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On-Water Silver(I)-Catalyzed Cycloisomerization of Acetylenic Free Amines/Amides towards 7-Azaindole/Indole/Isoquinolone Derivatives

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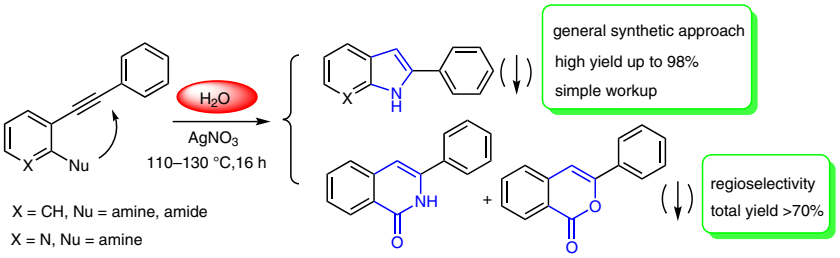

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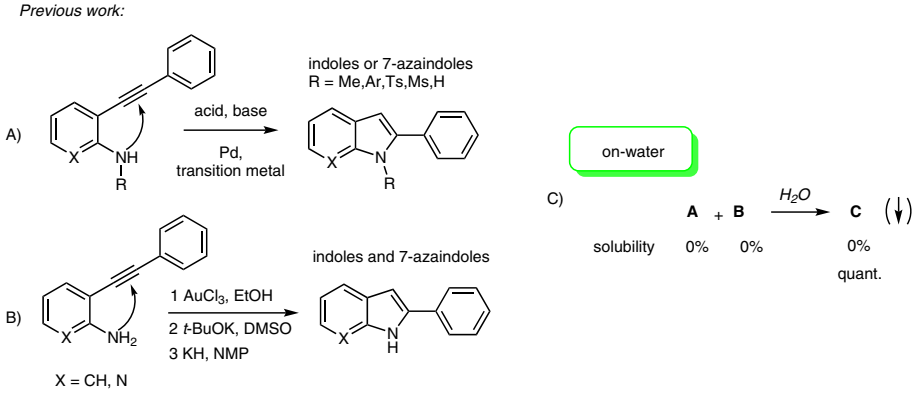
Abstract Silver-catalyzed on-water intramolecular cyclization of acetylenic free amines is reported, which affords 7-azaindoles in good to excellent yields. Neither strong base/acid catalysts nor N-substituted substrates are required to achieve this cycloisomerization. Hydrogen bonds between water medium and the substrates play an important role in improving chemical reactivity and regioselectivity. Furthermore, the on-water reaction is extendable to acetylenic amides for isoquinolone synthesis.

Key words on-water, cycloisomerization, 7-azaindoles, indoles, isoquinolones

7-Azaindole and indole derivatives have attracted considerable attention in organic synthesis because of their presence in many natural products and potent biological activities.[1,2] Intramolecular cyclization of 3-alkynylpyridylamines (generally obtained via an additional step, e.g., Sonogashira coupling) appears an effective strategy for the direct synthesis of 7-azaindoles or indoles, hence considerable efforts have been devoted in this direction.[3,4]

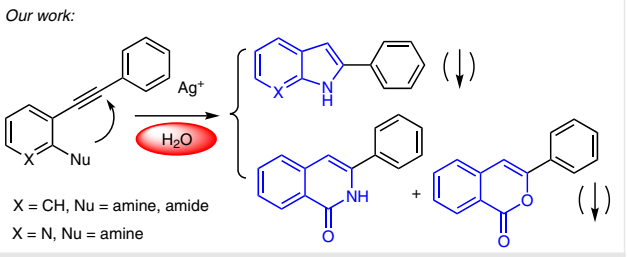
Mechanism of the intramolecular cyclization is that the amino group attacks activated triple bonds to afford N-containing heterocycles. Most reported reactions were focused on the synthesis of either indoles or 7-azaindoles (Scheme 1, A),[3] and only a few could be applied to both (Scheme 1, B).[4] Catalysts employed for this cyclization include strong bases (KH, *t*-BuOK, etc.),[3a–c] expensive transition-metal catalysts (Pd,[3d] $AuCl_3$,[4b] etc.), or strong acid (e.g., TFA).[3e] In addition, the reaction conditions suffered from other limitations, such as high catalyst loading, complicated operational procedures, harsh reaction conditions, and uses of toxic solvents (e.g., NMP, DMSO, toluene).[3,4] Thus, new synthetic protocols of wide substrate range, resource-saving conditions, and simple operations are needed to be explored.



Scheme 1 Previous work (A, B) and ideal green reactions (C)

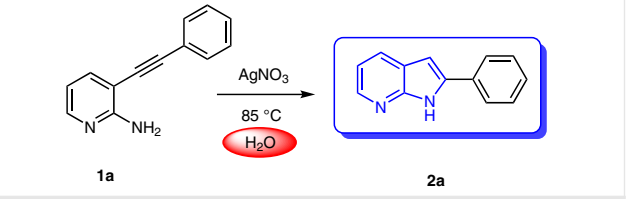
On-water reaction is a class of unique water-mediated reaction, in which insoluble reactants form aqueous suspension under vigorous stirring.[5] Sharpless and co-workers first reported such reactions in 2005 where water-insoluble reactants gave high yields of products in pure water.[5a] As presented in Scheme 1 (C), on-water reaction comes very close to the ideal green reaction.[5d] More importantly, the solvent effect of water (mainly hydrogen-bond) could play a key role in improving reactivity and regioselectivity.[5] Recently on-water reactions have been used to synthesize diverse frameworks.[5e–i]

Our aim was to develop a general and simple synthetic protocol employing acetylenic free amines as substrates to synthesize 7-azaindole and indole derivatives. Herein we report on the silver(I)-catalyzed on-water ring-closure reactions towards 7-azaindoles, indoles, isoquinolones, and isocoumarins (Scheme 2).



Scheme 2 Silver-catalyzed synthesis of 7-azaindoles, indoles, isoquinolones, and isocoumarins

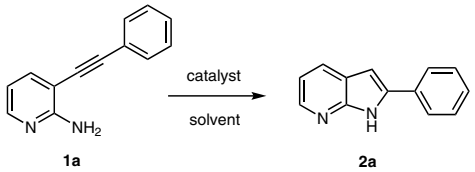
In initial reaction exploration, 3-(phenylethynyl)pyridine-2-amine (**1a**) was chosen as the substrate, which can be readily prepared from the corresponding alkynes and 2-amino-3-bromopyridine by Sonogashira coupling in satisfactory yield according to the literature protocol.[6] 3-(Phenylethynyl)pyridine-2-amine (**1a**) was stirred in water with $AgNO_3$ (10 mol%) at 85 °C (Scheme 3). The reaction was stopped at 48 hours with the starting material still remaining. Pure product 2-phenyl-7-azaindole (**2a**) was obtained in 33% yield after flash column chromatography, which encouraged us to further investigate the reaction conditions.



Scheme 3 Initial example of silver-catalyzed 7-azaindole synthesis

Subsequently, 3-(phenylethynyl)pyridine-2-amine (**1a**) was used as the model substrate to optimize reaction conditions including different catalysts and temperatures, and results are summarized in Table 1.

Table 1 Optimization of the Cyclization Conditions[a]



Entry	Catalyst (20 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$AgNO_3$ (10 mol%)	H_2O	85	48	33
2	$AgNO_3$ (10 mol%)	H_2O	100	36	42
3	$AgNO_3$ (10 mol%)	H_2O	110	36	51
4	$AgNO_3$	H_2O	100	24	63
5	$AgNO_3$	H_2O	110	24	87
6	$AgNO_3$	H_2O	130	16	96
7	–	H_2O	130	16	NR
8	$AgNO_3$	H_2O	130[c]	8	82
9	AgOTf	H_2O	130	16	trace
10	AgOAc	H_2O	130	16	trace
11	Ag_2CO_3	H_2O	130	16	trace
12	AgF	H_2O	130	16	92
13	$AgClO_4$	H_2O	130	16	93
14	ScOTf	H_2O	130	16	NR
15	$Cu(OAc)_2$	H_2O	130	16	NR
16	$FeCl_3$	H_2O	130	16	NR
17	concd HCl (1 equiv)	H_2O	130	16	NR
18	concd HNO_3 (1 equiv)	H_2O	130	16	NR
19	$Cu(OCOCF_3)_2 \cdot \times H_2O$ 1-ethylpiperidine (2 equiv)	H_2O	130	16	NR
20	$AuCl_3$	H_2O	130	16	95
21	$AuCl_3$ (10 mol%)	H_2O	130	16	81
22	$AgNO_3$	toluene	130	16	NR
23	$AgNO_3$	EtOH	100	16	30
24	$AgNO_3$	DMF	130	16	trace and complex
25	$AgNO_3$	neat	130	16	11

[a] Reaction conditions: **1a** (50 mg), solvent (2 mL), sealed tube in oil bath. Tf = triflate.
[b] Isolated yields. NR: No reaction.
[c] Microwave heating, detected by HPLC every 2 h.

Increasing the catalyst loading from 10 mol% to 20 mol% shortened the reaction time (Table 1, entries 2–5). Reaction temperature was also an important factor because the substrate was almost completely converted to 2-phenyl-7-azaindole (**2a**) after increasing the temperature from 100 to 130 °C (entries 4–6). No reaction occurred in the absence of catalyst at 130 °C (entry 7). We also tried to apply microwave irradiation to shorten the reaction time, but the result was unsatisfactory (entry 8). Some other silver(I) salts were screened (entries 9–13), among which $AgNO_3$ displayed the

highest catalytic activity with a yield of 96% (entry 6). Meanwhile, the other two water soluble silver salts (entries 12, 13) provided much better yields than the insoluble ones, the latter just gave a trace amount of cyclized product **2a** (entries 9–11). No reaction occurred when ScOTf, $FeCl_3$, $Cu(OAc)_2$, HCl,[3p] HNO_3, and $Cu(OCOCF_3)_2{\cdot}{\times}H_2O$[3q] were used as the catalysts (entries 14–19). Among them HCl and $Cu(OCOCF_3)_2{\cdot}xH_2O$ had been used to synthesize indoles,[3p,q] but they could not be applied to synthesize 7-azaindoles under our reaction conditions. One possible reason is that the pyridine N atom weakens the NH_2 moiety's nucleophilic reactivity. $AuCl_3$ also provided a yield of 95% under the same condition (entry 20), but a poorer yield was obtained at lower catalyst loading (entry 21). Thus, $AgNO_3$ was chosen as the catalyst for its relatively lower cost.

Additionally, we performed the model reaction in organic solvents, such as DMF, toluene, EtOH, and without solvent under the same conditions (Table 1, entries 22–25), none of them could effectively mediate the synthesis of desired product **2a**. We also observed the solubility of organic molecule in the progress of reaction (Figure 1). At the initial and final state, the organic phase was solid (Figure 1, P1, P3). During the progress of reaction, the organic phase was oily liquid under 130 °C, and this kind of oil-water state was beneficial to form aqueous suspension under vigorous stirring (Figure 1, P2). These results confirmed that the model reaction belonged to on-water reaction class.

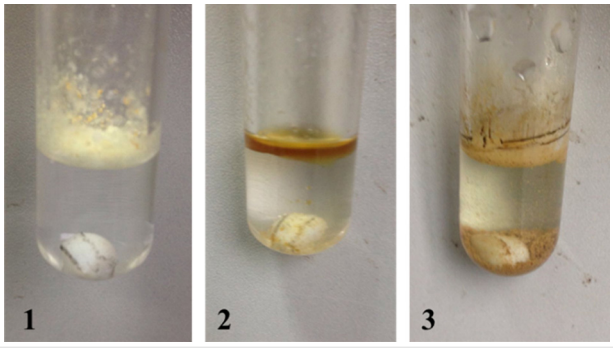
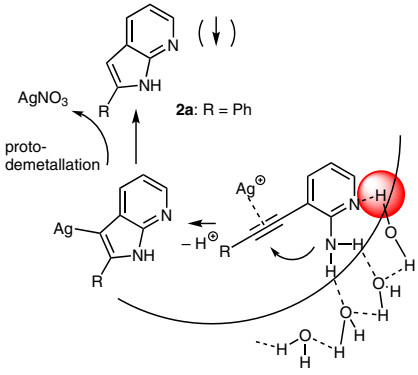


Figure 1 Appearance of solubility in the reaction progress. **P1**: Initial state. **P2**: Up to 130 °C. **P3**: Final state.

The on-water phenomenon is a unique chemistry that occurs at the water–oil phase boundary. Under vigorous agitation or high temperature, at large hydrophobic surfaces about 1 in 4 of the water molecules in the final layer has an OH-free group directed at the boundary. These bare protons act as both hydrogen-bond donors and acceptors, and therefore are involved in trans-phase hydrogen bonding with the transition state, which lowers the activation energy of the reaction.[5c]

On the basis of the results obtained above and previously reported literature,[5c] a plausible mechanism of this on-water reaction is illustrated in Scheme 4. A cooperative hydrogen bond network at the oil-water interface could stabilize the transition state as proposed by Marcus.[5c] More importantly, the hydrogen bond between water and N atom on pyridine ring strengthens the aromaticity of pyridine and then enhances NH_2 moiety's nucleophilic reactivity, which may explain why aprotic solvents like DMF and toluene cannot effectively mediate the synthesis of desired product **2a** (Scheme 4). It is certain that $AgNO_3$ as the catalyst also plays an important role in promoting the cyclization.

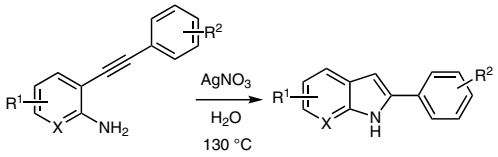


Scheme 4 Proposed mechanism of the on-water reaction

With the optimal conditions established, the substrate scopes including 2-(phenylethynyl)anilines were subsequently explored, and the results are shown in Table 2. Most products were obtained in good to excellent yields (80–98%) after simple filtration and drying process (**2a**–**p**). These cases were close to the ideal green reaction shown in Scheme 1 (C). Furthermore, this reaction condition was applied successfully to synthesize both 7-azaindoles **2a**–**h** and indoles **2i**–**p**. This reaction system also could be applied to the synthesis of 2-propyl-7-azaindole (**2r**) and provides 62% yield, while the product need to be isolated by column chromatography.

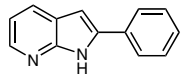
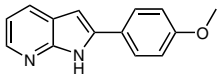
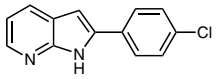
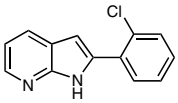
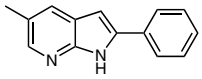
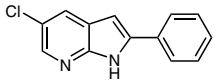
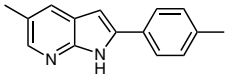
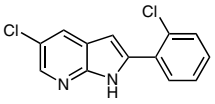
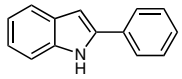
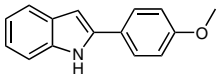
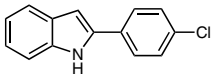
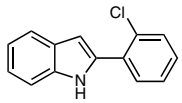
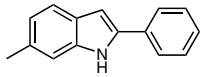
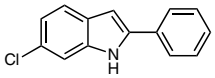
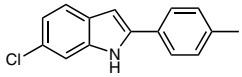
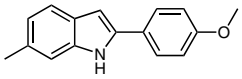
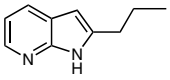
The excellent reactivity of amine as a nucleophile for this transformation prompted us to investigate amide group for the synthesis of isoquinolones (Table 3, **4a**–**d**). 2-(Phenylethynyl)benzamides were successfully cyclized to form isoquinolones, but the products were impure and the isolated yields (35–54%) were not as satisfactory as indoles or 7-azaindoles. Interestingly, another series of isocoumarin products were isolated (Table 3, **5a**–**d**) in comparable yields (24–42%). For each reaction, the yield of the isoquinolone and isocoumarin derivatives in total was higher than 70% (73–86%). Ketonic oxygen addition products were avoided because of the key hydrogen bond between the O atom and water, which reduces the nucleophilicity of the amide oxygen (Scheme 5). Additionally, aqueous $AgNO_3$ solution is acidic, and 6-*endo* cyclization product is the major product instead of 5-*exo* under acidic conditions.[7] To the best of our

Table 2 Synthesis of **2a–p** under Optimized Conditions[a]



1a–p
X = CH, N

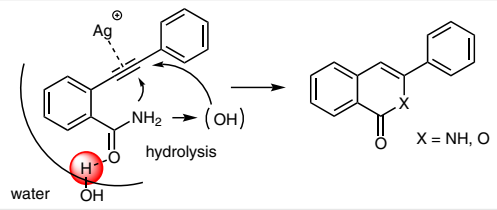
2a–p

 **2a**, 96%	 **2b**, 90%	 **2c**, 94%
 **2d**, 96%	 **2e**, 92%	 **2f**, 86%
 **2g**, 86%	 **2h**, 80%	 **2i**, 98%
 **2j**, 91%	 **2k**, 90%	 **2l**, 92%
 **2m**, 98%	 **2n**, 94%	 **2o**, 91%
 **2p**, 96%	 **2r**, 62%	

[a] Reaction conditions: **1a–p** (50 mg), $AgNO_3$ (20 mol%), H_2O (2 mL); 8–24 h, sealed tube in oil bath; isolated yields.

knowledge, the on-water synthetic method of isoquinolones has not been reported.[8]

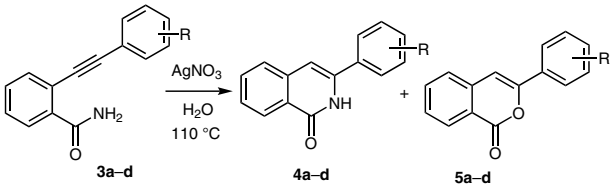
Recycling of the retained aqueous $AgNO_3$ medium was also investigated. Results from the recycling study on the reaction of 5-chloro-2-(*p*-tolylethynyl)aniline (**1o**) are shown in Table 4. After the third recycle, isolated yield still achieved 93% without $AgNO_3$ addition, but the reaction time was prolonged from 10 to 36 hours. The product of every recycle was simply obtained by filtration and the resulting colorless aqueous filtrate (containing $AgNO_3$) was used in the next recycle immediately.



Scheme 5 Proposed mechanism for on-water amide cyclization reaction

In summary, we have developed a general and simple method to synthesize N-containing benzoheterocycles (including 7-azaindoles, indoles, and isoquinolones) via Ag(I)-catalyzed on-water reaction. The products of 7-azaindoles and indoles displayed high yields and most of them were isolated by simple filtration. Isoquinolone derivatives could be successfully synthesized from amides by this on-water reaction, while the isolated yields were unsatisfactory due to amide hydrolysis. In addition, this reaction provided another way to synthesize isocoumarins.

Table 3 Synthesis of **4a–d** under Optimized Conditions[a]

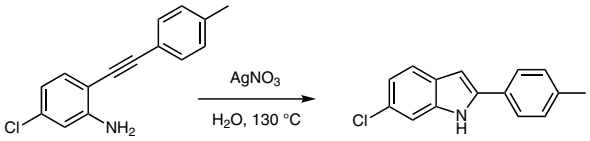


3a–d 4a–d 5a–d

R	**4** Yield (%)[b]	**5** Yield (%)[b]	Total yield (%)
H	**4a** (35)	**5a** (42)	77
4-Me	**4b** (50)	**5b** (24)	74
4-OMe	**4c** (48)	**5c** (25)	73
4-CO_2Me	**4d** (54)	**5d** (32)	86

[a] Reaction conditions: **3a–e** (50 mg), $AgNO_3$ (20 mol%), H_2O (2 mL), 10–16 h, in sealed tube.
[b] Isolated yields.

Table 4 Recycling of the Aqueous $AgNO_3$ Medium[a]



1o 2o

Entry	Recycle	Time (h)	Yield (%)[b]
1	1	10	96
2	2	16	94
3	3	36	93

[a] Reaction condition: **1o** (50 mg), $AgNO_3$ (20 mol%), H_2O (2 mL), in sealed tube.
[b] Isolated yields.

The ^{1}H NMR (400 MHz) spectra were recorded using Varian 400 MHz with TMS as internal standard, and the ^{13}C NMR (600 MHz) spectra were recorded using Bruker 600 MHz. MS data were recorded on Agilent Technologies 6120 quadrupole mass spectrometer. Purity was recorded on high-performance liquid chromatography (HPLC) using a Poroshell 120 column (50 mm × 4.6 mm). Conditions were as follows: MeOH/H_2O eluent at 1.2 mL/min flow (containing 0.1% TFA) at 30 °C, 8 min, gradient 40% MeOH to 60% MeOH, monitored by UV absorption at 254 nm. TLC was carried out with silica gel precoated glass plates. TLC spots were visualized under UV light. Melting point was recorded using WRS-1B digital instrument. All the solvents and reagents were used directly as obtained commercially, unless otherwise noted. Compounds **1a–p** and **3a–d** were prepared according to literature procedures.[4b,6,8i]

2-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2a); Typical Procedure

To a sealed tube (10 mL) was added 3-(phenylethynyl)pyridin-2-amine (**1a**; 50 mg, 0.26 mmol), H_2O (2 mL), and $AgNO_3$ (8.7 mg, 0.052 mmol). After ultrasonic oscillation for 5 min, the mixture was stirred at 130 °C for about 16 h. The reaction product was filtered, washed with H_2O, and dried to give a brown solid; yield: 48 mg (96%); mp 209–210 °C; HPLC purity 98%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.13 (s, 1 H), 8.30–8.20 (m, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H), 7.95–7.89 (m, 2 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.39–7.32 (m, 1 H), 7.12 (dd, *J* = 7.9, 4.6 Hz, 1 H), 6.96 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 149.1, 143.1, 138.2, 131.2, 128.8 (2 C), 128.5, 128.0, 125.2 (2 C), 121.3, 116.0, 97.2.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}N_2^+$: 195.0922; found: 195.0928.

2-(4-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2b)

Brown solid; yield: 45 mg (90%); mp 200–202 °C; HPLC purity 93%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.01 (s, 1 H), 8.15 (d, *J* = 4.7 Hz, 1 H), 7.89–7.85 (m, 3 H), 7.04–7.01 (m, 3 H), 6.78 (d, *J* = 2.0 Hz, 1 H), 3.79 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 148.7, 143.2, 134.8, 131.2, 130.9, 130.6, 130.3, 129.4, 128.2, 127.3, 120.0, 115.8, 101.4, 69.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}N_2O^+$: 225.1028; found: 225.1032.

2-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2c)

Brown solid; yield: 47 mg (94%); mp 235–236 °C; HPLC purity 94%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.19 (s, 1 H), 8.22 (s, 1 H), 7.94 (dd, *J* = 8.2, 5.9 Hz, 3 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 7.06 (dd, *J* = 7.8, 4.5 Hz, 1 H), 6.96 (s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 149.5, 143.0, 136.8, 132.3, 130.3, 128.8 (2 C), 127.9, 126.8 (2 C), 120.7, 116.0, 97.6.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{10}ClN_2^+$: 229.0533; found: 229.0541.

2-(2-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2d)

Brown solid; yield: 48 mg (96%); mp 238–239 °C; HPLC purity 94%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.04 (s, 1 H), 8.25 (dd, *J* = 4.7, 1.5 Hz, 1 H), 8.02–7.97 (m, 1 H), 7.74 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.62–7.58 (m, 1 H), 7.49–7.39 (m, 2 H), 7.09 (dd, *J* = 7.9, 4.7 Hz, 1 H), 6.85 (s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 159.1, 149.4, 142.1, 138.2, 127.2, 126.6 (2 C), 124.0, 121.1, 115.7, 114.2 (2 C), 95.5.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{10}ClN_2^+$: 229.0533; found: 229.0538.

5-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2e)

Brown solid; yield: 46 mg (92%); mp 248–250 °C; HPLC purity 99%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.00 (s, 1 H), 8.07 (s, 1 H), 7.92 (d, *J* = 7.8 Hz, 2 H), 7.74 (s, 1 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 147.9, 143.7, 138.3, 131.4, 128.7 (2 C), 128.1, 127.8, 125.1 (2 C), 124.4, 121.0, 96.6, 17.9.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}N_2^+$: 229.0533; found: 229.0538.

5-Chloro-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2f)

Brown solid; yield: 43 mg (86%); mp 240–241 °C; HPLC purity 99%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.38 (s, 1 H), 8.30–7.84 (m, 4 H), 7.60–7.29 (m, 3 H), 6.93 (s, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 147.8, 140.6, 140.2, 130.9, 128.8 (2 C), 128.3, 126.7, 125.4 (2 C), 122.6, 121.8, 96.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}N_2^+$: 229.0533; found: 229.0548.

5-Methyl-2-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2g)

Brown solid; yield: 43 mg (86%); mp 260–261 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.92 (s, 1 H), 8.03 (s, 1 H), 7.81 (d, *J* = 7.9 Hz, 2 H), 7.69 (d, *J* = 1.9 Hz, 1 H), 7.26 (d, *J* = 7.9 Hz, 2 H), 6.77 (d, *J* = 2.0 Hz, 1 H), 2.35 (d, *J* = 8.8 Hz, 6 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 148.1, 143.1, 138.3, 137.1, 129.2 (2 C), 128.8, 127.2, 125.0 (2 C), 124.1, 120.7, 95.7, 20.7, 18.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}N_2^+$: 223.1235; found: 223.1234.

5-Chloro-2-(2-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (2h)

Brown solid; yield: 40 mg (80%); mp 255–256 °C; HPLC purity 100%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.28 (s, 1 H), 8.24 (d, *J* = 2.3 Hz, 1 H), 8.11 (d, *J* = 2.3 Hz, 1 H), 7.73 (dd, *J* = 7.4, 2.0 Hz, 1 H), 7.62 (dd, *J* = 7.7, 1.6 Hz, 1 H), 7.50–7.40 (m, 2 H), 6.84 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 146.9, 141.2, 136.9, 131.3, 131.0, 130.4, 130.2, 129.8, 127.4, 127.2, 122.5, 120.9, 101.0.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9Cl_2N_2^+$: 263.0143; found: 263.0134.

2-Phenyl-1*H*-indole (2i)

Brown solid; yield: 49 mg (98%); mp 185–187 °C; HPLC purity 93%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.53 (s, 1 H), 7.86 (dt, *J* = 8.4, 1.7 Hz, 2 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.34–7.28 (m, 1 H), 7.10 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1 H), 7.00 (td, *J* = 7.5, 6.9, 1.1 Hz, 1 H), 6.90 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 137.4, 136.9, 132.0, 128.7 (2 C), 128.4, 127.2, 124.8 (2 C), 121.4, 119.8, 119.2, 111.1, 98.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N^+$: 194.0970; found: 194.0972.

2-(4-Methoxyphenyl)-1*H*-indole (2j)

Brown solid; yield: 45.5 mg (91%); mp 225–226 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.41 (s, 1 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.08–6.93 (m, 4 H), 6.76 (d, *J* = 2.1 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 158.6, 137.6, 136.7, 128.6, 126.2 (2 C), 124.7, 120.8, 119.5, 119.0, 114.2 (2 C), 110.9, 97.1, 55.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}NO^+$: 224.1075; found: 224.1077.

2-(4-Chlorophenyl)-1*H*-indole (2k)

Brown solid; yield: 45 mg (90%); mp 203–205 °C; HPLC purity 97%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37–8.20 (m, 1 H), 7.59 (dd, *J* = 20.4, 8.1 Hz, 3 H), 7.39 (dd, *J* = 8.2, 4.9 Hz, 3 H), 7.23–7.08 (m, 2 H), 6.80 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.3, 136.0, 132.8, 130.3, 128.6 (2 C), 128.5, 125.7 (2 C), 122.0, 120.1, 119.8, 110.3, 99.8.

LC-MS (ESI): *m*/*z* = 228 (M + H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClN^+$: 228.0580; found: 228.0580.

2-(2-Chlorophenyl)-1*H*-indole (2l)

Brown solid; yield: 46 mg (92%); mp 205–206 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1 H), 7.66 (dd, *J* = 7.7, 1.7 Hz, 2 H), 7.44 (ddd, *J* = 23.0, 8.0, 1.2 Hz, 2 H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.29–7.24 (m, 1 H), 7.23–7.19 (m, 1 H), 7.14 (m, 1 H), 6.86 (dd, *J* = 2.3, 1.1 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.3, 135.1, 131.3, 131.1, 130.8, 130.7, 128.8, 128.1, 127.2, 122.6, 120.7, 120.2, 111.0, 103.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClN^+$: 228.0580; found: 228.0577.

6-Methyl-2-phenyl-1*H*-indole (2m)

Brown solid; yield: 49 mg (98%); mp 190–192 °C; HPLC purity 91%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.65–7.59 (m, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.16 (s, 1 H), 6.95 (dd, *J* = 8.1, 1.4 Hz, 1 H), 6.77 (s, 1 H), 2.46 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 136.7, 136.6, 131.9, 131.6, 128.4 (2 C), 126.8, 126.5 (2 C), 124.4, 121.4, 119.7, 110.3, 99.2, 21.2.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{14}N^+$: 208.1126; found: 208.1135.

6-Chloro-2-phenyl-1*H*-indole (2n)

Brown solid; yield: 47 mg (94%); mp 175–177 °C; HPLC purity 94%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 7.69–7.62 (m, 2 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.41–7.31 (m, 2 H), 7.09 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.80 (dd, *J* = 2.1, 1.0 Hz, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.0, 136.5, 131.3, 128.5 (2 C), 127.4, 127.2, 124.5 (2 C), 120.8, 120.4, 110.2, 99.3.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClN^+$: 228.0580; found: 228.0578.

6-Chloro-2-(*p*-tolyl)-1*H*-indole (2o)

Brown solid; yield: 45.6 mg (91%); mp 145–146 °C; HPLC purity 91%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 7.57–7.48 (m, 3 H), 7.37 (d, *J* = 1.8 Hz, 1 H), 7.26–7.23 (m, 1 H), 7.08 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.74 (s, 1 H), 2.40 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.8, 138.0, 137.0, 129.8 (2 C), 129.1, 127.9, 127.7, 125.0 (2 C), 121.3, 120.9, 110.7, 99.3, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}ClN^+$: 242.0737; found: 242.0736.

2-(4-Methoxyphenyl)-6-methyl-1*H*-indole (2p)

Brown solid; yield: 48 mg (96%); mp 220–221 °C; HPLC purity 94%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.60–7.54 (m, 2 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.17 (td, *J* = 1.7, 0.9 Hz, 1 H), 6.95 (dd, *J* = 10.0, 8.3 Hz, 3 H), 6.66 (dd, *J* = 2.1, 1.0 Hz, 1 H), 3.85 (s, 3 H), 2.46 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.5, 136.7, 136.5, 131.1, 126.6, 125.7 (2 C), 124.8, 121.3, 119.3, 113.8 (2 C), 110.1, 98.0, 54.8, 21.2.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}NO^+$: 252.1263; found: 252.1258.

2-Propyl-7-azaindole (2r)

To a sealed tube (10 mL) was added 3-(pent-1-yn-1-yl)pyridin-2-amine (**1r**; 50 mg, 0.31 mmol), H_2O (2 mL), and $AgNO_3$ (10.5 mg, 0.062 mmol). After ultrasonic oscillation for 5 min, the mixture was stirred at 130 °C for about 16 h. The solid was filtered and purified by column chromatography to give a white solid; yield: 31 mg (62%); mp 66–67 °C; HPLC purity 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.82 (s, 1 H), 8.27–8.13 (m, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 7.05 (dd, *J* = 7.7, 4.8 Hz, 1 H), 6.21 (s, 1 H), 2.85 (t, *J* = 7.6 Hz, 2 H), 1.85 (sext, *J* = 7.5 Hz, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 148.7, 141.7, 140.1, 128.1, 122.2, 115.5, 97.4, 30.7, 22.3, 13.9.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}N_2^+$: 161.1079; found: 161.1083.

3-Phenylisoquinolin-1(2*H*)-one (4a)

Slight yellow solid; yield: 17.6 mg (35%); mp 203–204 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 7.75–7.71 (m, 2 H), 7.68 (dd, *J* = 7.0, 1.2 Hz, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.56–7.45 (m, 4 H), 6.81 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.2, 138.7, 137.7, 133.6, 132.3, 128.9, 128.7, 126.9 (2 C), 126.1, 125.9, 125.4 (2 C), 124.2, 103.9.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}NO^+$: 222.0919; found: 222.0919.

3-(*p*-Tolyl)isoquinolin-1(2*H*)-one (4b)

Slight yellow solid; yield: 25 mg (50%); mp 220–221 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.41 (s, 1 H), 8.40 (d, *J* = 8.1 Hz, 1 H), 7.69–7.62 (m, 3 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.47 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 6.77 (s, 1 H), 2.43 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.1, 139.7, 139.6, 138.5, 132.8, 131.4, 129.9 (2 C), 127.5, 126.5 (2×C), 126.0 (2 C), 124.8, 103.9, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}NO^+$: 236.1075; found: 236.1089.

3-(4-Methoxyphenyl)isoquinolin-1(2*H*)-one (4c)

Slight yellow solid; yield: 24 mg (48%); mp 241–242 °C; HPLC purity 94%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.14 (s, 1 H), 8.32 (d, *J* = 8.1 Hz, 1 H), 7.63–7.57 (m, 3 H), 7.51 (d, *J* = 8.1 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 6.98–6.90 (m, 2 H), 6.67 (s, 1 H), 3.80 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.5, 160.1, 138.6, 137.9, 132.3, 126.8, 126.7 (2 C), 126.0, 125.7 (2 C), 123.8, 114.1, 102.9, 54.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}NO_2^+$: 252.1025; found: 252.1042.

Methyl 4-(1-Oxo-1,2-dihydroisoquinolin-3-yl)benzoate (4d)

Slight yellow solid; yield: 27 mg (54%); mp 261–262 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.66 (s, 1 H), 8.22 (dd, *J* = 8.0, 1.1 Hz, 1 H), 8.09–8.02 (m, 2 H), 7.99–7.93 (m, 2 H), 7.78–7.72 (m, 2 H), 7.53 (ddd, *J* = 8.2, 4.9, 3.4 Hz, 1 H), 7.07 (s, 1 H), 3.89 (s, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 165.6, 162.5, 138.6, 137.9, 137.4, 132.6, 129.7, 129.3 (2×C), 126.8 (2×C), 126.8, 126.5, 125.1, 104.4, 52.1.

HRMS(ESI): *m*/*z* calcd for $C_{17}H_{14}NO_3^+$: 280.0974; found: 280.0980.

3-Phenyl-1*H*-isochromen-1-one (5a)

Slight yellow solid; yield: 21 mg (42%); mp 86–88 °C; HPLC purity 96%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.28 (m, 1 H), 7.91–7.86 (m, 2 H), 7.72 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.53–7.39 (m, 5 H), 6.96 (s, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.7, 153.0, 136.9, 134.3, 131.3, 129.4, 129.0, 128.2 (2 C), 127.5, 125.4, 124.6 (2 C), 119.9, 101.2.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_9O_2^+$: 222.0681; found: 222.0683.

3-(*p*-Tolyl)-1*H*-isochromen-1-one (5b)

Pale yellow solid; yield: 12 mg (24%); mp 110–112 °C; HPLC purity 97%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32–8.25 (m, 1 H), 7.79–7.73 (m, 2 H), 7.69 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.50–7.43 (m, 2 H), 7.24 (s, 2 H), 6.90 (s, 1 H), 2.39 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.8, 153.3, 139.6, 137.1, 134.2, 129.0, 128.9 (2 C), 128.6, 127.3, 125.2, 124.6 (2 C), 119.8, 100.4, 20.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{12}O_2^+$: 236.0837; found: 236.0832.

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (5c)

Pale yellow solid; yield: 13 mg (25%); mp 111–113 °C; HPLC purity 98%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.1 Hz, 1 H), 7.87–7.79 (m, 2 H), 7.70 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.46 (ddd, *J* = 8.1, 4.6, 3.2 Hz, 2 H), 7.00–6.94 (m, 2 H), 6.84 (s, 1 H), 3.87 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.8, 160.5, 153.1, 137.3, 134.2, 129.0, 127.0, 126.2 (2 C), 125.0, 123.9, 119.5, 113.6 (2 C), 99.6, 54.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{12}O_3^+$: 252.0786; found: 252.0784.

Methyl 4-(1-Oxo-1*H*-isochromen-3-yl)benzoate (5d)

Pale yellow solid; yield: 16 mg (32%); mp 136–138 °C; HPLC purity 99%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (ddd, *J* = 8.5, 1.3, 0.7 Hz, 1 H), 8.16–8.10 (m, 2 H), 7.99–7.94 (m, 2 H), 7.76 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.55 (td, *J* = 7.4, 1.1 Hz, 2 H), 7.07 (s, 1 H), 3.95 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.4, 152.4, 137.0, 136.0, 135.0, 131.2, 130.1 (2 C), 129.8, 128.8, 126.3, 125.1 (2 C), 120.9, 103.5, 52.3.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}O_4^+$: 280.0736; found: 280.0731.

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Supporting Information

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