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The first synthesis of *cis-N,N′*-dialkylisoindigo derivatives from 3-indolyl-2-oxindoles with DDQ

Da Young Seo, Hwa Jung Roh, Hwi Yul Jo, Sung Cho, Jae Nyoung Kim [*]

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

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ABSTRACT

cis-N,N′-Dialkylisoindigo derivatives were synthesized for the first time by the reaction of 3-indolyl-2-oxindoles with DDQ in aqueous 1,4-dioxane. *cis*-Isoindigo derivatives were completely isomerized to the corresponding *trans*-isomers by heating the solution in short time.

Isoindigo (3,3′-biindolylidene-2,2′-dione) and its derivatives have received much attention due to their biological activity such as anti-leukemia, antiproliferative, and anti-inflammatory activity (Fig. 1).[1] For example, *Meisoindigo* has been used for treatment of chronic myeloid leukemia in China[1h] and *Natura* (1-β-D-triacetylxylopyranosylisoindigo) has been proved to be an excellent inhibitor for cyclin-dependent kinases.[1i] In addition, isoindigo derivatives have been used as electron acceptor units for organic electronic materials[2] and key intermediates for the synthesis of natural products.[3]

Generally, isoindigo derivatives have been synthesized by an acid-catalyzed condensation reaction of isatin with oxindole,[4a–c] tris(diethylamino)phosphine-mediated carbene dimerization of isatin,[4d–f] palladium-catalyzed cascade dual annulations of diarybut-2-ynediamides,[4g] and other methods.[4h–j] Very recently, we reported a new method for the synthesis of isoindigo derivatives from 3-indolyl-2-oxindoles with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[5] Isoindigo derivatives including *Meisoindigo* and *Natura* have been synthesized as *trans*-isomers in all precedent reports including ours (Fig. 1).[1–5] Lunak and co-workers examined the isomerization of *trans*-isoindigo to *cis*-isoindigo; however, no evidence for the formation of *cis*-isoindigo has been found.[6] Literature survey revealed that there was no report on the synthesis or isolation of *cis*-isoindigo derivatives.

During our synthesis of *trans*-isoindigo derivatives from 3-indolyl-2-oxindoles with DDQ in refluxing aqueous 1,4-dioxane in the presence of trifluoroacetic acid (TFA),[5] the formation of a polar component was observed at the early stage of the reaction (<1 h), and the polar component was converted rapidly to *trans*-isoindigo. Thus, we thought that the polar component must be an intermediate for the formation of *trans*-isoindigo. However, isolation of the polar component failed due to its instability at that moment. To our pleased, we found that the polar component could be formed exclusively at room temperature. When we carried out the reaction of 3-indolyl-2-oxindole **1a** at room temperature for 1 h, the polar component was isolated in good yield (74%) along with small amount of *trans*-**2a** (6%), as shown in Scheme 1.

The polar component was found to be *cis*-**2a** based on its ^{1}H and ^{13}C NMR spectra along with its complete conversion to *trans*-**2a** in short time (50 min) by refluxing in aqueous 1,4-dioxane (*vide infra*). The proton at the 4-position (or 4′-position) of *cis*-**2a** appeared upfield ($\delta = 8.10$ ppm) compared to that of *trans*-**2a** ($\delta = 9.14$ ppm) by the absence of deshielding anisotropy of the carbonyl group present in *trans*-**2a**. The reaction at 10 °C afforded *cis*-**2a** in improved yield (79%) for 3 h; however, the formation of *trans*-**2a** was still observed, albeit in a trace amount (4%). The reaction proceeded even at 0 °C to give *cis*-**2a** (78%) along with *trans*-**2a** (4%) although somewhat long reaction time (12 h) was required. The ratio (*cis*-**2a**/*trans*-**2a**, >19:1) at low temperature (10 °C and 0 °C) stated that *cis*-**2a** might be a kinetically favored product (*vide infra*, Scheme 3).

Encouraged by the interesting results we synthesized some representative *cis*-isoindigo derivatives, and the results are summarized in Table 1. We carried out the reactions of various 3-indolyl-2-oxindoles **1b**–**1k** and DDQ (2.0 equiv.) in the presence

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[*] Corresponding author.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

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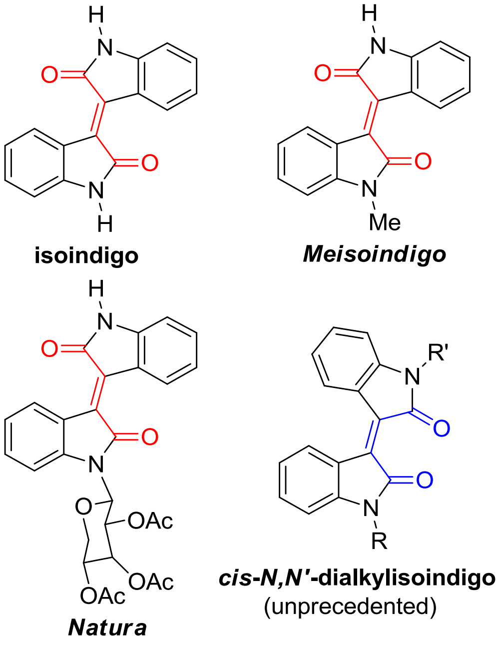

Fig. 1. Representative isoindigo derivatives.

of TFA (20 mol%) in aqueous 1,4-dioxane at 10 °C for 3 h, and *cis*-isoindigo derivatives **2b**–**2k** were obtained in good yields (72–80%).[7–9] *N,N′*-Unsubstituted *cis*-isoindigo **2l** was also synthesized in good yield (71%).[10]

It is interesting to note that isoindigo derivative **2h** could also be synthesized from **1h**′ (X = 5-Me, Y = H, $R^1 = R^2$ = Me) under the same reaction condition in a similar yield (74%), as shown in Scheme 2.

In order to confirm the structure of *cis*-isoindigo, we carried out NOE experiments with *cis*-**2d** (in CD_2Cl_2) and *trans*-**2d** (in $CDCl_3$), as shown in Fig. 2. Irradiation of H_4 (δ = 7.78 ppm) of *cis*-**2d** showed NOE increment of $H_{4'}$ (δ = 8.09 ppm). In contrast, irradiation of H_4 (δ = 8.89 ppm) of *trans*-**2d** showed NOE increment of the methyl group (δ = 2.31 ppm) only. X-ray crystal structure identification of *cis*-**2d** failed due to its rapid conversion to *trans*-**2d**.

The reaction mechanism could be proposed as shown in Scheme 3, which has been proposed in our previous paper.[5] An acid-catalyzed dehydration of **1a** would generate resonance-stabilized cation intermediate **I**.[11a] Addition of water at the 2-position of indole ring generated a cyclic hemiaminal intermediate **II**. A subsequent oxidation of **II** with DDQ would afford **2a**.[11,12] The stereochemistry of isoindigo **2a** might be determined in the cyclic hemiaminal intermediate stage. There could be a favorable hydrogen bonding in *cis*-**II**, thus *cis*-**2a** would be formed preferentially after DDQ oxidation. However, *cis*-**2a** was isomerized to more stable *trans*-**2a** under the previous refluxing condition (*vide infra*).

It is interesting to note that *cis*-**2a** was somewhat unstable in $CDCl_3$ and converted slowly to *trans*-**2a** even at room temperature. It was more stable in CH_2Cl_2 or 1,2-dichloroethane, and the formation of only a trace amount of *trans*-**2a** (<3%) was observed after 24 h. Thus, the ^1H and ^{13}C NMR spectra of **2a**–**2k** were obtained in CD_2Cl_2. The isomerization was accelerated by elevating temperature.

Actually, *cis*-**2a** was converted quantitatively to *trans*-**2a** in refluxing chloroform within 4 h, and the isomerization was completed within 50 min in aqueous 1,4-dioxane (Scheme 1).[13] The isomerization might occur via single bond rotation of the resonance form **III**, as shown in Scheme 4. The isomerization might also proceed by addition of water to form **IV**, single bond rotation, and elimination of water. Thus, the selective formation of *trans*-**2a** in our previous paper[5] might be the result of initial formation of *cis*-**2a** and a following double bond isomerization to *trans*-**2a**.

As an example, *cis*-**2a** was quite stable in solid state, and no isomerization occurred even after 20 days in a refrigerator. However, *cis*-**2a** was rapidly converted to *trans*-**2a** at 200 °C, and a complete conversion was observed within 5 min even in a solid state. Actually, the melting point of *cis*-**2a** (268–270 °C) was exactly same to that of *trans*-**2a**.[5] In addition, as noted above, *cis*-**2a** was converted slowly to *trans*-**2a** in $CDCl_3$ at room temperature, and the conversion was monitored by ^1H NMR, as shown in Fig. 3. The first spectrum of *cis*-**2a** (a) was taken in CD_2Cl_2, and the following three spectra (b)–(d) of *cis*-**2a** were taken on time progress in $CDCl_3$.

cis-**2a** was converted to *trans*-**2a** in about 17% after 1 day (c) and 34% after 3 days (d). The spectrum (e) is *trans*-**2a** in $CDCl_3$.

In summary, various *cis*-isoindigo derivatives were synthesized in good yields for the first time by the reaction of 3-indolyl-2-oxindoles with DDQ in aqueous 1,4-dioxane. The studies on the biological activity of *cis*-isoindigo derivatives and further studies on reaction mechanism are currently underway.[14]

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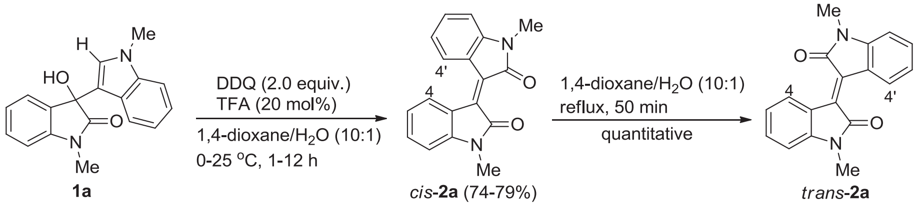

25 °C, 1 h: *cis*-**2a** (74%), *trans*-**2a** (6%)
10 °C, 3 h: *cis*-**2a** (79%), *trans*-**2a** (4%)
0 °C, 12 h: *cis*-**2a** (78%), *trans*-**2a** (4%)

Scheme 1. The first synthesis of *cis*-isoindigo **2a**.