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Synthesis of Isatins by I_2/TBHP Mediated Oxidation of Indoles

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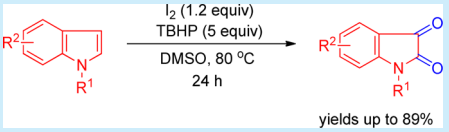
Supporting Information

ABSTRACT: An I_2/TBHP mediated oxidation of commercially available indoles has been developed, which affords isatins in moderate to good yields.



Isatins widely exist in natural products and pharmaceuticals. They are important heterocycles with diverse biological properties such as antimalarial,[1] anticancer,[2] anticonvulsant,[3] antifungal,[4] and anti-inflammatory agents.[5] Moreover, they are also important intermediates for the construction of valuable molecules such as the synthesis of SU5416 (VEGFR-2 inhibitor)[6] and donaxaridine[7] (Figure 1). Sustained attention has been paid to developing general and direct methods for the preparation of isatins.

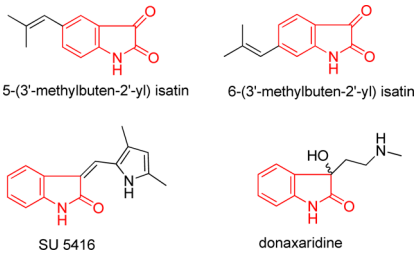
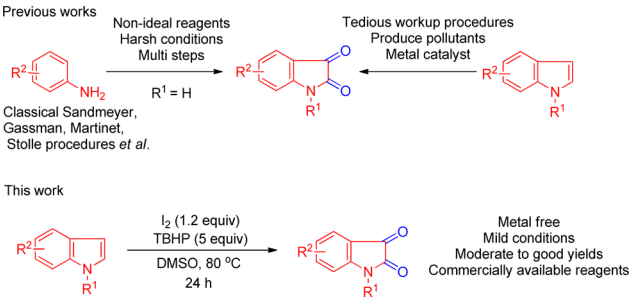


Figure 1. Pharmacologically active indoline-2,3-diones (isatins) and their derivatives.

Classical methods for the preparation of isatin derivatives include the Sandmeyer,[8] Gassman,[9] Martinet,[10] and Stollé[11] procedures. However, they typically suffer from harsh conditions or reagents, elevated temperatures, and nonideal solvents. Recently, several improved protocols for the construction of isatins have been reported such as aryne-based methods,[12] Sandmeyer modifications,[13] metal catalyzed oxidations,[14] sulfur ylide mediated carbonyl homologation,[15] and C−H amination.[16] Although few reports are available for the direct synthesis of isatins from commercially available indoles,[17] a mild and metal-free strategy for the direct synthesis of isatins from indoles is still desirable. More recently, we have reported an I_2/TBHP mediated amination of indoles with anilines.[18] In our continuous efforts to construct heterocycles under oxidative conditions,[19] herein, we demonstrate an I_2/TBHP mediated oxidation of commercially available indoles to give isatins in moderate to good yields (Scheme 1).

Our studies were initiated by the reaction of *N*-methylindole **1a** in DMSO at 80 °C in the presence of 1.2 equiv of I_2 and 2 equiv of TBHP. The desired product *N*-methyl isatin **2a** could

Scheme 1. Preparation of Isatins



be obtained in 38% LC-yield (Table 1, entry 1). To our surprise, the yield of **2a** could be increased to 83% LC-yield (82% isolated yield) (Table 1, entry 2). When the reaction was mediated by other iodine sources such as KI and TBAI instead of I_2, the yield of **2a** was decreased (Table 1, entries 3 and 4). Further screenings of the oxidant and reaction temperature (more details see Supporting Information) revealed no better results (Table 1, entries 5 to 12).

With the optimal reaction conditions in hand, we investigated the scope of the reaction utilizing indoles. As shown in Figure 2, all the reactions proceeded well to furnish the desired isatins. Isatin **2b** could be obtained in 65% yield by direct oxidation of indole **1b** under the optimized conditions. It should be noted that the reaction of 4-methylindole **1c** could lead to **2c** in 89% yield. The reactions of 5-methylindole **1d**, 6-methylindole **1e**, and 7-methylindole **1f** could also afford the desired isatins **2d**, **2e**, and **2f** in 64%, 87%, and 73% yields, respectively. The reactions of indole bearing electron-donating groups such as 4-(benzyloxy)-1*H*-indole **1g** and 5-methoxyindole **1h** proceeded well to give **2g** and **2h** in 57% and 59% yields, respectively. When an indole bearing electron-withdrowing group such as 5-bromo-1*H*-indole **1i** was subjected to the reaction, the yield of the corresponding product **2i** is decreased to 11% for its lower reactivity. Notably, *N*-methylindoles bearing either electron-donating or -withdrowing groups increased the yields of the desired products significantly.

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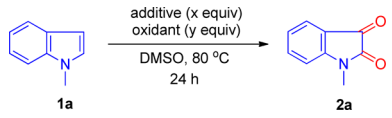
Table 1. Reaction Optimization[a]



entry	additive (equiv)	oxidant (equiv)	yield (%)[b]
1	I_2 (1.2)	TBHP (2)	38
2	I_2 (1.2)	TBHP (5)	83 (82[c])
3	KI (1.2)	TBHP (5)	14
4	TBAI (1.2)	TBHP (5)	12
5	I_2 (0.1)	TBHP (5)	trace
6	I_2 (1.5)	TBHP (5)	65
7	I_2 (1.2)	DTPB (5)	9
8	I_2 (1.2)	TBPB (5)	20
9	I_2 (1.2)	CPO (5)	20
10	I_2 (1.2)	PAA[d] (5)	11
11	I_2 (1.2)	TBHP (5)	57[e]
12	I_2 (1.2)	TBHP (5)	67[f]

[a]Reaction conditions: **1a** (0.5 mmol), I_2 (0.6 mmol), TBHP (2.5 mmol) in DMSO (6 mL), 80 °C, 24 h. [b]Determined by LC-MS analysis with biphenyl as the internal standard. [c]Isolated yield. [d]PAA = peracetic acid. [e]This reaction proceeded at room tempreture. [f]This reaction proceeded at 110 °C.

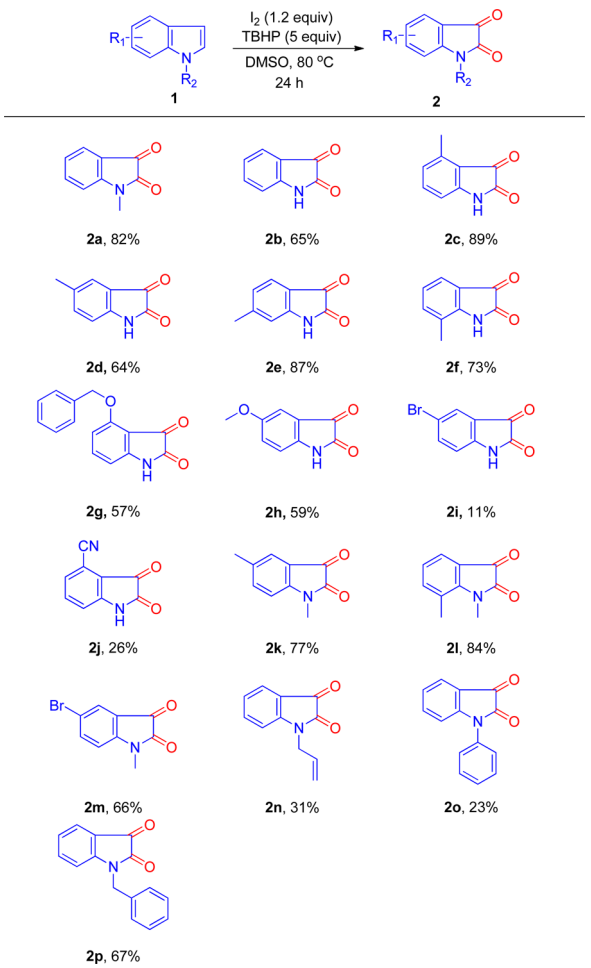
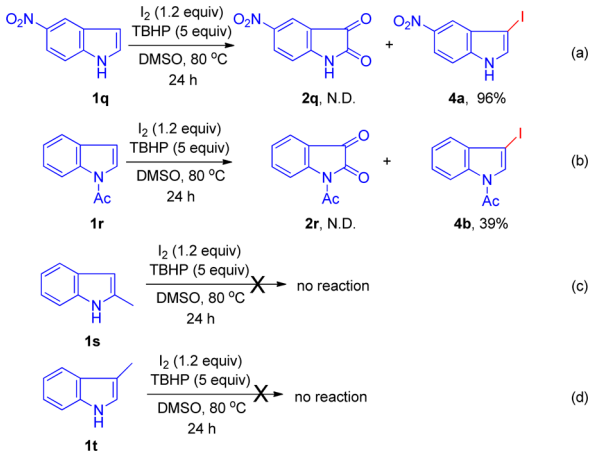


Figure 2. Substrate scope. Reaction conditions: **1** (0.5 mmol), I_2 (0.6 mmol), and TBHP (2.5 mmol) in DMSO (6 mL), 80 °C, 24 h. Isolated yields are shown.

The reaction of 1,7-dimethyl-1*H*-indole **1l** and 5-bromo-1-methyl-1*H*-indole **1m** lead to the desired isatins **2l** and **2m** in 84% and 66% yields, respectively. In addition, the reaction of 1-benzyl-1*H*-indole **1p** also proceeded well and could furnish the desired product **2p** in 67% yield. However, 1-allylindoline-2,3-dione **2n** and 1-phenylindoline-2,3-dione **2o** could only be obtained in 31% and 23% yields by oxidation of the corresponding indoles **1n** and **1o**, respectively.

When 5-nitroindole **1q** was subjected to the reaction under the optimal conditions, 3-iodo-5-nitroindole **4a** was obtained instead of 5-nitroisatin **2q** (Scheme 2, reaction a). Despite this,

Scheme 2. Oxidation Reaction of Other Indoles

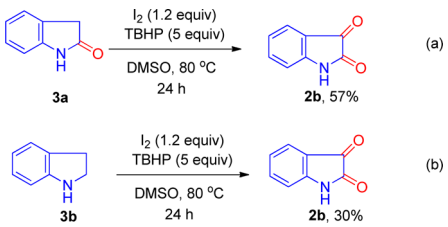


the 5-nitroisatin **2q** could be synthesized in excellent yield via a simple nitration of isatin **2b**.[20] However, the reaction of 1-acetylindole **1r** led to 1-acetyl-3-iodoindole **4b** in 39% yield instead of the isatin derivative **2r** under the identical conditions (Scheme 2, reaction b).

As expected, no desired product was obtained when 2-methyl-indole **1s** and 3-methyl-indole **1t** were subjected to the reaction under the optimized conditions (Scheme 2, reactions c and d).

To our delight, 2-indolone **3a** and indoline **3b** could also be oxidized under identical conditions to give the isatin **2b** in 57% and 30% yields, respectively (Scheme 3).

Scheme 3. Oxidation Reactions of 2-Indolone 3a and Indoline 3b



In order to better understand the mechanism of this reaction, we attempted several control experiments. When 3-iodo-1-methyl-indole **1u** was subjected to the reaction under similar conditions, **2a** could be obtained in 76% yield (Scheme 4, reaction a). This result indicated that 3-iodo-1-methyl-indole **1u** was the possible intermediate or its corresponding tautomer of the model reaction. As anticipated, when TEMPO (1.2 equiv) was added to the system, the reaction was completely

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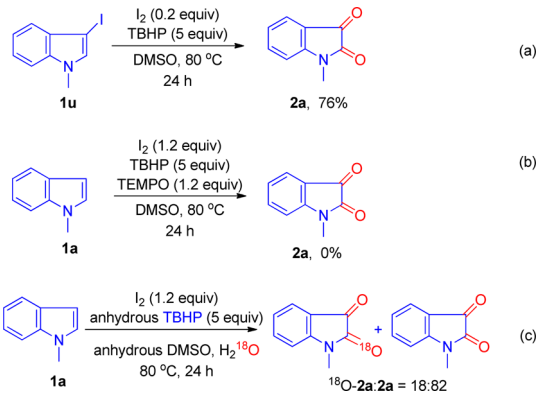
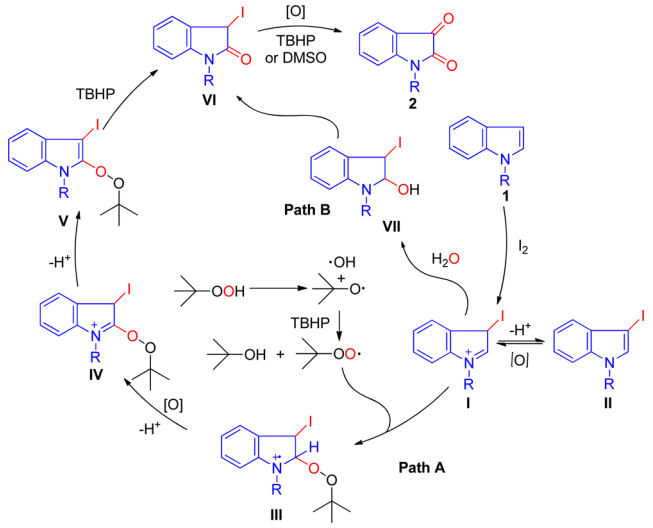
Scheme 4. Investigation into the Reaction Mechanism



suppressed (Scheme 4, reaction b), which indicated that the reaction involved radical processes. When the reaction was carried out with anhydrous DMSO and TBHP in the presence of $H_2{}^{18}O$, **2a** and ^{18}O labeled **2a** with the ratio of 82:18 could be obtained (Scheme 4, reaction c). This result meant that one of the oxygen atoms of the isatin comes from the water or TBHP.

Based on the above results and the literature,[21−23] a plausible mechanism for this reaction via two possible pathways is proposed in Scheme 5. First, indole reacts with I_2 to give the

Scheme 5. Plausible Reaction Mechanism



iminium intermediate **I**. Then, **I** reacts with a *tert*-butylperoxy free radical[22,22b] to furnish intermediate **III**,[22,22c,23] which can be oxidized by TBHP to give intermediate **IV**. After the isomerization of **IV** and oxidation by TBHP, 3-iodo-indolin-2-one **VI** can be generated (path A). On the other hand, water attacks the intermediate **I** to give intermediate **VII**. After simple oxidation of **VII** by TBHP, **VI** can also be performed (path B). After further oxidation of **VI** by TBHP or DMSO, isatin **2** is formed.[21,21e,f]

In conclusion, we have developed a convenient, simple, and metal-free protocol for the direct synthesis of isatins in moderate to good yields by the direct oxidation of commercially available indoles under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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