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Vinylogous *N*,*N*-dimethylaminomethylenation of 3-[(1-substituted)ethylidene]-oxindoles with *N*,*N*-dimethylformamide dimethylacetal

Hyun Ju Lee [a], Sangku Lee [b], Jin Yu [a], Jae Nyoung Kim [a,*]

[a] Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea
[b] Immune Modulator Research Center, KRIBB, Daejeon 305-806, Republic of Korea

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ABSTRACT

An efficient stereoselective synthesis of various 3-(3-dimethylaminoprop-2-enylidene)oxindoles has been disclosed. The compounds were synthesized via a vinylogous *N*,*N*-dimethylaminomethylenation at the γ-position of 3-[(1-substituted)ethylidene]oxindoles with DMF-DMA.

3-Alkylideneoxindole derivatives have been received much attention due to their diverse biological activities and synthetic applicability.[1–3] Recently, we also reported an efficient synthesis of 3-alkylideneoxindoles via Ti(O^iPr)$_4$/pyridine-mediated Knoevenagel condensation between oxindole and various carbonyl compounds.[4] In addition, the alkylidene moiety of 3-alkylideneoxindoles could be further functionalized to make biologically potent substances.[5,6] As some examples, Michael type C_β-functionalization to β-substituted oxindoles **I**,[5a,b] [3+2] trimethylenemethane cycloaddition to 3,3-spirocyclic compounds **II**,[2h,5c] and Michael/Michael/aldol annulation cascade to spirocycles **III**[5a,b] have been reported as depicted in Scheme 1. Very recently, Casiraghi and co-workers have reported an interesting vinylogous Michael addition to make **IV**[6a,b] and vinylogous Mukaiyama-type aldol reaction to **V**.[6c] The successful γ-functionalization of Casiraghi group could be achieved because of the vinylogous pro-nucleophilic character of the alkyl-group.[6a]

In addition, various 3-aminomethyleneoxindoles have been known to possess many interesting biological activities.[7] However, synthesis and biological activity of a two-carbon increased homolog, 3-(3-aminoprop-2-enylidene)oxindoles, have not been studied much.[8] Muller and co-workers reported the synthesis of 3-(3-aminoprop-2-enylidene)oxindoles via a sequential cyclocarbopalladation, Sonogashira coupling, and Michael addition.[8a,b] Balalaie and co-workers have also reported the synthesis via a sequential one-pot Ugi/Heck carbocyclization, Sonogashira coupling and Michael addition protocol.[8c]

In these contexts, we presumed that 3-(3-dimethylaminoprop-2-enylidene)oxindole **2** (Scheme 1) could be synthesized from 3-[(1-substituted)ethylidene]oxindole and *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA).[9,10] As exemplified with 3-alkylideneoxindole **1a** in Scheme 2, our rationale was based on the fact that the hydrogen of a methyl group of **1a** could be deprotonated easily by a trace amount of methoxide ion, present in small amount in DMF-DMA, to form the dienolate ion **VI**.[6,10] Subsequently, the dienolate **VI** could react with the iminium ion to form **2a** via a vinylogous *N*,*N*-dimethylaminomethylenation reaction.[9]

Thus, the reaction of **1a**-*E* and DMF-DMA (2.0 equiv) was examined in DMF at 80 °C for 1 h. In the reaction, a desired product **2a**-*E* was obtained in good yield (85%).[11] The stereochemistry of **2a**-*E* was confirmed by comparing its ^{1}H NMR data with the reported.[4,8] The proton at the C-4 position of **2a**-*E* appeared quite upfield (δ = 5.44 ppm) due to shielding effect of the phenyl ring. To our surprise, the corresponding **2a**-*Z* was not formed in any trace amount. The favorable electrostatic interaction between the dienolate **VI** and the iminium ion might be the reason for the stereoselective carbon—carbon bond formation. Accordingly, the reaction of **1a**-*Z*[4] and DMF-DMA was examined under the same reaction conditions. Compound **2a**-*E* was obtained again in a slightly lower yield (78%). The proton abstraction of **1a**-*Z* produced a dienolate

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

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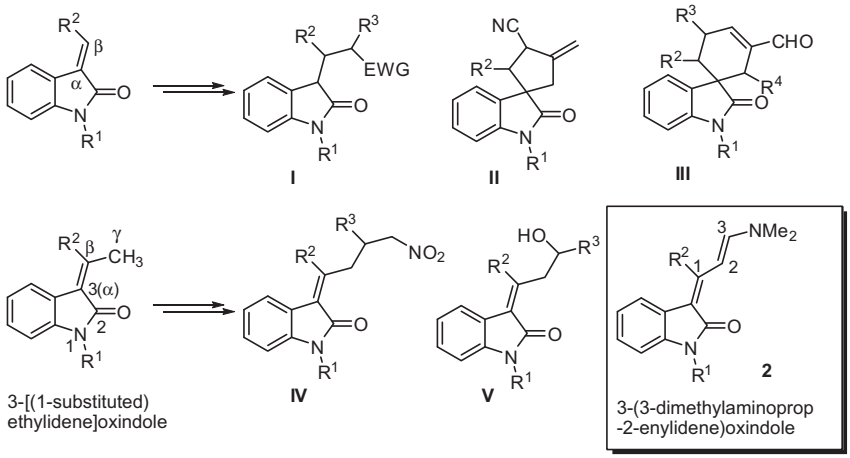
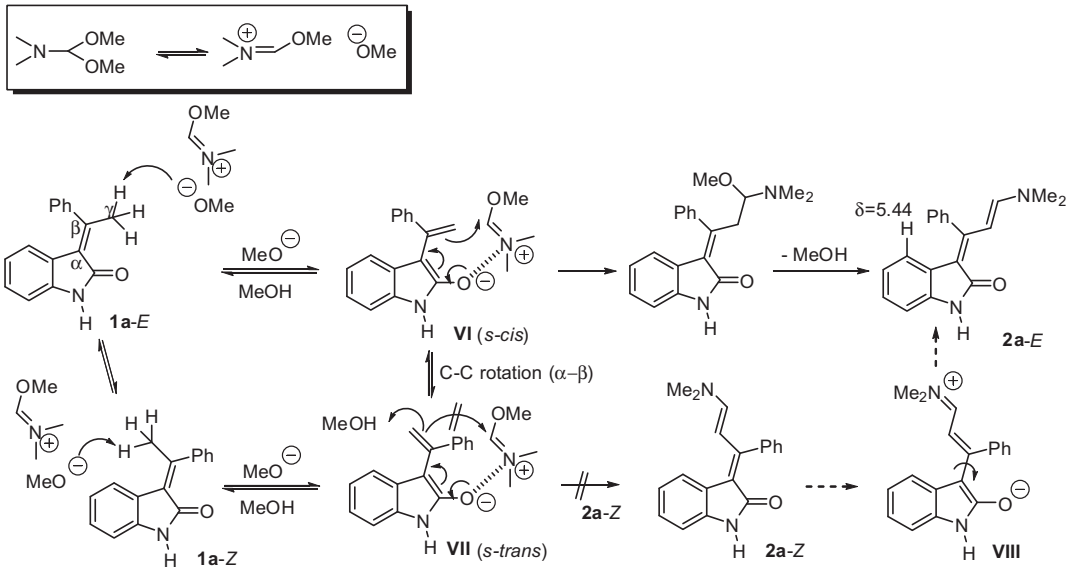


Scheme 1.



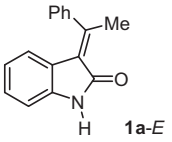
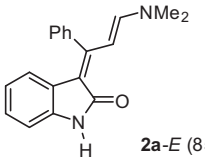
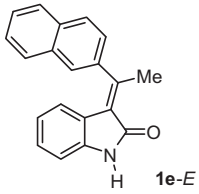
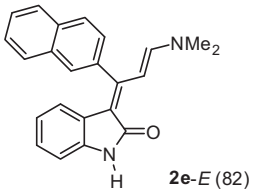
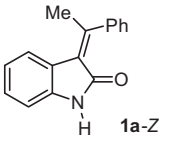
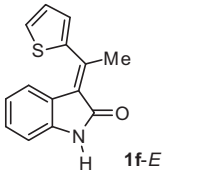
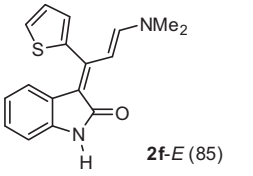
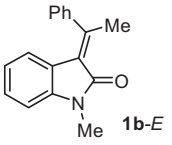
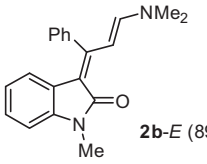
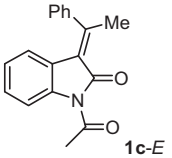
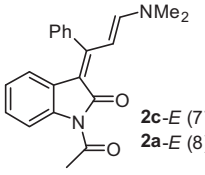
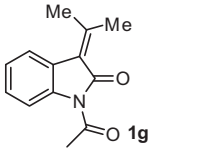
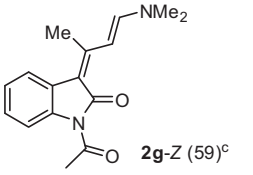
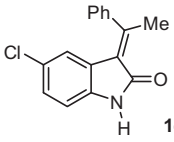
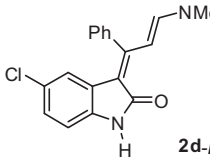
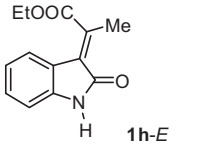
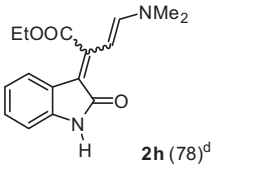
Scheme 2.

VII, but this dienolate cannot react with the iminium ion in its *s-trans* form. Thus *s-trans* dienolate **VII** has to be converted to *s-cis* dienolate **VI** via the C—C bond rotation. Otherwise, **1a**-*Z* has to be isomerized to **1a**-*E* by addition/elimination mechanism of some nucleophilic species such as methoxide ion.[4] Actually, **1a**-*Z* was isomerized to **1a**-*E* in the presence of DMF-DMA even at room temperature within 1 h, and the formation of **2a**-*E* was also observed during the isomerization process, albeit in a trace amount. The isomerization of **1a**-*Z* to **1a**-*E* occurred more rapidly in the presence of NaOMe in MeOH at room temperature. However, we could not exclude the following reaction pathway for the conversion of **1a**-*Z* to **2a**-*E* at this stage: the formation of a dienolate **VII**, the reaction of **VII** with iminium ion to form **2a**-*Z*, and an isomerization to **2a**-*E* via the mesomeric structure **VIII**.[9d]

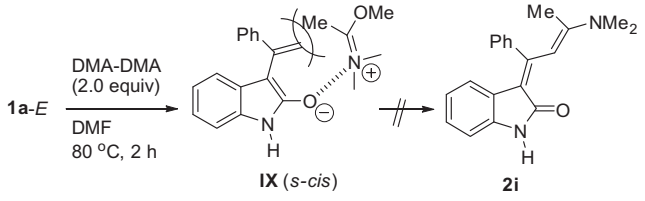
Encouraged by the results, the reactions of various 3-alkylideneoxindoles **1b**–**h** and DMF-DMA were examined. The results are summarized in Table 1. The reaction of *N*-methyl derivative **1b** (entry 3) afforded **2b** in good yield (89%). The reaction of *N*-acetyl derivative **1c** (entry 4) produced **2c** in good yield (77%) along with a low yield (8%) of N-deacetylated product **2a**-*E*. The reactions of 5-chlorooxindole derivative **1d** (entry 5), 1-(naphthalen-2-yl)ethylidene derivative **1e** (entry 6), and 1-(thiophen-2-yl)ethylidene derivative **1f** (entry 7) gave **2d**–**f** in high yields (82–85%). When we used the isopropylidene derivative **1g** (entry 8), the yield of **2g** was somewhat low (59%) due to the formation of some side products. The use of 1.0 equiv of DMF-DMA at 50 °C was crucial. Otherwise, further reactions of **2g** made the reaction mixture somewhat complex. In addition, a trace amount of **2g**-*E* was formed together in around 10% based on its ^{1}H NMR spectrum; however, we cannot separate them. The reaction of an ester derivative **1h**-*E* (entry 9) afforded the desired product **2h** in good yield (78%); however, **2h** was obtained as an inseparable mixture of *E*/*Z* isomers (1:1). The reason for the formation of *E*/*Z* mixture is not clear at this stage.

Unfortunately, the reaction of **1a** and *N*,*N*-dimethylacetamide dimethylacetal (DMA-DMA) failed, as shown in Scheme 3. The reaction was sluggish and almost no reaction was observed below 80 °C. A severe decomposition to intractable side products was observed at elevated temperature (>100 °C), and we could not identify nor isolate the expected compound **2i** in a reasonable yield.

Table 1
Synthesis of 3-(3-dimethylaminoprop-2-enylidene) oxindoles[a]

Entry	Substrate	Product (%)	Entry	Substrate	Product (%)
1	 **1a**-*E*	 **2a**-*E* (85)	6	 **1e**-*E*	 **2e**-*E* (82)
2	 **1a**-*Z*	**2a**-*E* (78)	7	 **1f**-*E*	 **2f**-*E* (85)
3	 **1b**-*E*	 **2b**-*E* (89)			
4	 **1c**-*E*	 **2c**-*E* (77) **2a**-*E* (8)[b]	8	 **1g**	 **2g**-*Z* (59)[c]
5	 **1d**-*E*	 **2d**-*E* (82)	9	 **1h**-*E*	 **2h** (78)[d]

[a] Conditions: **1** (0.5 mmol), DMF-DMA (2.0 equiv), DMF, 80 °C, 1 h.
[b] N-deacetylated product **2a**-*E* was isolated in low yield (8%).
[c] DMF-DMA (1.0 equiv) was used at 50 °C for 1 h, and **2g**-*E* (ca. 10%) was mixed together.
[d] *E*/*Z* mixture (1:1) based on ^{1}H NMR.

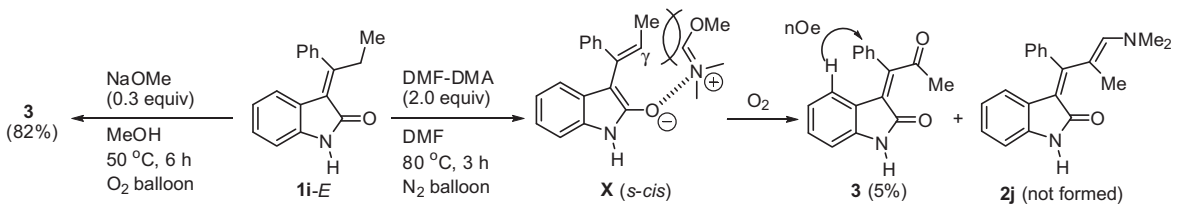


Scheme 3.

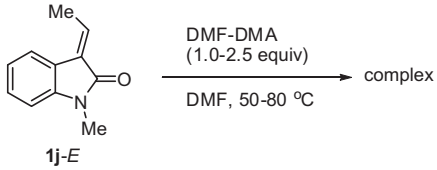
As shown in Scheme 3, an unfavorable steric hindrance between the γ-position of **IX** and the iminium ion would make the reaction difficult.

Similarly, the reaction of 1-phenylpropylidene derivative **1i** with DMF-DMA also failed presumably by the same steric reason, as shown in Scheme 4. It is interesting to note that an acetyl derivative **3** was formed, albeit in low yield (5%), presumably via an aerobic oxidation at the γ-position of the dienolate **X**, although the reaction was carried out under N_2 balloon atmosphere.[12,13] Actually, the oxidation of **1i** proceeded in good yield (82%) in MeOH in the presence of NaOMe (0.3 equiv) under O_2 balloon atmosphere at 50 °C for 6 h. The aerobic oxidation proceeded even at room temperature although somewhat slowly.

As a next entry, we examined the reaction of 3-[(1-unsubstituted)ethylidene]oxindole such as ethylidene derivative **1j** under the same reaction conditions, as shown in Scheme 5. Unfortunately, we could not obtain the corresponding product in a reasonable yield because of the formation of many side products. Casiraghi and co-workers also did not examine such an entry in their vinylogous functionalizations.[6] The different reactivity of ethylidene

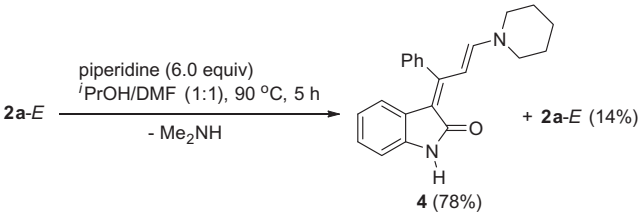


Scheme 4.



1j-*E*

Scheme 5.



4 (78%)

Scheme 6.

derivative **1j** as compared to that of 3-[(1-substituted)ethylidene]oxindoles **1a**–**h** is not clear at this stage.

As a last entry, we examined the synthesis of piperidinyl derivative **4** from *N*,*N*-dimethyl derivative **2a** and piperidine, as shown in Scheme 6. The reversible reaction afforded **4** in good yield (78%) when we used 6.0 equiv of piperidine, along with recovered starting material in 14% yield.[7d–f]

In summary, an efficient and stereoselective synthesis of various 3-(3-dimethylaminoprop-2-enylidene)oxindoles has been carried out by the vinylogous *N*,*N*-dimethylaminomethylenation at the γ-position of 3-alkylideneoxindoles with DMF-DMA.

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11. The starting materials **1a**–**j** were prepared according to the reported methods.[3,4]

Typical procedure for the synthesis of ***2a****-E:* A mixture of **1a**-*E* (118 mg, 0.5 mmol) and DMF-DMA (120 mg, 1.0 mmol) in DMF (1.0 mL) was heated to 80 °C for 1 h under N_2 balloon atmosphere. After the aqueous extractive workup and column chromatographic purification process (CH_2Cl_2/EtOAc, 2:1) compound **2a**-*E* was obtained as an orange solid, 123 mg (85%). Other compounds **2b**–**h** were synthesized analogously and the selected spectroscopic data of **2a**, **2b**, **2e**, **2f**, **3**, and **4** are as follows. It is interesting to note that the ^{13}C NMR peak of the carbon atom of *N*,*N*-dimethylamino group was not observed due to severe line-broadening effect.[14]

Compound ***2a****-E:* 85%; orange solid, mp 266–268 °C; IR (KBr) 1646, 1620, 1515, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (s, 6H), 5.44 (d, J = 7.8 Hz, 1H), 6.39 (d, J = 13.2 Hz, 1H), 6.51 (t, J = 7.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.89 (t, J = 7.8 Hz, 1H), 7.20–7.30 (m, 2H), 7.44–7.54 (m, 3H), 7.62 (d, J = 13.2 Hz, 1H), 7.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 100.52, 108.27, 109.69, 120.36, 120.79, 124.00, 125.98, 127.96, 128.65, 128.88, 136.95, 138.90, 153.23, 156.42, 169.74; ESIMS m/z 291 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.37; H, 6.46; N, 9.51.

Compound ***2b****-E:* 89%; orange solid, mp 174–176 °C; IR (KBr) 1649, 1615, 1528, 1336 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.96 (s, 6H), 3.33 (s, 3H), 5.47 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 13.2 Hz, 1H), 6.54 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.22–7.30 (m, 2H), 7.45–7.53 (m, 3H), 7.71 (d, J = 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.46, 100.47, 106.69, 109.81, 120.34, 120.51, 124.03, 124.95, 127.87, 128.67, 128.81, 138.94, 139.85, 152.84, 155.71, 168.43; ESIMS m/z 305 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.86; H, 6.80; N, 8.99.

Compound ***2e****-E:* 82%; orange solid, mp 244–246 °C; IR (KBr) 1649, 1618, 1514, 1263 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.89 (s, 6H), 5.11 (d, J = 7.5 Hz, 1H), 6.20 (t, J = 7.5 Hz, 1H), 6.38 (d, J = 13.2 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.52–7.64 (m, 2H), 7.63 (d, J = 13.2 Hz, 1H), 7.77 (s, 1H), 7.94–8.12 (m, 3H), 10.23 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 99.64, 108.19, 109.04, 119.29, 119.67, 123.73, 125.36, 126.42, 126.52, 126.74, 126.84, 127.92, 128.16, 128.70, 132.40, 133.17, 136.06, 138.13, 152.91, 154.94, 168.92; ESIMS m/z 341 $[M+H]^+$. Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.97; H, 5.97; N, 8.04.

Compound ***2f****-E:* 85%; orange solid, mp 254–256 °C; IR (KBr) 1649, 1619, 1508, 1403 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.95 (s, 6H), 5.42 (d, J = 7.8 Hz, 1H), 6.48 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 13.2 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.84 (t, J = 7.8 Hz, 1H), 6.97 (dd, J = 3.6 and 0.9 Hz, 1H), 7.24 (dd, J = 5.1 and 3.6 Hz, 1H), 7.51 (d, J = 13.2 Hz, 1H), 7.77 (dd, J = 5.1 and 0.9 Hz, 1H), 10.21 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 100.24, 108.21, 110.40, 119.59, 120.02, 124.10, 124.95, 126.90, 127.16, 127.78, 138.16, 138.55, 146.58, 152.52, 168.50; ESIMS m/z 297 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 69.08; H, 5.73; N, 9.36.

Compound ***3****:* 82%; yellow solid, mp 172–174 °C; IR (KBr) 1706, 1613, 1465, 1229 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.40 (s, 3H), 6.47 (d, J = 7.5 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.44–7.51 (m, 2H), 7.52–7.62 (m, 3H), 10.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.08, 110.29, 121.33, 121.95, 123.53, 124.27, 127.79, 129.32, 129.89, 130.18, 132.87, 142.05, 151.65, 168.46, 204.00; ESIMS m/z 264 $[M+H]^+$. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.80; H, 5.21; N, 5.27.

Compound ***4****:* 78%; orange solid, mp 250–252 °C; IR (KBr) 1654, 1601, 1520, 1243 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.55 (br s, 6H), 3.22 (br s, 4H), 5.21 (d, J = 7.5 Hz, 1H), 6.30 (d, J = 13.5 Hz, 1H), 6.34 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 7.10–7.30 (m, 2H), 7.40–7.65 (m, 3H), 7.73 (d, J = 13.5 Hz, 1H), 10.19 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 23.51, 25.23, 98.76, 108.11, 109.00, 119.28, 119.80, 123.70, 125.34, 127.98, 128.13, 129.03, 138.08, 138.51, 151.59, 155.32, 168.92; ESIMS m/z 331 $[M+H]^+$. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.82; H, 6.94; N, 8.39.

12. The starting material **1i**-*E* was recovered (67%) in the reaction (80 °C, 3 h). For the similar aerobic oxidation of oxindole derivatives, see: (a) Lee, H. S.; Kim, K. H.; Kim, Y. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 1761–1764; (b) Lee, H. J.; Lee, S.; Lim, J. W.; Kim, J. N. *Bull. Korean Chem. Soc.* **2013**, *34*, 2446–2450.
13. The stereochemistry of **3** was confirmed as *cis*-form based on the NOE experiment.
14. For the peak-broadening of similar compounds, see: (a) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561; (b) Wypych, J.-C.; Nguyen, T. M.; Benechie, M.; Marazano, C. *J. Org. Chem.* **2008**, *73*, 1169–1172; (c) Lee, K. Y.; Lee, C. G.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 69–74.