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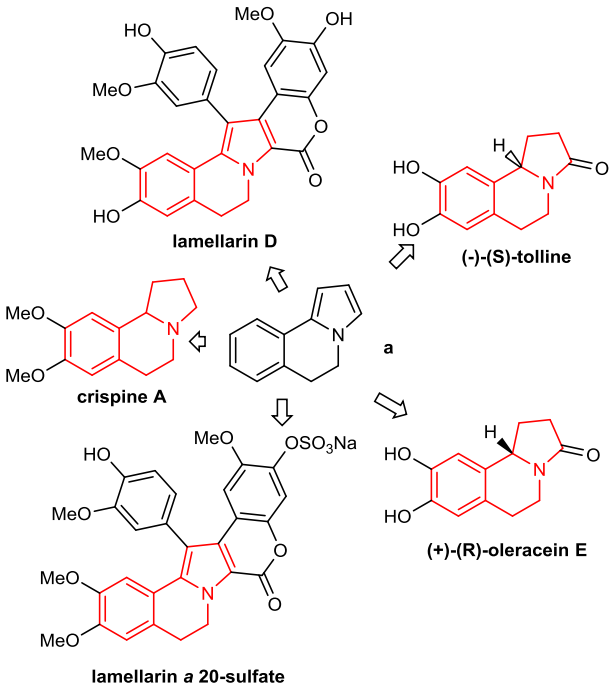
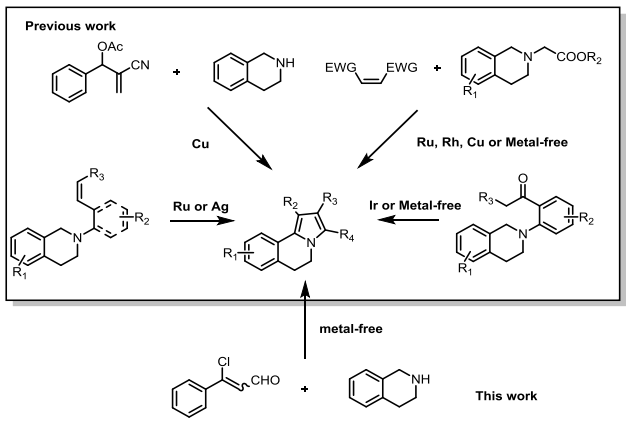
Metal-free! 20 examples, up to 97% yield.

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%).

Scheme 1 Representative natural products.

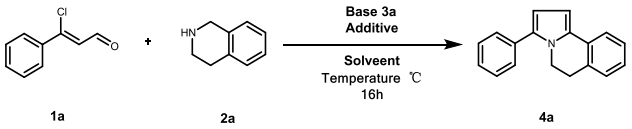


Scheme 2 Existing Strategies for the synthesis of pyrrolo[2,1-*a*]isoquinolines.



Pyrrolo[2,1-*a*]isoquinoline[1-4] (Scheme 1 **a**) framework is ubiquitous in various natural products and some biologically 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 have activities of anticancer[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 works (Scheme 2) using metal catalysis (e.g., Ir, Ru, Rh, Ag, Cu etc.) were accomplished by several research groups[19-27].

Table 1 Optimization of reaction conditions[a]



1a 2a 4a

Entry	T(℃)	Base	Addi-tive	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	4Å	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 ℃ 16 h, under Ar protect. [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.

In recent years, metal-free catalysis has been of great interests in the construction of 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 concerted reaction followed by oxidation in 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(1H)-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 of pyrrolo[2,1-*a*]isoquinolines which include intermolecular cascade cyclization of substituted 3-aryl(heteroaryl)-3-chloroacrylaldehydes and tetrahydroisoquinolines in 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 complicated by-products (Table 1, entry 1). Surprisingly, reducing 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]; more details please see SI). 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 extremely decrease (26%, entry 8), it might due to DMAP is a weak nucleophile but strong base[33]. Thus we used TEA as the optimal base for further optimization including screening of solvents, reaction temperature, additives and the loading of substrates. As results shown in Table 1, compared with DMF, 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 relative 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 have apparent effect on the reaction, both lower and higher temperature would depress the conversion of substrates (entries 14 and 15). In addition, some additives such as activated 4Å 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; 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 equivalents of TEA, 4 equivalents of THIQ, DMF used as solvents, and the reaction temperature of 120 ℃.

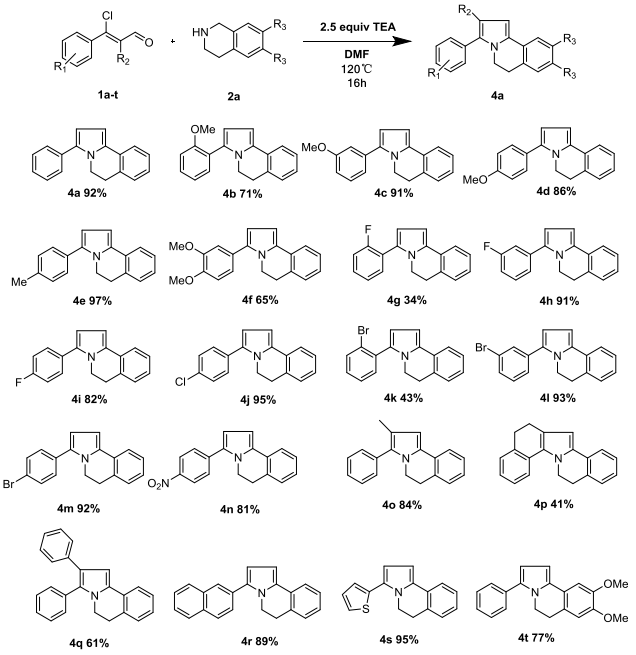
With optimized conditions in hand (Table 1, entry 20), we next explored the scope and limitations of this reaction by employing various (*Z*)-3-aryl(heteroaryl)-3-chloroacrylaldehydes 1 and THIQs 2 (Scheme 2). An assembly of 20 compounds was synthesized using this protocol and gave the best yield up 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 phenyl ring, the corresponding product was obtained in a high yield (up to 97%, entry 4e). However, *ortho*-substituents such as F and Br due to their steric hindrance are no beneficial to the reaction (34% 4g and 43% 4k); surprisingly the substrate which involve *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 get insight on the reaction mechanism we performed some additional experiments (Scheme 3). In experiment A, a mixture *Z* and *E* isomers of 3-chloro-3-(2-fluorophenyl)acrylaldehyde

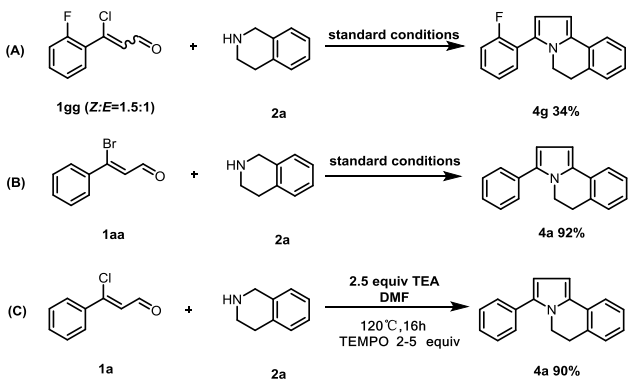
(1gg, *Z*/*E*=1.5:1 detected by ^{1}H NMR see SI) in place of 1g was used to investigate the effect of *E*/*Z* configuration on the reaction. Interestingly, product 4g was obtained in 34% yield (Scheme 3, A). The result is similar to the data of 4g which derived from (*Z*)-3-chloro-3-(2-fluorophenyl)acrylaldehyde (1g) used as the substrate in Table 2, and showed that 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 in this protocol and give 4a in a similar high yield (92%, Scheme 3, B). In Yan's work[28], intramolecular dehydrative coupling of tertiary amines and ketones 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 possible radical intermediate under argon atmosphere was not successful, and the product was still obtained in a high yield (90%, Scheme 3, C).

Table 2 Scope of tandem reaction[a]

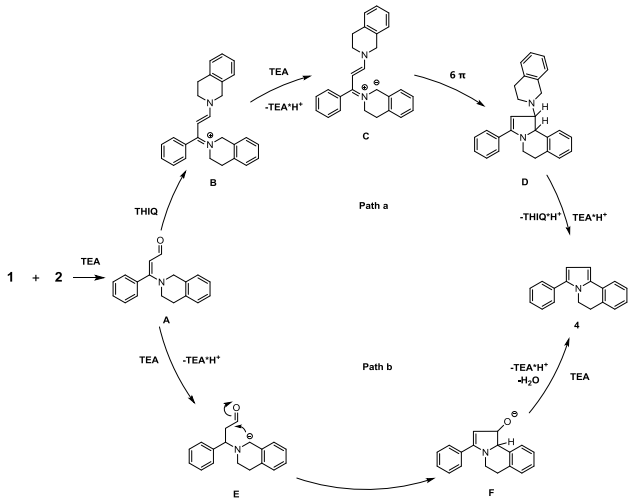


[a]Reaction conditions: 1a (1.20 mmol), 2a (4.80 mmol), 3a (3.00 mmol), solvent (3 mL), at 120 ℃ 16 h, without Ar protection.

Scheme 3 Mechanistic Studies



Scheme 4 Suggested mechanism



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 base circumstance. **B** prompted by TEA was transformed to intermediate **C** in situ, then **D** was generated by 6π-electrocyclization and subsequent elimination of THIQ (Path a); or through path b, **A** firstly prompted by TEA to give intermediate **E**, then **F** might be formed through a nucleophilic addition. Final product **4** was generated after the dehydration of **F**.

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 MHz 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 *N*,*N*-Dimethylformamide was added dropwise to the $POCl_3$/DMF complex. The reaction mixture was stirred for 1 h at 0 ℃ then heated at 65 ℃ for 8 h. Cooled at

room temperature and finally poured in an ice-cold saturated NaOAc water solution (20 mL). The resulting mixture was extracted with ethyl acetate (3×15 mL). The organic phase was washed with water (3×10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Thus 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 added TEA (3.00 mmol) slowly. Then heated to 120 ℃ for 16 h. The residue was treated with water (30 mL) and then extracted with EA (3×15 mL), 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 4f (238mg, 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 4n (282 mg, 81%); ^{1}H NMR (400 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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 ℃; 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

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. This material is available free of charge via the Internet at http://pubs.acs.org.

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

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