methyl group at the C-6 position (Table 3, **4e**). This is in sharp contrast to our previous observation that 2-amino-6-methylpyridine was an excellent substrate to methyl acetoacetate (Table 3, **4d'**).[37] The results show that the reaction with phenylacetone or phenylacetophenone derivatives is sensitive to the presence of a substituent at the carbon adjacent to the N-atom of the pyridine ring, in contrast to methyl acetoacetate. The sluggish reaction rate for C-6 methyl-substituted aminopyridines in the synthesis of 3-phenylimidazo[1,2-*a*]pyridine derivatives has been reported in literature and was attributed to steric hindrance.[50–52]

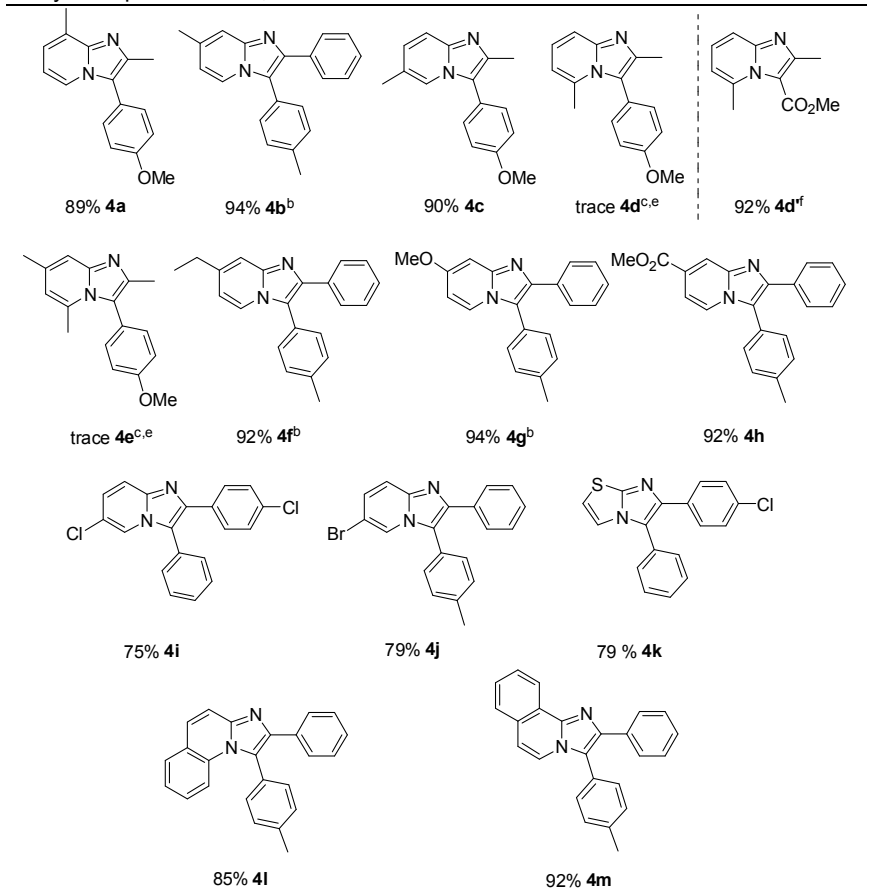
Table 3. Scope of reaction (2-aminopyridine derivatives).[a]



1 **2** **4**

Phenylacetones: R^1 = Ar, R^2 = Me

Phenylacetophenones: R^1, R^2 = Ar



89% **4a** | 94% **4b**[b] | 90% **4c** | trace **4d**[c,e] | 92% **4d'**[f]

trace **4e**[c,e] | 92% **4f**[b] | 94% **4g**[b] | 92% **4h**

75% **4i** | 79% **4j** | 79 % **4k**

85% **4l** | 92% **4m**

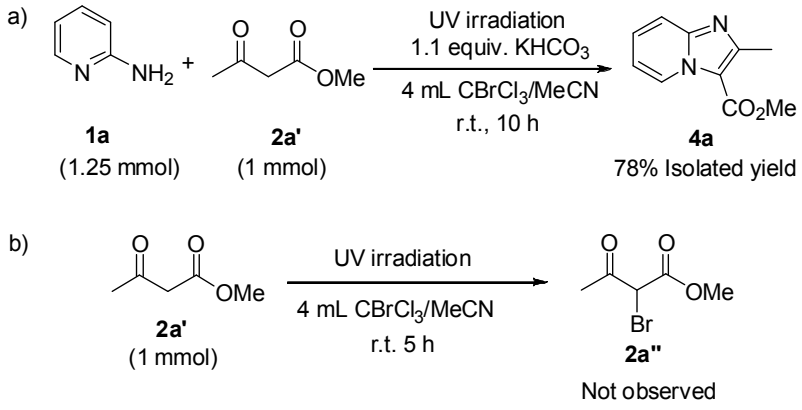
[a]Reaction conditions: **1** (1.1 equiv. with **2**), **2** (1.0 mmol), and $KHCO_3$ (1.0 equiv. with **2**) in 2 mL of 1:9 (v/v) $CBrCl_3$/MeCN mixture (2.0 equiv. wrt **2**) at 80 °C for 5 h. Percentage isolated yields. [b]After 4 h. [c]Additional experiments with $CsHCO_3$ and with 4-methylbenzyl phenyl ketone also gave trace amounts of products. [d]7 h reaction time. [e]10 h reaction time. [f]Isolated yield of **4d'** from previous work[37] for comparison with **4d**.

Both electron-donating and electron-withdrawing substituents, including OMe, Cl, Br, and CO_2Me, on the 2-aminopyridine substrate were well tolerated when coupled to various derivatives of phenylacetophenones, with good to excellent yields of 75 – 95 % (Table 3, **4g** - **4j**). Heteroaromatic derivatives, including 2-aminothiazole, 2-aminoquinoline and 1-aminoiso-

quinolines, also reacted smoothly with these derivatives to give their respective desired products with isolated yields of up to 92 % (Table 3, **4k** - **4m**).

The formation of imidazo[1,2-*a*]pyridines from 2-aminopyridine and 1,3-dicarbonyl was shown to occur via a radical pathway rather than an ionic one.[37] The reaction was severely inhibited by the addition of the radical scavenger 2,2,6,6-tetramethyl piperidinoxyl (TEMPO). Hence, we anticipate that the reaction should be able to proceed under UV irradiation. As $CBrCl_3$ absorbs in the UV range with maxima at ~240 and 280 nm,[53–57] homolytic fission to CCl_3• and Br• is possible. A reaction mixture of 2-aminopyridine and methyl acetoacetate in $CBrCl_3$/MeCN was irradiated with UV light (30 W, UVC) at room temperature. Gratifyingly, when the reaction mixture was worked up after 10 h, **4a** was obtained in 78 % isolated yield. (Scheme 2a). The possibility to use UV light instead of heat for the reaction is useful for substrates that are thermally labile. We also investigated if direct α-bromination of methyl acetoacetate **2a'** can occur under UV irradiation (Scheme 2b). However, this can be discounted as no mono-brominated products were observed after 5 h.

Scheme 2. Reactions under UV irradiation.



Based on these observations, the proposed mechanism is as follows (Figure 1). Upon UV irradiation or thermal activation, chain initiation occurs with cleavage of the C-Br bond in $CBrCl_3$, forming CCl_3• and Br• (see Supporting Information).[58] The CCl_3• removes a H• from the NH_2 moiety of 2-aminopyridine to form C_6H_5NH• and $CHCl_3$. The C_6H_5NH• abstracts a Br• from another $CBrCl_3$ molecule to form the intermediate **A.** Intermediate **A** then couples to the enol form of the dielectrophile **2** via an addition reaction to form the bromo-hemiaminal intermediate **B.** A similar intermediate has been postulated in the one-pot synthesis of 3-arylimidazo[1,2-*a*]pyridines employing NIS as the *α*-iodination source.[32] The 2-aminopyridine **1a** thus functions as an *α*-bromination shuttle, transferring Br from $CBrCl_3$ to the enol tautomer of **2**. Dehydration of **B** leads to the *α*-bromo imine intermediate **C** which undergoes intramolecular cyclization to form the ionic salt **D**. This step involves an S_N2-type nucleophilic attack at the *α*-carbon. The trace amounts of products obtained with the coupling of 2-amino 6-methylpyridine with phenylacetones or phenylacetophenones can be explained by the close

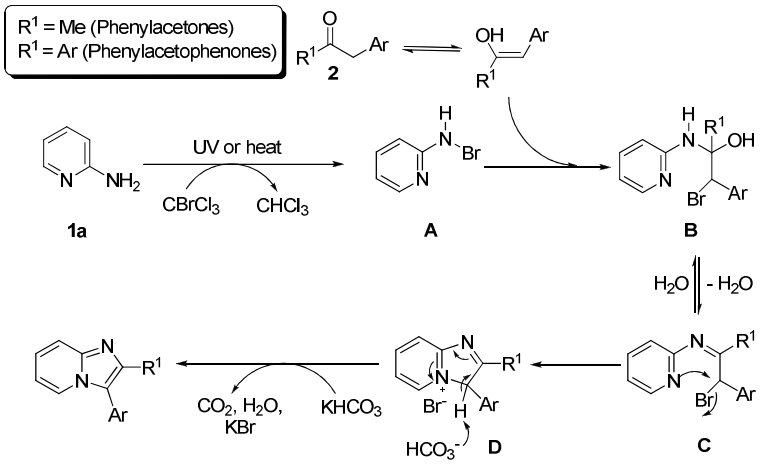


Figure 1. Proposed mechanism.

proximity of the phenyl H to the CH_3 moiety of 2-amino 6-methylpyridine which prevents the pyridine N atom from attacking the α-carbon (Figure 2). In contrast, this steric effect is absent when the phenyl group is replaced by an ester moiety, hence, high product yields are obtained with methyl acetoacetate. Deprotonation by HCO_3^- affords the desired product.

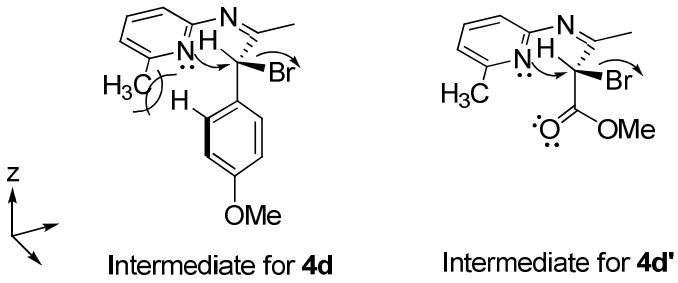


Figure 2. Steric interactions during intramolecular cyclization of **C**.

Support for the mechanism comes from *in-situ* ^{1}H NMR studies (Figure 3). As proposed, $CHCl_3$ should be formed in the initial bromination of **1a** to intermediate **A**. A mixture of 0.5 mmol each of 2-aminopyridine and methyl acetoacetate together with 3 equivalents of $CBrCl_3$ were added into 0.65 mL of CD_3CN in an NMR tube and a spectrum recorded at room temperature (Run 1). A very small chloroform peak at 7.62 ppm could be observed which is due to trace amounts of $CHCl_3$ in the $CBrCl_3$ solvent. The chemical shift of the $CHCl_3$ peak in CD_3CN agrees with reported literature.[59] The temperature was raised to 50 °C and the spectrum measured again (Run 2). The chloroform peak became more pronounced indicating the formation of additional $CHCl_3$. The chemical shift of ~ 0.006 ppm is due to the higher temperature. To confirm that this peak was indeed that of $CHCl_3$, the reaction mixture was spiked with chloroform (Run 3). The area of the peak at 7.61 ppm increased significantly, showing unambiguously that $CHCl_3$ was indeed formed as postulated.

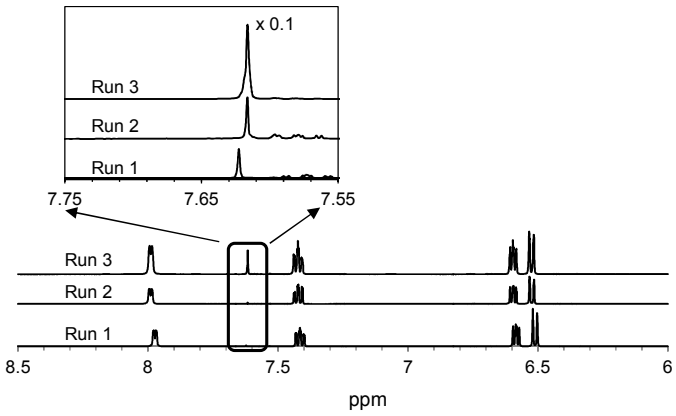
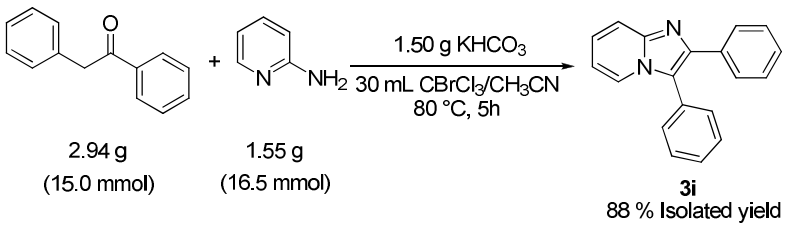


Figure 3. *In-situ* ^{1}H kinetic study using 0.5 mmol **1a**, 0.5 mmol **2a'**, 3 equiv. $CBrCl_3$ in 0.65 mL CD_3CN. Run 1 at room temperature, Run 2 at 50 °C and Run 3 at 50 °C spiked with $CHCl_3$. Inset: chloroform peak.

To demonstrate the practicality and versatility of this methodology, a scaled-up synthesis of **3i** was conducted (Scheme 3). Using 15 mmol of phenylacetophenone and 16.5 mmol of 2-aminopyridine, 2,3-diphenylimidazo[1,2-*a*]pyridine, **3i**, was obtained as a light yellow solid with an isolated yield of 88 % (3.55 g) after work-up, purification via column chromatography and recrystallization from ethanol.

Scheme 3. Scaled-up synthesis of 3-phenylimidazo[1,2-*a*]pyridine **3i**



In comparison, reported protocols for the synthesis of **3i** require Cu(I) or Pd(II) catalysts for the coupling of bromo or iodobenzene with 2-phenylimidazo[1,2-*a*]pyridine.[60–62] Another protocol uses Pd(II)-catalyzed Suzuki coupling of phenylboronic acid and bromo- or 3-iodo-2-phenylimidazo[1,2-*a*]pyridine.[63–65] The phenylimidazo[1,2-*a*]pyridines substrates in these

protocols are not commercially available and need to be presynthesized. In comparison, the present protocol using commercially available inexpensive reagents without requiring any transition metals is straightforward and offers a much greener alternative with comparable yields to previous methodologies found in the literature. The ease of scale up together with the wide scope of substrates it useful for applications in the industry. However, one limitation is that it cannot be extended to the use of 2-aminopyridines with a substituent at the C-6 position due to steric hindrance.

CONCLUSION

In conclusion, we have demonstrated a novel and efficient protocol employing a unique α-bromination system of 2-aminopyridine/$CBrCl_3$ to synthesize disubstituted 3-phenylimidazo[1,2-*a*]pyridines by C-N/C-N bond formation. 2-Aminopyridines and phenylacetones, phenylacetophenones or β-tetralones are coupled in this one-pot synthesis to give good to excellent yields at a relatively low temperature of 80 °C. Being radical-based, the reaction can also proceed under UV radiation at room temperature. The 2-aminopyridine acts both as the substrate and an α-bromination shuttle, transferring a Br atom to the α-carbon of its coupling partner for *in-situ* bromination. The synthesis was successfully scaled up to gram quantity with 88 % yield of **3i** as an example. Hence, this protocol offers a practical and economical alternative to the syntheses disclosed in earlier literature.

EXPERIMENTAL SECTION

General information: Thin layer chromatography (TLC) was performed using TLC silica gel 60 F_{254} glass plates. Silica gel 60 (230 – 400 mesh) was used for column chromatography. The ^{1}H NMR and ^{13}C NMR of samples in $CDCl_3$, DMSO-d_6 or CD_3CN were measured using a

300 MHz or 500 MHz spectrometer with tetramethylsilane (TMS) as an internal standard. For ^{1}H NMR spectra, chemical shifts were reported in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constant (Hz). Detection and analysis of compounds by gas chromatography and gas chromatography mass spectrometry were performed. Mass spectra measurements were recorded on TOFQ under electrospray ionization (ESI) mode. Melting points were recorded with samples in capillary tubes using an automated melting point system. The following chemicals were purchased and used as received: $CBrCl_3$, $KHCO_3$, $CsHCO_3$, MeCN, and derivatives of phenylacetones, phenylacetophenones and 2-aminopyridine.

Representative procedure for formation of 3-phenylimidazo[1,2-*a*]pyridines: A 10 mL round-bottomed flask was charged with 2-aminopyridine **1a** (104 mg, 1.1 mmol), 4-methoxyphenylacetone **2a** (107.9 μL, 1 mmol) and $KHCO_3$ (100 mg, 1.0 mmol in 2 mL of $CBrCl_3$/MeCN solvent mixture (1/9 v/v). The reaction mixture was stirred at 80 °C for 5 h. Thereafter, the reaction was diluted with H_2O and extracted with EtOAc (15 mL × 5). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the residue was cleaned up by column chromatography using ethyl acetate and hexane (v/v = 4/1) as eluent to afford **3a** in 91 % yield.

Scaled-up synthesis for compound 3i: A 100 mL round-bottomed flask was charged with 2-aminopyridine **1a** (1.55 g, 16.5 mmol), 2-phenylacetophenone (2.94, 15.0 mmol) and $KHCO_3$ (1.50 g, 15.0 mmol) in 300 mL of $CBrCl_3$/MeCN solvent mixture (1/9 v/v). The reaction mixture was stirred at 80 °C for 5 h. Thereafter, the reaction was diluted with H_2O and extracted with EtOAc (200 mL × 5). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the

residue was cleaned up by column chromatography using hexane and ethyl acetate (v/v = 4/1) as eluent. Further recrystallization with ethanol afforded **3i** in 88 % yield.

3-(4-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (**3a**): Obtained as a brown amorphous solid; yield: 216 mg (91 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.9 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.68 (t, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.4, 144.2, 140.5, 130.9, 123.8, 123.0, 121.5, 121.1, 116.8, 114.6, 111.7, 55.3, 13.7. HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$: 239.1179; found 239.1181.

3-(3-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3b): Obtained as a brown amorphous solid; yield: 210 mg (88 %).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.96-6.89 (m, 2H), 6.65 (t, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.0, 144.3, 140.8, 130.6, 130.1, 123.9, 123.0, 121.5, 121.1, 116.8, 115.0, 113.2, 111.7, 55.2, 13.8. HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$: 239.1179; found 239.1182.

3-(2-Methoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3c): Obtained as a brown amorphous solid; yield: 215 mg (90 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.6 Hz, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.12-6.99 (m, 3H), 6.63 (t, *J* = 6.8 Hz, 1H), 3.72 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.4, 144.5, 141.2, 132.3, 130.0, 124.5, 123.5, 120.8, 118.6, 117.8, 116.4, 111.1, 110.9, 55.2, 13.8. HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$: 239.1179; found 239.1181.

3-(3,4-diMethoxyphenyl)-2-methylimidazo[1,2-*a*]pyridine (3d): Obtained as a brown amorphous solid; yield: 231 mg (86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.9 Hz, 1H),

7.53 (d, *J* = 9.0 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H), 7.00 (s, *2*H), 7.00 (s, *2*H), 6.92 (s, 1H), 6.70 (t, *J* = 6.8 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.4, 149.0, 144.0, 140.3, 124.0, 123.0, 122.4, 121.6, 121.3, 116.7, 112.6, 111.9, 111.7, 56.0, 55.9, 13.7. HRMS (ESI) calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$: 269.1285; found 269.1286.

2-Methyl-3-phenylimidazo[1,2-*a*]pyridine (3e):[66] Obtained as a brown oil; yield: 177 mg (85 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.57-7.47 (m, 3H), 7.46-7.36 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 6.9 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.3, 140.8, 129.4, 129.3, 129.1, 128.0, 124.0, 122.9, 121.4, 116.8, 111.8, 13.8. HRMS (ESI) calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.1073; found 209.1075.

3-(4-Chlorophenyl)-2-methylimidazo[1,2-*a*]pyridine (3f):[66] Obtained as a brown amorphous solid; yield: 196 mg (81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.9 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.74 (t, *J* = 6.9 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.5, 141.1, 134.1, 130.7, 129.5, 127.8, 124.5, 122.8, 120.3, 117.0, 112.2, 13.8. HRMS (ESI) calcd for $C_{14}H_{12}ClN_2$ $[M+H]^+$: 243.0684; found 243.0682.

3-(4-Bromophenyl)-2-methylimidazo[1,2-*a*]pyridine (3g): Obtained as a brown solid; yield: 245 mg (85 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 9.3 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.68 (t, *J* = 6.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.5, 141.1, 132.3, 130.8, 128.2, 124.2, 122.7, 122.0, 120.1, 116.9, 112.0, 13.7. HRMS (ESI) calcd for $C_{14}H_{12}ClN_2$ $[M+H]^+$: 243.0684; found 243.0682.

2,3-Dihydronaphthylimidazo[1,2-*a*]pyridine (3h): Obtained as a yellowish-brown amorphous solid; yield: 196 mg (89 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.9 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.15 (q, *J* = 6.6 Hz, 2H), 6.87 (t, *J* = 6.9 Hz, 1H), 3.05 (s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.6, 145.9, 135.3, 128.8, 128.1, 126.7, 124.0, 123.5, 119.5, 118.6, 117.6, 112.7, 30.1, 23.9. HRMS (ESI) calcd for $C_{15}H_{13}N_2$ $[M+H]^+$: 221.1073; found 221.1072.

2,3-Diphenylimidazo[1,2-*a*]pyridine (3i):[50] Obtained as a light yellow solid; yield: 257 mg (95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.3 Hz, 1H), 7.71-7.57 (m, *3*H), 7.43-7.29 (m, *5*H), 7.25-7.13 (m, *3*H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.57 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.4, 142.0, 133.9, 130.2, 129.4, 129.1, 128.5, 127.9, 127.7, 127.1, 124.2, 122.8, 120.6, 117.0, 111.8. HRMS (ESI) calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1230; found 271.1229.

2-Phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine (3j):[61] Obtained as a light yellow solid; yield: 275 mg (97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.9 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.30-7.18 (m, *7*H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.61 (t, *J* = 6.9 Hz, 1H) 2.40 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.4, 141.9, 138.5, 134.1, 130.3, 130.0, 128.0, 127.8, 127.1, 126.5, 124.2, 123.0, 120.9, 117.2, 111.9, 21.2. HRMS (ESI) calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1386; found 285.1384.

2-(4-Chlorophenyl)-3-phenylimidazo[1,2-*a*]pyridine (3k):[66] Obtained as a light yellow solid; yield: 276 mg (91 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 6.6 Hz, 1H), 7.47-7.39 (m, *3*H), 7.30-7.11 (m, *5*H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.90 (t, *J* = 7.7 Hz, 1H), 6.40 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.1, 140.5, 132.6, 132.3, 129.9, 129.0, 128.8, 128.6,

128.4, 127.8, 124.2, 122.5, 120.5, 116.7, 111.7. HRMS (ESI) calcd for $C_{19}H_{14}Cl\,N_2$ $[M+H]^+$: 305.0840; found 305.0843.

2-(4-Bromophenyl)-3-phenylimidazo[1,2-*a*]pyridine (3l):[67] Obtained as a yellow solid; yield: 321 mg (92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 6.9 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.55-7.46 (m, *5*H), 7.43-7.35 (m, *4*H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.71 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.1, 141.0, 133.1, 131.3, 130.5, 129.6, 129.5, 129.4, 129.0, 128.7, 124.9, 123.2, 121.5, 117.4, 112.4. HRMS (ESI) calcd for $C_{19}H_{14}Br\,N_2$ $[M+H]^+$: 349.0335; found 349.0338.

3-(4-Methoxyphenyl)-2,8-dimethylimidazo[1,2-*a*]pyridine (4a): Obtained as a brown amorphous solid; yield: 226 mg (89 %). ^{1}H NMR (300 MHz, $CDCl_3$) 7.81 (d, *J* = 6.6 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 6.6 Hz, 1H), 6.53 (t, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 2.56 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.2, 144.3, 139.4, 130.7, 129.4, 126.2, 122.7, 121.5, 120.7, 114.4, 111.6, 55.1, 16.9, 13.5. HRMS (ESI) calcd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335; found 253.1337.

7-Methyl-2-phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine (4b): Obtained as a light yellow solid; yield: 281 mg (94 %); m.p. 150 - 152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 6.9 Hz, 2H), 7.39 (s, 1H), 7.27-7.15 (m, 7H), 6.44 (d, *J* = 6.9 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.9, 141.5, 138.3, 135.2, 134.2, 130.2, 129.9, 127.9, 127.7, 126.9, 126.7, 122.2, 120.3, 115.5, 114.5, 21.1, 21.0. HRMS (ESI) calcd for $C_{21}H_{19}N_2$ $[M+H]^+$: 299.1543; found 299.1545.

3-(4-Mehoxyphenyl)-2,6-dimethylimidazo[1,2-*a*]pyridine (4c): Obtained as a brown amorphous solid; yield: 227 mg (90 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.9 Hz, 1H), 7.37-7.27 (m, 3H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.3, 144.4, 139.6, 135.1, 130.8, 122.3, 121.6, 120.6, 115.1, 114.6, 114.5, 55.3, 21.2, 13.6. HRMS (ESI) calcd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335; found 253.1333.

7-Ethyl-2-phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine (4f): Obtained as a light yellow solid; yield: 288 mg (92 %).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.9 Hz, 1H), 7.69 (d, *J* = 6.9 Hz, 2H), 7.44 (s, 1H), 7.28-7.17 (m, 7H), 6.51 (d, *J* = 7.2 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 145.2, 141.8, 141.5, 138.5, 134.4, 130.5, 130.1, 128.1, 127.9, 127.1, 126.9, 122.6, 120.5, 114.3, 113.7, 28.3, 21.4, 14.4. HRMS (ESI) calcd for $C_{22}H_{21}N_2$ $[M+H]^+$: 313.1699; found 313.1703.

7-Methoxy-2-phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine (4g): Obtained as a yellow solid; yield: 297 mg (94 %); m.p. 149 - 151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.59 (m, 3H), 7.23-7.10 (m, 7H), 6.86 (s, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.6, 145.7, 141.0, 138.2, 134.1, 130.2, 129.8, 127.8, 127.4, 126.8, 126.5, 123.4, 119.7, 106.7, 94.1, 55.0, 21.0. HRMS (ESI) calcd for $C_{21}H_{19}N_2O$ $[M+H]^+$: 315.1492; found 315.1494.

Methyl 2-phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine-7-carboxylate (4h): Obtained as a light yellow solid; yield: 315 mg (92 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.29-7.19 (m, 8H), 3.88 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.4, 144.6, 143.3, 139.1, 133.5, 130.2, 130.1, 128.1, 127.9, 127.6, 125.8,

125.4, 122.6, 122.5, 119.9, 111.2, 52.2, 21.2. HRMS (ESI) calcd for $C_{22}H_{19}N_2O_2$ $[M+H]^+$: 343.1441; found 343.1444.

6-Chloro-2-(4-chlorophenyl)-3-phenylimidazo[1,2-*a*]pyridine (4i): Obtained as a light yellow solid; yield: 254 mg (75 %); m.p. 187 - 189 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.63-7.50 (m, 6H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.1, 142.2, 133.6, 132.2, 130.5, 129.8, 129.5, 129.2, 128.9, 128.5, 126.2, 121.7, 121.1, 120.8, 117.9. HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_2$ $[M+H]^+$: 339.0450; found 339.0451.

6-Bromo-2-phenyl-3-*p*-tolylimidazo[1,2-*a*]pyridine (4j): Obtained as a yellow solid; yield: 288 mg (79 %); m.p. 214 - 216 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 9.3 Hz, 1H), 7.33-7.19 (m, 8H), 2.45 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.9, 142.9, 139.2, 133.7, 130.3, 128.2, 127.8, 127.7, 127.6, 126.0, 123.2, 121.4, 118.0, 106.9, 21.4. HRMS (ESI) calcd for $C_{20}H_{16}BrN_2$ $[M+H]^+$: 363.0491; found 363.0494.

6-(4-chlorophenyl)-5-phenylimidazo[2,1-*b*]thiazole (4k): Obtained as a yellow solid; yield: 246 mg (79 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.45-7.37 (m, 5H), 7.32 (d, *J* = 4.5 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.0, 142.1, 132.8, 132.8, 130.0, 129.2, 129.0, 128.6, 128.5, 128.3, 122.9, 117.3, 112.7. HRMS (ESI) calcd for $C_{17}H_{12}ClN_2S$ $[M+H]^+$: 311.0404; found 311.0407.

2-Phenyl-1-*p*-tolylimidazo[1,2-*a*]quinoline (4l): Obtained as a yellow solid; yield: 284 mg (85 %); m.p. 182 - 184 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 6.9 Hz, 2H), 7.49-7.41 (m, 3H), 7.38-7.26 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.1 Hz,

2H), 6.79 (d, *J* = 9.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 181.2, 155.5, 140.1, 138.1, 137.6, 137.0, 134.8, 130.9, 129.3, 129.2, 128.5, 128.4, 127.8, 127.3, 127.2, 125.3, 122.3, 118.7, 115.8, 21.0. HRMS (ESI) calcd for $C_{24}H_{19}N_2$ $[M+H]^+$: 335.1543; found 335.1545.

2-Phenyl-3-*p*-tolylimidazo[2,1-*a*]isoquinoline (4m): Obtained as a yellow solid; yield: 306 mg (92 %); m.p. 138 - 140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 6.9 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.39-7.25 (m, 7H), 6.93 (d, *J* = 7.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.2, 140.2, 138.7, 134.5, 130.6, 130.1, 129.5, 128.2, 128.0, 127.9, 127.8, 127.0, 126.7, 126.7, 123.8, 123.4, 123.0, 121.0, 112.6, 21.4. HRMS (ESI) calcd for $C_{24}H_{19}N_2$ $[M+H]^+$: 335.1543; found 335.1545.

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Supporting Information

^{1}H, ^{13}C NMR and HSQC spectra and a proposed reaction mechanism for the initial bromination are given in the Supporting Information.

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