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Synthesis of 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione derivatives by cyclization of 3-alkylideneoxindoles with enaminone

Peng Hui Yang

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Abstract The reaction between 3-alkylideneoxindoles **1** and 3-aminocyclohex-2-enone **2** was studied, and an efficient synthesis of 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione derivatives was developed by a sequential Michael addition followed by intramolecular condensation catalyzed by nickel dichloride hexahydrate. The reaction mechanism is discussed.

Keywords Biindoles · 3-Alkylideneoxindoles · Synthesis

Introduction

Biindoles are the core structure of many naturally occurring alkaloids and have important biological activities including antioxidation activity [1], plant growth-promoting activity [2], protein kinase C inhibiting activity [3, 4], etc. Among these, the anticancer activity is the most notable [5, 6]. Therefore, they are the research targets for many organic and pharmaceutical chemists [7–10].

3-Alkylideneoxindoles are readily available building blocks for construction of various heterocycles. They are usually attacked by nucleophiles on exocyclic double bond. Spanish scientists reported controlled generation of three contiguous stereocenters in the Michael addition of 1-pyrrolidinocyclohexene to *N*-methyl-3-phenacylideneoxindole [11]; Bergman and colleague [12] reported efficient synthesis of highly substituted pyrrole by the reaction between 3-aminocrotonates and 3-acetonylideneoxindole in refluxing toluene; More recently, Perumal and colleague [13] reported an $InCl_3$-catalyzed one-pot synthesis of 2-pyrrolo-3′-yloxindoles via three-component reaction of 3-phenacylideneoxindole, β-keto ester, and ammonium acetate at reflux in ethanol.

P. H. Yang (✉)
College of Chemistry and Chemical Engineering, Xi'an Shiyou University, Xi'an 710065, China
e-mail: yaph2001@iccas.ac.cn

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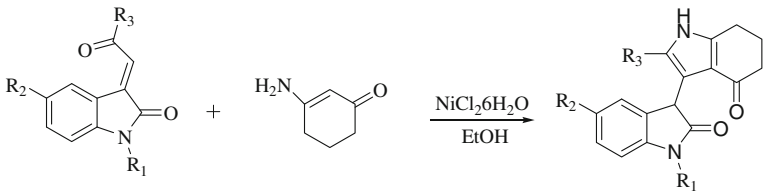


Scheme 1 Synthesis of 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione derivatives

As a continuation of our program on the development of new methodologies for preparation of biologically active heterocycles, we developed an efficient synthesis of hereto-unknown 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione derivatives by cyclization of 3-alkylideneoxindole **1** with 3-aminocyclohex-2-enone **2** catalyzed by nickel dichloride hexahydrate (Scheme 1).

Results and discussion

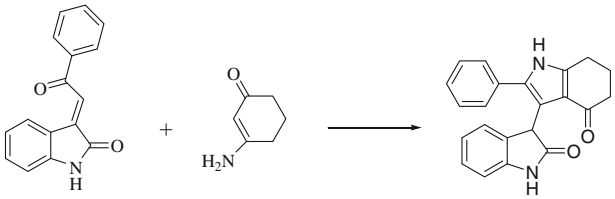
To optimize the reaction conditions, we first examined the reaction between 3-alkylideneoxindole **1a** and 3-aminocyclohex-2-enone **2**. When 3-alkylideneoxindole **1a** and 3-aminocyclohex-2-enone were heated in ethanol, the expected 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione **3a** was formed in 66.8 % yield after 60 h of reflux. Higher reaction temperature when using high-boiling-point solvents such as *n*-butanol caused decreased yields due to side-reactions. Perumal reported that $InCl_3$ was an efficient catalyst for this type of reaction, but $InCl_3$ is expensive and moisture sensitive. We tried to find a cheap and stable catalyst. After several trials, we found that nickel dichloride hexahydrate was suitable for the reaction. As can be seen from Table 1, the reaction of **1a** and 3-aminocyclohex-2-enone **2** catalyzed by nickel dichloride hexahydrate in refluxing ethanol afforded the expected 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione in 80.7 % yield.

Then, the scope and limitations of the reaction involving various 3-alkylideneoxindoles **1** and 3-aminocyclohex-2-enone **2** were explored. The results are presented in Table 2. It can be seen from Table 2 that 3-alkylideneoxindoles with various substituents were all good substrates for the reaction. When substituent R_3 was phenyl, the reaction yield was high, while when R_3 was methyl, the reaction yield was relatively low.

The proton nuclear magnetic resonance (NMR) spectrum of the products seemed to be complex because two sets of signals were observed due to the keto–enol tautomerization. However, the proton signals from different tautomers could be distinguished after careful study. The ratio of keto to enol varied for different compounds as indicated in Table 2.

The proposed mechanism of the reaction is shown in Scheme 2. 3-Aminocyclohex-2-enone **2** behaved as a 1,3-dinucleophile when reacted with 3-alkylideneoxindole. The reaction started with 3-aminocyclohex-2-enone **2** attacking the 3-alkylideneoxindole **1a** at the exocyclic methylene carbon via Michael addition

Table 1 Optimization of reaction conditions



1a **2** **3a**

Entry	Product	Catalyst	Solvent	Time (h)	Yield (%)
1	**3a**	None	EtOH	60	66.8
2	**3a**	None	Toluene	30	60.9
3	**3a**	None	*n*-Butanol	30	18.7
4	**3a**	$B(OH)_3$	EtOH	72	80.1
5	**3a**	$B(OH)_3$	Toluene	24	65.8
6	**3a**	$NiCl_26H_2O$	EtOH	60	80.7
7	**3a**	$CuCl_22H_2O$	EtOH	60	Messy

Table 2 1,3,1′,5′,6′,7′-Hexahydro-3,3′-biindolyl-2,4′-dione **3**

Entry	Product (keto:enol)[a]	R_1	R_2	R_3	Yield[b] (%)
1	**3a** (4:1)	H	H	C_6H_5	80.7
2	**3b** (3:1)	H	Me	C_6H_5	82.0
3	**3c** (4:1)	Me	H	C_6H_5	84.3
4	**3d** (3:1)	Et	H	C_6H_5	78.4
5	**3e** (4:5)	H	H	Me	66.2
6	**3f** (2:3)	H	Me	Me	65.1
7	**3g** (3:2)	Me	H	Me	69.5

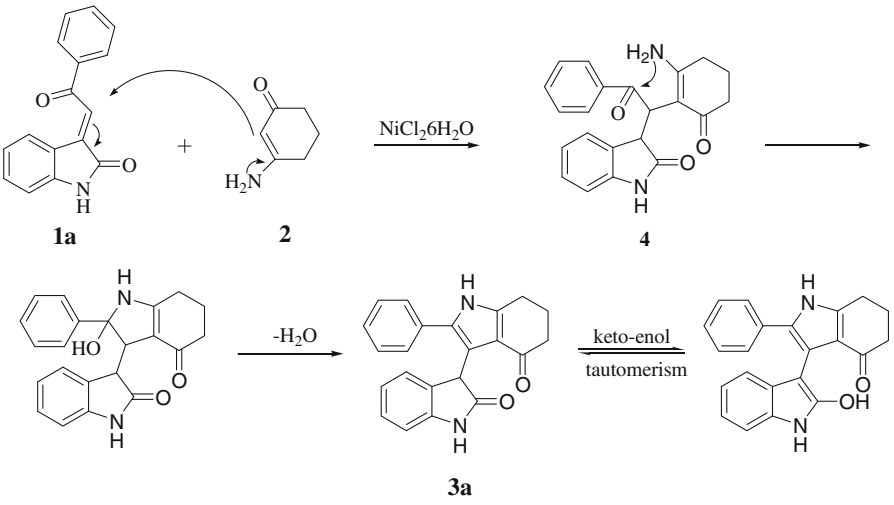
[a] Ratio obtained from ^{1}H nuclear magnetic resonance (NMR) analysis of the NH protons

[b] Isolated yield

to give the intermediate **4**. The intermediate **4** underwent ring closure followed by elimination of one molecule of water to afford the 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione **3a**.

Conclusions

The reaction between 3-alkylideneoxindoles **1** and 3-aminocyclohex-2-enone **2** was studied, and an efficient synthesis of 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione derivatives was developed by a sequential Michael addition followed by intramolecular condensation catalyzed by nickel dichloride hexahydrate. The reaction mechanism was discussed.



Scheme 2 The proposed mechanism

Experimental

Melting points were uncorrected and determined on a WRS-1A digital melting-point apparatus. ^{1}H NMR spectra were recorded on an INOVA-400 using tetramethylsilane (TMS) as internal reference. Elemental analysis was recorded on a VarioEL III elemental analysis device. All reagents and solvents were obtained from commercial sources and were used without purification.

General procedure for preparing 1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione **3a–h**

To a mixture of 3-alkylideneoxindole **1** (1.0 eq.) and 3-aminocyclohex-2-enone **2** (1.2 eq.) in 25 mL of anhydrous EtOH was added nickel dichloride hexahydrate (0.3 eq.). Then the mixture was stirred and refluxed for 40–82 h. The mixture was cooled to room temperature. The precipitated product was collected by filtration, or the mixture was poured into water and extracted with ethyl acetate. The extracts were dried and evaporated, and the residue was crystallized to give the pure products.

2′-Phenyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3a***

M.p. >290 °C; ^{1}H NMR (DMSO-d^6) δ: 11.70 (s, 1H), 10.27 (s, 1H), 7.46–7.52 (m, 3H), 7.35–7.37 (m, 1H), 7.08–7.12 (m, 2H), 6.78–6.79 (m, 3H), 4.52 (s, 1H), 2.77 (s, 2H), 2.09 (s, 2H), 1.94 (s, 2H). Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18 %. Found: C, 76.82; H, 5.14; N, 7.90 %.

5-Methyl-2′-phenyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3b***

M.p. 253–255 °C; ^{1}H NMR (DMSO-d^6) δ: 11.70 (s, 1H), 10.17 (s, 1H), 7.47–7.55 (m, 3H), 7.37 (t, 1H, $J = 6.4$ Hz), 7.14 (d, 1H, $J = 4.8$ Hz), 6.90 (d, 1H, $J = 8.0$ Hz), 6.65–6.74 (m, 2H), 4.51 (s, 1H), 2.80 (t, 2H, $J = 5.2$ Hz), 2.16 (s, 3H), 2.11–2.13 (m, 2H), 1.95–1.99 (m, 2H); Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86 %. Found: C, 77.20; H, 5.42; N, 7.59 %.

1-Methyl-2′-phenyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3c***

M.p. 270–272 °C; ^{1}H NMR (DMSO-d^6) δ: 11.73 (s, 1H), 7.37–7.58 (m, 4H), 7.13–7.21 (m, 2H), 6.87–6.99 (m, 3H), 4.62 (s, 1H), 3.15 (s, 3H), 2.78 (t, 2H, $J = 6.0$ Hz), 2.07–2.13 (m, 2H), 1.92–1.96 (m, 2H); Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86 %. Found: C, 77.15; H, 5.48; N, 7.85 %.

1-Ethyl-2′-phenyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3d***

M.p. 269–270 °C; ^{1}H NMR (DMSO-d^6) δ: 11.74 (s, 1H), 7.46–7.56 (m, 3H), 7.37 (t, 1H, $J = 7.2$ Hz), 7.10–7.25 (m, 2H), 6.86–7.03 (m, 3H), 4.58 (s, 1H), 3.71 (q, 2H, $J = 7.2$ Hz), 2.79 (t, 2H, $J = 5.6$ Hz), 2.08–2.13 (m, 2H), 1.93–1.96 (m, 2H), 1.23 (t, 3H, $J = 6.4$ Hz); Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56 %. Found: C, 77.46; H, 5.83; N, 7.22 %.

2′-Methyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3e***

M.p. >290 °C; ^{1}H NMR (DMSO-d^6) δ: 11.10 (s, 1H), 10.44 (s, 1H), 6.67–7.15 (m, 4H), 5.49 (s, 1H), 2.72 (t, 2H, $J = 6.0$ Hz), 2.35 (t, 1H, $J = 6.0$ Hz), 1.99–2.05 (m, 2H), 1.87–1.90 (m, 1H), 1.58 (s, 3H); Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99 %. Found: C, 74.42; H, 5.54; N, 9.66 %.

5,2′-Dimethyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3f***

M.p. >290 °C; ^{1}H NMR (DMSO-d^6) δ: 11.10 (s, 1H), 10.34 (s, 1H), 6.93 (d, 1H, $J = 8.0$ Hz), 6.72 (d, 1H, $J = 8.0$ Hz), 6.68 (s, 1H), 5.45 (s, 1H), 2.72 (t, 2H, $J = 5.2$ Hz), 2.35 (t, 1H, $J = 5.6$ Hz), 2.17 (s, 3H), 2.01–2.05 (m, 2H), 1.86–1.91 (m, 1H), 1.58 (s, 3H); Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52 %. Found: C, 72.99; H, 5.88; N, 9.19 %.

1,2′-Dimethyl-1,3,1′,5′,6′,7′-hexahydro-3,3′-biindolyl-2,4′-dione ***3g***

M.p. 260–262 °C; ^{1}H NMR (DMSO-d^6) δ: 11.16 (s, 1H), 7.16 (t, 1H, $J = 8.0$ Hz), 6.93 (t, 2H, $J = 8.0$ Hz), 6.75 (d, 1H, $J = 8.0$ Hz), 4.54 (s, 1H), 3.14 (s, 3H), 2.65 (t, 2H, $J = 5.2$ Hz), 2.35 (t, 1H, $J = 6.0$ Hz), 2.27 (s, 3H), 1.98–2.07 (m, 2H), 1.85–1.90 (m, 1H); Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52 %. Found: C, 73.02; H, 5.96; N, 9.31 %.

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