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PII: S0040-4020(16)30146-6

DOI: 10.1016/j.tet.2016.03.014

Reference: TET 27554

To appear in: *Tetrahedron*

Received Date: 12 January 2016

Revised Date: 29 February 2016

Accepted Date: 2 March 2016

Please cite this article as: Bai R, Yang J, Min L, Liu C, Wu F, Gu Y, Facile synthesis of 3,4-fused tricyclic indoles with a seven-membered ring through a three-component reaction of 4-hydroxyindole, aldehyde, and malonodinitrile or ethyl cyanoacetate, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.03.014.

Graphic Abstract

Facile synthesis of 3,4-fused tricyclic indoles with a seven-membered ring through a three-component reaction of 4-hydroxyindole, aldehyde, and malonodinitrile or ethyl cyanoacetate

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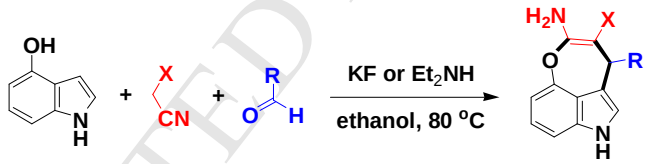

X = CN, CO_2Et, C(O)Ph
R = aryl and alkyl

29 examples, 49~98% yields

Salient features: (i) High efficiency and wide scope of substrate.
(ii) Simple operation.
(iii) Mild and environmentally benign conditions.

Facile synthesis of 3,4-fused tricyclic indoles with a seven-membered ring through a three-component reaction of 4-hydroxyindole, aldehyde, and malonodinitrile or ethyl cyanoacetate

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Ⓢ *Supporting Information*

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ABSTRACT: Three-component reactions of 4-hydroxyindole, aldehydes, and malonodinitrile or ethyl cyanoacetate were developed for the first time by using either potassium fluoride or diethylamine as a catalyst, which provided an easy access to 3,4-fused tricyclic indoles in good to excellent yield. The merits of this synthesis route are attributed to its simplicity, practicality, efficiency, and eco-friendliness, as well as the easy availability of the catalyst.

KEYWORDS: three-component reaction; 4-hydroxyindole; 3,4-fused tricyclic indole; seven-membered heterocycle

■ INTRODUCTION

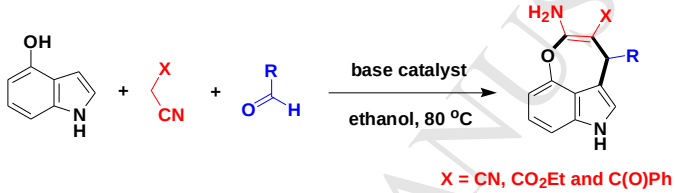
The synthesis of complex organic compounds exhibiting particular properties and chemical structures is always a central research target for organic chemists. Multicomponent reactions (MCRs) comprise an efficacious method to construct valuable and complex organic compounds owing to atomic economy, convergence, and high bond-forming index.[1-4] At present, MCRs play a very important role in synthetic methodology. In this context, many sequential multistep synthesis reactions can be replaced by MCRs, especially for pharmaceutical and heterocyclic molecular synthesis.[1, 2] Therefore, considering the advantages of MCRs, the search and development of novel MCRs remain a central topic in organic synthetic chemistry.

The molecule-containing indole nucleus is one of the most important heterocyclic compounds extensively existing in nature, agrochemicals, and pharmaceuticals.[5, 6] Furthermore, indole and its derivatives can be widely applied in optic-electronic materials, intercellular signal molecules, scavengers of free radicals, plant growth regulators, medicine, and so forth.[7-9] Therefore, the synthesis and framework embellishment of indoles have attracted broad and continuous attention. The 3,4-fused indole is particularly noteworthy because it presents a key structural motif of numerous bioactive natural products, such as lysergic acid,[10] dehydrobufotenine,[11] hapalindole U,[12] chuangxinmycin,[13] aurantioclavine,[14] N-methylwelwistatin,[15] communesin F,[16] and dragmacidin E.[17] Thus, continued interest is present in the development of new methods to access this scaffold.[18] Although many methods have been developed for the synthesis of 3,4-fused indoles,[19-26] these methods heavily rely

on the usage of noble metal catalysts. Such methods also suffered from limitations of substrate generality, availability of starting materials, multistep synthesis, low product yields, and harsh reaction conditions. Hence, the design of improved and environmentally benign approaches allowing for rapid and cost-effective synthesis of 3,4-fused indoles from readily available precursors would be highly desired.

Bisnucleophiles are often used to establish MCRs.[27-29] C,O- and C,N-based 1,3-bisnucleophiles, such as 1,3-dicarbonyl compounds,[30] activated phenols,[31] and anilines,[32] have been extensively used in conjunction with aldehydes to synthesize heterocycles through MCRs. However, 1,4-bisnucleophiles have been rarely adopted to develop MCRs, probably because the common 1,4-bisnucleophiles, such as 2-aminothiophenol, *o*-phenylenediamine, and glycinamide, tended to react with aldehyde alone to form a two-component adduct, thus precluding the possibility of establishing MCRs with them.[33-38] We have recently been engaged in developing MCRs of aldehyde and two different nucleophiles,[39-43] and some of our works were also associated with the use of bisnucleophiles.[44-46] On the basis of our previous results, we envisioned that 4-hydroxyindole, an easily available and inexpensive indole derivative, may act as a C,O-based 1,4-bisnucleophile because the C3 position of indole and the OH group are both reactive. However, given that the two reactive sides exist in the two fused aromatic rings, these 1,4-bisnucleophiles, if they work, may not behave like the conventional one because of their rigid structure. Therefore, the possibility of using 4-hydroxyinole as a 1,4-bisnucleophile is of particular interest. Consequently, a research program has started to explore new MCRs by using

4-hydroxyindoles as building blocks. This paper reports the preliminary results on the use of 4-hydroxyindole as a 1,4-bisnucleophile, which reacted readily with an aromatic aldehyde and malonodinitrile or ethyl cyanoacetate, providing a 3,4-fused indole with a seven-membered ring by using a base catalyst (**Scheme 1**). This three-component reaction did not only provide an easy access to a class of highly useful indole derivatives but also displayed a good scope of substrates under environmentally benign conditions.



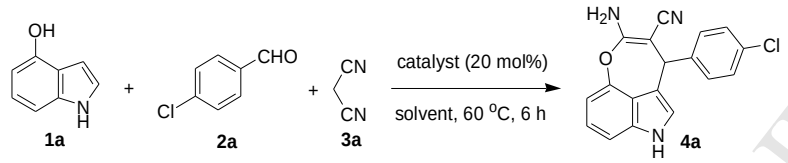
Scheme 1. Three-component reaction of 4-hydroxyindole, aldehyde, and α-electron-withdrawing group-substituted acetonitrile.

■ RESULTS AND DISCUSSION

A mixture of 4-hydroxyindole **1a**, 4-chlorobenzaldehyde **2a**, and malonodinitrile **3a** was initially treated with different organic and inorganic bases, and the results are listed in **Table 1**. The reaction was performed in ethanol at 60 °C for 6 h. In the absence of any catalyst, no reaction occurred (entry 1). An addition of 20 mol% of piperidine significantly changed the result of the model reaction, and a 3,4-fused indole with a seven-membered ring **4a** was obtained in 83% yield (entry 2). Diethylamine showed a better catalytic activity than piperidine under the same conditions, and the yield of **4a** reached 91% (entry 3). Triethylamine and morphoine were also examined, but their yields were slightly inferior compared with the two

former systems (entries 4 and 5). *L*-Proline and pyridine were proven inappropriate for this reaction (entries 6 and 7).

Table1. Effect of basic catalysts on the three-component reaction of **1a**, **2a**, and **3a**.[a]



Entry	Catalyst	Solvent	Yield (%)[b]
1	—	EtOH	0
2	piperidine	EtOH	83
3	diethylamine	EtOH	91
4	triethylamine	EtOH	76
5	morpholine	EtOH	70
6	L-proline	EtOH	12
7	pyridine	EtOH	14
8	K_2CO_3	EtOH	66
9	KOH	EtOH	51
10	Cs_2CO_3	EtOH	24
11	KF	EtOH	98
12	KF	CH_3NO_2	84
13	KF	CH_3CN	79
14	KF	DCE	83
15	KF	1,4-dioxane	28
16	KF	Toluene	< 5
17	KF	EtOH (*aqu*. 95%)	81

[a] Reaction conditions: **1a**, 0.4 mmol; **1a**/**2a**/**3a**: = 1:1:1; catalyst: 0.08 mmol; 60 °C, anhydrous ethanol, 2.0 mL, 6 h. [b] Isolated yield.

Inorganic bases, such as K_2CO_3, KOH, and Cs_2CO_3, were then examined, and the

maximum yield of **4a** only reached 66% (entries 8-10). When KF was used, the reaction proceeded very well, and **4a** can be obtained at 98% (entry 11). As such, the effect of solvent on the synthesis of **4a** was investigated using KF as a catalyst. Among the various solvents that were screened, anhydrous ethanol was recognized to be the most feasible medium for this reaction (entries 11-16). An aqueous solution of ethanol (95%) was also examined, but the yield declined to 81% (entry 17). Therefore, anhydrous ethanol was used as the solvent of choice.

Figure 1 shows the effect of the amount of KF on the model three-component reaction. As shown in the figure, the performance of the model reaction was influenced quite notably by the dosage of KF catalyst. The increase of the catalyst amount significantly improved the reaction yield when it is lower than 20 mol%. The yield reached the maximum level when 20 mol% KF was used.

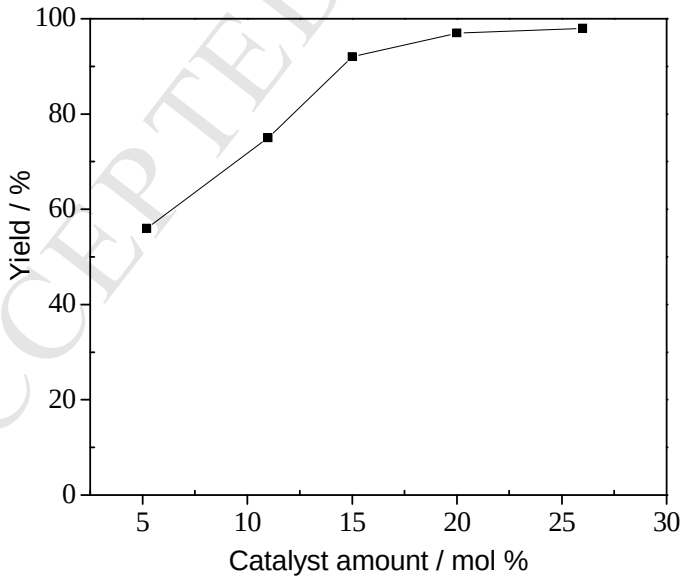


Figure 1. Effect of KF amount on the model reaction.(**1a**, 0.4 mmol; **2a**, 0.4 mmol; **3a**, 0.4 mmol; anhydrous ethanol 2.0 mL; 60 °C, 12 h).

Figure 2 presents the effects of reaction time on the model reaction. The yield

increased quickly with the escalation of the reaction time from 2 h to 6 h. Thereafter, the yield remained at an almost constant level. The maximum yield of **4a** was achieved after 6 h of reaction.

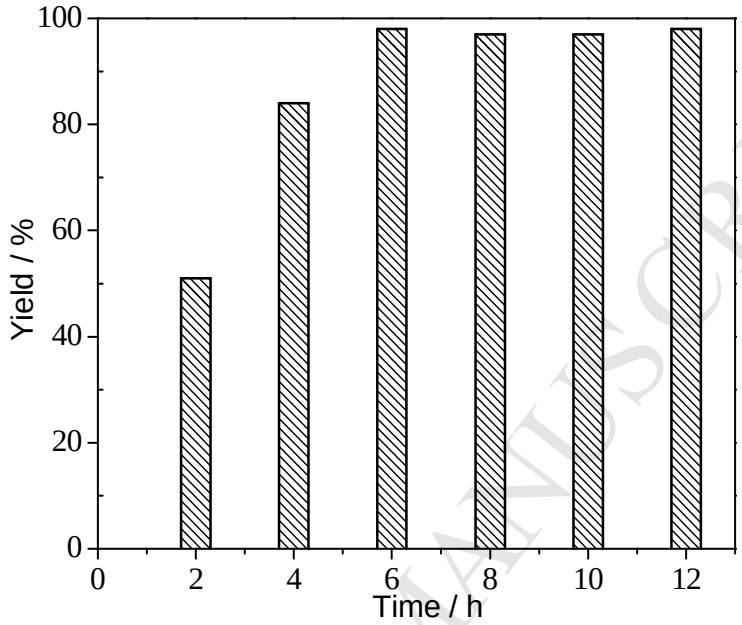
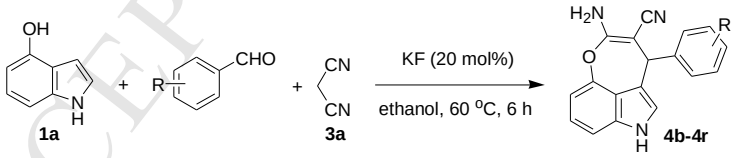


Figure 2. Effect of reaction time on the synthesis (**1a**, 0.4 mmol; **2a**, 0.4 mmol; **3a**, 0.4 mmol, anhydrous ethanol 2.0 mL; 60 °C).

Considering the optimized conditions, the scope and generality of this three-component reaction were then investigated. First, the scope with respect to the benzaldehyde component was studied, and the results are listed in **Table 2**. A set of benzaldehydes spanning a convenient spectrum of lipophilicity and reactivity was selected to react with **1a** and **3a**. In all cases, excellent yields were obtained with the aid of a KF catalyst, regardless of the nature of the substituent present on the aldehyde (electron-donating or electron-withdrawing). Benzaldehydes containing sterically demanding substituents, such as 2-methoxybenzaldehyde, 4-methyl-2-bromobenzaldehyde, 4-fluoro-2-bromobenzaldehyde,

2-chlorobenzaldehyde, 2-chloro-6-fluorobenzaldehyde, and 2-nitrobenzaldehyde, also participated in this reaction readily (entries 4, 6–9, and 15). However, in some cases, the obtained yields were slightly inferior compared with those of the *para*-substituted congener aldehydes. Nevertheless, moderate product yield can be achieved when 2-chloro-6-fluorobenzaldehyde, in which the reactive formyl group blocked by two substituents in this molecule, was used as a substrate (**4j**). This result implied that the existence of an *ortho*-substituent group in benzaldehyde only demonstrated a slight detrimental effect on the synthetic efficiency of the desired indole. In some cases, the generated 3,4-fused indoles, such as **4l** and **4m**, precipitated out from the reaction solution, thus facilitating the isolation of the product. These reactions can also be effectively scaled up with similar efficiency. For example, a 10 mmol scale reaction of **1a**, 3,4,5-trimethoxybenzaldehyde, and **3a** gave the corresponding indole derivative **4l** in a 96% yield (3.6 g).

Table 2. KF-catalyzed three-component reaction of **1a**, **3a**, and different aldehydes.[a]

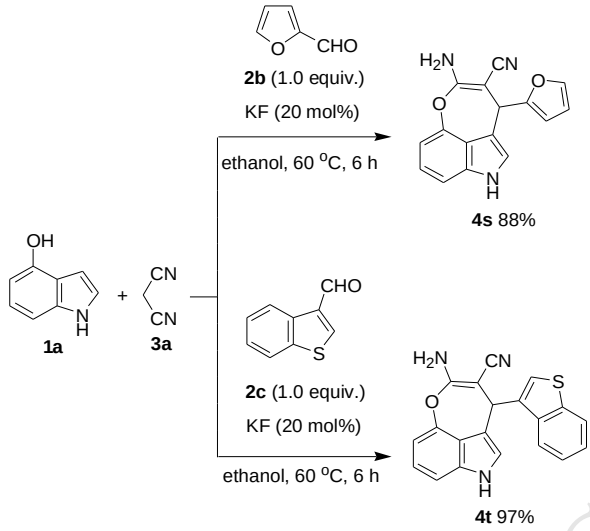


Entry	R	Product	Yield (%)[b]
1	H	**4b**	71
2	4-Me	**4c**	95
3	4-OMe	**4d**	84
4	2-OMe	**4e**	78
5	4-Br	**4f**	96
6	4-Me-2-Br	**4g**	85

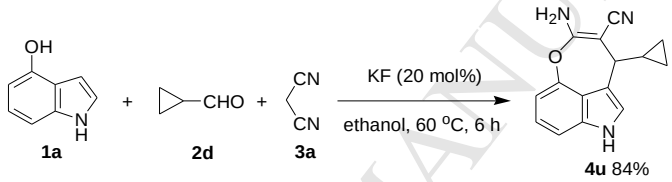
7	4-F-2-Br	**4h**	87
8	2-Cl	**4i**	67
9	2-Cl-6-F	**4j**	67
10	3,4-$(OMe)_2$	**4k**	77
11	3,4,5-$(OMe)_3$	**4l**	94 (96)[c]
12	4-OMe-3-Bn	**4m**	92
13	4-SCF_3	**4n**	81
14	4-NO_2	**4o**	86
15	2-NO_2	**4p**	80
16	4-CN	**4q**	90
17	4-CF_3	**4r**	79

[a] Reaction conditions: **1a**, 0.4 mmol; **3a**, 0.4 mmol; aldehyde, 0.4 mmol, KF, 0.08 mmol, anhydrous ethanol, 2.0 mL, 60 °C, 6 h. [b] Isolated yield. [c] 10 mmol scale reaction.

Aldehydes with heterocyclic substituent, such as furfural **2b** and 1-benzothiophene-3-carbaldehyde **2c**, can also be used to synthesize the 3,4-fused indole derivatives in the KF/ethanol system. In these cases, the desired products, **4s** and **4t**, were obtained in 88% and 97% yields, respectively (**Scheme 2**). In the presence of KF, cyclopropanecarboxaldehyde **2d**, which is an aliphatic aldehyde, also reacted smoothly with **1a** and **3a**, producing a 3,4-fused indole **4u** in ethanol in an 84% yield (**Scheme 3**).



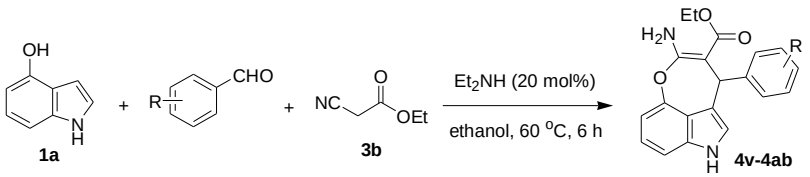
Scheme 2. KF-catalyzed three-component reaction of **1a**, **3a**, and **2b** or **2c**.



Scheme 3. KF-catalyzed three-component reaction of **1a**, **3a**, and **2d**.

We found that as well as being able to use malonodinitrile **3a,** it was also possible to use ethyl cyanoacetate **3b**. But, KF catalyst had to be replaced by diethylamine; otherwise, a low yield would be obtained. In ethanol solvent, the similar 3,4-fused indole products were obtained in moderation to acquire a good yield with this reaction (**Table 3**). In this reaction, benzaldehydes contain sterically demanding substituents, such as 4-chloro-2-bromobenzaldehyde, also worked well.

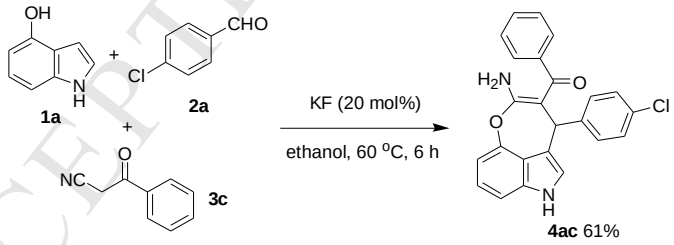
Table 3. Et_2NH-catalyzed three-component reaction of **1a**, **3b** and aldehyde.[a]



Entry	R	Product	Yield (%)[b]
1	4-OMe	**4v**	70
2	3,4,5-$(OMe)_3$	**4w**	49
3	4-Cl	**4x**	86 (20)[c]
4	4-Cl-2-Br	**4y**	60
5	4-NO_2	**4z**	72
6	4-CN	**4aa**	84
7	4-CH_3	**4ab**	71

[a] Reaction conditions: **1a**, 0.4 mmol; **3b**, 0.4 mmol; aldehyde, 0.4 mmol, diethylamine, 0.08 mmol, anhydrous ethanol, 2.0 mL, 60 °C, 6 h. [b] Isolated yield. [c] KF was used as catalyst.

The KF/ethanol system was also discovered to be able to promote the reaction of benzoylacetonitrile **3c**, **1a,** and **2a**. With the established three-component reaction, a 3,4-fused indole **4ac** was obtained in 61% yield (**Scheme 4**), thereby introducing the substrate scope of the reaction.



Scheme 4. Three-component reaction of **3c**, **1a**, and **2a**.

In the reaction of 3,4,5-trimethoxybenzaldehyde, **1a,** and **3a**, an interesting phenomenon was observed. Before starting the reaction, all substrates dissolved very well in ethanol solvent (**Figure 3**, photo **a**). Once the stirring was triggered, a large amount of yellow solid appeared immediately (photo **b**). However, the reaction

mixture became gradually transparent with the progress of the reaction (photo **c**). Finally, some insoluble species appeared again in the vial at the end of the reaction (photo **d**). To obtain the inside information, the stepwise reaction of **1a**, **3a**, and 3,4,5-trimethoxybenzaldehyde was selected to scale up. The reaction was performed under identical conditions, and the yellow solid was isolated. Spectroscopic analysis revealed that the compound was 2-(3,4,5-trimethoxybenzylidene)malononitrile **5a.** Literature survey indicated that malonodinitrile can react easily with aromatic aldehyde even in the absence of any catalyst.[47] **5a** was also found to react with **1a** in the presence of a catalytic amount of KF in ethanol at 60 °C, providing **4l** in an almost quantitative yield after 6 h (**Scheme 5**).

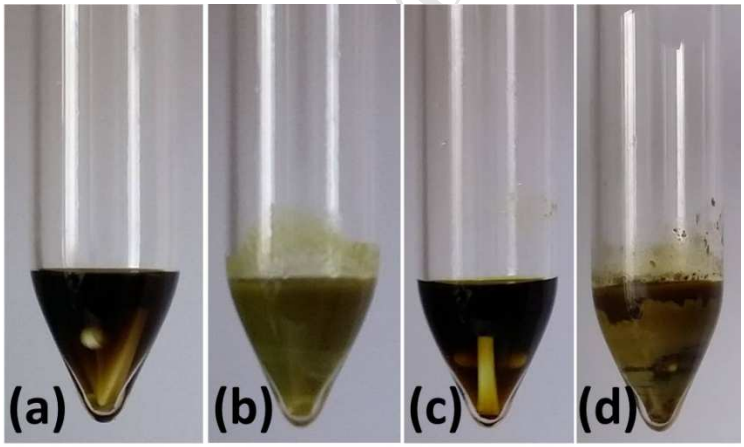
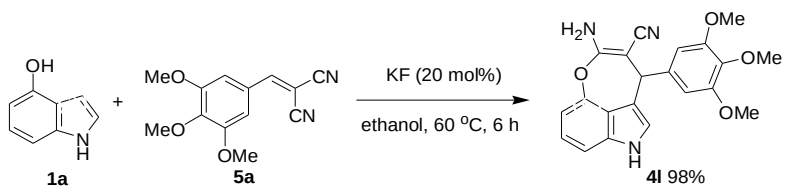


Figure 3. A progressive view of the three-component reaction of 3,4,5-trimethoxybenzaldehyde, **1a**, and **3a**: (**a**) before starting the reaction; (**b**) after starting the stirring; (**c**) after 3 h of reaction; (**d**) at the end of the reaction.



Scheme 5. Reaction of **5a** and **1a**.

On the basis of the above results, a plausible mechanism for the model reaction is proposed in **Figure 4**. The initial event of the reaction should be the formation of arylidenenitrile (**I**) through a Knoevenagel reaction between the aldehyde and malonodinitrile in the presence of a basic catalyst; A Michael-type addition reaction of **1a** to this intermediate led to the formation of intermediates (**II**); Then, **4a** was formed through a tandem reaction involving an intramolecular nucleophilic addition of the phenolic OH group to one of the cyano groups, which provided intermediates (**III**); And finally, tautomerization of (**III**) to form the final product **4a**.

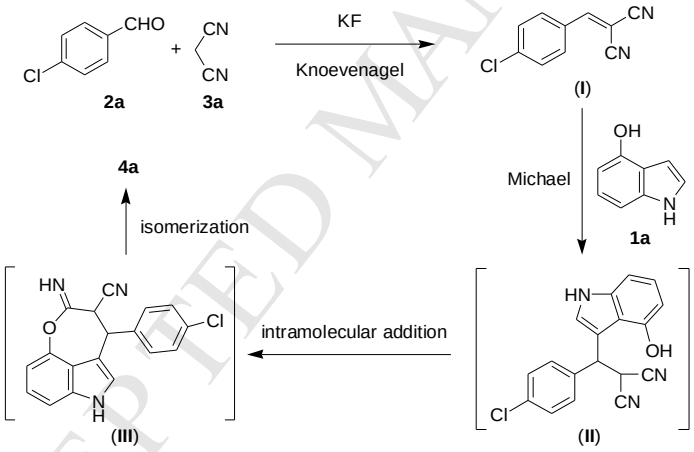


Figure 4. Plausible mechanism of the model reaction.

■ CONCLUSION

In summary, a three-component reaction of 4-hydroxyindole, aldehyde, and malonodinitrile or ethyl cyanoacetate was developed for the first time, providing an expedient way to access 3,4-fused indoles with a seven-membered ring. All reactions were conducted under mild and environment-friendly conditions by using either KF

or diethylamine as catalyst. The three-component reaction displayed a good scope of substrates. In some cases, the products can be easily isolated by simple filtration. This experiment is the first to demonstrate that 4-hydroxyindole can be used as a C,O-based 1,4-bisnucleophile for organic synthesis. This observation inspires synthetic chemists to use this easily available indole in many other reactions, which can be adopted to synthesize other valuable indole-containing compounds.

■ EXPERIMENTAL SECTION

Chemicals. Reagents and starting materials were directly purchased from commercial resources and used as received without further purification. All chemicals were of reagent grade.

Typical procedure for the three-component reaction of 4-hydroxyindole, aldehydes, and malonodinitrile. The reaction was performed in a 20 mL V-type tube equipment with a triangle magnetic stirring bar. In a typical reaction, 4-hydroxyindole (0.4 mmol) was mixed with malonodinitrile (0.4 mmol) and aldehydes (0.4 mmol) in 2.0 mL of ethanol. KF (0.08 mmol) was then added. The mixture was subsequently heated to 60 °C under stirring for 6 h. After the reaction, the mixture was cooled to room temperature, and the target product was isolated using a preparative thin-layer chromatograph (TLC) with eluting solution [petroleum ether/ethyl acetate = 3/1 (v/v)]. Test for substrate scope expansion was the same as the abovementioned analogous procedure.

Stepwise three-component reaction of 4-hydroxyindole, malonodinitrile, and 3,4,5-trimethoxybenzaldehyde. The reaction was performed similar to the

abovementioned typical procedure. Malonodinitrile (4 mmol) was mixed with 3,4,5-trimethoxybenzaldehyde (4 mmol) and KF (0. 4 mmol) in 20 mL of ethanol. The mixture was then heated to 60 °C under stirring for 0.5 h. After the reaction, the mixture was cooled to room temperature, and the precipitated solid was separated by filtration. The acquired solid was washed with cold ethanol (4×4.0 mL) and dried at 100 °C for 1 h. Thereafter, 4-hydroxyindole (2 mmol) was mixed with the aforementioned acquired solid (2 mmol) and KF (0. 4 mmol) in 10 mL of ethanol. The mixture was then stirred at 60 °C for 6 h. After the reaction, the mixture was cooled to room temperature, and the target product was isolated by filtration.

Product analysis. Melting points were determined on an electrothermal type (Yuhua X-4) melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance instrument by using TMS as an internal reference, and chemical shifts were expressed in ppm. Infrared spectra were recorded (KBr pellets) on a Bruker Equinox 55 spectrometer with a resolution of 0.4 cm^{-1}. HRMS was recorded on a Bruker MicrOTOF-Q II instrument.

Spectral data for the products

2-Amino-4-(4-chlorophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4a): Yellow solid; m.p. 196–198 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 4.84 (s, 1H), 6.51 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.35–7.38 (m, 3H), 11.33 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.9, 146.3, 141.2, 136.8, 131.6, 129.8, 129.0, 126.1, 122.1, 121.3, 116.9, 111.7, 109.1, 98.0, 56.8, 28.7 ppm; IR: ν = 3451, 3354, 2179, 1659, 1602, 1490, 1398, 1349, 1223, 1088, 887, 793, 770, 737, 490 cm^{-1}; HRMS (TOF, ESI): m/z calcd for $C_{18}H_{13}ClN_3O$, $[M + H]^+$ 322.0747, found 322.0741.

2-Amino-4-phenyl-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4b): Yellow solid; m.p. 188–190 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 4.69 (s, 1H), 6.41 (s, 1H), 6.60 (d, *J* = 12.0 Hz, 1H), 6.84 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.06–7.12 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.9, 147.4, 141.2, 136.8, 129.0, 128.0, 127.0, 126.1, 122.2, 121.4, 116.9, 112.3, 109.0, 98.0, 57.2, 41.3 ppm; IR: ν = 3394, 3310, 2201, 1656, 1487, 1453, 1390, 1349, 1221, 1089, 882, 771, 741, 699, 587, 526, 482 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{14}N_3O$, $[M + H]^+$ 288.1137, found 288.1132.

2-Amino-4-(*p*-tolyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4c): Yellow solid; m.p. 187–189^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 2.26 (s, 3H), 4.74 (s, 1H), 6.59 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 2H), 7.09–7.16 (m, 5H), 7.38 (s, 1H), 11.27 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.8, 144.3, 141.0, 136.6, 136.3, 129.6, 127.8, 126.0, 122.2, 121.6, 112.3, 109.0, 98.1, 79.3, 57.4, 40.8, 21.0 ppm; IR: ν = 3339, 2189, 1654, 1607, 1509, 1401, 1350, 1254, 1220, 1174, 1089, 1029, 798, 756, 733, 567 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{16}N_3O$, $[M + H]^+$ 302.1293, found 302.1289.

2-Amino-4-(4-methoxyphenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4d): Yellow solid; m.p. 132–134 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 21 ^{o}C, TMS): δ = 3.60 (s, 3H), 4.63 (s, 1H), 6.40 (s, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 2H), 7.00–7.03 (m, 3H), 7.26 (t, *J* = 2.8 Hz, 1H), 11.20 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.7, 158.4, 141.1, 139.6, 136.7, 129.0, 126.0, 122.3, 121.5, 116.9, 114.3, 112.5, 108.9, 97.9, 57.6, 55.5, 28.7 ppm; IR: ν = 3338, 2186, 1654, 1606, 1509, 1401, 1350, 1254, 1220, 1174,1089, 1029, 798, 756, 733, 678, 523 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{16}N_3O_2$, $[M + H]^+$ 318.1243, found 318.1242.

2-Amino-4-(2-methoxyphenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carbonitrile (4e): Yellow solid; m.p. 134–136 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 3.83 (s, 3H), 5.25 (s, 1H), 6.52 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.87 (s, 2H), 6.98–7.03 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.10–7.18 (m, 1H), 7.36 (s, 1H),

11.28 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.6, 156.6, 141.5, 136.7, 135.2, 129.3, 128.2, 125.9, 121.7, 121.3, 116.9, 112.6, 111.9, 108.9, 97.9, 79.6, 56.4, 56.1, 34.1 ppm; IR: ν = 3452, 3325, 2192, 1696, 1652, 1492, 1407, 1352, 1224, 1098, 1026, 884, 761, 734, 585, 535 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{16}N_3O_2$, $[M + H]^+$ 318.1243, found 318.1249.

2-Amino-4-(4-bromophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4f): Yellow solid; m.p. 213–215^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 4.82 (s, 1H), 6.50 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.38 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H) 11.32 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.9, 146.8, 141.2, 136.8, 131.9, 130.2, 126.1, 122.1, 121.3, 120.1, 116. 9, 111.6, 109.1, 98.0, 56.7, 40.6 ppm; IR: ν = 3444, 3354, 2180, 1658, 1602, 1488, 1401, 1349, 1222, 1088, 1009, 887, 791, 769, 736, 487 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{13}BrN_3O$, $[M + H]^+$ 366.0242, found 366.0233.

2-Amino-4-(2-bromo-4-methylphenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carbonitrile (4g): Yellow solid; m.p. 197–199 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 2.12 (s, 3H), 5.23 (s, 1H), 6.43 (s, 1H), 6.56 (d, *J* = 12.0 Hz, 1H), 6.89 (s, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 2H), 7.28 (s, 1H), 7.31 (s, 1H) 11.24 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.0, 142.8, 141.2, 138.9, 136.9, 133.2, 131.3, 129.7, 126.1, 122.5, 121.4, 121.1, 116.9, 111.4, 109.1, 98.1, 56.3, 28.7, 20.5 ppm; IR: ν = 3435, 3336, 2188, 1653, 1628, 1490, 1403, 1350, 1221, 1090, 1039, 886, 801, 760, 734, 492 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{15}BrN_3O$, $[M + H]^+$ 380.0398, found 380.0385.

2-Amino-4-(2-bromo-4-fluorophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4h): Yellow solid; m.p. 203–205^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 5.35 (s, 1H), 6.51 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 11.34 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.0, 160.8 (d, *J* = 246.0 Hz), 141.2, 136.9, 132.9 (d, *J* = 8 Hz), 128.7. 128.2, 126.2, 122.6 (d, *J* = 10.0

Hz), 121.2, 120.9, 119.8 (d, *J* = 25.0 Hz), 116.9, 116.2 (d, *J* = 21.0 Hz), 111.0, 109.2, 98.0, 55.9, 28.6 ppm; ^{19}F NMR (400 Mz, DMSO): δ = - 113.68 ppm; IR: ν = 3441, 3334, 2189, 1653, 1631, 1601, 1486, 1352, 1218, 1088, 884, 856, 763, 733, 514, 452 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{12}BrFN_3O$, $[M + H]^+$ 384.0148, found 384.0137.

2-Amino-4-(2-chlorophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4i): Yellow solid; m.p. 200–202 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 5.37 (s, 1H), 6.53 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.26–7.32 (m, 3H), 7.41 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 11.36 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.2, 144.0, 141.3, 136.9, 132.1, 131.4, 130.0, 128.9, 126.2, 121.4, 121.0, 116.9, 111.1, 109.1, 98.0, 55.8, 38.1 ppm; IR: ν = 3450, 3353, 2270, 1658, 1612, 1489, 1399, 1348, 1225, 1086, 887, 795, 767, 737, 491 cm^{-1}; HRMS (TOF, ESI): m/z calcd for $C_{18}H_{13}ClN_3O$, $[M + H]^+$ 322.0747, found 322.0752.

2-Amino-4-(2-chloro-6-fluorophenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carbonitrile (4j): Yellow solid; m.p. 254–256 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 21 ^{o}C, TMS): δ = 5.55 (s, 1H), 6.50 (s, 1H), 6.60 (s, 1H), 7.02 (s, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.32–7.38 (m, 3H), 11.32 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.5, 141.6, 137.0, 130.0 (d, *J* = 10.0 Hz), 126.2, 120.9 (d, *J* = 10.0 Hz), 116.8, 115.9, 109.0, 97.9, 53.3, 32.5 ppm; ^{19}F NMR (400 Mz, DMSO): δ = - 112.71 ppm; IR: ν = 3303, 2198, 1657, 1577, 1494, 1453, 1397, 1349, 1263, 1222, 1170, 1096, 1061, 896, 787, 730, 679, 582, 528, 461 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{12}ClFN_3O$, $[M + H]^+$ 340.0653, found 340.0644.

2-Amino-4-(3,4-dimethoxyphenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carbonitrile (4k): Yellow solid; m.p. 215–217 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 25 ^{o}C, TMS): δ = 3.60 (d, *J* = 2.8 Hz, 6H), 4.64 (s, 1H), 6.39 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 6.73–6.76 (m, 2H), 6.79 (s, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 11.19 (s, 1H); ^{13}C NMR (100 Mz, DMSO): 160.8, 149.1, 148.0, 141.0, 140.0, 136.7, 128.7, 128.2, 126.0, 122.2, 121.5, 120.1, 116.9, 112.4, 111.9, 108.8, 98.0, 57.4, 55.9, 40.8 ppm; IR:

ν = 3449, 3386, 3329, 2195, 1666, 1603, 1513,1493, 1464, 1401, 1351, 1261, 1225, 1141, 1089, 1022, 889, 791, 738, 570, 527 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{20}H_{18}N_3O_3$, $[M + H]^+$ 348.1348, found 348.1339

2-Amino-4-(3, 4, 5-trimethoxyphenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4l): Yellow solid; m.p. 235–237 ^oC; ^1H NMR (400 MHz, DMSO, 25 ^oC, TMS): δ = 3.64 (s, 3H), 3.72 (s, 6H), 4.79 (s, 1H), 6.51 (s, 1H), 6.56 (s, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 2.4 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.9, 153.4, 143.0, 141.0, 136.8, 136.6, 126.0, 122.2, 121.5, 116.9, 112.0,108.9, 106.2, 98.0, 60.4, 56.9, 56.3, 41.4 ppm; IR: ν = 3453, 3383, 3334, 2193, 1659, 1667, 1595, 1505, 1463, 1425, 1401, 1352, 1326, 1231, 1124, 1093, 1004, 891, 802, 746, 689, 574, 530 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{21}H_{20}N_3O4$, $[M + H]^+$ 378.1454, found 378.1455.

2-Amino-4-(3-benzyl-4-methoxyphenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4m): Yellow solid; m.p. 236–238 ^oC; ^1H NMR (400 MHz, DMSO, 21 ^oC, TMS): δ = 3.72 (s, 3H), 4.71 (s, 1H), 4.99 (q, *J* = 12.0 Hz, 2H), 6.48 (s, 1H), 6.65 (d, *J* = 4.0 Hz, 1H), 6.75 (dd, J_a = 1.6 Hz, J_b = 8.0 Hz, 1H), 6.89 (s, 2H), 6.91–6.93 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.30–7.41 (m, 6H), 11.29 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.8, 148.4, 148.1, 141.0, 139.9, 137.4, 136.7, 128.8, 128.6, 128.3, 125.9, 122.2, 121.5, 120.4, 116.9, 113.9, 112.7, 112.4, 108.8, 97.9, 70.5, 57.2, 56.1, 40.7 ppm; IR: ν = 3395, 3335, 2183, 1654, 1601, 1513, 1402, 1350, 1225, 1086, 889, 794, 772, 741, 699, 478 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{26}H_{22}N_3O_2$, $[M + H]^+$ 408.1712, found 408.1704.

2-Amino-4-(4-((trifluoromethyl) thio) phenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4n): Yellow solid; m.p. 174–176 ^oC; ^1H NMR (400 MHz, DMSO, 21 ^oC, TMS): δ = 4.91 (s, 1H), 6.52 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 1H),7.38 (d, *J* = 8.0 Hz, 3H), 7.66 (d, *J* = 8.0 Hz, 2H), 11.36 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.0, 150.9, 141.3, 137.0, 136. 9, 131.6, 129.5, 128.6, 126.2, 122.0, 121.3 (d, *J* = 7.0 Hz), 116.9, 111.4, 109.2, 97.9, 56.5, 40.9 ppm; ^{19}F NMR (400 Mz, DMSO): δ = - 42.16 ppm; IR: ν = 3388, 3305, 3192, 2201,

1655, 1627, 1488, 1393, 1350, 1222, 1166, 1117, 1083, 1015, 884, 794, 773, 740, 654, 596, 519, 493 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{13}F_3N_3OS$, $[M + H]^+$ 388.0731, found 388.0718.

2-Amino-4-(4-nitrophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4o): Yellow solid; m.p. 202–204 ^oC; ^1H NMR (400 MHz, DMSO, 25 ^oC, TMS): δ = 5.04 (s, 1H), 6.54 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 2H), 7.15 (d, *J* = 12.0 Hz, 1H), 7.41 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 2H), 11.38 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.0, 154.8, 146.7, 141.3, 137.0, 129.2, 126.3, 124.4, 122.0, 121.1, 117.0, 110.9, 109.2, 98.0, 56.1, 40.9 ppm; IR: ν = 3441, 3395, 3335, 2184, 1655, 1513, 1402, 1350, 1225, 1087, 889, 772, 741, 700, 479 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{13}N_4O_3$, $[M + H]^+$ 333.0988, found 333.0980.

2-Amino-4-(2-nitrophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4p): Yellow solid; m.p. 224–226 ^oC; ^1H NMR (400 MHz, DMSO, 25 ^oC, TMS): δ = 5.37 (s, 1H), 6.54 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.41–7.47 (m, 2H), 7.60–7.64 (m, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 11.38 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.1, 149.1, 141.5, 140.5, 137.0, 133.9, 132.0, 128.5, 126.4, 124.0, 121.6, 120.8, 116.9, 110.6, 109.4, 98.1, 56.2, 36.0 ppm; IR: ν = 3443, 3342, 2189, 1656, 1521, 1408, 1350, 1224, 1091, 860, 773, 744, 682, 635, 483 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{18}H_{13}N_4O_3$, $[M + H]^+$ 333.0988, found 333.0983.

2-Amino-4-(4-cyanophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4q): Yellow solid; m.p. 210–212 ^oC; ^1H NMR (400 MHz, DMSO, 25 ^oC, TMS): δ = 4.85 (s, 1H), 6.43 (s, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 11.27 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.1, 152.8, 141.3, 137.0, 133.1, 129.0, 126.3, 122.0, 121.1, 119.3, 117.0, 111.1, 109.9, 109.2, 98.0, 56.2, 41.2 ppm; IR: ν = 3334, 2231, 2185, 1654, 1627, 1488, 1401, 1350, 1222, 1164, 1089, 1061, 888, 741, 864, 798, 749, 659, 493 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{13}N_4O$, $[M + H]^+$ 313.1089, found 313.1094.

2-Amino-4-(4-(trifluoromethyl) phenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4r): Yellow solid; m.p. 169–171 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 21 ^{o}C, TMS): δ = 4.96 (s, 1H), 6.53 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 2H), 7.15 (d, *J* = 8.0 Hz, 1H),7.40 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H),7.69 (d, *J* = 8.0 Hz, 2H), 11.36 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.0, 151.9, 141.3, 136.9, 128. 8, 127.7 (q, *J* = 31 Hz), 126.2, 126.0 (d, *J* = 3.0 Hz), 123.4, 122.0, 121.2, 116.9, 111.3, 109.2, 98.0, 56.4, 41.0 ppm; ^{19}F NMR (400 Mz, DMSO): δ = - 60.81 ppm; IR: ν = 3448, 3423, 3354, 3199, 2189, 1658, 1579, 1491, 1402, 1352, 1328, 1254, 1224, 1162, 1111, 1066, 1018, 888, 864, 848, 799, 754, 732, 668, 608, 488 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{19}H_{13}F_3N_3O$, $[M + H]^+$ 356.1011, found 356.1005.

2-Amino-4-(furan-2-yl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carbonitrile (4s): Yellow solid; m.p. 177–179 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 21 ^{o}C, TMS): δ = 4.83 (s, 1H), 6.08 (d, *J* = 4.0 Hz, 1H), 6.24–6.25 (m, 1H), 6.38 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 4.0 Hz, 1H), 11.24 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.6, 158.0, 142.7, 141.5, 137.0, 126.1, 121.8, 121.2, 117.0, 110.8, 109.6, 108.8, 105.9, 97.9, 54.1, 34.9 ppm; IR: ν = 3431, 3369, 3328, 2193, 1655, 1627, 1492, 1404, 1349, 1216, 1150, 1084, 1007, 750, 598, 479 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{16}H_{12}N_3O_2$, $[M + H]^+$ 278.0930, found 278.0927.

2-Amino-4-(benzo[b]thiophen-3-yl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4t): Yellow solid; m.p. 217–219 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 5.33 (s, 1H), 6.55 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.21–7.30 (m, 2H), 7.39 (t, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 160.9, 141.2, 140.2, 137.5, 137.0, 126.1, 124.8, 124.6, 124.4, 123.7, 122.4, 121.7, 110.5, 108.9, 100.1, 98.0, 55.8, 36.1 ppm; IR: ν = 3467, 3416, 3327, 2194, 1659, 1657, 1489, 1399, 1349, 1218, 1092, 1060, 1015, 760, 737, 505 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{20}H_{14}N_3OS$, $[M + H]^+$ 344.0858, found 344.0855.

2-Amino-4-cyclopropyl-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3-carbonitrile (4u):

Yellow solid; m.p. 147–149 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 21 ^{o}C, TMS): δ = 0.26–0.38 (m, 4H), 0.78–0.83 (m, 1H), 2.88 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 6.65 (s, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 11.15 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 161.7, 141.6, 136.8, 125.8, 122.1, 121.4, 117.0, 113.1, 108.5, 97.8, 55.3, 38.4, 21.6, 3.34 ppm; IR: ν = 3460, 3346, 2186, 1665, 1607, 1490, 1400, 1352, 1224, 1090, 797, 763, 721, 497 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{15}H_{14}N_3O$, $[M + H]^+$ 252.1137, found 252.1121.

Ethyl 2-amino-4-(4-methoxyphenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carboxylate (4v): Yellow solid; m.p. 207–209 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 1.06 (t, *J* = 8.0 Hz, 3H), 3.62 (s, 3H), 3.95 (q, *J* = 8.0 Hz, 2H), 4.85 (s, 1H), 6.46 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 12.0 Hz, 3H), 7.30 (s, 1H), 7.58 (s, 2H), 11.19 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 169.1, 161.5, 157.7, 141.8, 141.2, 136.5, 128.5, 125.8, 122.3, 116.9, 115.6, 113.8, 108.6, 97.8, 77.8, 59.0, 55.4, 39.3, 14.8 ppm; IR: ν = 3417, 3315, 1672, 1609, 1509, 1487, 1351, 1254, 1212, 1169, 1092, 1061, 1030, 797, 751, 726, 541 cm^{-1}. HRMS (TOF, ESI): m/z calcd for $C_{21}H_{21}N_2O_4$, $[M + H]^+$ 365.1501, found 365.1492.

Ethyl 2-amino-4-(3, 4, 5-trimethoxyphenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indole-3- carboxylate (4w): Yellow solid; m.p. 231–233 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 1.07 (t, *J* = 8.0 Hz, 3H), 3.54 (s, 3H), 3.64 (s, 6H), 3.96 (q, *J* = 4.0 Hz, 2H), 4.87 (s, 1H), 6.45 (s, 2H), 6.47(s, 1H), 6.90 (d, *J* = 12.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.61 (s, 2H), 11.21 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 169.1, 161.7, 153.0, 145.4, 141.2, 136.6, 136.1, 125.8, 122.3, 116.9, 115.1, 108.7, 104.9, 97.9, 77.3, 60.4, 59.0, 56.2, 40.4, 14.8 ppm; IR: ν = 3433, 3365, 1680, 1615, 1506, 1486, 1461, 1422, 1352, 1326, 1289, 1235, 1212, 1125, 1094, 1064, 1002, 726, 693, 661, 598. HRMS (TOF, ESI): m/z calcd for $C_{23}H_{25}N_2O_6$, $[M + H]^+$ 425.1713, found 425.1706.

Ethyl 2-amino-4-(4-chlorophenyl)-4,6-dihydrooxepino [4, 3, 2-cd] indole-3-carboxylate (4x): Yellow solid; m.p. 181–183 ^{o}C; ^{1}H NMR (400 MHz,

$CDCl_3$, 22 °C, TMS): δ = 1.17 (t, *J* = 8.0 Hz, 3H), 4.07 (q, *J* = 4.0 Hz, 2H), 5.00 (s, 1H), 6.64 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.13–7.19 (m, 5H), 7.25 (s, 2H), 8.37 (s, 1H); ^{13}C NMR (100 Mz, $CDCl_3$): δ = 169.0, 160.4, 147.4, 141.4, 136.2, 131.4, 129.2, 128.1, 124.2, 123.0, 116.9, 115.1, 108.0, 99.0, 79.1, 59.5, 30.3, 14.4 ppm; IR: ν = 3438, 3369, 2978, 2904, 1669, 1605, 1528, 1504, 1404, 1365, 1351, 1313, 1290, 1247, 1211, 1159, 1086, 1059, 1018, 891, 790, 761, 733, 484, 454. HRMS (TOF, ESI): m/z calcd for $C_{20}H_{18}ClN_2O_3$, $[M + H]^+$ 369.1006, found 369.1002.

Ethyl 2-amino-4-(2-bromo-4-chlorophenyl)-4,6-dihydrooxepino [4, 3, 2-cd] indole-3- carboxylate (4y): Yellow solid; m.p. 157–159 °C; ^{1}H NMR (400 MHz, DMSO, 22 °C, TMS): δ = 0.98 (t, *J* = 8.0 Hz, 3H), 3.89 (q, *J* = 4.0 Hz, 2H), 5.48 (s, 1H), 6.48 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 7.06–7.09 (m, 2H), 7.33 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 2H), 11.28 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 168.8, 161.7, 151.1, 140.7, 136.9, 134.5, 132.9, 129.9, 128.1, 126.1, 120.9, 116.9, 109.1, 103.3, 98.0, 76.0, 59.1, 39.1, 14.6 ppm; IR: ν = 3425, 3314, 1671, 1606, 1488, 1302, 1213, 1165, 1097, 1063, 1024, 736. HRMS (TOF, ESI): m/z calcd for $C_{20}H_{17}BrClN_2O_3$, $[M + H]^+$ 447.0111, found 447.0101.

Ethyl

2-amino-4-(4-nitrophenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carboxylate (4z): Yellow solid; m.p. 141–143 °C; ^{1}H NMR (400 MHz, DMSO, 22 °C, TMS): δ = 1.07 (t, *J* = 7.2 Hz, 3H), 3.97 (q, *J* = 6.8 Hz, 2H), 5.13 (s, 1H), 6.54 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 2.8 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.80 (s, 2H), 8.11 (d, *J* = 8.0 Hz, 2H), 11.32 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 168.7, 161.6, 157.3, 146.0, 141.2, 136.9, 128.9, 126.1, 124.0, 122.2, 117.0, 113.5, 109.0, 97.9, 76.3, 59.1, 30.6, 14.7 ppm; IR: ν = 3443, 3311, 2981, 1737, 1675, 1604, 1510, 1406, 1346, 1294, 1243, 1213, 1163, 1105, 894, 827, 741, 583, 531, 481; HRMS (TOF, ESI): m/z calcd for $C_{20}H_{18}N_3O_5$, $[M + H]^+$ 380.1246, found 380.1239.

Ethyl

2-amino-4-(4-cyanophenyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carboxylate

(4aa): Yellow solid; m.p. 165–167 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 1.02 (t, *J* = 4.0 Hz, 3H), 3.92 (q, *J* = 4.0 Hz, 2H), 5.02 (s, 1H), 6.48 (s, 1H), 6. 79 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz,1H), 7.32–7.36 (m, 3H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 2H), 11.25 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 168.7, 161.6, 155.2, 141.2, 136.8, 132.6, 128.7, 126.1, 122.2, 119.5, 116.9, 113.8, 108.9, 108.9, 97. 9, 76.4, 59.1, 30.5, 14.7 ppm; IR: ν = 3503, 3305, 2983, 2916, 2225, 1675, 1605, 1526, 1486, 1405, 1350, 1300, 1257, 1209, 1160, 1104, 1060, 1025, 891, 787, 746, 673, 582, 454. HRMS (TOF, ESI): m/z calcd for $C_{21}H_{18}N_3O_5$, $[M + H]^+$ 360.1348, found 360.1332.

Ethyl 2-amino-4-(*p*-tolyl)-4,6-dihydrooxepino[4,3,2-cd]indole-3-carboxylate (4ab): Yellow solid; m.p. 220–222 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 1.10 (t, *J* = 8.0 Hz, 3H), 2.18 (s, 3H), 3.98 (q, *J* = 4.0 Hz, 2H), 4.92 (s, 1H), 6.53 (s, 1H), 6. 83 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 7.36 (s, 1H), 7.66 (s, 2H), 11.26 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 169.1, 161.6, 146.7, 141.3, 136.6, 134.9, 129.0, 127.5, 125.8, 122.4, 116.9, 115.5, 108.6, 103.4, 97.8, 77.6, 59.0, 21.0, 14.8 ppm; IR: ν = 3413, 3313, 2984, 2904, 1664, 1638, 1599, 1504, 1482, 1402, 1351, 1315, 1294, 1247, 1210, 1158, 1099, 1060, 1018, 892, 751, 727, 580, 505, 456; HRMS (TOF, ESI): m/z calcd for $C_{21}H_{21}N_2O_3$, $[M + H]^+$ 349.1552, found 349.1539.

2-Amino-4-(4-chlorophenyl)-4, 6-dihydrooxepino [4, 3, 2-cd] indol-3-yl) (phenyl)methanone (4ac): Yellow solid; m.p. 132–134 ^{o}C; ^{1}H NMR (400 MHz, DMSO, 22 ^{o}C, TMS): δ = 5.00 (s, 1H), 6.55 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.08–7.13 (m, 5H), 7.32–7.39 (m, 4H), 9.26 (s, 2H), 11.31 (s, 1H); ^{13}C NMR (100 Mz, DMSO): δ = 193.9, 163.7, 147.9, 142.5, 140.7, 136.8, 130.7, 129.1, 128.9, 128.5, 128.5, 126.5, 126.2, 122.0, 117.0, 115.3, 109.0, 97.8, 88.1, 31.1 ppm; IR: ν = 3421, 1692,1596, 1491, 1448, 1352, 1261, 1092, 1015, 789, 699, 508. HRMS (TOF, ESI): m/z calcd for $C_{24}H_{18}ClN_2O_2$, $[M + H]^+$ 401.1057, found 401.1056.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENT

This work was supported by National Natural Science Foundation of China (21373093) and the Fundamental Research Funds for the Central Universities of China (2014ZZGH019). The authors thank for Analytical and Testing Center of HUST, Chutian Scholar Program of the Hubei Provincial Government and the Cooperative Innovation Center of Hubei Province.

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