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Cyclization and oxidation of *o*-bromophenylacetamides for the synthesis of oxindoles and isoindigoes

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ABSTRACT

N-substituted oxindoles were obtained through a facile KOH/DMSO promoted intramolecular cyclization of *o*-bromophenylacetamides in good yields. Furthermore, isoindigo derivatives were readily synthesized through sequential intramolecular cyclization, oxidation and condensation of *o*-bromophenylacetamide in the presence of copper (II) acetate monohydrate, iodobenzene diacetate and KOH/DMSO. This method provides a convenient synthesis of a range of oxindoles and symmetrical biologically important (*E*)-bisindole-2-ones using *o*-bromophenylacetamide as sole starting material. The reaction mechanism is elucidated in light of the control experiment results.

1. Introduction

Isoindigoes are active ingredients in some traditional Chinese medicines and constitute the scaffold of some recently identified molecules with antileukemia activities.[1] Meisoindigo (1-methylisoindigo) and Natura™ (1-β-D-triacetylxylopyranosyl isoindigo) are isoindigo derivatives of which meisoindigo is a therapeutic agent used for the treatment of chronic myelocytic leukemia (CML) in China, and Natura™ exhibit anti-cancer activity (Fig. 1). Besides, isoindigoes such as DAD have important applications in organic electronics as one of the latest reported amide-based acceptors, and their perfect planar π-conjugated structure, together with a strong electron-withdrawing effect, make them ideal monomers for the synthesis of donor/acceptor low bandgap conjugated polymer for varied electronic applications in organic photovoltaics (OPVs) and organic field effect transistors (OFETs).[2] Therefore, the development of effective methods for their synthesis is a research topic of great interest.[3] Facile synthesis of functionalized aryl-containing isoindigo derivatives via dimerization of substituted indolin-2-one carbenens have been reported.[3a] Bogdanov group have reported the synthesis of long-chain *N*-alkyl isoindigo via the reaction of substituted isatins with tris(diethylamino)phosphine.[3b] Recently, Huang reported palladium (II) acetate-catalyzed dual C–H functionalization for the synthesis of (*E*)-bisindole-2-ones from diarylbut-2- ynediamides.[3d]

Oxindole skeleton is the key structural motif in isoindigoes and numerous natural products,[4] and also the important starting material for the synthesis of isoindigoes. Common method for the synthesis of oxindole involves the derivatization of relevant heterocycles, such as reduction of isatins or oxidation of indoles.[5] Another classical approach to the oxindole is the Friedel-Crafts cyclization of α-haloacetanilides and related variations.[6] Transition-metal catalyzed synthesis of oxindoles via intramolecular arylation or alkylation of anilide derivatives have also been developed.[7] In addition, metal catalyzed C–H activation has emerged as a highly atom-economic strategy to oxindoles,[8] as exemplified by the direct Pd-catalyzed intramolecular oxidative coupling method developed by Kündig for the synthesis of 3,3-disubstitued oxindoles.[8a] Moreover, Bolm et al. have reported the synthesis of oxindoles by t-BuOK-promoted intramolecular arylations of fluoro- and chloro-substituted anilides under transition metal-free conditions.[9]

As part of our continued efforts in developing efficient protocols for the synthesis of useful heterocycle,[10] herein we report an efficient base-promoted intramolecular cyclization of *o*-halophenylacetamide for the facile synthesis of oxindoles in good

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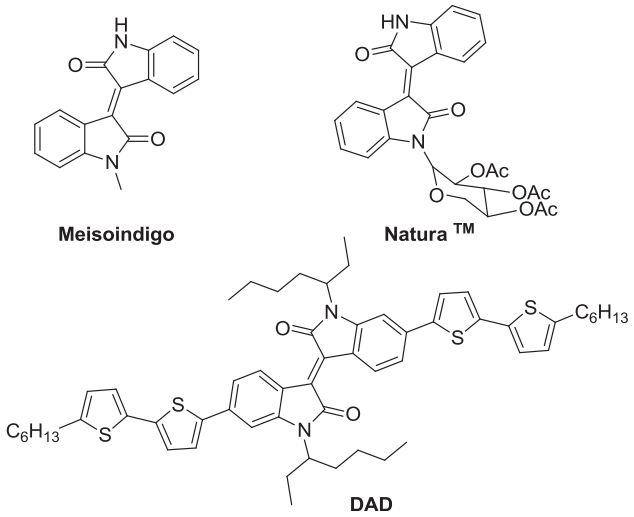


Fig. 1. Representative examples of isoindigoes.

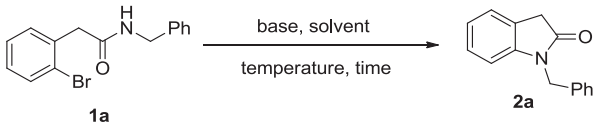
yields. Furthermore, isoindigo derivatives could be obtained by sequential cyclization, oxidation and condensation of *o*-halophenylacetamide in the presence of copper acetate monohydrate and iodobenzene diacetate as oxidizer in KOH/DMSO system.

2. Results and discussion

In our initial attempt to prepare 1-benzylindolin-2-one (**2a**) from *N*-benzyl-2-(2-bromophenyl)acetamide (**1a**) by intramolecular *N*-arylation in the superbasic medium consisting of KOH and DMSO at 50 °C, 35% **2a** was obtained (Table 1, entry 1). The effects of base, solvent, temperature and time were further investigated and the results were summarized in Table 1. Reaction temperature had a significant effect on this reaction. The yield was improved to 84% when the reaction was conducted at 120 °C (entry 4). However, no significant improvement in the yield was observed by increasing the temperature further. Solvent also played an important role in the reaction. Various common solvents such as DMF, diglyme, dioxane, and toluene are inferior to DMSO (Table 1, entries 6–9). Then, a variety of bases were examined. While strong bases such as KOH, KO^{t}Bu and NaOH exhibited high reactivity to the reaction in DMSO (Table 1, entries 9–14), weak ones like Na_2CO_3, K_2CO_3, and K_3PO_4 were ineffective. When the amount of KOH was decreased to 1 equiv, the yield decreased to 60%. The reaction became sluggish under air and a lower yield was obtained. Thus, the reaction was best performed in the presence of KOH in DMSO at 120 °C under argon.

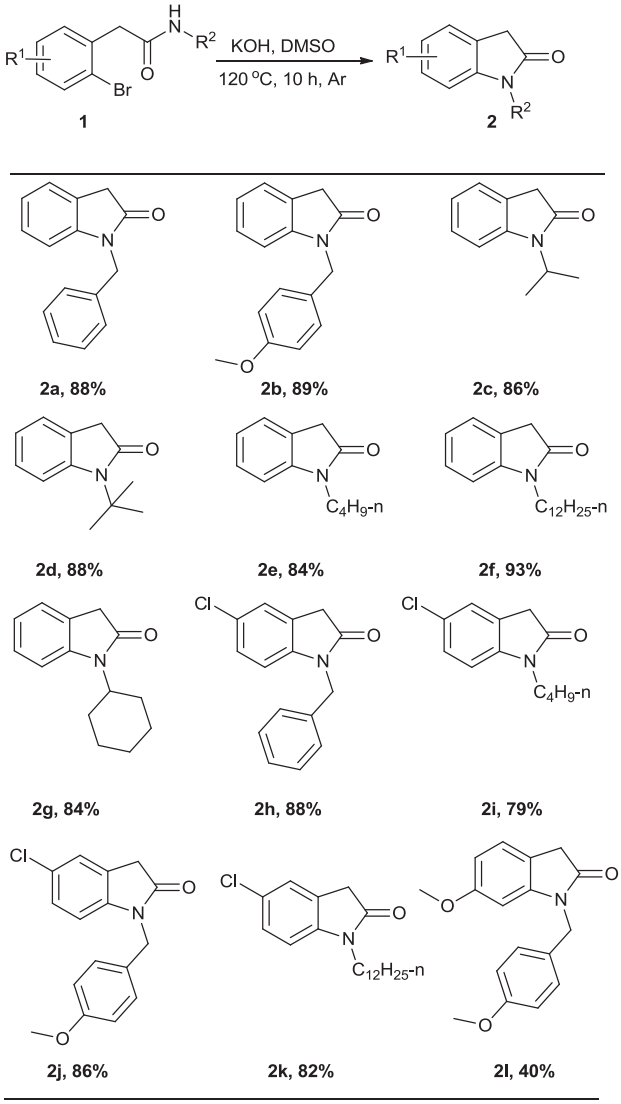
With the optimized conditions in hand, the scope of the substrates was screened. Twelve oxindole derivatives were obtained, and the best yield is up to 93% (Scheme 1). We found that the electronic nature of the substituent group R^1 of substrates had an obvious effect on the yields, and electron-withdrawing substituents

Table 1
Optimization of the reaction conditions.[a]



Entry	Base	Solvent (mL)	T (°C)	Yield (%)[b]
1	KOH	DMSO (2)	50	35
2	KOH	DMSO (2)	80	65
3	KOH	DMSO (2)	100	70
4	KOH	DMSO (2)	120	84
5	KOH	DMSO (2)	130	84
6	KOH	Diglyme (2)	100	43
7	KOH	DMF (2)	100	nr
8	KOH	Dioxane (2)	100	nr
9	KOH	DMSO (4)	120	88
10[c]	KOH	DMSO (4)	120	65
11	Na_2CO_3	DMSO (4)	120	nr
12	KO^{t}Bu	DMSO (4)	120	88
13	NaOH	DMSO (4)	120	87
14[d]	KOH	DMSO (4)	120	60
15[e]	KOH	DMSO (4)	120	Trace

[a] Reaction conditions: **1a** (0.50 mmol), base (2.0 equiv), stirred under argon for 10 h.
[b] Isolated yield.
[c] Reaction time: 5 h.
[d] KOH (1.0 equiv).
[e] KOH (4.0 equiv).



[a]Reaction conditions: *o*-bromophenylacetamides **1** (0.50 mmol), KOH (2.0 equiv) in DMSO (4 mL) at 120 °C under argon for 10 h.

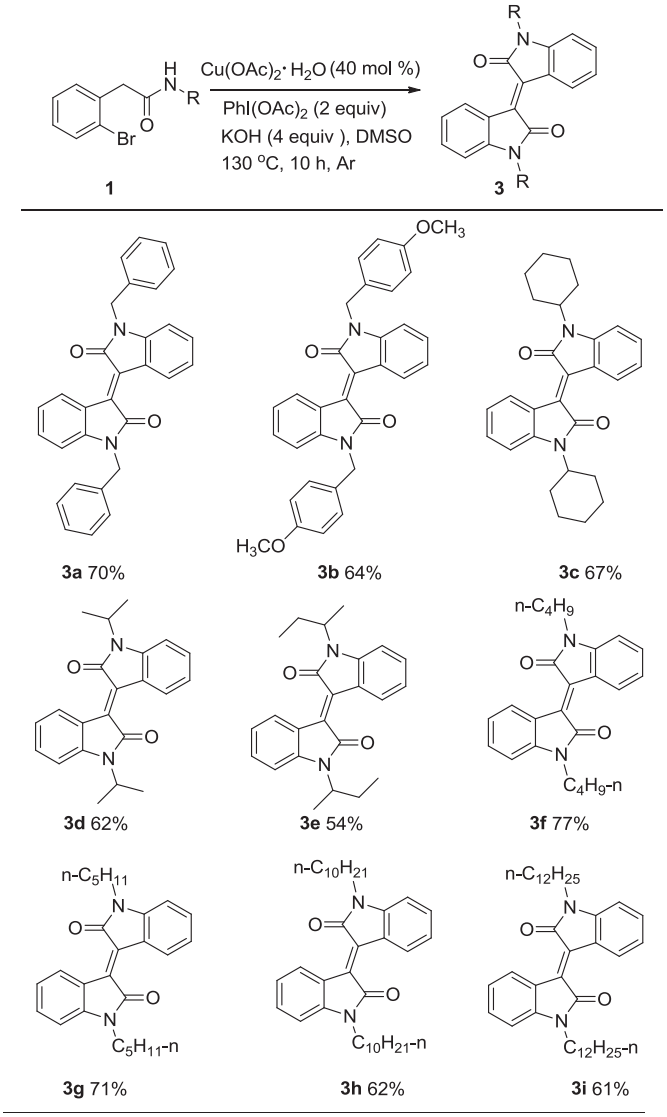
Scheme 1. Scope of the synthesis of oxindoles.[a]

on the aromatic ring are clearly favored (**2h**, **2i**, **2j** and **2k**). Comparing the cyclization results of 2-bromoderivatives **1b** (R^1=H), **1j** (R^1=Cl), and **1l** (R^1=OCH_3) revealed that the latter process was the most difficult one leading to product **2l** in only 40% yield. With respect to the *N*-substituent R,[2] we observed there to be a significant effect of amide substitution on the cyclization. We were pleased to find that both alkyl and benzyl groups were tolerated. However, attempted reaction of the *N*-aryl substituted substrates 2-(2-bromophenyl)–*N*-(*p*-tolyl)acetamide revealed a limitation of the method, no cyclization occurred, and only trace of oxidation product of the starting material characterized as α-hydroxyl amide by NMR was observed, which might be due to the existence of *p*-π conjugation in the *N*-aryl substituted amide. The findings demonstrated that the cyclization is highly dependent on the nitrogen substituents.

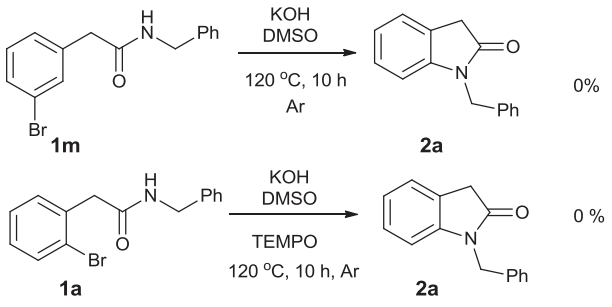
Only a trace amount of product **2a** was formed in 4 equiv KOH (Table 1, entry 15). The reaction became sluggish under air and a lower yield of **2a** was obtained. This inspired us to expand the reaction conditions in order to obtain more interesting results. Our literature perusal on this aspect revealed that an efficient copper-catalyzed synthesis of *N*-substituted isatins had been developed in good yields from arylacetamides in the presence of TBAB using 3.0 equiv of K_2CO_3 as the base under air.[11]

To test the oxidative cyclization reaction of *o*-bromophenylacetamides in KOH/DMSO system, a series of experiments were conducted. To our surprise, with iodobenzene diacetate [$PhI(OAc)_2$] as the oxidant, copper (II) salt exhibit remarkable catalytic activity toward the selective oxidation of oxindoles and isoindigo **3a** could be obtained. $Cu(OAc)_2 \cdot H_2O$ proved to be the best promoter among various copper sources that were examined. No desired product was observed in the absence of copper salt or iodobenzene diacetate. Reactions in the presence of other bases, such as K_2CO_3, and K_3PO_4, did not proceed well. This protocol provides a facile way to a library of isoindigo derivatives with the advantages of easily available starting materials and operational simplicity (Scheme 2).

To gain some insights into the mechanism of this transformation, several control experiments were performed under the standard conditions (Scheme 3). In view of the importance of trace metals present in commercially available metal salts can catalyze various reactions,[12] especially some known palladium-catalyzed related cyclizations, additional experiments were performed to further examine this issue. No difference in the yield was noted in experiments when KOH from different sources was used. The yield of **2a** remained essentially unchanged when high-purity KOH (>99.995%) was applied in the reactions with new glassware and magneton, indicating that metal residues in the base were not critical. Also, when *N*-benzyl-2-(3-bromophenyl)acetamide (**1m**), a regioisomer of **1a**, was subjected to the KOH/DMSO system, no cyclization product was detected, but only the starting material was recovered. This result renders less probable the involvement of aryne intermediates in the cyclization process. Notably, the addition of a typical radical scavenger tetramethylpiperidine *N*-oxide (TEMPO) to the reaction system completely inhibited the reaction. On the basis of the above findings, a plausible radical-nucleophilic aromatic substitution ($S_{RN}1$) mechanism is involved in the cyclization reaction. The reaction may initiate with the deprotonation of N–H by KOH leading to intermediate **I**, which might be transformed into aryl radical intermediate **II**.[13] The aryl radical reacts with nitrogen nucleophile to a new radical anion **III** which goes on to form the intramolecular substituted product **2** by transferring its electron to intermediate **I**. The resulted oxindole **2** then undergoes oxidation to isatins by iodobenzene diacetate and $Cu(OAc)_2$. Finally, isoindigo **3** was obtained by the base-promoted isatin/oxindole condensation reaction (see Scheme 4).



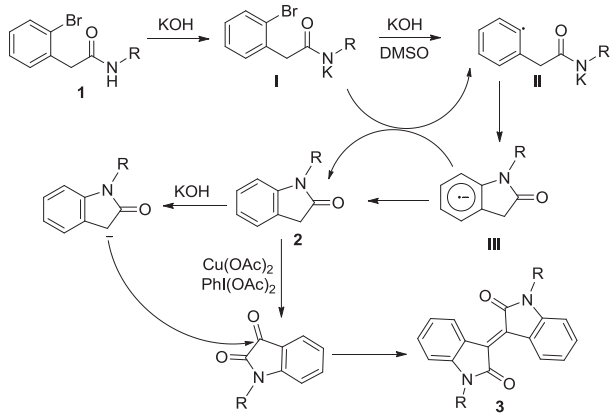
Scheme 2. Synthesis of isoindigoes.



Scheme 3. Control Experiments.

3. Conclusion

In conclusion, we have successfully developed an efficient method for the synthesis of oxindole, and isoindigo derivatives sequential intramolecular cyclization, oxidation and condensation of *o*-bromophenylacetamide. Further studies towards the synthetic applications of base promoted intramolecular cyclization and



Scheme 4. Plausible Mechanism.

oxidation of carboxylic acid derivatives are in progress.

4. Experiment section

4.1. General

All reactions were carried out under argon atmosphere using pre-dried glassware. Cyclization substrates *o*-halophenylacetamides **1** were prepared from *o*-halophenylacetic acid and amine in analogy to previously described methodologies.[14] All starting materials and reagents were commercially available and used directly without further purification. KOH (99.995%) was purchased from Sigma Aldrich. All known products gave satisfactory analytical data by NMR spectra, which corresponding to the reported literature values. Unknown compounds were confirmed by HRMS additionally. All melting points were taken on an X-4 Digital Melting Point Apparatus without correction. NMR spectra were recorded on Bruker Avance 300 or 500 instruments in the solvent indicated with tetramethylsilane (TMS) as an internal standard; chemical shifts (δ) are given in ppm, the coupling constants J are given in Hz. High-resolution mass spectral (HRMS) were obtained on Agilent 6200 LC/MS TOF using APCI or ESI in positive mode.

4.2. General procedure for the synthesis of oxindoles

A mixture of *N*-alkyl-2-(2-halogenphenyl)acetamide **1** (0.5 mmol), KOH (1.0 mmol) was stirred in DMSO (4.0 mL) at 120 °C in an oil bath in Ar for 10 h. Upon completion, the resulting mixture was cooled to room temperature and then extracted with EtOAc (2 × 15 mL). The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After that the organic phase was filtered, and the filtrate was evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel using appropriate eluent to afford the desired product **2a**-**2l**.

4.3. General procedure for the synthesis of isoindigoes

A mixture of *N*-alkyl-2-(2-halogenphenyl)acetamide **1** (0.25 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol, 40 mol %), iodobenzene diacetate (0.5 mmol) and KOH (1.0 mmol) was stirred in DMSO (4.0 mL) at 130 °C in an oil bath under Ar for 10 h. The resulting mixture was cooled to room temperature and then extracted with EtOAc (2 × 10 mL). The organic phases were combined and dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography to give the corresponding products **3a**-**3i**.

4.4. Characterization data of product

All the products were characterized by ^{1}H NMR, ^{13}C NMR, GCMS, and HRMS (for new products). The copies of NMR charts were reported in supplementary data.

4.4.1. 1-Benzylindolin-2-one (**2a**)[15]

White solid (98 mg, 88% yield); m. p. 67–69 °C (Lit. 66–67 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.10 (m, 7H), 6.98 (t, J = 7.2, 1H), 6.69 (d, J = 7.8, 1H), 4.87 (s, 2H), 3.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 144.3, 136.0, 128.8, 127.8, 127.7, 127.4, 124.5, 124.5, 122.4, 109.1, 43.7, 35.8.

4.4.2. 1-(4-methoxybenzyl)indolin-2-one (**2b**)[15]

White solid (113 mg, 89% yield); m. p. 107–109 °C (Lit. 105–107 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.27–7.14 (m, 4H), 6.99 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 7.5 Hz, 1H), 4.84 (s, 2H), 3.75 (s, 3H), 3.59 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.1, 159.0, 144.3, 128.8, 127.9, 124.5, 122.3, 114.1, 109.1, 55.3, 43.2, 35.8.

4.4.3. 1-Isopropylindolin-2-one (**2c**)[16]

Colorless oil (75 mg, 86% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.03–6.98 (m, 2H), 4.74–4.70 (m, 1H), 3.49 (s, 2H), 1.48 (d, J = 7.2 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.7, 143.8, 127.5, 125.0, 124.5, 121.7, 109.8, 43.5, 36.0, 19.3. HRMS (ESI) calcd for $C_{11}H_{14}NO$ ($[M+H]^+$) 176.1072, found 176.1075.

4.4.4. 1-(tert-butyl)indolin-2-one (**2d**)

Yellowish oil (83 mg, 88% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.18 (m, 3H), 6.98 (t, J=7.0, 1H), 3.46 (s, 2H), 1.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 145.5, 127.1, 125.6, 124.3, 121.4, 113.1, 57.6, 37.4, 29.1. HRMS (ESI) calcd for $C_{12}H_{16}NO$ ($[M+H]^+$) 190.1232, found 190.1236.

4.4.5. 1-Butylindolin-2-one (**2e**)[15]

Colorless oil (79 mg, 84% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 3.70 (t, J = 7.2 Hz, 2H), 3.50 (s, 2H), 1.70–1.60 (m, 2H), 1.46–1.33 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 144.7, 127.8, 124.7, 124.4, 122.1, 108.3, 39.8, 35.8, 29.5, 20.2, 13.8.

4.4.6. 1-Dodecylindolin-2-one (**2f**)

Yellow solid (140 mg, 93% yield); m. p. 32–34 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.28–7.22 (m, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 3.69 (t, J = 7.4 Hz, 2H), 3.50 (s, 2H), 1.68–1.64 (m, 2H), 1.33–1.25 (m, 18H), 0.88 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 144.7, 127.8, 124.7, 124.4, 122.1, 108.3, 40.1, 35.8, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 27.5, 27.0, 22.7, 14.2. HRMS (ESI) calcd for $C_{20}H_{32}NO$ ($[M+H]^+$) 302.2484, found 302.2484.

4.4.7. 1-Cyclohexylindolin-2-one (**2g**)

White solid (90 mg, 84% yield); m. p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 7.07–6.98 (m, 2H), 4.26–4.18 (m, 1H), 3.50 (s, 2H), 2.22–2.09 (m, 2H), 1.92–1.88 (m, 2H), 1.78–1.74 (m, 3H), 1.49–1.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 144.2, 127.4, 125.0, 124.5, 121.6, 110.1, 51.9, 36.0, 29.0, 26.0, 25.4. HRMS (ESI) calcd for $C_{14}H_{18}NO$ ($[M+H]^+$) 216.1388, found 216.1387.

4.4.8. 1-Benzyl-5-chloroindolin-2-one (**2h**)[17]

White solid (113 mg, 88% yield); m. p. 96–99 °C (Lit. 103–104 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.31–7.23 (m, 6H), 7.13 (d,

J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 4.89 (s, 2H), 3.61 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 142.8, 135.4, 128.9, 127.8, 127.3, 124.9, 109.9, 43.8, 35.7.

*4.4.9. 1-Butyl-5-chloroindolin-2-one (**2i**)*

Yellow oil (88 mg, 79% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.10 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 3.68 (t, J = 7.2 Hz, 2H), 3.51 (s, 2H), 1.68–1.59 (m, 2H), 1.44–1.32 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 143.3, 127.7, 127.4, 126.3, 124.9, 109.1, 39.9, 35.6, 29.4, 20.2, 13.7; HRMS (ESI) calcd for $C_{12}H_{15}NOCl$ ($[M+H]^+$) 224.0842, found 224.0837.

*4.4.10. 5-Chloro-1-(4-methoxybenzyl)indolin-2-one (**2j**)*

White solid (111 mg, 86% yield); m. p. 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21–7.12 (m, 4H), 6.84 (d, J = 7.2 Hz, 2H), 6.64 (d, J = 7.8 Hz, 1H), 4.82 (s, 2H), 3.76 (s, 3H), 3.58 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.5, 159.1, 142.8, 128.7, 127.7, 127.5, 126.1, 124.8, 114.2, 109.9, 55.3, 43.3, 35.7. HRMS (ESI) calcd for $C_{16}H_{15}NO_2Cl$ ($[M+H]^+$) 288.0791, found 288.0789.

*4.4.11. 5-Chloro-1-dodecylindolin-2-one (**2k**)*

Yellow solid (138 mg, 82% yield); m. p. 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.22 (m, 2H), 6.74 (d, J = 7.8 Hz, 1H), 3.67 (t, J = 7.2 Hz, 2H), 3.50 (s, 2H), 1.31–1.25 (m, 20H), 0.87 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 143.3, 127.7, 126.3, 124.9, 109.1, 40.2, 35.7, 31.9, 29.6, 29.5, 29.5, 29.3, 29.3, 27.3, 26.9, 22.7, 14.1; HRMS (ESI) calcd for $C_{20}H_{31}NOCl$ ($[M+H]^+$) 336.2094, found 336.2089.

*4.4.12. 1-(4-methoxybenzyl)-6-methoxyindolin-2-one (**2l**)*

Colorless oil (57 mg, 40% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.52–6.48 (m, 1H), 6.35 (d, J = 2.1 Hz, 1H), 4.82 (s, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.54 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 159.8, 159.0, 145.5, 128.8, 127.9, 124.8, 116.3, 114.1, 105.9, 97.4, 55.4, 55.3, 43.2, 35.2. HRMS (ESI) calcd for $C_{17}H_{18}NO_3$ ($[M+H]^+$) 284.1287, found 284.1281.

*4.4.13. (E)-1,1′-dibenzyl-[3,3′-biindolinylidene]-2,2′-dione (**3a**)[3c]*

Red solid (77 mg, 70% yield); m. p. 248–249 °C (Lit. 242–244 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.23 (d, J = 15 Hz, 1H), 7.34–7.26 (m, 6H), 7.05 (t, J = 12.5 Hz, 1H), 6.72 (d, J = 12.5 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 144.9, 136.1, 133.9, 132.9, 130.4, 129.3, 128.0, 127.6, 122.9, 122.0, 109.0, 44.1.

*4.4.14. (E)-1,1′-bis(4-methoxybenzyl)-[3,3′-biindolinylidene]-2,2′-dione(**3b**)*

Red solid (80 mg, 64% yield); m. p. 274–275 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, J = 8 Hz, 1H), 7.30–7.27 (m, 3H), 7.04 (t, J = 8 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8 Hz, 1H), 4.95 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.5, 144.9, 134.0, 132.8, 130.3, 129.0, 128.2, 122.8, 122.1, 114.6, 109.0, 55.7, 43.6. HRMS (APCI) calcd for $C_{32}H_{27}N_2O_4$ ($[M+H]^+$) 503.1971, found: 503.1970.

*4.4.15. (E)-1,1′-dicyclohexyl-[3,3′-biindolinylidene]-2,2′-dione(**3c**)*

Red solid (71 mg, 67% yield); m. p. 81–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, J = 7.5 Hz, 1H), 7.26–7.23 (m, 1H), 6.96–6.91 (m, 2H), 2.19–2.12 (m, 1H), 1.85 (d, J = 12.5 Hz, 2H), 1.74–1.67 (m, 2H), 1.40–1.32 (m, 2H), 1.26–1.21 (m, 2H), 0.82–0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 144.8, 134.0, 132.3, 130.2, 122.2, 122.0, 109.5, 30.0, 29.4, 26.5, 25.7. HRMS (APCI) calcd for $C_{28}H_{31}N_2O_2$ ($[M+H]^+$) 427.2385, found: 427.2380.

*4.4.16. (E)-1,1′-diisopropyl-[3,3′-biindolinylidene]-2,2′-dione (**3d**)[18]*

Red solid (54 mg, 62% yield); m. p. 183–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (d, J = 7.5 Hz, 1H), 7.34–7.31 (m, 1H), 7.04–7.01 (m, 1H), 6.94 (d, J = 8 Hz, 1H), 4.72–4.66 (m, 1H), 1.53 (d, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 144.5, 134.1, 132.5, 130.3, 122.3, 122.1, 109.5, 44.3, 19.8. HRMS (APCI) calcd for $C_{22}H_{23}N_2O_2$ ($[M+H]^+$) 347.1759, found: 347.1754.

*4.4.17. (E)-1,1′-di-sec-butyl-[3,3′-biindolinylidene]-2,2′-dione (**3e**)*

Red solid (51 mg, 54% yield); m. p. 155–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, J = 8 Hz, 1H), 7.32–7.29 (m, 1H), 7.04–7.01 (m, 1H), 6.93 (d, J = 8 Hz, 1H), 2.12–2.06 (m, 1H), 1.87–1.79 (m, 2H), 1.52–1.50 (m, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 144.7, 134.0, 132.5, 130.2, 122.3, 122.1, 109.6, 50.4, 26.9, 18.1, 11.8. HRMS (APCI) calcd for $C_{24}H_{27}N_2O_2$ ($[M+H]^+$) 375.2072, found: 375.2067.

*4.4.18. (E)-1,1′-dibutyl-[3,3′-biindolinylidene]-2,2′-dione (**3f**)[18]*

Red solid (72 mg, 77% yield); m. p. 145–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, J = 8 Hz, 1H), 7.39–7.33 (m, 1H), 7.09–7.06 (m, 1H), 6.82 (d, J = 8 Hz, 1H), 3.81 (t, J = 7.5 Hz, 2H), 1.75–1.69 (m, 2H), 1.49–1.41 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 145.1, 134.0, 132.7, 130.3, 122.5, 122.1, 108.3, 40.2, 30.0, 20.7, 14.2. HRMS (APCI) calcd for $C_{24}H_{27}N_2O_2$ ($[M+H]^+$) 375.2072, found: 375.2072.

*4.4.19. (E)-1,1′-dipentyl-[3,3′-biindolinylidene]-2,2′-dione (**3g**)*

Red solid (71 mg, 71% yield); m. p. 97–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, J = 8 Hz, 1H), 7.37–7.33 (m, 1H), 7.06–7.03 (m, 1H), 6.79 (d, J = 7.5 Hz, 1H), 3.77 (t, J = 7.5 Hz, 2H), 1.74–1.68 (m, 2H), 1.38–1.36 (m, 4H), 0.90 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 145.1, 134.0, 132.7, 130.3, 122.5, 122.1, 108.3, 40.5, 29.5, 27.6, 22.8, 14.4. HRMS (APCI) calcd for $C_{26}H_{31}N_2O_2$ ($[M+H]^+$) 403.2385, found: 403.2380.

*4.4.20. (E)-1,1′-didecyl-[3,3′-biindolinylidene]-2,2′-dione (**3h**)[3b]*

Red solid (84 mg, 62% yield); mp: 90–91 °C (Lit. 107–108 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, J = 8 Hz, 1H), 7.37–7.34 (m, 1H), 7.06–7.03 (m, 1H), 6.79 (d, J = 7.5 Hz, 1H), 3.77 (t, J = 7.5 Hz, 2H), 1.73–1.67 (m, 2H), 1.40–1.28 (m, 14H), 0.87 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 145.1, 133.9, 132.6, 130.2, 122.5, 122.0, 108.2, 40.4, 32.2, 30.0, 29.8, 29.7, 29.6, 27.8, 27.4, 23.0, 14.4. HRMS (APCI) calcd for $C_{36}H_{51}N_2O_2$ ($[M+H]^+$) 543.3950, found: 543.3945.

*4.4.21. (E)-1,1′-didodecyl-[3,3′-biindolinylidene]-2,2′-dione (**3i**)[3b]*

Red solid (101 mg, 67% yield); m. p. 87–88 °C (Lit. 111 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, J = 8 Hz, 1H), 7.37–7.34 (m, 1H), 7.06–7.03 (m, 1H), 6.79 (d, J = 8 Hz, 1H), 3.77 (t, J = 7.5 Hz, 2H), 1.73–1.67 (m, 2H), 1.42–1.25 (m, 18H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 145.1, 134.0, 132.7, 130.3, 122.5, 122.1, 108.3, 40.5, 32.3, 30.1, 30.0, 30.0, 29.9, 29.7, 27.9, 27.6, 27.5, 23.1, 14.5. HRMS (APCI) calcd for $C_{40}H_{59}N_2O_2$ ($[M+H]^+$) 599.4576, found: 599.4571.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.12.005.

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