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Base-Promoted Intermolecular Cyclization of Substituted 3-Aryl(Heteroaryl)-3-chloroacrylaldehydes and Tetrahydroisoquinolines: An Approach to Access Pyrrolo[2,1-*a*]isoquinolines

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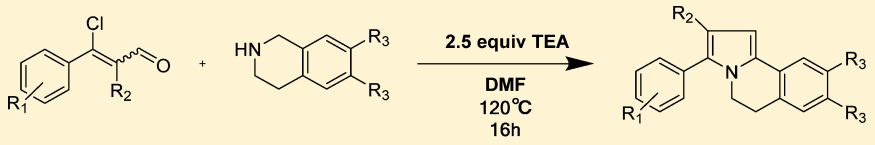
Supporting Information

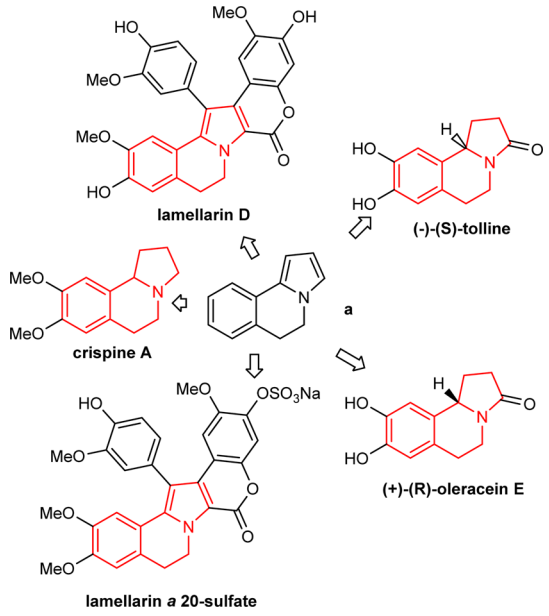


Metal-free! 20 examples, up to 97% yield.

ABSTRACT: We have developed a new base-promoted intermolecular cascade cyclization reaction of substituted 3-aryl(heteroaryl)-3-chloroacrylaldehydes and tetrahydroisoquinolines in one pot. The reaction provides a facile and practical synthesis of pyrrolo[2,1-*a*]isoquinolines. A number of pyrrolo[2,1-*a*]isoquinolines were synthesized in moderate to high yields (up to 97%).

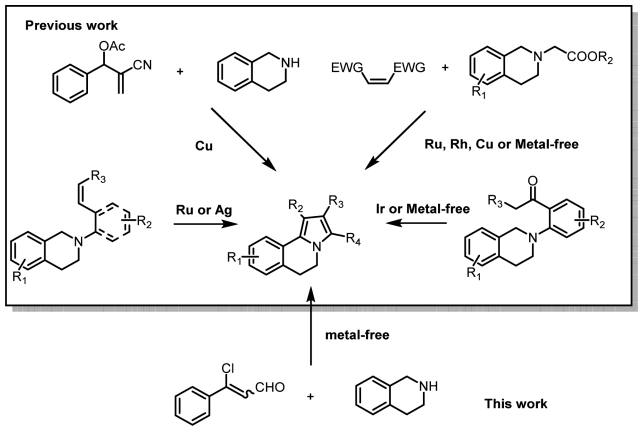
Pyrrolo[2,1-*a*]isoquinoline[1−4] (Scheme 1a) framework is ubiquitous in various natural products and some bio-

Scheme 1. Representative Natural Products



logically active molecules. Representative compounds such as lamellarin D, lamellarin *a* 20-sulfate, and derivatives crispine A, trolline, and oleracein E are depicted in Scheme 1. Among them, lamellarin D is a potent inhibitor of human topoisomerase I,[5] lamellarin *a* 20-sulfate is an inhibitor of HIV integrase,[6] and even other lamellarins exhibit anticancer activity;[7−9] in addition, crispine A emerged as a target of great interest, due to potential biological and pharmaceutical activities.[10,11] The synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives has been the focus of organic chemists' research for a long time.[12−18] Accordingly, a number of synthetic methods which include metal and metal-free catalysis have been reported. Sequential elegant studies (Scheme 2) using metal catalysis (e.g., Ir, Ru, Rh, Ag, Cu, etc.) were accomplished by several research groups.[19−27]

Scheme 2. Existing Strategies for the Synthesis of Pyrrolo[2,1-*a*]isoquinolines



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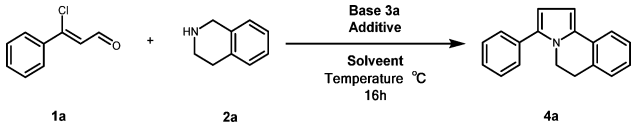
In recent years, metal-free catalysis has been of great interest in the construction of the pyrrolo[2,1-*a*]isoquinoline framework. These metal-free catalysis pathways involve stepwise coupling of radicals, which were in situ formed in the presence of *t*-BuOK/DMF,[28] or a concerted reaction followed by oxidation in the I_2/H_2O_2,[29] KI/TBHP,[30] or TBAI/TBHP[31] system, such as [3 + 2] cycloaddition between 1,4-dicarbonyl-2-butenes and alkyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetates. Although aforementioned successful synthetic methods have been developed, new and facile approaches are still desirable in terms of great structural diversity of pyrrolo[2,1-*a*]isoquinoline derivatives. In this context, we developed a new and facile synthetic method for pyrrolo[2,1-*a*]isoquinolines which include an intermolecular cascade cyclization of substituted 3-aryl-(heteroaryl)-3-chloroacrylaldehydes and tetrahydroisoquinolines in a one-pot reaction promoted by Et_3N/DMF.

Initially, the optimal reaction conditions in Yan's work[28] were also used to examine the reaction of (*Z*)-3-chloro-3-phenylacrylaldehyde (**1a**) with THIQ (1,2,3,4-tetrahydroisoquinoline, **2a**). Unfortunately, 3-phenyl-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline (**4a**) has not been detected, and the substrate **1a** was transformed to complex byproducts (Table 1, entry 1). Surprisingly, reducing the basicity of inorganic bases is beneficial to the reaction; for example, when NaOH or K_2CO_3 was used as the base, the product **4a** was obtained in 34% and 42% isolated yields respectively (entries 2 and 3), and **4a** was confirmed by crystal structure (CCDC: 1421171;[32] for more details please see Supporting Information). Encouraged by these preliminary results, a variety of organic bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DABCO (1,4-diazabicyclo[2.2.2]octane), DIPEA (*N*,*N*-diisopropylethylamine), DMAP (4-dimethylaminopyridine), TMEDA (tetramethylethylenediamine), and TEA (trimethylamine) were used instead of K_2CO_3. Obviously, among these bases, TEA gave the best yield (56%, entry 4), and remarkably, DMAP gave us an extreme decrease in yield (26%, entry 8), which might due to DMAP being a weak nucleophile but a strong base.[33] Thus, we used TEA as the optimal base for further optimization including in the screening of solvents, reaction temperature, additives, and the loading of substrates. As results show in Table 1, compared with DMF, the high polarity of solvents such as DMSO was also beneficial to the reaction (48%, entry 10); however, compared with DMF or DMSO, other solvents of relatively low polarity, such as, CH_2Cl_2, THF, and CH_3CN (entries 11, 12, and 13), gave a trace amount of product **4a**. The results showed that the reaction temperature has an apparent effect on the reaction; both a lower and higher temperature would depress the conversion of substrates (entries 14 and 15). In addition, some additives such as activated 4 Å molecular sieves and silica or the oxidant MnO_2 could not apparently improve the yields (separately 55%, 55%, entries 16, 17, and 18); Gratifyingly, increasing the amount of THIQ and TEA led to a high yield (93%, entry 19; for more details, see SI Table 1); Further experiments exhibited that oxygen had no impact on this reaction in which a radical pathway might not be involved. Ultimately, the optimal reaction conditions identified were as follows: 2.5 equiv of TEA, 4 equiv of THIQ, DMF used as solvent, and a reaction temperature of 120 °C.

Table 1. Optimization of Reaction Conditions[a]



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

entry	*T* (°C)	base	additive	solvent	yield[b](%)
1	90/120	*t*-BuOK	–	DMF	N.D.[c]
2	120	NaOH	–	DMF	34
3	120	K_2CO_3	–	DMF	42
4	120	TEA	–	DMF	56
5	120	DBU	–	DMF	31
6	120	DABCO	–	DMF	45
7	120	DIPEA	–	DMF	50
8	120	DMAP	–	DMF	26
9	120	TMEDA	–	DMF	47
10	120	TEA	–	DMSO	48
11	reflux	TEA	–	DCE	trace[d]
12	reflux	TEA	–	THF	trace
13	reflux	TEA	–	MeCN	trace
14	100	TEA	–	DMF	38
15	150	TEA	–	DMF	42
16	120	TEA	4 Å	DMF	55[e]
17	120	TEA	silica	DMF	55[e]
18	120	TEA	MnO_2	DMF	38[e]
19	120	TEA	–	DMF	93[f]
20	120	TEA	–	DMF	92[g]

[a]Reaction conditions: **1a** (1.20 mmol), **2a** (1.80 mmol), **3a** (1.80 mmol), solvent (3 mL), at 120 °C 16 h, under Ar protection. [b]Isolated yield of **4a**. [c]No desired product; detected by HRMS. [d]Detected by HRMs. [e]Additive/**1a** (m/m = 1:1). [f]**1a** (1.20 mmol), **2a** (4.80 mmol), **3a** (3.00 mmol). [g]**1a** (1.20 mmol), **2a** (4.80 mmol), **3a** (3.00 mmol), without Ar protection.

With optimized conditions in hand (Table 1, entry 20), we next explored the scope and limitations of this reaction by employing various (*Z*)-3-aryl(heteroaryl)-3-chloroacrylaldehydes **1** and THIQs **2** (Scheme 2). An assembly of 20 compounds were synthesized using this protocol and gave the best yield up to 97%. The results indicated that compounds **1** with electron-withdrawing (F, Cl, Br, and NO_2) or electron-donating groups (Me and OMe) were well tolerated and provided the corresponding products in moderate to high yields. As shown in Table 2, when R_1 is a *meta*- or *para*-substituted group on the phenyl ring, the corresponding product was obtained in a high yield (up to 97%, **4e**). However, *ortho*-substituents such as F and Br due to their steric hindrance are not beneficial to the reaction (34% **4g** and 43% **4k**); surprisingly the substrate which involves *ortho*-substituent OMe gave a satisfying yield of 71% (**4b**). Substrates with the substituent R_2 such as Me and phenyl all provided corresponding products in good to excellent yields respectively (84% **4o** and 61% **4q**).

Similarly, 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde also gave corresponding product **4p** in 41% yield. Subsequently, when condensed 3-aryl- and 3-heteroaryl-substituted 3-chloroacrylaldehydes including naphthalene and thiophene frameworks were subjected to the optimized conditions, products **4r** and **4s** were obtained in excellent isolated yields (89% and 95%). Finally, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in place of THIQ reacted with **1a**; this reaction also led to the corresponding product **4t** in a satisfactory yield (77%). Unfortunately, while *N*-methylbenzylamine and piperidine were used, corresponding products were not detected.

To gain insight into the reaction mechanism we performed some additional experiments (Scheme 3). In experiment A, a

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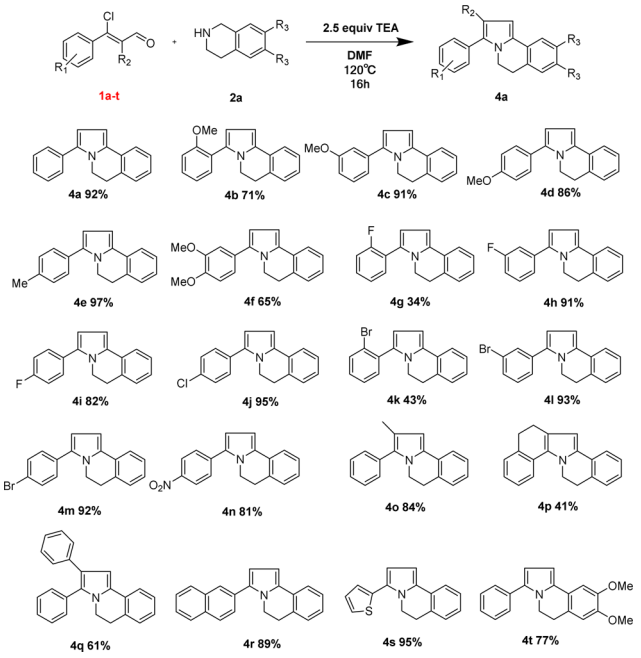
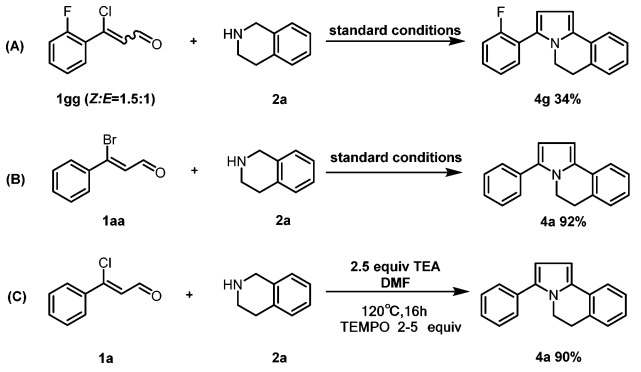
Table 2. Scope of Tandem Reaction[a]



[a]Reaction conditions: **1a** (1.20 mmol), **2a** (4.80 mmol), **3a** (3.00 mmol), solvent (3 mL), at 120 °C 16 h, without Ar protection.

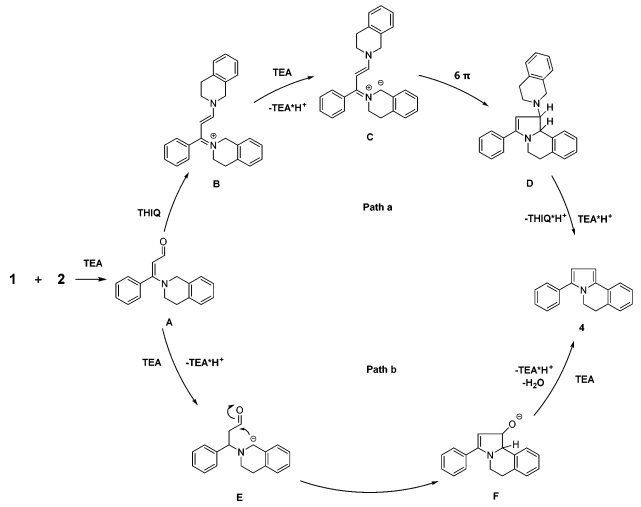
Scheme 3. Mechanistic Studies



mixture of *Z* and *E* isomers of 3-chloro-3-(2-fluorophenyl)-acrylaldehyde (**1gg**, *Z*/*E* = 1.5:1 detected by ^{1}H NMR see SI) in place of **1g** was used to investigate the effect of the *E*/*Z* configuration on the reaction. Interestingly, product **4g** was obtained in 34% yield (Scheme 3A). The result is similar to the data for **4g** which derived from (*Z*)-3-chloro-3-(2-fluorophenyl)acrylaldehyde (**1g**) used as the substrate in Table 2 and showed that the geometric configuration might have no effect on the reaction result. Compared with (*Z*)-3-chloro-3-phenylacrylaldehyde (**1a**), (*Z*)-3-bromo-3-phenylacrylaldehyde (**1aa**) also might undergo the same intermediate step in this protocol and give **4a** in a similarly high yield (92%, Scheme 3B). In Yan's work,[28] intramolecular dehydrative coupling of tertiary amines and ketones was promoted by *t*-BuOK/DMF through a radical process;[34] however, under the same conditions, the reaction of (*Z*)-3-chloro-3-phenylacrylaldehyde (**1a**) with tetrahydroisoquinoline could not afford corresponding product **4a** (Table 1, entry 1). In addition, another investigation using TEMPO to catch a possible radical intermediate under an argon atmosphere was not successful, and the product was still obtained in a high yield (90%, Scheme 3C).

Thus, based on these experiment results, a plausible mechanism for this reaction is tentatively proposed in Scheme 4. Initially, intermediate **A** was first formed from compounds **1** and **2** via a Michael addition, then nucleophilic substitution between **A** and THIQ gave an intermediate **B** under basic conditions. **B** prompted by TEA was transformed to intermediate **C** in situ, and then **D** was generated by 6π-electrocyclization and subsequent elimination of THIQ (path a). Through path b, **A** was first prompted by TEA to give intermediate **E**, and then **F** might be formed through a nucleophilic addition. Final product **4** was generated after the dehydration of **F**.

Scheme 4. Suggested Mechanism



In conclusion, we have developed a new TEA-prompted intermolecular cascade cyclization reaction of substituted 3-aryl(heteroaryl)-3-chloroacrylaldehydes and tetrahydroisoquinolines in one pot. The reaction provides a facile and practical synthesis of pyrrolo[2,1-*a*]isoquinolines. A number of pyrrolo[2,1-*a*]isoquinolines were synthesized in moderate to high yields, and the mechanism of the reaction was tentatively proposed.

EXPERIMENTAL SECTION

General Information. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF254). Visualization of the developed plates was performed under UV light (254 nm). Flash column chromatography was performed on silica gel (200−300 mesh). ^{1}H and ^{13}C NMR were recorded at 400 and 101 MHz, respectively; chemical shifts were reported in ppm referenced to the H_2O (δ 3.33) in DMSO standard for ^{1}H NMR. Chemical shifts of ^{13}C NMR are reported relative to $CDCl_3$ (δ 77.0). Coupling constants, *J*, were reported in hertz (Hz). High resolution mass spectra (HRMS) were obtained on an ESI-Q-TOF mass spectrometer. And DMF was freshly distilled from CaH_2, and TEA was freshly distilled from KOH.

General Procedure for the Synthesis of Substrate 1. Phosphorus oxychloride (5.10 g, 33.29 mmol) was added dropwise over 15 min to an ice-cooled stirred solution of dry *N*,*N*-dimethylformamide (10 mL). After 30 min, the appropriate acetophenone derivative (8.32 mmol) dissolved in 5 mL of *N*,*N*-dimethylformamide was added dropwise to the $POCl_3$/DMF complex. The reaction mixture was stirred for 1 h at 0 °C and then heated at 65 °C for 8 h. Then, it was cooled to room temperature and finally poured into an ice-cold saturated NaOAc water solution (20 mL). The

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resulting mixture was extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was subjected to column chromatography purification on silica gel eluting with petroleum ether/ethyl acetate (95:0.5) to give *cis*-products.[35]

General Procedures for the Synthesis of 4. To a suspension of β-chlorovinyl aldehydes **1** (1.20 mmol) and THIQ **2** (4.80 mmol) in DMF 3 mL of TEA (3.00 mmol) were added slowly, followed by heating to 120 °C for 16 h. The residue was treated with water (30 mL) and then extracted with EA (3 × 15 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1) to afford the desired compound **4**.

*3-Phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4a**).* White solid, mp 109−111 °C; **4a** (271 mg, 92%); ^{1}H NMR (400 MHz, DMSO) δ 7.58 (d, *J* = 7.7 Hz, 1H), 7.49−7.41 (m, 4H), 7.38−7.29 (m, 1H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.5, 1.1 Hz, 1H), 6.65 (d, *J* = 3.7 Hz, 1H), 6.30 (d, *J* = 3.7 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.2, 132.8, 130.9, 130.6, 129.8, 128.5, 128.4, 127.7, 127.0, 126.7, 125.5, 122.5, 109.4, 104.2, 42.0, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}N$ $[M + H]^+$ 246.1277, found 246.1270.

*3-(2-Methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4b**).* White solid, mp 108−110 °C; **4b** (235 mg, 71%); ^{1}H NMR (400 MHz, DMSO) δ 7.55 (d, 1H), 7.38 (t, 1H), 7.30−7.19 (m, 3H), 7.09 (t, *J* = 12.5, 4.8 Hz, 2H), 7.02 (t, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 3.87−3.71 (m, 5H), 2.94 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 131.9, 130.8, 130.7, 130.2, 130.0, 129.1, 127.7, 126.9, 125.3, 122.4, 122.0, 120.6, 110.8, 109.6, 103.7, 55.3, 42.2, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1383, found 276.1372.

*3-(3-Methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4c**).* White solid, mp 81−83 °C; **4c** (301 mg, 91%); ^{1}H NMR (400 MHz, DMSO) δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 11.1, 3.7 Hz, 1H), 7.01 (3, *J* = 15.6, 5.0 Hz, 2H), 6.91 (d, *J* = 8.2, 2.2 Hz, 1H), 6.64 (d, *J* = 3.7 Hz, 1H), 6.31 (d, *J* = 3.7 Hz, 1H), 4.14 (t, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 134.0, 133.9, 130.9, 130.6, 129.7, 129.3, 127.6, 127.0, 125.5, 122.4, 120.8, 114.1, 112.0, 109.4, 104.2, 55.0, 41.9, 29.4. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1383, found 276.1383.

*3-(4-Methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4d**).* White solid, mp 100−102 °C; **4d** (284 mg, 86%); ^{1}H NMR (400 MHz, DMSO) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 3.7 Hz, 1H), 6.20 (d, *J* = 3.7 Hz, 1H), 4.07 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 2.99 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 134.0, 130.5, 130.3, 129.9, 129.8, 127.7, 127.0, 125.4, 125.4, 122.4, 113.8, 108.7, 104.0, 55.2, 41.8, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}NO$ $[M + H]^+$ 276.1383, found 276.1379.

*3-(p-Tolyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4e**).* White solid, mp 103−105 °C; **4e** (302 mg, 97%); ^{1}H NMR (400 MHz, DMSO) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.28−7.19 (m, 4H), 7.11 (t, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 6.24 (d, *J* = 3.7 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 134.3, 130.6, 130.6, 130.0, 129.9, 129.1, 128.5, 127.7, 127.0, 125.4, 122.5, 109.0, 104.1, 41.9, 29.6, 21.1. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1434, found 260.1434.

*3-(3,4-Dimethoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4f**).* Yellow solid, mp 115−117 °C; **4f** (238 mg, 65%); ^{1}H NMR (400 MHz, DMSO) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.96 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.61 (d, *J* = 3.7 Hz, 1H), 6.23 (d, *J* = 3.7 Hz, 1H), 4.11 (t, *J* = 6.5 Hz, 2H), 3.80 (d, *J* = 6.9 Hz, 6H), 2.99 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 148.2, 134.0, 130.5, 130.4, 129.8, 127.6, 127.0, 125.6, 125.4, 122.4, 121.0, 112.2, 111.1, 108.7, 103.9, 55.8, 55.8, 41.8, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.1489, found 306.1486

*3-(2-Fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4g**).* Yellow solid, mp 53−55 °C; **4g** (107 mg, 34%); ^{1}H NMR (400 MHz, DMSO) δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.50−7.40 (m, 2H), 7.38−7.21 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 3.7 Hz, 1H), 6.29 (d, *J* = 3.6 Hz,1H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (d, *J* = 246.8 Hz), 131.7 (d, *J* = 3.0 Hz), 131.2, 130.7, 129.7, 129.1 (d, *J* = 8.1 Hz), 127.8, 127.7, 127.1, 125.7, 124.1 (d, *J* = 3.6 Hz), 122.5, 120.8 (d, *J* = 15.1 Hz), 115.7 (d, *J* = 22.4 Hz), 110.7, 104.2, 42.2 (d, *J* = 4.7 Hz), 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}FN$ $[M + H]^+$ 264.1183, found 264.1182.

*3-(3-Fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4h**).* White solid, mp 102−104 °C; **4h** (288 mg, 91%); ^{1}H NMR (400 MHz, DMSO) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.52−7.43 (m, 1H), 7.34−7.21 (m, 4H), 7.19−7.10 (m, 2H), 6.66 (d, *J* = 3.8 Hz, 1H), 6.38 (d, *J* = 3.8 Hz, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.01 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 245.8 Hz), 134.9 (d, *J* = 8.3 Hz), 132.9 (d, *J* = 2.3 Hz), 131.5, 130.7, 129.9 (d, *J* = 8.7 Hz), 129.6, 127.7, 127.1, 125.8, 124.0 (d, *J* = 2.8 Hz), 122.7, 115.1 (d, *J* = 22.0 Hz), 113.4 (d, *J* = 21.1 Hz), 110.0, 104.4, 42.1, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}FN$ $[M + H]^+$ 264.1183, found 264.1183.

*3-(4-Fluorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4i**).* White solid, mp 106−108 °C; **4i** (259 mg, 82%); ^{1}H NMR (400 MHz, DMSO) δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 8.3, 5.7 Hz, 2H), 7.32−7.20 (m, 3H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 3.6 Hz, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.00 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 246.7 Hz), 133.1, 130.9, 130.6, 130.2 (d, *J* = 8.0 Hz), 129.8, 129.0 (d, *J* = 3.3 Hz), 127.7, 127.1, 125.6, 122.5, 115.3 (d, *J* = 21.5 Hz), 109.3, 104.2, 41.9, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}FN$ $[M + H]^+$ 264.1183, found 264.1178.

*3-(4-Chlorophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4j**).* Yellow solid, mp 100−102 °C; **4j** (319 mg, 95%); ^{1}H NMR (400 MHz, DMSO) δ 7.59 (d, *J* = 7.6 Hz, 1H), 7.49 (s, 4H), 7.25 (t, *J* = 9.7, 7.5 Hz, 2H), 7.13 (t, *J* = 7.4, 1.0 Hz, 1H), 6.66 (d, *J* = 3.8 Hz, 1H), 6.33 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 132.6, 131.3, 131.2, 130.6, 129.6, 129.6, 128.6, 127.7, 127.1, 125.7, 122.6, 109.7, 104.4, 42.0, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}ClN$ $[M + H]^+$ 280.0888, found 280.0887.

*3-(2-Bromophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4k**).* Yellow solid, mp 87−89 °C; **4k** (167 mg, 43%); ^{1}H NMR (400 MHz, DMSO) δ 7.77 (b, 1H), 7.60 (b, 1H), 7.51−7.42 (m, 2H), 7.39−7.32 (m, 1H), 7.25 (t, *J* = 9.8, 4.1 Hz, 2H), 7.12 (t, *J* = 7.5, 1.1 Hz, 1H), 6.64 (d, *J* = 3.7 Hz, 1H), 6.19 (d, *J* = 3.7 Hz, 1H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 132.8, 132.7, 132.5, 130.6, 130.2, 129.6, 129.4, 127.8, 127.1, 127.0, 125.6, 125.2, 122.5, 109.9, 103.5, 42.1, 29.3. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}BrN$ $[M + H]^+$ 324.0382, found 324.0380.

*3-(3-Bromophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4l**).* White solid, mp 128−130 °C; **4l** (362 mg, 93%); ^{1}H NMR (400 MHz, DMSO) δ 7.65 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 14.9, 7.8 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.25 (3, *J* = 9.5, 7.7 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 3.8 Hz, 1H), 6.38 (d, *J* = 3.8 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 2H), 3.01 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 132.5, 131.5, 131.1, 130.6, 129.9, 129.6, 129.5, 127.7, 127.1, 126.9, 125.8, 122.7, 122.5, 110.1, 104.4, 42.0, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}BrN$ $[M + H]^+$ 324.0382, found 324.0385.

*3-(4-Bromophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4m**).* White solid, mp 120−122 °C; **4m** (358 mg, 92%); ^{1}H NMR (400 MHz, DMSO) δ 7.67−7.54 (m, 3H), 7.46−7.37 (m, 2H), 7.28−7.20 (m, 2H), 7.16−7.09 (m, 1H), 6.66 (d, *J* = 3.8 Hz, 1H), 6.34 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 131.7, 131.5, 131.4, 130.6, 129.9, 129.6, 127.7, 127.1, 125.8, 122.6, 120.7, 109.7, 104.4, 42.0, 29.5. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}BrN$ $[M + H]^+$ 324.0382, found 324.0379.

*3-(4-Nitrophenyl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4n**).* Brown solid, mp 168−170 °C; **4n** (282 mg, 81%); ^{1}H NMR (400

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MHz, DMSO) δ 8.27 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 7.4 Hz, 1H), 7.28 (t, J = 11.4, 7.4 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.05 (t, J = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 145.6, 139.2, 133.3, 132.2, 131.7, 129.3, 128.5, 128.4, 127.6, 126.8, 124.4, 123.2, 112.8, 106.0, 42.6, 29.1. HRMS (ESI) m/z calcd for $C_{18}H_{15}N_2O_2$ $[M + H]^+$ 291.1128, found 291.1131.

*2-Methyl-3-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4o**).* Yellow oil; **4o** (261 mg, 84%); ^{1}H NMR (400 MHz, DMSO) δ 7.41 (t, J = 7.5 Hz, 2H), 7.29 (dd, J = 19.0, 7.3 Hz, 3H), 7.21 (d, J = 7.4 Hz, 1H), 6.98 (t, J = 6.8 Hz, 1H), 6.92−6.82 (m, 2H), 6.72 (s, 1H), 3.98 (t, J = 6.5 Hz, 2H), 3.00 (t, J = 6.4 Hz, 2H), 1.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 131.5, 130.3, 129.6, 128.4, 127.8, 126.5, 126.2, 125.2, 125.1, 123.6, 121.9, 118.7, 118.4, 44.2, 30.1, 10.5. HRMS (ESI) m/z calcd for $C_{19}H_{18}N$ $[M + H]^+$ 260.1434, found 260.1436.

*5,6,12,13-Tetrahydrobenzo[6,7]indolo[2,1-a]isoquinoline (**4p**).* Yellow solid, mp 170−172 °C; **4p** (133 mg, 41%); ^{1}H NMR (400 MHz, DMSO) δ 7.83 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.27−7.09 (m, 4H), 7.05 (dd, J = 7.3, 6.5 Hz, 1H), 6.75 (s, 1H), 3.95 (t, J = 6.3 Hz, 2H), 3.00 (t, J = 6.3 Hz, 2H), 2.81−2.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 132.9, 132.3, 130.1, 128.3, 127.9, 126.7, 126.1, 125.8, 125.0, 124.5, 124.0, 123.9, 122.6, 117.4, 115.9, 44.4, 31.5, 30.4, 21.2. HRMS (ESI) m/z calcd for $C_{20}H_{18}N$ $[M + H]^+$ 272.1434, found 272.1434.

*2,3-Diphenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4q**).* Yellow solid, mp 64−66 °C; **4q** (235 mg, 61%); ^{1}H NMR (400 MHz, DMSO) δ 7.41−7.33 (m, 3H), 7.24 (t, J = 6.3 Hz, 3H), 7.19 (s, 1H), 7.17−7.11 (m, 2H), 7.04 (dt, J = 15.9, 5.7 Hz, 4H), 6.89 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 4.13 (t, J = 6.4 Hz, 2H), 3.07 (t, J = 6.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 135.5, 131.8, 130.9, 129.5, 128.5, 128.0, 128.0, 127.9, 126.6, 126.5, 126.1, 125.5, 125.3, 124.5, 124.0, 120.3, 119.0, 44.6, 30.1. HRMS (ESI) m/z calcd for $C_{24}H_{20}N$ $[M + H]^+$ 322.1590, found 322.1596.

*3-(Naphthalen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4r**).* Yellow solid, mp 51−53 °C; **4r** (315 mg, 89%); ^{1}H NMR (400 MHz, DMSO) δ 8.00 (t, J = 13.1, 5.4 Hz, 2H), 7.84−7.76 (m, 1H), 7.67−7.47 (m, 5H), 7.32−7.21 (m, 2H), 7.12 (t, J = 7.4, 1.1 Hz, 1H), 6.76 (d, J = 3.6 Hz, 1H), 6.31 (d, J = 3.6 Hz, 1H), 3.74 (t, J = 6.1 Hz, 2H), 2.96 (t, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6, 132.9, 131.9, 130.6, 130.5, 130.4, 129.8, 128.5, 128.2, 128.2, 127.8, 127.1, 126.3, 125.9, 125.9, 125.5, 125.2, 122.4, 110.8, 103.9, 42.0, 29.4. HRMS (ESI) m/z calcd for $C_{22}H_{18}N$ $[M + H]^+$ 296.1434, found 296.1434.

*3-(Thiophen-2-yl)-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4s**).* Yellow solid, mp 72−74 °C; **4s** (287 mg, 95%) ^{1}H NMR (400 MHz, DMSO) δ 7.59 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 4.5, 1.8 Hz, 1H), 7.30−7.21 (m, 2H), 7.20−7.09 (m, 3H), 6.64 (d, J = 3.8 Hz, 1H), 6.35 (d, J = 3.8 Hz, 1H), 4.18 (t, J = 6.7 Hz, 2H), 3.04 (t, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 131.2, 130.4, 129.4, 127.7, 127.4, 127.1, 126.8, 125.8, 125.1, 124.6, 122.6, 110.6, 104.3, 41.5, 29.3. HRMS (ESI) m/z calcd for $C_{16}H_{14}NS$ $[M + H]^+$ 252.0841, found 252.0841.

*8,9-Dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline (**4t**).* White solid, mp 173−175 °C; **4t** (282 mg, 77%); ^{1}H NMR (400 MHz, DMSO) δ 7.48−7.39 (m, 4H), 7.36−7.26 (m, 1H), 7.15 (s, 1H), 6.89 (s, 1H), 6.57 (d, J = 3.6 Hz, 1H), 6.26 (d, J = 3.6 Hz, 1H), 4.08 (t, J = 6.4 Hz, 2H), 3.78 (d, J = 15.5 Hz, 6H), 2.93 (t, J = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.3, 133.8, 132.9, 131.0, 128.4, 128.3, 126.6, 123.2, 122.7, 111.1, 109.1, 106.0, 102.9, 56.0, 55.9, 42.2, 29.1. HRMS (ESI) m/z calcd for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.1489, found 306.1486.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01781.

Crystallographic data for **4a** (CIF)

Experimental details on the optimization of the reaction conditions and X-ray data, along with copies of ^{1}H and ^{13}C NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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