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A new route to the synthesis of ellipticine quinone from isatin

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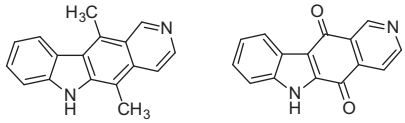
ABSTRACT

1-(2-Oxo-2-(pyridin-4-yl)ethyl)indoline-2,3-dione can be prepared and converted by treatment with sodium hydroxide into 2-isonicotinoyl-1*H*-indole-3-carboxylic acid as a key intermediate which can be transformed into ellipticine quinone in a two step sequence.

Pyrido[4,3-*b*]carbazole[1] containing alkaloids comprise a group of naturally occurring biologically active compounds and have attracted a broad interest in chemistry, biology, and pharmacology. Ellipticine **1** (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, Fig. 1)[2] and its congeners are well-known for their biological activities such as anticancer,[3] antineoplastic[4] and their use of treatment for myeloblastic leukemia, advanced breast cancer, and solid tumors.[5] Ellipticine quinone **2** (5*H*-pyrido[4,3-*b*]carbazole-5,11(6*H*)-dione, Fig. 1)[6] is an important synthetic intermediate and it can easily be converted into ellipticine **1** by known methods.[7]

Condensation of *ortho*-aminophenylcarbonyl compounds with α-halomethylketones is a versatile route for the synthesis of indoles possessing an acyl group at C(2).[8] *ortho*-Aminophenylglyoxylic acids are readily generated in situ by the effect of an alkali (usually NaOH) on isatins. The reaction of *ortho*-aminophenylglyoxylic acids with α-halomethylketones can be formulated into a general synthesis for 2-acylindole-3-carboxylic acids and their *N*-alkyl derivatives.[9] However, because of the low reactivity of the salts with respect to N-alkylation, this reaction does not occur either in aprotic solvents at increased temperature or in strongly basic media or with phase transfer catalysis.[10]

Isatin (indoline-2,3-dione) **3** is commercially available, a multifunctional heterocycle containing nitrogen atom whose behavior in alkylation reactions is strongly based on the reaction conditions and nature of the alkylating agents used.[11] Isatin may react with α-halomethylketones at the *β*-CO or *NH* group. If the reaction proceeds with N-alkylation, the products formed smoothly isomerize to give 2-acylindole-3-carboxylic acids as a result of the facile opening of the five-membered isatin ring in aqueous alkali solutions, super basic media, and alcoholic solutions of sodium alkoxides.[9–12]



Ellipticine **1** Ellipticine quinone **2**

Figure 1. Structures of ellipticine (**1**) and ellipticine quinone (**2**).

The indoledione-indole rearrangement[8–12] is one of the best methods for the synthesis of 2-acylindole-3-carboxylic acids since it is atom economic and requires a simple base to promote the reaction. It can be described as the isomerization of 1-[2-oxoalkyl(aryl or heteroaryl)]indole-2,3-diones into 2-acylindole-3-carboxylic acids.

Directed *ortho*-metallation[13] (DoM) plays a vital role in the modern organic synthesis. Syntheses of various heterocyclic quinones are reported by using tandem metallation in situ cyclization of (het)arylpyridylketones bearing an alkyl carboxylate or a lithium carboxylate group at a remote position from the pyridine ring.[14] To the best of our knowledge, there are no reports concerning the synthesis of ellipticine quinone from isatin until now. Our interest of using 1-(2-oxo-2-(pyridin-4-yl)ethyl)indoline-2,3-dione **9** as synthetic precursor for the synthesis of ellipticine quinone is described in this Letter.

Our synthetic approach for the synthesis of ellipticine quinone is outlined in Scheme 1. We envisioned that ketone **9** can be

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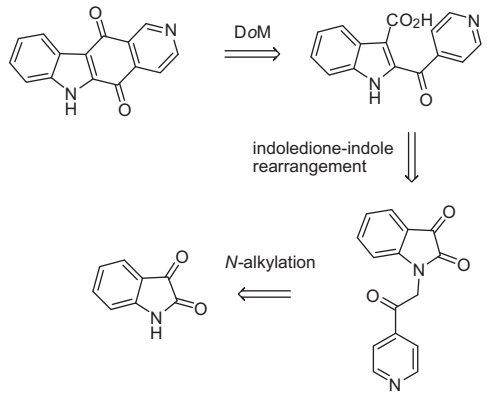
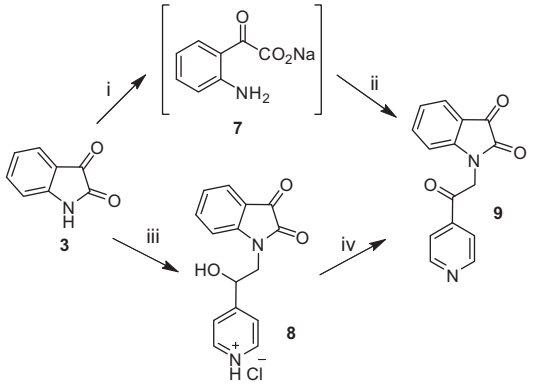
synthesized from isatin using appropriate N-alkylating reagents which can easily be converted to 2-isonicotinoyl-1*H*-indole-3-carboxylic acid **11** under basic condition via indoledione-indole rearrangement. Finally, ellipticine quinone **2** could be obtained from **11** by exploiting *ortho*-lithiation strategy (Scheme 2).

The first key step in the synthesis of ellipticine quinone is the synthesis of **9** from isatin **3** using various alkylating reagents shown in Figure 2 which were prepared from known procedures.[15] We initially performed reaction between sodium 2-(2-aminophenyl)-2-oxoacetate **7** (derived from isatin **3** upon treatment with NaOH/MeOH) and 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide **4** in DMF at 70 °C for 5 h affording **9** in 17% yield. Many attempts to increase yield of **9** under various conditions were less than satisfactory due to low reactivity of salts **4** and **7**. However, treatment of **3** with other alkylating reagents such as 2-bromo-1-(pyridin-4-yl)ethanol **5** or 4-(oxiran-2-yl)pyridine **6** in NaH/DMF gave 1-(2-hydroxy-2-(pyridin-4-yl)ethyl)indoline-2,3-dione



Scheme 1. Retrosynthetic analysis of ellipticine quinone (**2**).



Scheme 2. Synthesis of 1-(2-oxo-2-(pyridin-4-yl)ethyl)indoline-2,3-dione (**9**). Reagents and conditions: (i) NaOH, MeOH, reflux, 5 h (ii) 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide, DMF, 70 °C, 5 h, 19% (iii) NaH, 2-bromo-1-(pyridin-4-yl)ethanol or 4-(oxiran-2-yl)pyridine, DMF, rt, overnight, 76–81% (iv) IBX, DMSO, rt, 6 h, 84%.

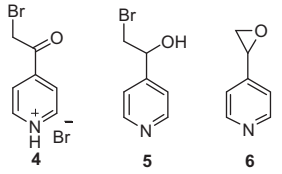
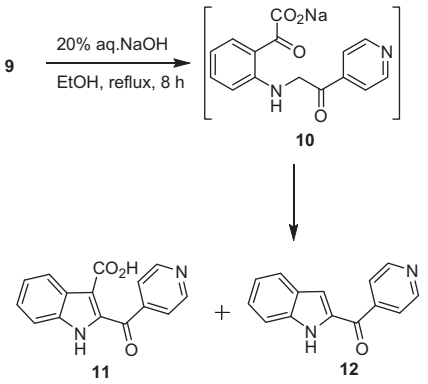
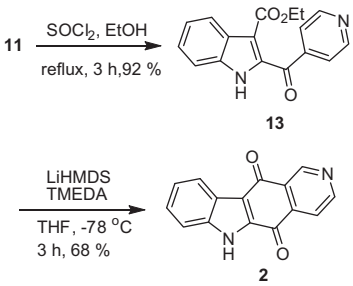


Figure 2. N-alkylating reagents of isatin (**3**).



Scheme 3. Indoledione-indole rearrangement of **9** to carboxylic acid (**11**).



Scheme 4. Synthesis of ellipticine quinone (**2**). (LiHMDS = lithium *bis*(trimethylsilyl)azanide).

hydrochloride **8** in 78% yield which was then oxidized to **9** by IBX/DMSO (Scheme 3).

The next key step is the rearrangement of ketone **9** to carboxylic acid **11**. Hydrolysis of compound **9** using 20% aqueous NaOH in ethanol at reflux for 8 h afforded **11** through an intermediate **10** along with easily separable decarboxylated product **12** in 76% and 24% yields respectively (Scheme 4).

The key intermediate **11** was subjected to esterification with ethanol to give corresponding ester **13** in 92% yield. Then we conducted directed *ortho*-lithiation of **13** by utilizing 5 equiv of LiHMDS/TMEDA in THF at −78 °C for 3 h producing our target ellipticine quinone **2** in 68% yield.

In summary, we reported a simple and efficient route to the synthesis of ellipticine quinone (**2**) from isatin. Key reactions included N-alkylation of isatin, indoledione-indole rearrangement, and directed *ortho*-lithiation. In addition, this synthetic route may be used as a model for similar pyrido[4,3-*b*]carbazole alkaloids.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.098.

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