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Is the 2,3-carbon–carbon bond of indole really inert to oxidative cleavage by Oxone? – Synthesis of isatoic anhydrides from indoles†

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A recent report has indicated that the oxidizing agent Oxone does not possess the ability to cleave the 2,3-carbon–carbon bond of indole. Work in our laboratory shows that this is not the case. Indole and a variety of aryl ring substituted derivatives readily react to form synthetically important isatoic anhydrides.

Oxone, a potassium triple salt containing potassium peroxymonosulfate, is a powerful oxidant. Compared to other oxidation reagents Oxone is particularly attractive in part due to its stability, nontoxic nature and environmentally benign by-products, namely K_2SO_4 and $KHSO_4$. Oxone is a very versatile oxidant that induces numerous oxidation reactions.[1]

In the presence of Oxone, indole derivatives are susceptible to oxidative functionalization. Isatin compounds, such as 1-methylisatin (**1**, Fig. 1) and oxindole (**2**), have been reported to be synthesized from the reaction of indoles with Oxone.[2] Umemoto and co-workers showed that indole-2,3-dicarboxylic acid degrades in a Hunsdiecker-type reaction to form the 3,3-dibrominated indole analog (**3**).[3] Chandramohan and co-workers disclosed that the oxidation of 3-indole acetic acid in the presence of Oxone results in 2-hydroxy-3-indole-methanol (**4**).[4] While the aldehyde **5** was reported to be the product of the reaction of 2,3-dimethyl indole with Oxone,[5] Wu and co-workers have shown that a thiocyanate group can be introduced regioselectively into the 3-position of indoles to give analogs such as compound **6**.[6] Considered together, these examples give the impression that given the presence of Oxone as the sole oxidant, the 2,3-carbon–carbon bond of indole compounds is chemically inert to oxidative cleavage. This is surprising since oxidizing agents milder than Oxone can induce such a transformation, yielding anthranilic acid derivatives.[7]

Recently, Lian and co-workers disclosed a very elegant approach for the preparation of phenylbenzoxazinone

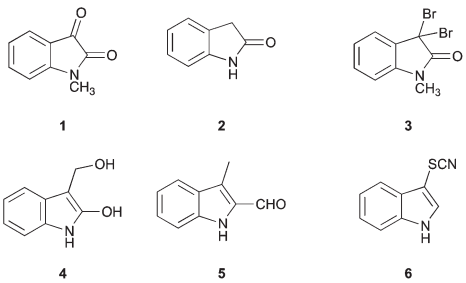
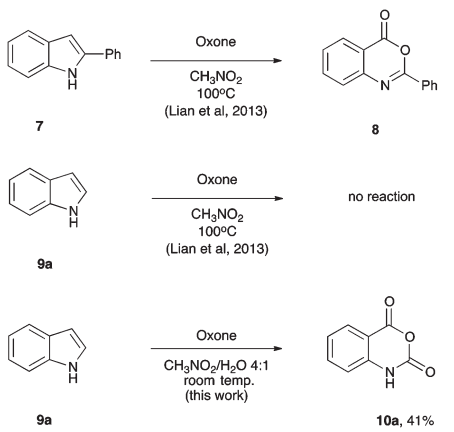


Fig. 1 Examples of indole derivative products formed upon Oxone induced oxidation.



Scheme 1 The ability of Oxone to cleave the 2,3-carbon–carbon bond of indole compounds appears to be dependent on substrate and reaction conditions.

(**8**, Scheme 1) by Oxone induced oxidation of 2-phenyl indole (**7**).[8] This reaction clearly shows that Oxone has the ability to break the 2,3-carbon–carbon bond of 2-substituted indoles. The authors also indicated that even at 100 °C in nitromethane (CH_3NO_2) the parent compound indole **9a** is chemically inert to Oxone and no cleavage reaction occurs.

Work in our laboratory indicates that a simple addition of water to the reaction mixture is sufficient to induce a reaction

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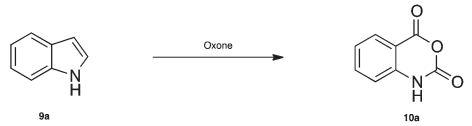
Table 1 Optimization reaction conditions for oxidation of indoles[a]



Entry	Solvent	Yield of **10a**
1	CH_3NO_2–H_2O 4 : 1	41%
2	CH_3OH–H_2O 4 : 1	47%
3	CH_3CN–H_2O 4 : 1	53%
4	DMF–H_2O 4 : 1	83%
5	CH_3CN–H_2O 4 : 1	80%

[a] Reaction conditions: 10 ml solvent mixture, 4 eq. Oxone. Entries 1–4: room temp., 16 h. Entry 5: 1 h, 40 °C. Isolated yields.

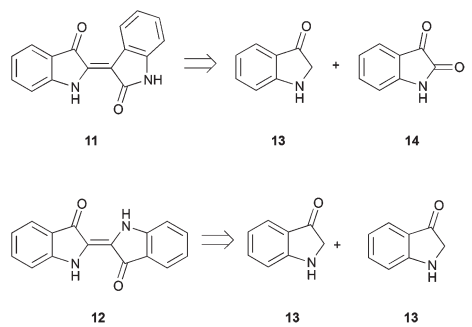


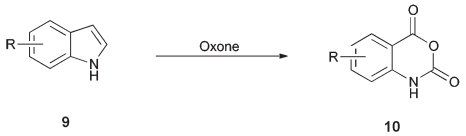
Fig. 2 Structures and retro-synthesis of indirubin (**11**) and indigo (**12**).

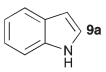
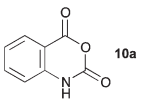
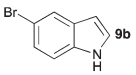
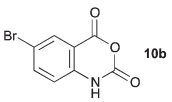
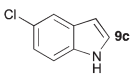
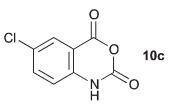
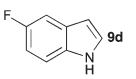
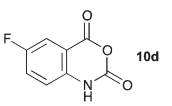
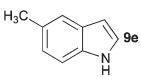
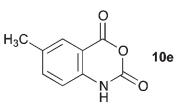
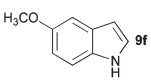
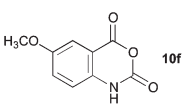
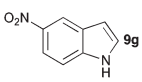
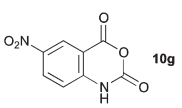
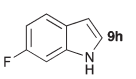
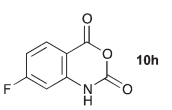
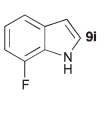
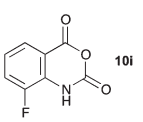
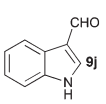
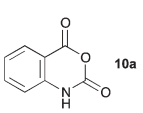
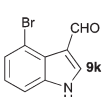
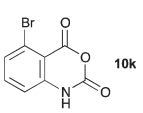
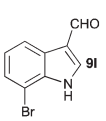
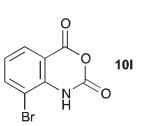
at room temperature. Under these conditions an oxygen atom was inserted between the C-2/C-3 carbon atoms of **9a** and isatoic anhydride (**10a**) was formed with a 41% yield.

We had earlier considered 4 : 1 CH_3OH–H_2O and 4 : 1 CH_3CN–H_2O mixtures (Table 1, entries 2 and 3). Both of these mixtures gave **10a** in yields of 47% and 53%, respectively. Our preliminary results indicate that a 4 : 1 DMF–H_2O solvent mixture (entry 4) is by far more superior. Under these conditions **10a** was isolated in 83% yield. Alternatively, we discovered that we were able to achieve a similar yield by gently heating the reaction mixture to 40 °C in 4 : 1 CH_3CN–H_2O for an hour (entry 5).

We can explain the significantly lower yields for entries 1–3 (Table 1) by the formation of a dark blue resin that is sparingly soluble in organic solvents. To gain an initial insight into the intermediates of this reaction we decided to examine more closely the resin obtained from the reaction in a 4 : 1 mixture of CH_3CN–H_2O (entry 3). The TLC of this material revealed the presence of several highly colored compounds. From the ^1H NMR spectrum of this complex mixture we were able to identify indirubin (**11**, Fig. 2) and indigo (**12**) by comparison with authentic samples. The formation of indirubin (**11**) under the reaction conditions can be envisioned by the condensation of indolin-3-one (**13**, Fig. 2) and isatin (**14**). Indigo (**12**), on the other hand, is the product of the oxidative coupling of two molecules of indolin-3-one (**13**). Thus **13** and **14** clearly have to be present in the reaction mixture to form these two side products.

Table 2 Reactions of derivatives



Entry	Substrate **9**	Product **10**	Yield[a]
1			83%
2			89%
3			75%
4			74%
5			69%
6			<10%[b]
7			84%
8			67%
9			32%
10			85%
11			54%
12			78%

[a] Reaction conditions: 10 ml solvent mixture, 4 eq. Oxone. Entries 1–5, 7 and 10. DMF–H_2O 4 : 1, room temp., 16 h. Entries 6, 8, 9, 11–12: CH_3CN–H_2O, 40 °C, 1 h. Isolated yields. [b] Complex mixture.

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When we treated **14** with 2 equivalents of Oxone at room temperature in a mixture of 4 : 1 CH_3CN–H_2O, isatoic anhydride (**10a**) was isolated in 78% yield. The reaction appeared to be regioselective. Indolin-3-one (**13**) is unstable in air and readily dimerizes to form indigo (**12**). When **12** was heated at 60 °C in a 2 : 1 mixture of CH_3CN–H_2O in the presence of 4 equivalents of Oxone for one hour, the resulting product was isatoic anhydride (**10a**) in 76% yield. Indirubin (**11**), on the other hand, was very stable towards the oxidation with Oxone and was oxidized only slowly. Therefore, based on the information available to us we hypothesize that under the reaction conditions **13** is formed as an initial oxidation product. This compound either dimerizes to form indigo (**12**) or alternatively converts into isatin (**14**) directly. Further oxidation of **12** and **14** leads to isatoic anhydride (**10a**).

With the optimized reaction conditions in place, we tested the applicability of this reaction to aryl-substituted derivatives of indoles (Table 2, entries 2–9). In general the yields are high and numerous functional groups are tolerated. In the 5-position halogens, alkyl and nitro groups can be present on the ring (entries 2–9); 6-flouroindole (**9h**) and 7-fluoroindole (**9i**) also reacted smoothly. Only for 5-methoxy indole (**9f**) the yield was significantly lower.

Entries 10–12 (Table 2) indicate that indole-3-carbaldehydes can also be used as alternative starting materials for the synthesis of isatoic anhydrides. In the presence of Oxone these compounds readily react under decarboxylation to give the corresponding isatoic anhydrides: **10a**, **10k** and **10l**. The aldehyde **9j** gave isatoic anhydride (**10a**) in similar yield as the parent indole **9a**.

In summary, contrary to work done by other groups we have shown that in the presence Oxone simple indoles react very well *via* the cleavage of the 2,3-carbon–carbon bond. The main products of this reaction are isatoic anhydrides – very important intermediates for the synthesis of numerous heterocycles.[9] Our preliminary results indicate that isatin compounds may also be used as starting materials for this transformation. Both indoles and isatins are readily commercially available. Currently, the most common reaction to synthesize isatoic anhydrides is with anthranilic acids and phosgene. Phosgene is known to be poisonous and dangerous to use. Our results open up a new avenue for the preparation of isatoic anhydrides by using a solid, environmentally benign reagent.

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