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Synthesis of Aza-Fused Isoquinolines through Domino Cross-Aldol Condensation and Palladium-Catalyzed Intramolecular Direct Arylation

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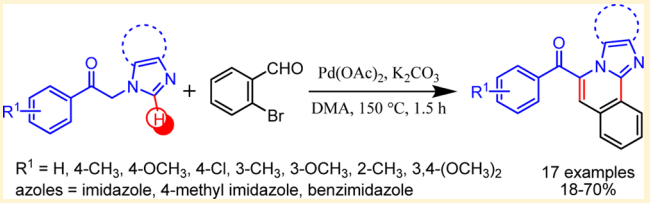
Supporting Information

ABSTRACT: A straightforward method has been developed for the synthesis of aroyl-substituted imidazo-/benzimidazo-fused isoquinolines. The cascade reaction proceeds via a cross-aldol condensation of 2-(1*H*-imidazol-1-yl/benzimidazolyl-1-yl)-1-arylethanones and 2-bromobenzaldehyde followed by palladium-catalyzed intramolecular C−H functionalization. This approach offers a simple and efficient alternative one-pot protocol for the assembly of imidazo/benzimidazo[2,1-*a*]isoquinolines in moderate to good yields.



INTRODUCTION

In recent years much attention has been directed toward the development of more efficient and straightforward transition-metal-catalyzed multiple-bond-forming methods for the construction of heterocyclic molecules from simple precursors.[1] By exploitation of these advances, traditional retrosynthetic methods can be modified to detach fused heterocycles, which can be reconnected using techniques such as domino/cascade reactions[1d] and multicomponent reactions,[2] together with well-received atom-economical approaches such as C−H functionalizations.[3] To date, several elegant methods have been reported where traditional C−C bonding approaches such as aldol condensation were amalgamated with sophisticated techniques such as C−H functionalization, which delivered fused heterocycles with high complexity and substitutions.[4]

Nitrogen-containing heterocycles are privileged structures due to their potential applications in medicinal chemistry.[5] Their ubiquity in several natural products and pharmacologically important molecules as well as in commercially available drugs has attracted the interest of synthetic chemists. Among them, isoquinolines and imidazo[1,2-*a*]pyridines are the important class of heterocycles which are present in several alkaloids (papaverine and jamtine) and marketed drugs (zolpidem and alpidem) with a wide range of bioactivities (Figure 1).[6,7] Similarly, imidazo[2,1-*a*]isoquinolines have been found to exhibit antitumor and platelet activating factor (PAF) antagonist activities.[8] 1*H*-Phenanthro[9,10-*d*]imidazoles with an imidazo[2,1-*a*]isoquinoline moiety have been used in the synthesis of useful fluorophores and organic semiconductors.[9] The synthesized benzimidazo[2,1-*a*]isoquinoline scaffold is structurally very similar to indoloquinoline alkaloids such as cryptolepine, neocryptolepine, and isocryptolepine (Figure 1). These isomeric indoloquinolines act as DNA intercalating agents and have been found to exhibit topoisomerase inhibition activity.[10]

It was believed that fusion of two or more bioactive heterocyclic scaffolds could generate novel hybrid leads for a variety of biological targets. In this context, several methodologies have been reported for the synthesis of azole-fused isoquinolines.[3d,11] For example, the Yanada group achieved these motifs via microwave-assisted tandem reactions among 2-haloarylaldehydes, alkynes, and *o*-phenylenediamines (Scheme 1a).[12] Very recently, Li and co-workers reported the reaction of benzimidazoles with alkynyl bromides in the presence of palladium to give benzo[4,5]imidazo[2,1-*a*]isoquinolines in good yields (Scheme 1b).[13] An aroyl functionality is reported to be crucial for the potential bioactivities of various heterocycles.[14] However, aroyl-functionalized imidazo[2,1-*a*]-isoquinolines have been less explored, which might be due to the dearth of direct approaches to obtain these moieties. As a result of our continuing interest in the development of new synthetic strategies for the construction of novel N-fused heterocycles using C−H functionalizations,[7,15] herein we wish to disclose our recent findings on the assembly of azole-fused isoquinolines by the palladium-catalyzed tandem reactions of 2-(1*H*-imidazol-1-yl/benzimidazolyl-1-yl)-1-arylethanones with 2-bromobenzaldehyde (Scheme 1c).

RESULTS AND DISCUSSION

Our initial investigations commenced by recognizing a suitable catalytic system for the envisioned domino approach, and the results are summarized in Table 1. Initially, 2-(1*H*-imidazol-1-yl)-1-phenylethanone (**1a**) was treated with 2-bromobenzaldehyde (**2**) in the presence of $Pd(OAc)_2$ (5 mol %) and Cs_2CO_3 (2.5 equiv) in *N*,*N*-dimethylacetamide (DMA) at 150 °C for 1.5 h. Gratifyingly, imidazo[2,1-*a*]isoquinolin-5-yl(phenyl)-

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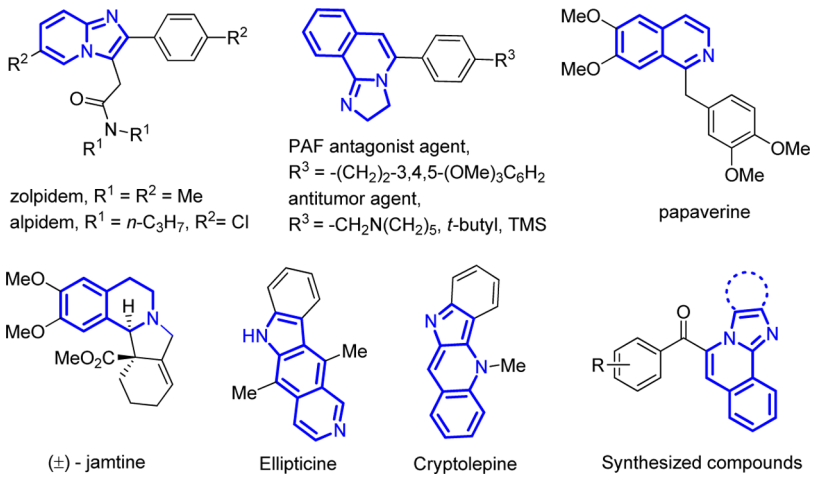


Figure 1. Selected bioactive aza-heterocycles.

Scheme 1. Synthesis of Azole-Fused Isoquinolines

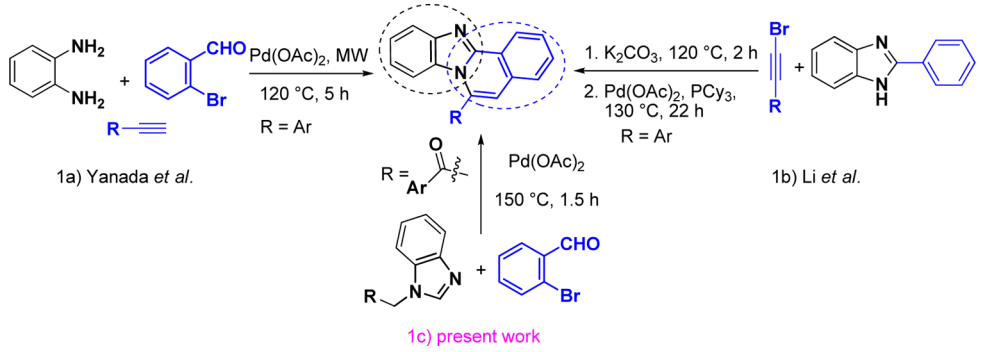
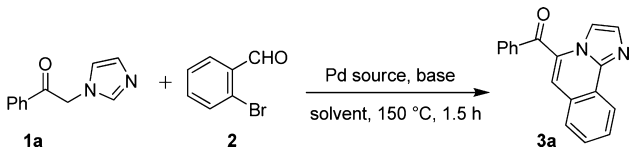


Table 1. Optimization of Reaction Conditions[a]



1a 2 3a

entry	catalyst	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	Cs_2CO_3	DMA	59
2	**$Pd(OAc)_2$**	**K_2CO_3**	**DMA**	**68**
3	$Pd(OAc)_2$	^tBuOK	DMA	traces
4	$Pd(OAc)_2$	KOH	DMA	52
5	$Pd(PPh_3)_4$	K_2CO_3	DMA	22
6	$PdCl_2$	K_2CO_3	DMA	25
7	$Pd(PPh_3)_2Cl_2$	K_2CO_3	DMA	20
8	$Pd(PCy_3)_2Cl_2$	K_2CO_3	DMA	33
9	$Pd(OAc)_2$	K_2CO_3	DMF	40
10	$Pd(OAc)_2$	K_2CO_3	DMSO	17
11[c,d,f]	$Pd(OAc)_2$	K_2CO_3	toluene	NR
12[d–f]	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	NR
13		K_2CO_3	DMA	*e*
14	$Pd(OAc)_2$		DMA	traces
15[g]	$Pd(OAc)_2$	K_2CO_3	DMA	49
16[h]	$Pd(OAc)_2$	K_2CO_3	DMA	58

[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.55 mmol), catalyst (5 mol %), base (1.25 mmol), solvent (2 mL), 1.5 h, 150 °C, N_2 atmosphere. [b]Isolated yields. [c]At 120 °C. [d]No reaction (NR). [e]At 110 °C. [f]Only aldol product was isolated after 16 h. [g]10 mol % of PPh_3 was used. [h]30 mol % of pivalic acid was used.

methanone (**3a**) was isolated in 59% yield (entry 1). The structure of **3a** was characterized by its spectral data (IR, MS, and NMR). In the IR spectrum of **3a**, a strong peak appeared at 1636 cm^{-1} for C=O stretching. In the ^1H NMR spectrum of **3a**, a singlet appeared at δ 9.20 ppm for the highly deshielded C_6-*H* along with other protons at their respective positions. The ketonic carbon of **3a** appeared at δ 190.42 along with all other expected carbons in the ^{13}C NMR spectrum. The total number of ^{13}C signals observed was one less than the total number of nonequivalent carbon atoms, and this may be due to slower relaxation of the quaternary carbon or an overlapping resonance due to the accidental equivalence of two carbon atoms. The peak at *m*/*z* 273.1058 for the $[M + H]^+$ ion in the mass spectrum of **3a** further confirmed its structure.

Encouraged by this result, we further screened various palladium catalysts, bases, and solvents to improve the yield of tandem product **3a**. A survey of various bases such as K_2CO_3, KO^tBu, and KOH suggested that K_2CO_3 is suitable for the present methodology, which afforded **3a** in 68% yield (Table 1, entry 2). Among all palladium catalysts screened for the reaction, viz. $Pd(OAc)_2$, $Pd(PPh_3)_4$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(PCy_3)_2Cl_2$, the highest yield for **3a** was obtained using $Pd(OAc)_2$ (entries 2 and 5–8). Surprisingly, changing the reaction solvent to toluene or 1,4-dioxane failed to produce **3a**, whereas with DMF or DMSO yields were diminished (entries 9–12). The reaction was restricted to the intermediate stage (aldol adduct) without Pd catalyst, and only starting materials were recovered with traces of **3a** in the absence of base (entries 13 and 14). The use of PPh_3 as a ligand and pivalic acid as an

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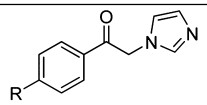
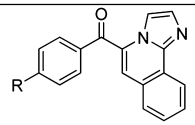
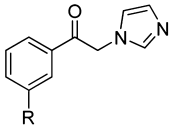
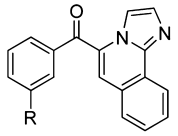
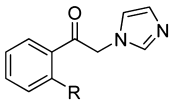
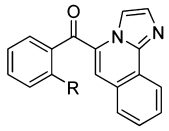
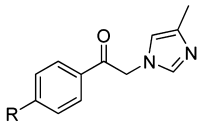
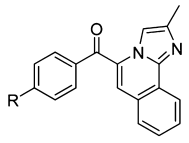
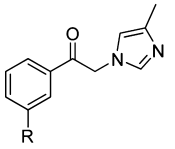
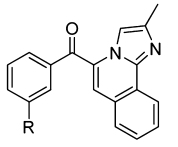
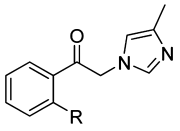
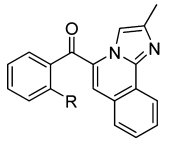
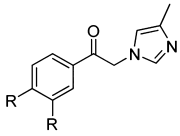
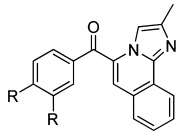
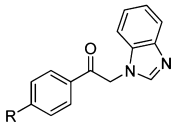
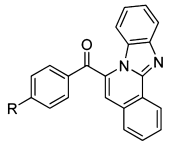
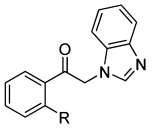
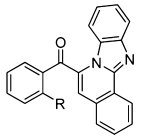
Table 2. Substrate Scope for the Tandem Synthesis of Azole-Fused Isoquinolines 3[a]

entry	substrate			product		yield (%)[b]
1		R = H	**1a**		**3a**	68
		R = Me	**1b**		**3b**	69
		R = OMe	**1c**		**3c**	58
		R = NO_2	**1d**		**3d**	0
		R = Cl	**1e**		**3e**	18
2		R = Me	**1f**		**3f**	55
		R = OMe	**1g**		**3g**	64
3		R = Me	**1h**		**3h**	56
4		R = H	**1i**		**3i**	54
		R = Me	**1j**		**3j**	59
		R = OMe	**1k**		**3k**	48
5		R = Me	**1l**		**3l**	56
		R = OMe	**1m**		**3m**	51
6		R = Me	**1n**		**3n**	70
7		R = OMe	**1o**		**3o**	53
8		R = H	**1p**		**3p**	49
		R = OMe	**1q**		**3q**	47
9		R = Me	**1r**		**3r**	49

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), K_2CO_3 (1.25 mmol), $Pd(OAc)_2$ (5 mol %), DMA (2 mL), 150 °C, 1.5 h. [b]Yields of the isolated products.

additive also did not improve the yield of **3a** (entries 15 and 16).

With the established reaction conditions in hand (Table 1, entry 2), we further studied the scope of the cascade reaction. As shown in Table 2, diversely substituted azolyl aryl ethanones (**1**) produced **3** in moderate to good yields under the optimized reaction conditions. Though the aryl group in substrate **1** is not in the vicinity of reactive sites, substituents on the aryl moiety greatly influenced the outcome of the cascade process. For example, substrates with electron-rich arenes resulted in higher yields of tandem products (**3**) in comparison to arenes with electron-withdrawing groups. It is important to mention that 4-chlorophenyl-substituted azole **1e** gave **3e** in poor yield (Table 2, entry 1), whereas only starting material was recovered in the case of 4-nitrophenyl-substituted azole **1d** (Table 2, entry 1). Similarly, starting material was recovered along with product

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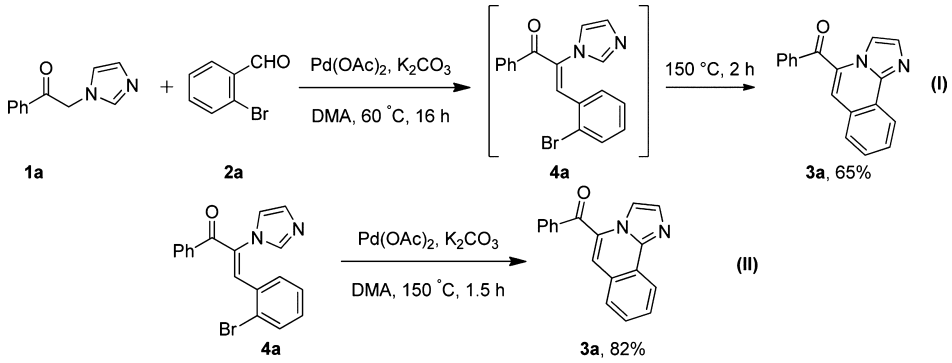
Scheme 2. Control Experiments



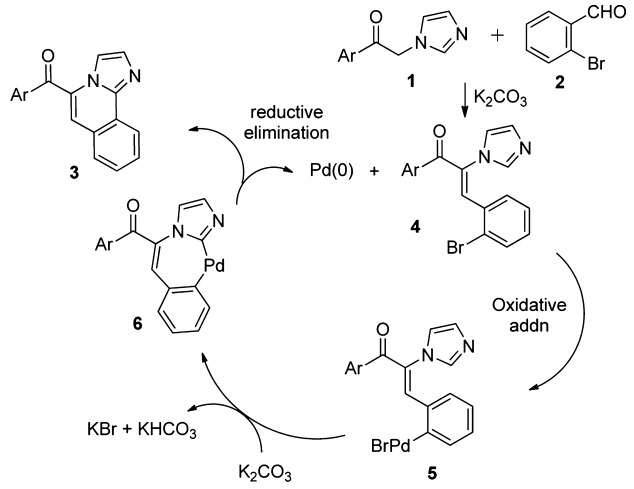
and some other inseparable mixtures of compounds in the case of electron-withdrawing substituents on the aryl group (entry 1, **3e**). Aroyl groups with substituents at ortho, meta, and para-positions (**3b**–**h**) were well tolerated under the reaction conditions (Table 2, entries 1–3) to give good yields of the cascade products (**3f**–**r**). Similarly, 4-methylimidazole analogues (**1i**–**o**) underwent smooth conversion to afford the corresponding tandem products (**3i**–**o**) in good yields (Table 2, entries 4–7). To our delight, substrates with benzimidazole moieties (**1p**–**r**) also smoothly participated in the domino process and provided good yields of the corresponding benzimidazo-fused isoquinolines **3p**–**r** (Table 2, entries 8 and 9). An attempt to replace 2-bromobenzaldehyde with 2-chlorobenzaldehyde was not successful. In this case, aldol adduct and dechlorinated aldol adduct were formed along with an inseparable mixture of compounds. The desired tandem product was not observed even after the reaction was continued overnight under optimized reaction conditions.

Control experiments were performed to investigate the likely synthetic pathway of designed tandem sequences (Scheme 2). When the standard reaction was performed at 60 °C, only aldol adduct **4a** was detected as a major product after 16 h. Further continuation of the reaction for 2 h at 150 °C led to **3a**, confirming the intermediacy of aldol adduct **4a** in this tandem reaction (eq I, Scheme 2). To further validate this pathway, aldol adduct **4a** was treated under similar reaction conditions to afford the tandem product **3a** in 82% yields (eq II, Scheme 2). The reaction is a tandem process, and we did not find any intermediate left after completion of the reaction. However, when intermediate aldol adduct **4a** was isolated from the reaction, we found only one isomer (as analyzed by LCMS; data provided in the Supporting Information). In some reactions, minor amounts of a nonpolar side product were detected by TLC, which was not isolable and hence could not be characterized.

On the basis of previous literature[3a,16] and our observations, we believe that the reaction proceeds via initial cross-aldol condensation between **1** and **2** in the presence of base that provides the aldol adduct **4** (Scheme 3). Oxidative insertion of palladium(0) into **4** gives the arylpalladium bromide intermediate **5**. The Pd(II) intermediate **5** is believed to be responsible for the intramolecular C–H activation of the azole C_2 position to give palladacyclic intermediate **6**. Finally, reductive elimination of **6** affords the domino products, azole-fused isoquinolines (**3**) with the regeneration of active palladium(0) for the next cycle.

In conclusion, we have demonstrated a straightforward cascade approach for the synthesis of imidazo/benzimidazo-

Scheme 3. Plausible Mechanism for the Formation of 3



[2,1-*a*]isoquinolines via cross-aldol condensation/palladium-catalyzed intramolecular C–H functionalization. This method gives an alternative route for the assembly of imidazo/benzimidazo[2,1-*a*]isoquinolines with the hitherto unknown aroyl moiety at the C-5 position. The key precursors, 2-(1*H*-imidazol/benzimidazolyl-1-yl)-1-aryl ethanones, could be obtained through readily available phenacyl halides and azoles in a single step.

EXPERIMENTAL SECTION

General Information. 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 determined by their NMR spectra (^{1}H and ^{13}C NMR). Chemical shifts are reported in parts per million (ppm) using the deuterated solvent peak or tetramethylsilane as an internal standard. IR spectra were recorded on a FTIR spectrophotometer, and the ν_{max} values are expressed in cm^{-1}. The HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. 2-(1*H*-Imidazol-1-yl/benzimidazolyl-1-yl)-1-arylethanones (**1**) were synthesized by the reaction between phenacyl halides and azoles following procedures reported earlier.[17] All other chemicals were obtained from commercial suppliers and used without further purification.

General Procedure for the Synthesis of 3a. A clean oven-dried 10 mL round-bottom flask was charged with **1a** (93 mg, 0.5 mmol), 2-bromobenzaldehyde (**2**; 102 mg, 0.55 mmol), K_2CO_3 (172 mg, 1.25 mmol), $Pd(OAc)_2$ (11 mg, 5 mol %), and DMA (2 mL). The resulting solution was stirred at 150 °C for 1.5 h under an N_2 atmosphere. On completion, the reaction mass was cooled to ambient temperature and

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then diluted with water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc/hexanes) to afford **3a** in 68% (93 mg) yield.

*Imidazo[2,1-a]isoquinolin-5-yl(phenyl)methanone (**3a**):* yield 68% (93 mg); yellow solid; mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.90 (d, J = 7.5 Hz, 2H), 7.76−7.55 (m, 5H), 7.47 (t, J = 7.6 Hz, 1H), 7.41 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 137.4, 133.0, 132.3, 131.4, 129.7, 129.3, 129.2, 128.7, 127.2, 126.7, 125.8, 125.2, 122.5, 121.1; IR (KBr) 3070, 1636, 1412, 1227 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{13}N_2O$ 273.1022, found 273.1034 $[M + H]^+$.

*Imidazo[2,1-a]isoquinolin-5-yl(p-tolyl)methanone (**3b**):* yield 69% (99 mg); yellow solid; mp 201−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.76−7.69 (m, 1H), 7.58 (s, 1H), 7.55−7.49 (m, 1H), 7.45 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 144.2, 134.6, 132.2, 131.2, 130.0, 129.5, 129.4, 129.1, 127.2, 126.7, 125.3, 125.0, 122.5, 121.1, 21.8; IR (KBr) 3055, 2924, 1643, 1458, 1257 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O$ 287.1179, found 287.1189 $[M + H]^+$.

*Imidazo[2,1-a]isoquinolin-5-yl(4-methoxyphenyl)methanone (**3c**):* yield 58% (88 mg); yellow solid; mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.97−7.93 (m, 3H), 7.66 (t, J = 8.3 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.34 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9, 163.9, 132.3, 131.0, 129.7, 128.9, 127.2, 126.5, 125.4, 123.8, 122.5, 121.1, 114.0, 55.6; IR (KBr) 3065, 2948, 1631, 1482, 1278, 1221 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O_2$ 303.1128, found 303.1152 $[M + H]^+$.

*(4-chlorophenyl)(imidazo[2,1-a]isoquinolin-5-yl)methanone (**3e**):* yield 18% (27 mg); yellow solid; mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.71−7.61 (m, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.51−7.43 (m, 1H), 7.37 (s, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 189.1, 139.6, 135.7, 131.6, 131.1, 129.2, 129.1, 129.1, 127.3, 126.8, 125.7, 125.1, 122.5, 121.3; IR (KBr) 2926, 2864, 1651, 1459, 1255 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{12}ClN_2O$ 307.0633, found 307.0612 $[M + H]^+$.

*Imidazo[2,1-a]isoquinolin-5-yl(m-tolyl)methanone (**3f**):* yield 55% (79 mg); yellow solid; mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 7.71 (s, 1H), 7.70−7.62 (m, 3H), 7.53−7.43 (m, 3H), 7.40 (s, 1H), 2.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 138.8, 137.4, 133.8, 132.3, 131.3, 130.1, 129.5, 129.2, 128.7, 128.5, 127.2, 126.9, 126.7, 125.6, 125.2, 122.5, 121.0, 21.4; IR (KBr) 2916, 2854, 1643, 1458, 1265 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O$ 287.1179, found 287.1155$[M + H]^+$.

*Imidazo[2,1-a]isoquinolin-5-yl(3-methoxyphenyl)methanone (**3g**):* yield 64% (97 mg); yellow solid; mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, J = 2.6 Hz, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.96 (d, J = 6.3 Hz, 1H), 7.70−7.57 (m, 2H), 7.52−7.36 (m, 5H), 7.22 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 159.8, 138.6, 132.2, 131.4, 129.6, 129.3, 129.2, 128.6, 127.2, 126.7, 125.8, 125.1, 122.4, 122.2, 121.0, 119.3, 114.2, 55.5; IR (KBr) 3070, 2962, 1628, 1466, 1285, 1126 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O_2$ 303.1128, found 303.1112 $[M + H]^+$.

*Imidazo[2,1-a]isoquinolin-5-yl(o-tolyl)methanone (**3h**):* yield 56% (80 mg); yellow solid; mp 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.71−7.63 (m, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.54−7.47 (m, 1H), 7.44−7.42 (m, 2H), 7.40−7.31 (m, 2H), 7.29 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 137.6, 137.0, 132.7, 131.7, 131.3, 130.9, 130.2, 129.4, 128.7, 128.4, 127.5, 127.1, 127.1, 125.5, 125.1, 122.4, 121.2, 19.7; IR (KBr) 3186, 3055, 1651, 1458, 1211 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O$ 287.1187, found 287.1168 $[M + H]^+$.

*(2-Methylimidazo[2,1-a]isoquinolin-5-yl)(phenyl)methanone (**3i**):* yield 54% (77 mg); orange solid; mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.17−8.12 (m, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.73−7.64 (m, 2H), 7.61−7.55 (m, 3H), 7.41 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 1.4 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 137.5, 133.0, 131.7, 131.3, 129.9, 129.7, 129.3, 129.0, 128.7, 128.3, 126.1, 126.0, 125.4, 123.3, 122.6, 16.6; IR (KBr) 3055, 2916, 1636, 1458, 1257 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O$ 287.1179, found 287.1192 $[M + H]^+$.

*(2-Methylimidazo[2,1-a]isoquinolin-5-yl)(p-tolyl)methanone (**3j**):* yield 59% (88 mg); orange solid; mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.73−7.62 (m, 3H), 7.60 (d, J = 7.3 Hz, 1H), 7.53−7.34 (m, 3H), 7.29 (s, 1H), 2.85 (s,3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 138.7, 137.5, 133.8, 131.7, 131.2, 130.1, 129.9, 129.4, 129.3, 128.4, 128.2, 126.9, 126.0, 125.7, 125.4, 123.2, 122.5, 21.4, 16.6; IR (KBr) 2916, 2854, 1643, 1456, 1265 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}N_2O$ 301.1335, found 301.1326 $[M + H]^+$.

*(4-Methoxyphenyl)(2-methylimidazo[2,1-a]isoquinolin-5-yl)-methanone (**3k**):* yield 48% (76 mg); orange solid; mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8, 163.8, 132.2, 131.5, 130.8, 129.7, 129.7, 129.5, 129.0, 127.9, 126.0, 125.6, 123.9, 123.2, 122.5, 114.0, 55.6, 16.6; IR (KBr) 2952, 2928, 1647, 1461, 1261, 1189 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}N_2O_2$ 317.1285, found 317.1268 $[M + H]^+$.

*(2-Methylimidazo[2,1-a]isoquinolin-5-yl)(m-tolyl)methanone (**3l**):* yield 56% (84 mg); orange solid; mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.69−7.63 (m, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.44−7.34 (m, 3H), 7.27 (s, 1H), 2.85 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 144.1, 134.7, 131.6, 131.0, 129.9, 129.9, 129.5, 129.4, 129.1, 128.1, 126.0, 125.5, 125.1, 123.2, 122.5, 21.7, 16.6; IR (KBr) 2916, 2854, 1643, 1458, 1257 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}N_2O$ 301.1335, found 301.1362 $[M + H]^+$.

*(3-Methoxyphenyl)(2-methylimidazo[2,1-a]isoquinolin-5-yl)-methanone (**3m**):* yield 51% (80 mg); orange solid; mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.70−7.65 (m, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.49−7.39 (m, 4H), 7.34 (s, 1H), 7.22 (ddd, J = 7.9, 2.5, 1.5 Hz, 1H), 3.90 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1, 159.8, 138.8, 131.7, 131.3, 129.9, 129.6, 129.3, 128.3, 126.1, 125.9, 125.4, 123.2, 122.6, 122.2, 119.3, 114.2, 55.5, 16.6; IR (KBr) 2962, 2924, 1643, 1458, 1257, 1180 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}N_2O_2$ 317.1285, found 317.1298 $[M + H]^+$.

*(2-Methylimidazo[2,1-a]isoquinolin-5-yl)(o-tolyl)methanone (**3n**):* yield 70% (110 mg); orange solid; mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.68 (t, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.49 (t, 1H), 7.46−7.31 (m, 4H), 7.21 (s, 1H), 2.87 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 137.8, 137.0, 131.8, 131.6, 131.2, 130.8, 130.4, 130.1, 129.5, 128.6, 128.4, 127.7, 126.0, 125.5, 125.3, 123.3, 122.5, 19.7, 16.7; IR (KBr) 3163, 3032, 1651, 1458, 1250 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}N_2O$ 301.1335, found 301.1312 $[M + H]^+$.

*(3,4-Dimethoxyphenyl)(2-methylimidazo[2,1-a]isoquinolin-5-yl)-methanone (**3o**):* yield 53% (80 mg); orange solid; mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.71−7.65 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H), 7.46−7.39 (m, 1H), 7.28 (s, 2H), 6.98 (d, J = 8.1 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 2H), 2.87 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 156.4, 152.0, 134.2, 133.4, 132.4, 132.2, 132.1, 131.5, 130.6, 128.7, 128.2, 127.4, 126.3, 125.8, 125.2, 114.5, 112.6, 58.8, 58.7, 19.1; IR (KBr) 3070, 2962, 1628, 1466, 1288, 1211 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O_3$ 303.1128, found 303.1152 $[M + H]^+$.

*Compound **3p**:* yield 49% (79 mg); yellow solid; mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 7.2 Hz, 2H), 8.04 (d, J = 8.2 Hz, 1H), 7.84−7.68 (m, 4H), 7.61 (t, J = 7.7 Hz, 2H), 7.56−7.47 (m, 2H), 7.31−7.25 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 147.6, 144.1, 135.9, 134.6, 133.5, 130.6, 130.3, 130.0, 129.8, 129.5, 129.0, 127.9, 125.3, 124.7, 124.6, 122.2, 120.0,

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116.9, 114.1; IR (KBr) 2924, 2854, 1651, 1450, 1288 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{15}N_2O$ 323.1179, found 323.1156 $[M + H]^+$.

Compound ***3q:*** yield 47% (86 mg); yellow solid; mp 172−173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.1 Hz, 1H), 7.81−7.68 (m, 3H), 7.55−7.44 (m, 2H), 7.31−7.24 (m, 1H), 7.21 (s, 1H), 7.05 (d, J = 8.9 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.8, 165.0, 147.6, 144.1, 133.6, 133.1, 130.3, 129.8, 129.7, 129.6, 128.6, 127.7, 125.3, 124.6, 124.4, 122.2, 119.9, 115.4, 114.4, 114.0, 55.7; IR (KBr) 2924, 2847, 1643, 1450, 1257, 1165 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{17}N_2O_2$ 353.1285, found 353.1256 $[M + H]^+$.

Compound ***3r:*** yield 49% (87 mg); yellow solid; mp 158−160 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.82−7.73 (m, 2H), 7.72−7.67 (m, 3H), 7.59−7.50 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.38−7.31 (m, 2H), 7.18 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 147.6, 144.1, 140.3, 135.9, 135.3, 132.9, 132.1, 131.4, 130.3, 130.2, 130.1, 129.5, 128.1, 125.8, 125.3, 124.9, 124.7, 122.2, 120.0, 118.5, 114.6, 21.1; IR (KBr) 3055, 2924, 1659, 1450, 1211 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{17}N_2O$ 337.1335, found 337.1362 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H NMR and ^{13}C NMR spectra for compounds **3a−r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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