NRC Research Press

ARTICLE

Copper-catalyzed oxidative trimerization of indoles by using TEMPO to construct quaternary carbon centers: the synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-ones

Yu-Bo Kong, Jia-Yi Zhu, Zheng-Wang Chen, and Liang-Xian Liu

Abstract: A simple, convenient, and efficient synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives has been developed by the oxidative trimeric reaction of indoles using the TEMPO/$CuCl_2$ catalyst system under ambient air. This methodology provides an alternative approach for the direct generation of all-carbon quaternary centers at the C-2 position of indoles.

Key words: indoles, TEMPO, biomimetic synthesis, trimerization.

Résumé : On a élaboré une méthode simple, commode et efficace de synthèse de dérivés de la 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one par la réaction de trimérisation oxydative d'indoles en utilisant un système catalyseur TEMPO/$CuCl_2$ dans l'air ambiant. Cette méthode offre une approche de rechange pour la génération directe de centres quaternaires totalement carbonés à la position C-2 des indoles. [Traduit par la Rédaction]

Mots-clés : indoles, TEMPO, synthèse biomimétique, trimérisation.

Introduction

The radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) and its derivatives are well-established catalysts for oxidation processes and now used extensively in organic synthesis and industrial applications as a mild, safe, and economical alternative to heavy metal reagents due to their high selectivity and pronounced versatility.[1]

Indolin-3-ones with a chiral center at the 2 position are encountered in a large variety of natural products and can be used in the total synthesis of biologically active alkaloids.[2–4] For example, 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one (**1**) (Fig. 1) was isolated as the product of indole oxidation by a strain of *Claviceps purpurea*.[4a] This compound has also been characterized from natural (bacterial) sources such as *Vibrio parahaemolyticus*[2a] and *Haemophilus influenzae*.[4b] In addition, isatisine A (**2**), an oxindole system having indole 2-substituents, is present in the roots and leaves of *Isatis indigotica* (Cruciferae). This biennial herbaceous plant is widely cultivated in China and East Asia for the prevention and treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.[5] Therefore, developing convenient methods for the construction of 2,2-disubstituted indolin-3-ones are of considerable interest.[3d,5b,6] In 2008, Ganachaud and co-workers reported the biocatalytic synthesis of **1** by trimerisation of indole.[7a] However, the chemical synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one (**1**) and its derivatives from indoles has been rarely reported up to now.[7b–7c]

Recently, we have developed an novel, operationally simple, and practical biomimetic synthetic method for the trimerization of indoles toward a variety of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives by using TEMPO in air as oxidant with excellent regioselectivity under mild conditions (Scheme 1).[8] However, extensive study in this group revealed several drawbacks: first, substrates with a strong electron-withdrawing group, such as NO_2 and CN, do not lead to the desired products. Consequently, it is difficult to synthesize 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives containing strong electron-withdrawing groups with this method. Second, a high loading of TEMPO is required (0.7 equiv.). Third, a long reaction time of 3 days is needed. Thus, the development of new catalyst systems for the oxidative trimerization of indoles continues to be of interest.

In the last decade, many TEMPO/metal systems have been discovered for using molecular oxygen as an environmentally friendly oxidant for the selective oxidation of alcohols. Copper, among transition metals, is particularly attractive in organic synthesis because of its low price, slight toxicity, and environmentally benign feature.[9] Among the existing TEMPO/metal systems, the TEMPO/copper systems have been well investigated.[10] Inspired by these reports, we envisioned that TEMPO/copper systems could be applied to the oxidative trimeric reaction of indoles. We report herein on the construction of all-carbon quaternary centers at the C2 position of indoles using TEMPO/$CuCl_2$ in air as the oxidants.

Results and discussion

Initially, the trimeric reaction of indole **5a** was studied as a model reaction to examine the suitable reaction conditions (Scheme 2; Table 1). TEMPO itself is an expensive chemical, so it is desirable to be able to decrease the loading of TEMPO by using a copper co-catalyst. Cocatalyst screening experiments with various copper sources indicated that $CuCl_2$ was the best catalyst, which gave trimer **6a** in a moderate yield under the reaction conditions (55%) (Table 1, entry 7). Other copper catalysts such as $CuSO_4{\cdot}5H_2O$, $Cu(OAc)_2$, $Cu(OH)_2$, and Cu_2O were observed to be inferior to $CuCl_2$ (Table 1, entries 1–3 and 5). As can be seen in entries 4 and 6, CuI and $Cu(OTf)_2$ are not useful as a cocatalyst in the oxidative trimerization of **5a**. It is worth noting that the acid additive is critical to the trimeric reaction; the desired product **6a** could not be obtained in the absence of an acid catalyst (entry 8). Thus, different

Received 22 September 2013. Accepted 14 November 2013.

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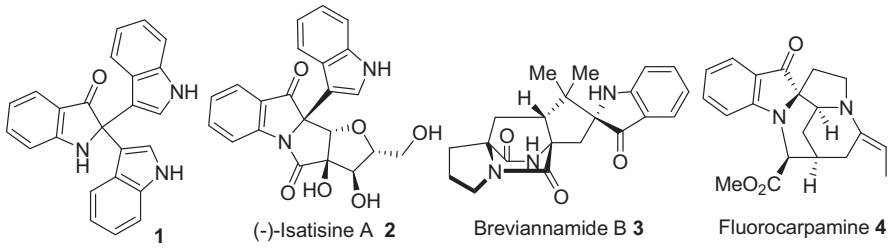
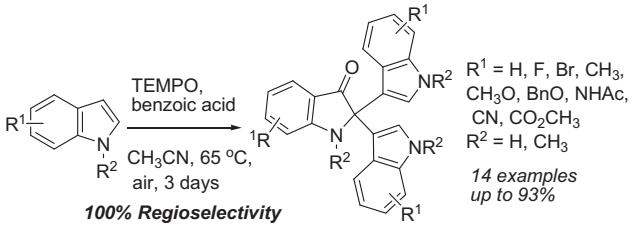
Published at www.nrcresearchpress.com/cjc on 5 December 2013.

Fig. 1. Representative natural products with a 2,2′-disubstituent indolin-3-one structural unit.



Scheme 1. Synthesis of 2,2-disubstituted oxindoles by using TEMPO in air as oxidant.



Scheme 2. Synthesis of **6a**.

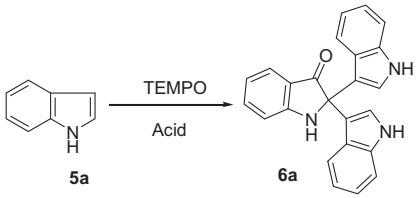


Table 1. Optimization of the reaction conditions.

Entry	Copper catalyst (mmol)	Acid (mmol)	Temperature (°C)	% **6a**[a]
1	$CuSO_4·5H_2O$ (0.1)	Benzoic acid (0.1)	50	35
2	$Cu(OAc)_2$ (0.1)	Benzoic acid (0.1)	50	26
3	$Cu(OH)_2$ (0.1)	Benzoic acid (0.1)	50	20
4	CuI (0.1)	Benzoic acid (0.1)	50	Trace
5	Cu_2O (0.1)	Benzoic acid (0.1)	50	17
6	$Cu(OTf)_2$ (0.1)	Benzoic acid (0.1)	50	Trace
7	$CuCl_2$ (0.1)	Benzoic acid (0.1)	50	55
8	$CuCl_2$ (0.1)		50	Trace
9	$CuCl_2$ (0.1)	Oxalic acid (0.1)	50	33
10	$CuCl_2$ (0.1)	CF_3CO_2H (0.1)	50	Trace
11	$CuCl_2$ (0.1)	HBF_4 (0.1)	50	Trace
12	$CuCl_2$ (0.05)	Benzoic acid (0.1)	50	24
13	$CuCl_2$ (0.15)	Benzoic acid (0.1)	50	62
14	$CuCl_2$ (0.2)	Benzoic acid (0.1)	50	73
15	$CuCl_2$ (0.25)	Benzoic acid (0.1)	50	72
16	$CuCl_2$ (0.3)	Benzoic acid (0.1)	50	70
17	$CuCl_2$ (0.2)	Benzoic acid (0.15)	50	76
18	$CuCl_2$ (0.2)	Benzoic acid (0.2)	50	79
19	$CuCl_2$ (0.2)	Benzoic acid (0.25)	50	78
20	$CuCl_2$ (0.2)	Benzoic acid (0.2)	40	67
21	$CuCl_2$ (0.2)	Benzoic acid (0.2)	25	Trace
22	$CuCl_2$ (0.2)	Benzoic acid (0.2)	60	83
23	$CuCl_2$ (0.2)	Benzoic acid (0.2)	70	75
24	$CuCl_2$ (0.2)	Benzoic acid (0.2)	80	63

Note: Reaction conditions: indole (0.5 mmol), TEMPO (0.1 mmol), and CH_3CN (0.6 mL) for 6 h.

[a]Isolated yield.

acid additives were screened to improve the yield. Benzoic acid was found to be the best choice for the oxidative trimeric reaction of **5a**, since other acid additives such as oxalic acid are not as effective as benzoic acid under similar reaction conditions (Table 1, entry 9). Stronger Brønsted acids, CF_3CO_2H and HBF_4, were ineffective for this transformation (Table 1, entries 10 and 11).

With respect to the loading of $CuCl_2$, it was also established that 40 mol% of $CuCl_2$ was indeed the preferred amount with lower or higher loading giving poor yields (Table 1, entries 12–16). Similarly, when 40 mol% of benzoic acid was used, the desired **6a** was obtained in good yield (Table 1, entry 18). The reaction temperature also had great influence on the reaction. When the reaction was treated at 25 °C, trace amounts of **6a** were obtained (Table 1, entry 21). When the reaction mixture was warmed to 60 °C, the desired product was formed in 83% yield (Table 1, entry 22). A higher temperature (80 °C) led to a significant decreased yield possibly due to other side reactions (Table 1, entry 24). After a great deal of screening on different parameters, we found that the oxidative trimeric reaction of indole by using TEMPO (20 mol%) as an oxidant, $CuCl_2$ (40 mol%) as a cocatalyst, and benzoic acid (40 mol%) as an acid in CH_3CN at 60 °C led to the highest efficiency (83% yield) (Table 1, entry 22).

The scope of the protocol was further tested after the optimal reaction conditions were established. A variety of representative indole derivatives were subjected to the optimized conditions, as depicted in Scheme 3 and Table 2. Thus, a trimeric reaction of substituted indoles proceeded smoothly to provide the corresponding 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives in moderate to excellent yields. The reaction can tolerate a variety of functional groups at the 1, 4, 5, 6, and 7 positions of indoles, such as F, Cl, Br, CH_3, CH_2CH_3, CH_3O, BnO, CO_2CH_3, CN, and NO_2, providing opportunities for further synthetic elaboration.

The scope of the indole counterpart in this reaction has also been evaluated. Indoles with electron-donating groups or electron-withdrawing groups on C-5, C-6, C-7, and C-4 all worked well under the present reaction conditions. In contrast, indole with OCH_3 on C-4 gave relatively low product yield (Table 2, entry 17). We were delighted to note that the substrates with strongly electron-withdrawing groups, such as NO_2 or CN, smoothly underwent the reaction to afford the corresponding products in moderate yields. For example, 5-nitro-1*H*-indole was transformed into trimer **6j** in 55% yield (Table 2, entry 9). In our previous work on the oxidative trimeric reaction of indoles,[8] the efficiency of this transformation is highly dependent upon the electronic properties of R^1 groups. Electron-rich groups showed better results than electron-withdrawing groups in this trimerization. In contrast, the strongly electron-withdrawing group NO_2 totally inhibited the process.

With the promising results for the oxidative dimer of indoles, we further explored the possibility of extending the reaction to the more challenging 2-substituted indoles, and the results are summarized in Scheme 4 and Table 3. In general, the TEMPO/$CuCl_2$ system displayed higher catalytic activity than when TEMPO alone was used. It was interesting to find that 2-substituted indoles with electron-donating groups, such as 2-methyl-1*H*-indole, 2-phenyl-1*H*-indole, 1-methyl-2-methyl-1*H*-indole, 1-butyl-2-phenyl-1*H*-indole, and 1-methyl-2-phenyl-1*H*-indole, all reacted very well under the present reaction conditions. However, much lower yields were obtained in the case of methyl 1*H*-indole-2-carboxylate and methyl 5-chloro-1*H*-indole-2-carboxylate (Table 3, entries 4

Scheme 3. Synthesis of **6a–6s**.

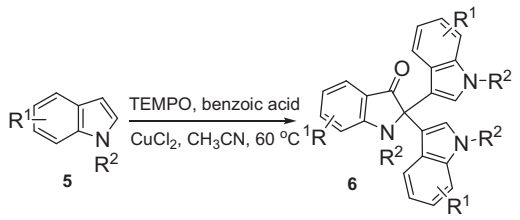


Table 2. Trimeric reaction of indoles by using TEMPO/$CuCl_2$ in air.

Entry	R^1	R^2	Time (h)	Product	Yield (%)[a]
1	H	H	6	**6a**	83
2	5-Br	H	6	**6b**	83
3	5-F	H	6	**6c**	75
4	5-CH_3	H	6	**6d**	76
5	5-OCH_3	H	6	**6e**	74
6	5-OBn	H	6	**6f**	70
7	5-NHAc	H	6	**6g**	93
8	5-CO_2CH_3	H	10	**6h**	69
9	5-NO_2	H	24	**6i**	55
10	5-CN	H	25	**6j**	52
11	6-Cl	H	6	**6k**	80
12	6-F	H	6	**6l**	73
13	6-CO_2CH_3	H	10	**6m**	65
14	7-CH_3	H	6	**6n**	79
15	7-OCH_3	H	6	**6o**	70
16	7-NO_2	H	24	**6p**	41
17	4-OCH_3	H	10	**6q**	62
18	H	CH_3	6	**6r**	68
19	H	C_2H_5	6	**6s**	66

Note: Reaction conditions: indole (0.5 mmol), TEMPO (0.1 mmol), $CuCl_2$ (0.2 mmol), benzoic acid (0.2 mmol), and CH_3CN (0.6 mL).
[a]Isolated yield.

Scheme 4. Synthesis of **7a–7j**.

Table 3. Dimeric reaction of 2-substituted indoles by using TEMPO in air.

Entry	R^1	R^2	R^3	Time (h)	Temperature (°C)	Product	Yield (%)[a]
1	H	H	CH_3	6	25	**7a**	90 (30)
2	H	H	Ph	6	25	**7b**	92 (23)
3	H	CH_3	Ph	6	25	**7c**	65 (15)
4	H	H	CO_2Et	72	120	**7d**	43 (13)
5	5-Cl	H	CO_2Et	72	120	**7e**	36 (10)
6	5-CH_3	H	CH_3	6	25	**7f**	80 (31)
7	H	CH_3	CH_3	24	25	**7g**	89 (61)
8	H	*n*-Bu	Ph	24	65	**7h**	70 (48)
9	H	Boc	CH_3	72	120	**7i**	Trace (0)
10	H	Boc	Ph	72	120	**7j**	Trace (0)

Note: Reaction conditions: indole (0.5 mmol), TEMPO (0.1 mmol), $CuCl_2$ (0.2 mmol), benzoic acid (0.2 mmol), and CH_3CN (0.6 mL). Boc, *tert*-butoxycarbonyl.
[a]Isolated yield. The yield in parentheses was obtained under the conditions of indole (0.5 mmol)/TEMPO (0.35 mmol)/benzoic acid (0.25 mmol)/CH_3CN (0.6 mL).

and 5). Interestingly, we observed that indoles with electron-withdrawing substituents at the 1 positions of indoles, such as *tert*-butoxycarbonyl, could not provide the corresponding products and the starting materials were completely recovered (Table 3, entries 9 and 10).

Conclusions

In summary, we have developed an operationally simple and efficient method to construct all-carbon quaternary centers at the C2 position of indoles via a copper-catalyzed oxidative trimeric reaction of indoles. These precursors offer distinct advantages in substrate scope, TEMPO loading, and reaction time over previously reported methods. It is noteworthy that the substrates with a strongly electron-withdrawing group, such as NO_2 or CN, smoothly underwent the reaction to afford the corresponding products in moderate yields. Moreover, it is highly regioselective (2,3′ linkage). Importantly, the broad group tolerance, less expensive metal catalyst, and aerobic reaction conditions made this method useful to construct such unique scaffolds from commercially available indole and its derivatives.

Experimental section

General comments

Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively. Chemical shifts were reported in parts per million relative to TMS for ^{1}H and ^{13}C NMR spectra. $CDCl_3$ or DMSO-d_6 was used as the NMR solvent. Mass spectra were recorded with Bruker Dalton Esquire 3000 plus LC-MS apparatus. Elemental analyses were carried out on a Perkin-Elmer 240B instrument. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate – petroleum ether (PE) (60–90 °C) mixture.

General procedure for the preparation of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-ones

To a solution of indole (0.5 mmol), TEMPO (0.1 mmol) and $CuCl_2$ (0.2 mmol) in CH_3CN (0.6 mL) was added benzoic acid (0.2 mmol) under atmosphere and the mixture was stirred at 25–120 °C for 6–72 h (monitored by TLC). The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent EtOAc–PE = 1:2) to yield the corresponding product.

5,5′-Dinitro-2-(5-nitro-1H-indol-3-yl)-2,3′-biindolin-3-one (6i)

Yellow solid, mp 214–216 °C (from EtOAc–PE = 1:2). IR (KBr) ν_{max}: 3388, 1621, 1332 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.00 (s, 1H, NH), 11.99 (s, 1H, NH), 9.98 (s, 1H, NH), 8.42 (dd, *J* = 9.1, 2.4 Hz, 1H, Ar-H), 8.37 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.22 (d, *J* = 2.2 Hz, 2H, Ar-H), 7.98 (dd, *J* = 9.0, 2.2 Hz, 2H, Ar-H), 7.62 (d, *J* = 2.4 Hz, 2H, Ar-H), 7.59 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.12 (d, *J* = 9.1 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 198.6, 162.9, 141.0, 140.7, 138.8, 133.7, 128.4, 124.7, 122.8, 117.5, 117.4, 116.7, 115.1, 113.1, 112.3, 68.9. MS (ESI): 499 (M+H$^+$, 100), 521 (M+Na$^+$, 25). Anal. calcd. for $C_{24}H_{14}N_6O_7$: C 57.84, H 2.83, N 16.86; found: C 57.52, H 3.17, N 16.49.

2-(5-Cyano-1H-indol-3-yl)-3-oxo-2,3′-biindoline-5,5′-dicarbonitrile (6j)

Yellow amorphous solid. IR (KBr) ν_{max}: 3415, 2223, 1626, 1119 cm^{-1}. ^{1}H NMR (100 MHz, DMSO-d_6) δ: 11.80 (s, 2H, NH), 9.44 (s, 1H, NH), 8.03 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.87 (dd, *J* = 8.6, 1.6 Hz, 1H, Ar-H), 7.63 (d, *J* = 1.6 Hz, 2H, Ar-H), 7.57 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.47 (s, 1H, Ar-H), 7.46 (s, 1H, Ar-H), 7.42 (dd, *J* = 8.5, 1.6 Hz, 2H, Ar-H), 7.07 (d, *J* = 8.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 198.5, 161.7, 141.0, 139.3, 131.3, 127.1, 125.8, 125.4, 124.6, 121.0, 119.7, 117.5,

113.9, 113.8, 113.0, 101.4, 99.4, 67.9. MS (ESI): 439 ($M+H^+$, 100). Anal. calcd. for $C_{27}H_{14}N_6O$: C 73.96, H 3.22, N 19.17; found: C 73.63, H 3.49, N 18.84.

6,6′-Dichloro-2-(6-chloro-1H-indol-3-yl)-2,3′-biindolin-3-one (6k)

Yellow solid, mp 197–199 °C (from EtOAc–PE = 1:2). IR (KBr) ν_{max}: 3412, 1668, 1611, 1452, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.43 (s, 2H, NH), 8.50 (s, 1H, NH), 7.66 (d, J = 7.6 Hz, 1H, Ar-H), 7.57 (d, J = 7.6 Hz, 1H, Ar-H), 7.31 (d, J = 8.0 Hz, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.18 (d, J = 7.6 Hz, 2H, Ar-H), 6.94 (t, J = 8.0 Hz, 2H, Ar-H), 6.89 (t, J = 7.6 Hz, 1H, Ar-H), 5.60 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.5, 161.1, 142.9, 137.8, 126.8, 126.5, 125.6, 124.6, 122.0, 119.4, 118.1, 116.7, 114.1, 111.8, 111.5, 68.2. MS (ESI): 466 ($M+H^+$, 100), 468 ($M+H^+$, 100), 470 ($M+H^+$, 30). Anal. calcd. for $C_{24}H_{14}Cl_3N_3O_1$: C 61.76, H 3.02, N 9.00; found: C 62.08, H 2.84, N 8.75.

7,7′-Dimethoxy-2-(7-methoxy-1H-indol-3-yl)-2,3′-biindolin-3-one (6o)

Yellow solid, mp 209–210 °C (from EtOAc–PE = 1:2). IR (KBr) ν_{max}: 3406, 1660, 1615, 1452, 1116, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30 (s, 2H, NH), 7.37 (d, J = 7.8 Hz, 1H, Ar-H), 7.16 (s, 1H, Ar-H), 7.15 (s, 1H, Ar-H), 7.05 (d, J = 8.1 Hz, 2H, Ar-H), 6.99 (d, J = 7.8 Hz, 1H, Ar-H), 6.92 (t, J = 8.1 Hz, 2H, Ar-H), 6.86 (t, J = 7.8 Hz, 1H, Ar-H), 6.62 (d, J = 7.8 Hz, 2H, Ar-H), 5.58 (s, 1H, NH), 3.95 (s, 6H, 2 × OCH_3), 3.88 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.0, 151.9, 146.7, 146.2, 127.6, 127.1, 123.5, 120.6, 120.2, 119.3, 116.7, 115.8, 115.7, 113.3, 102.0, 68.6, 55.4, 55.3. MS (ESI): 454 ($M+H^+$, 100). Anal. calcd. for $C_{27}H_{23}N_3O_4$: C 71.51, H 5.11, N 9.27; found: C 71.43, H 5.30, N 8.92.

7,7′-Dinitro-2-(7-nitro-1H-indol-3-yl)-2,3′-biindolin-3-one (6p)

Yellow solid, mp 302–305 °C (from EtOAc–PE = 1:2). IR (KBr) ν_{max}: 3411, 1630, 1513, 1478, 1309 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 2H, NH), 8.47 (dd, J = 7.5, 2.2 Hz, 1H, Ar-H), 8.19 (d, J = 8.0 Hz, 2H, Ar-H), 8.08 (d, J = 7.5 Hz, 1H, Ar-H), 7.92 (s, 1H, NH), 7.76 (d, J = 8.0, Hz, 2H, Ar-H), 7.47 (d, J = 2.2 Hz, 2H, Ar-H), 7.15 (t, J = 8.0 Hz, 2H, Ar-H), 7.05 (t, J = 7.5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 152.0, 133.4, 133.0, 131.9, 130.5, 128.7, 128.5, 126.1, 126.0, 122.9, 120.1, 120.0, 118.5, 115.0, 67.7. MS (ESI): 499 ($M+H^+$, 100), 521 ($M+Na^+$, 20). Anal. calcd. for $C_{24}H_{14}N_6O_7$: C 57.84, H 2.83, N 16.86; found: C 60.03, H 2.52, N 16.67.

1,1′-Diethyl-2-(1-ethyl-1H-indol-3-yl)-2,3′-biindolin-3-one (6s)

Yellow solid, mp 238–241 °C (from EtOAc–PE = 1:2). IR (KBr) ν_{max}: 3413, 1699, 1609, 1486, 1463, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 7.4 Hz, 1H, Ar-H), 7.56 (dt, J = 8.3, 1.2 Hz, 1H, Ar-H), 7.35 (t, J = 7.9 Hz, 4H, Ar-H), 7.18 (t, J = 7.9 Hz, 2H, Ar-H), 7.06 (s, 2H, Ar-H), 6.97 (t, J = 7.4 Hz, 2H, Ar-H), 6.86 (d, J = 8.3 Hz, 1H, Ar-H), 6.76 (t, J = 7.4 Hz, 1H, Ar-H), 4.13 (q, J = 7.3 Hz, 4H, 2 × CH_2), 3.59 (q, J = 7.1 Hz, 2H, CH_2), 1.43 (t, J = 7.3 Hz, 6H, 2 × CH_3), 0.67 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.7, 158.7, 137.5, 136.7, 128.2, 126.6, 125.9, 121.8, 121.5, 119.2, 118.7, 116.4, 111.9, 109.3, 108.0, 72.7, 41.0, 38.2, 15.5, 13.3. MS (ESI): 448 ($M+H^+$, 100). Anal. calcd. for $C_{30}H_{29}N_3O$: C 80.51, H 6.53, N 9.39; found: C 80.17, H 6.74, N 9.25.

2,2′-Dimethyl-2,3′-biindolin-3-one (7a)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3425, 1672, 1614, 1117 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.99 (s, 1H, NH), 7.72 (d, J = 7.7 Hz, 1H, Ar-H), 7.53 (dt, J = 1.0, 8.5 Hz, 1H, Ar-H), 7.38 (d, J = 8.1 Hz, 1H, Ar-H), 7.24 (d, J = 8.1 Hz, 1H, Ar-H), 7.07 (dt, J = 1.0, 8.1 Hz, 1H, Ar-H), 6.96 (dt, J = 1.0, 8.1 Hz, 1H, Ar-H), 6.89 (t, J = 7.7 Hz, 1H, Ar-H), 6.88 (d, J = 8.5 Hz, 1H, Ar-H), 5.30–4.80 (s, 1H, NH), 2.36 (s, 3H, CH_3), 1.93 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 204.2, 159.5, 137.4, 134.9, 132.5, 127.5, 125.3, 121.3, 119.8, 119.7, 119.5, 119.1, 112.4, 110.4, 109.6, 67.1, 29.7, 25.1. MS (ESI): 277 ($M+H^+$, 100). Anal. calcd. for $C_{18}H_{16}N_2O$: C 78.24, H 5.84, N 10.14; found: C 77.95, H 6.02, N 9.87.

2,2′-Diphenyl-2,3′-biindolin-3-one (7b)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3427, 3312, 1673, 1610, 1151, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.36 (s, 1H, NH), 8.35 (s, 1H, NH), 7.51 (dt, J = 8.1, 1.0 Hz, 1H, Ar-H), 7.38 (m, 2H, Ar-H), 7.34 (d, J = 8.1 Hz, 1H, Ar-H), 7.25 (d, J = 7.6 Hz, 1H, Ar-H), 7.15 (m, 3H, Ar-H), 7.05 (m, 6H, Ar-H), 6.98 (d, J = 8.1 Hz, 1H, Ar-H), 6.76 (t, J = 7.6 Hz, 1H, Ar-H), 6.71 (t, J = 7.6 Hz, 1H, Ar-H), 6.61 (d, J = 8.1 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 200.9, 160.5, 140.3, 138.4, 137.9, 136.2, 133.6, 130.0, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 124.8, 121.6, 120.8, 119.1, 119.0, 117.9, 112.4, 111.7, 111.5, 71.6. MS (ESI): 401 ($M+H^+$, 100). Anal. calcd. for $C_{28}H_{20}N_2O$: C 83.98, H 5.03, N 7.00; found: C 84.05, H 4.72, N 6.81.

1,1′-Dimethyl-2,2′-diphenyl-2,3′-biindolin-3-one (7c)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3440, 1616, 1123 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42 (dt, J = 1.3, 8.4 Hz, 2H, Ar-H), 7.35 (d, J = 8.2 Hz, 2H, Ar-H), 7.31–7.25 (s, 4H, Ar-H), 7.24–7.18 (s, 3H, Ar-H), 7.13 (d, J = 7.2 Hz, 1H, Ar-H), 6.93 (dt, J = 1.3, 7.6 Hz, 1H, Ar-H), 6.91 (dt, J = 1.3, 7.2 Hz, 1H, Ar-H), 6.82 (d, J = 7.6 Hz, 1H, Ar-H), 6.65 (d, J = 8.2 Hz, 1H, Ar-H), 6.58 (d, J = 8.4 Hz, 1H, Ar-H), 6.55 (t, J = 7.2 Hz, 1H, Ar-H), 3.47 (s, 3H, CH_3), 2.80 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.1, 159.4, 140.0, 138.5, 137.2, 136.9, 131.4, 131.3, 130.7, 128.3, 128.2, 127.7, 127.6, 126.9, 125.2, 121.9, 121.5, 119.5, 119.4, 116.4, 109.8, 109.4, 107.7, 76.2, 30.5, 29.6. MS (ESI): 429 ($M+H^+$, 100). Anal. calcd. for $C_{30}H_{24}N_2O$: C 84.08, H 5.65, N 6.54; found: C 83.87, H 5.96, N 6.25.

Diethyl 3-oxo-2,3′-biindoline-2,2′-dicarboxylate (7d)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3416, 1728, 1688, 1612, 1264, 1143 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.10 (s, 1H, NH), 7.79 (d, J = 7.5 Hz, 1H, Ar-H), 7.52 (t, J = 8.6 Hz, 1H, Ar-H), 7.49 (d, J = 8.6 Hz, 1H, Ar-H), 7.39 (d, J = 8.3 Hz, 1H, Ar-H), 7.28 (t, J = 7.4 Hz, 1H, Ar-H), 7.05 (t, J = 7.4 Hz, 1H, Ar-H), 6.96 (d, J = 8.3 Hz, 1H, Ar-H), 6.95 (t, J = 7.4 Hz, 1H, Ar-H), 5.98 (s, 1H, NH), 4.35 (q, J = 7.1 Hz, 2H, OCH_2), 4.25 (q, J = 7.1 Hz, 2H, OCH_2), 1.38 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 168.2, 161.9, 138.0, 135.7, 130.1, 128.4, 125.7, 125.5, 125.4, 125.3, 122.3, 121.2, 120.0, 119.9, 113.1, 112.0, 72.8, 62.8, 61.5, 14.3, 13.9. MS (ESI): 393 ($M+H^+$, 100). Anal. calcd. for $C_{22}H_{20}N_2O_5$: C 67.34, H 5.14, N 7.14; found: C 67.68, H 4.83, N 6.91.

Diethyl 5,5′-dichloro-3-oxo-2,3′-biindoline-2,2′-dicarboxylate (7e)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3428, 1725, 1705, 1615, 1252, 1139 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 12.38 (s, 1H, NH), 8.27 (s, 1H, NH), 7.64 (d, J = 2.2 Hz, 1H, Ar-H), 7.55 (dd, J = 8.8, 2.2 Hz, 1H, Ar-H), 7.50 (d, J = 8.8 Hz, 1H, Ar-H), 7.26 (dd, J = 8.8, 3.0 Hz, 1H, Ar-H), 7.21 (d, J = 3.0 Hz, 1H, Ar-H), 7.02 (d, J = 8.8 Hz, 1H, Ar-H), 4.30 (q, J = 7.1 Hz, 2H, OCH_2), 4.08 (q, J = 7.1 Hz, 2H, OCH_2), 1.30 (t, J = 7.1 Hz, 3H, CH_3), 1.07 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 194.4, 167.6, 161.3, 161.2, 138.5, 134.7, 127.8, 125.9, 125.3, 125.2, 123.9, 122.7, 120.5, 119.2, 115.2, 114.9, 114.7, 73.5, 62.3, 61.6, 14.5, 14.2. MS (ESI): 461 ($M+H^+$, 100), 463 ($M+H^+$, 60). Anal. calcd. for $C_{22}H_{18}Cl_2N_2O_5$: C 57.28, H 3.93, N 6.07; found: C 56.96, H 4.11, N 5.79.

2,2′,5,5′-Tetramethyl-2,3′-biindolin-3-one (7f)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 3260, 1688, 1625, 1499 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.73 (s, 1H, NH), 7.45 (s, 1H, NH), 7.33 (d, J = 8.4 Hz, 1H, Ar-H), 7.24 (s, 1H, Ar-H), 7.11 (s, 1H, Ar-H), 7.09 (d, J = 8.4 Hz, 1H, Ar-H), 6.81 (d, J = 8.3 Hz, 1H, Ar-H), 6.76 (d, J = 8.3 Hz, 1H, Ar-H), 2.32 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 1.72 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 204.4, 159.0, 139.2, 133.6, 133.2, 128.0, 126.8, 126.2, 124.0, 121.8, 120.0, 118.3, 112.3, 110.6, 108.7, 67.1, 25.1, 22.1, 20.6, 14.4. MS (ESI): 305 ($M+H^+$, 100). Anal. calcd. for $C_{22}H_{20}N_2O$: C 78.92, H 6.62, N 9.20; found: C 78.57, H 6.95, N 8.90.

1,1′,2,2′-Tetramethyl-2,3′-biindolin-3-one (7g)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 1692, 1613, 1319 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (dd, J = 1.4, 7.2 Hz, 1H, Ar-H), 7.55 (dt, J = 1.4, 8.1 Hz, 1H, Ar-H), 7.47 (t, J = 7.8 Hz, 1H, Ar-H), 7.26 (d, J = 8.1 Hz, 1H, Ar-H), 7.14 (dt, J = 1.0, 8.1 Hz, 1H, Ar-H), 7.00 (dt, J = 1.0, 8.1 Hz, 1H, Ar-H), 6.80 (d, J = 7.8 Hz, 1H, Ar-H), 6.77 (t, J = 7.2 Hz, 1H, Ar-H), 3.64 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.92 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.9, 158.9, 137.8, 136.8, 135.7, 130.2, 128.5, 125.5, 120.7, 119.6, 119.5, 118.3, 116.8, 109.0, 108.1, 71.2, 29.5, 27.8, 22.0, 11.9. MS (ESI): 305 (M+H$^+$, 100). Anal. calcd. for $C_{22}H_{20}N_2O$: C 78.92, H 6.62, N 9.20; found: C 78.63, H 6.86, N 8.87.

1,1′-Dibutyl-2,2′-diphenyl-2,3′-biindolin-3-one (7h)

Straw yellow amorphous solid. IR (KBr) ν_{max}: 1708, 1613, 1488, 1462, 744 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (s, 1H, Ar-H), 7.44 (t, J = 7.5 Hz, 1H, Ar-H), 7.40 (d, J = 8.1 Hz, 1H, Ar-H), 7.36–7.25 (m, 8H, Ar-H), 7.16 (d, J = 7.5 Hz, 1H, Ar-H), 6.97 (d, J = 7.5 Hz, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.92 (t, J = 7.5 Hz, 1H, Ar-H), 6.75 (d, J = 8.1 Hz, 1H, Ar-H), 6.59 (d, J = 8.4 Hz, 1H, Ar-H), 6.57 (t, J = 7.5 Hz, 1H, Ar-H), 3.93 (dt, J = 2.6, 8.6 Hz, 2H, Ar-H), 3.46 (dt, J = 4.9, 11.1 Hz, 1H, Ar-H), 3.14 (dt, J = 4.9, 11.1 Hz, 1H, Ar-H), 1.65–1.55 (m, 2H, Ar-H), 1.20–1.10 (m, 3H, Ar-H), 1.08–0.90 (m, 3H, Ar-H), 0.79 (t, J = 7.2 Hz, 3H, CH_3), 0.58 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.6, 158.4, 139.1, 139.0, 137.0, 136.1, 131.7, 131.6, 130.7, 129.1, 128.3, 127.7, 127.6, 127.5, 126.9, 125.4, 122.1, 121.4, 119.3, 116.1, 110.5, 109.8, 107.9, 76.4, 44.1, 43.5, 32.1, 29.6, 20.2, 20.0, 13.7, 13.4. MS (ESI): 513 (M+H$^+$, 100). Anal. calcd. for $C_{36}H_{36}N_2O$: C 84.34, H 7.08, N 5.46; found: C 84.26, H 6.97, N 5.25.

Supplementary material

Supplementary material is available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0435.

Acknowledgements

The authors are grateful to the National Science Foundation of China (Nos. 21162001 and 21202023), the National Key Technology R&D Program of China (No. 2009BAI78B01), Jiangxi Province Key Support Program (No. 2009BNB06200), Natural Science Foundation of Jiangxi Province (No. 20132BAB203007), and Jiangxi Province Office of Education Support Program (No. GJJ13666) for financial support.

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