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IBX-promoted domino reaction of α-hydroxy amides: a facile one-pot synthesis of isatins†

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A novel and temperature-controlled oxidation of α-hydroxy amides in the presence of IBX is described. The divergent one-pot synthesis of isatins and α-formyl amides was achieved in good to excellent yields under metal-free conditions. And these two mild methods can tolerate a variety of functional groups, and are operationally simple.

Isatins(indoline-2,3-diones) are one of the most important and widely occurring structural units in many natural products and drug intermediates.[1] They are also known to act as PET imaging agents,[2] antipsychotic drugs,[3] anticancer drugs[4] and antiepileptic drugs (Fig. 1).[5] Moreover, isatins are versatile building blocks for the construction of many significant heterocycles and spiro-fused frameworks which occur in many natural products and bioactive molecules such as spirotryprostatins, horsfiline, gelsemine, gelseverine, rhynchophylline, and elacomine.[6] Consequently, much attention has been paid to their preparation and many methods are available. Traditionally, there are two practical approaches to their synthesis: one involves strong acid- (often H_2SO_4) or base-mediated condensation of aniline with diethyl ketomalonate (Martinet procedure),[7] oxalyl chloride (Stollé procedure),[8] or chloral hydrate (Sandmeyer procedure),[9] and the other involves introduction of substituents onto a preexisting aromatic ring.[10] Later, several improved protocols for the construction of isatins have been reported such as aryne-based methods,[11] Sandmeyer modifications,[12] metal catalyzed oxidations,[13] sulfur ylide mediated carbonyl homologation,[14] and C–H amination.[15] Recently, Ilangovan and co-workers reported a molecular iodine-promoted synthesis of isatins from easily accessible 2′-aminophenylacetylenes, 2′-aminostyrenes, and 2′-amino-β-ketoesters.[16] Just later, Bredenkamp *et al.* reported the synthesis of isatins through direct oxidation of indoles with IBX-SO_3K/NaI.[17] However, all these reported methods suffer from one or more drawbacks, like the use of expensive or toxic catalyst, longer reaction time, tedious synthetic procedures, and low yield of product. Therefore, the development of effective and direct strategies for the preparation of isatins, particularly involving a metal-free reaction, would be highly desirable.

On the other hand, hypervalent iodine reagents are extensively used for various transformations in organic synthesis. For example, iodoxybenzoic acid (IBX) is widely used in oxidation reactions because of its high efficiency, easy availability, mild reaction conditions and its stability to moisture and air.[18] During the past decades, the use of IBX as the oxidant has been dramatically increased. Nicolaou *et al.* have reported a series of IBX-based synthetic technology: (1) the oxidation of benzylic sites,[19] (2) the cyclization of functionalized anilides to their heterocyclic counterparts[20] and (3) dehydrogenating ketones, aldehydes and silyl enol ethers to their corresponding α,β-unsaturated carbonyl compounds.[21] And recently, several IBX or IBX analogues based methodology in water/organic solvent biphasic system has been established.[22]

From last year, we have been focusing on the application of α-formyl amides[23] which can be easily synthesized from

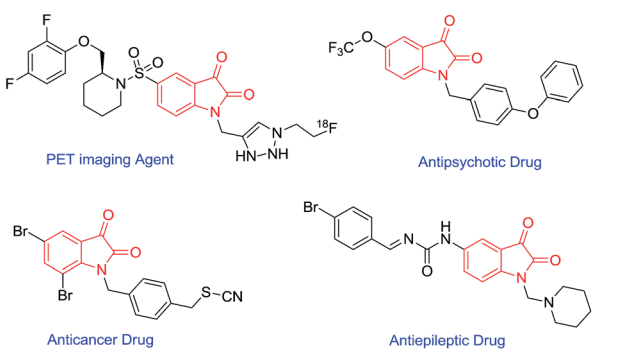

Fig. 1 Biologically active molecules containing an isatin moiety.

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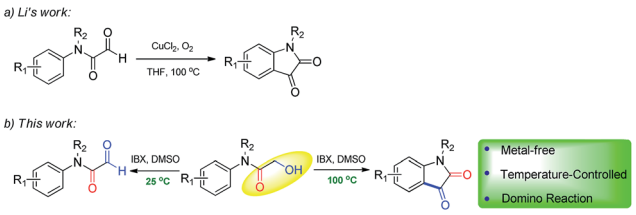
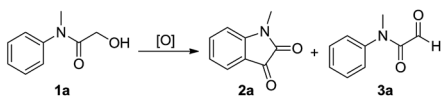


Scheme 1 Preparation of isatins.

α-hydroxy amides *via* Swern oxidation. Although Li *et al.* developed a copper-catalyzed intramolecular C–H oxidation/acylation protocol for the synthesis of isatins from α-formyl amides (Scheme 1a),[24] the synthetic method for isatins using α-hydroxy amides as starting materials hasn't been reported before. Besides, α-hydroxy amides are important substances in organic synthesis and valuable agents in medicinal chemistry.[25] Therefore, we were very interested in realizing an efficient and metal-free method for the preparation of isatins from α-hydroxy amides. During the course of our investigation, unexpectedly, we found that the reaction conditions were critical for the products formed (Scheme 1b). When IBX was used as oxidant and the reaction was conducted in DMSO at 100 °C, the expected isatins were obtained in good to excellent yields. Nonetheless, when reaction temperature dropped to 25 °C, α-formyl amides were produced as the only products. Here we wish to disclose the results of the investigation.

Table 1 Optimization of reaction conditions[a]



Entry	Oxidant	Solvent	Temp. (°C)	Yield[b] (%) 3a	3b
1	IBX	DMSO	100	91	0
2	DMP	DMSO	100	78	0
3	$PhI(CF_3COO)_2$	DMSO	100	41	6
4	$PhI(OAc)_2$	DMSO	100	27	0
5	SeO_2	DMSO	100	30	11
6	CrO_3	DMSO	100	0	0
7	NaClO	DMSO	100	0	0
8[c]	IBX	DMSO	100	63	0
9[d]	IBX	DMSO	100	90	0
10	IBX	DMF	100	29	50
11	IBX	Dioxane	100	17	72
12	IBX	Toluene	100	11	61
13	IBX	DMSO	120	87	0
14	IBX	DMSO	90	71	16
15	IBX	DMSO	50	0	61
16	IBX	DMSO	25	0	93
17[e]	IBX	DMSO/EA	0	0	0
18[d]	IBX	DMSO	90	85	16

[a] Reaction conditions: **1a** (1 mmol) and oxidant (1 mmol) in solvent (2 mL) under the corresponding temperature for 3 h. [b] Isolated yield. [c] IBX (0.5 mmol). [d] IBX (2 mmol). [e] DMSO/EA (v/v = 1 : 2.5).

At the beginning of our investigation, experiments were carried out using 2-hydroxy-*N*-methyl-*N*-phenylacetamide (**1a**) as a model substrate. After extensive screenings, we were pleased to find that IBX was the optimized oxidant for the synthesis of isatin (Table 1, entries 1–7). Notably, the isatin **2a** was exclusively obtained under this condition (Table 1, entry 1). For the optimization of the amount of IBX used in the model reaction, one equivalent was found to be adequate, as neither larger nor smaller amount showed better yields (Table 1, entries 8–9). Among various solvents examined, DMSO turned out to be the best choice, while others such as DMF, dioxane and toluene were less effective (Table 1, entries 10–12). It might be because IBX only dissolves in DMSO. Further investigation indicated that temperature was important for this transformation. An excellent yield has been obtained when the reaction was carried out at 100 °C (Table 1, entry 1). However, with the temperature increasing to 120 °C, the yield of **2a** dropped to 87% (Table 1, entry 13). And no isatin was obtained when the reaction was conducted below 90 °C (Table 1, entries 15–17). To our surprise, when **1a** reacted with IBX at 25 °C, the oxidant product **3a** was exclusively obtained in 93% yield (Table 1, entry 16). Therefore, as observed in this study, the optimized conditions for the synthesis of isatins tend to be: α-hydroxy amides (1.0 mmol) and IBX (1.0 mmol) in DMSO at 100 °C. And the optimized conditions for the synthesis of α-formyl amides tend to be: α-hydroxy amides (1.0 mmol) and IBX (1.0 mmol) in DMSO at 25 °C.

To further define the scope of this new method for the synthesis of isatins, a wide range of α-hydroxy amides were reacted under the optimized conditions. And the results were summarized in Fig. 2. A host of α-hydroxy amides bearing either the electron-donating groups such as methyl, methoxy, or electron-withdrawing groups such as nitro, halogen, were well

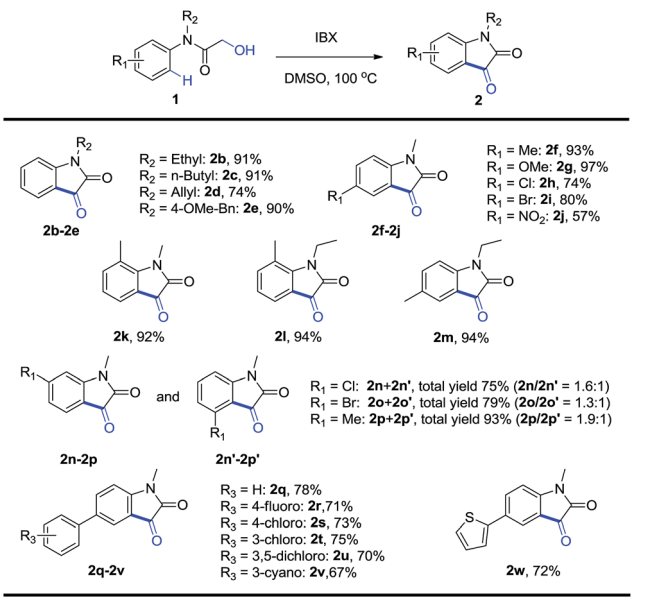
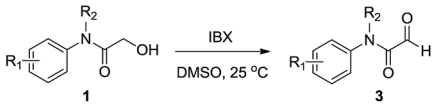


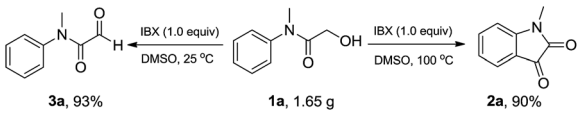
Fig. 2 Transformation of α-hydroxy amides (**1**) to isatins (**2**). Reaction conditions: α-hydroxy amides (**1**, 1.0 mmol), IBX (1.0 mmol) in DMSO (2 mL) at 100 °C for 3 h.

Table 2 Synthesis of α-formyl amides from α-hydroxy amides[a]



Entry	R_1	R_2	3	Yield[b] (%)
1	H	Ethyl	**3b**	95
2	4-MeO	Me	**3c**	90
3	4-Cl	Me	**3d**	91
4	4-(2-Thienyl)	Me	**3e**	82
5	4-(3-$NO_2C_6H_4$)	Me	**3f**	89

[a] Reaction conditions: α-hydroxy amides (**1**, 1.0 mmol), IBX (1.0 mmol) in DMSO (2 mL) at 25 °C for 3 h. [b] Isolated yield.



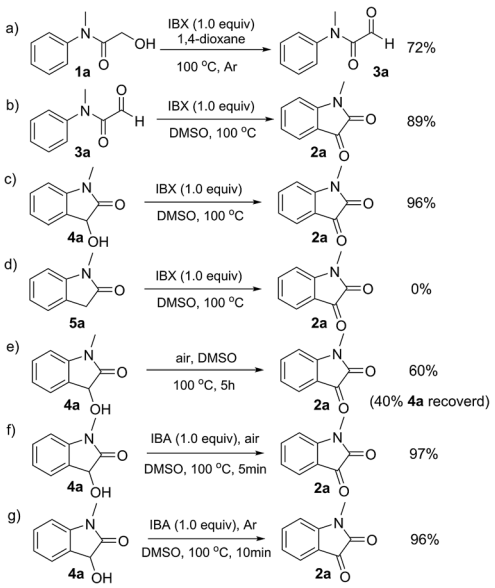
Scheme 2 Large-scale divergent synthesis.

tolerated during the course of the reaction providing the desired compounds **2b–2m** in moderate to excellent yields. And the results showed that electron-donating groups could improve the reaction yields. Notably, the substrates with *meta*-methyl or halogens on N-substituted aromatic ring provided a mixture of 4-substituted and 6-substituted isatins, and **2n–2p** were major products from the transformation, which indicated that steric hindrance had significant effect on this reaction. Besides, synthetically useful biphenyl, thienyl and allyl were tolerated in this transformation, giving **2d** and **2o–2w** in good yields. Furthermore, a variety of functional groups such as ether, nitro, halogen, cyano and allyl were well-suited for this reaction.

Under the optimal conditions as for **3a**, a range of reactions of various α-hydroxy amides (**1**) with IBX (1.0 equiv.) were carried out in DMSO at room temperature, and the results are summarized in Table 2. All the reactions proceeded smoothly to afford the corresponding α-formyl amides **3b–f** in excellent yields, indicating that the reaction is not sensitive to electronic effects (Table 2, entries 1–5). And a variety of functional groups such as ether, nitro and halogen were well-suited for this reaction. Besides, synthetically useful thienyl and biphenyl were tolerated in this transformation, giving **3e** and **3f** in good yields (Table 2, entries 4–5).

Moreover, considering the general application of these two transformations, we demonstrated the gram-scale progress, and an example of large-scale reaction with excellent yield of the desired product is shown in Scheme 2.

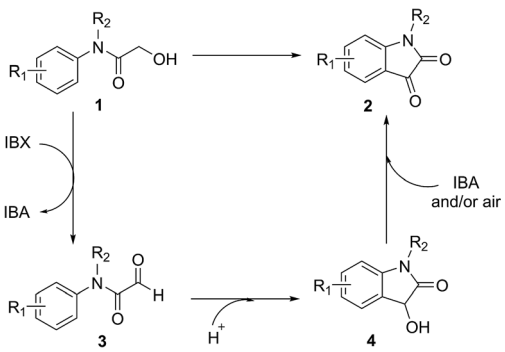
A series of control experiments have also been performed to explore the mechanism of the synthesis of isatins (Scheme 3). When 2-hydroxy-*N*-methyl-*N*-phenylacetamide (**1a**) was treated with IBX in 1,4-dioxane under Ar at 100 °C, the target product **3a** was obtained in 72% yield (Scheme 3a). And isatin **2a** could be



Scheme 3 Control experiments for the reaction mechanism.

synthesized from **3a** under the optimized conditions in good yield (Scheme 3b). These results suggested that α-formyl amide (**3a**) should be an important intermediate in the synthesis of isatin. When 3-hydroxy-1-methylindolin-2-one (**4a**), the expected product from **3a** *via* Friedel–Crafts reaction, was reacted under the optimized conditions, 96% yield of **2a** was obtained (Scheme 3c). In contrast, when compound **4a** was replaced by 1-methylindolin-2-one (**5a**), the expected product from the Friedel–Crafts reaction of **1a**, no isatin was formed (Scheme 3d). These showed that compound **4a** instead of **5a** played the role of intermediate in this transformation. Furthermore, IBA and air should be the oxidants of the transformation from **4a** to **2a** (Scheme 3e–g).

On the basis of the above results, a possible mechanism was proposed and depicted in Scheme 4. α-Hydroxy amides (**1**) was first converted into α-formyl amides (**3**) by way of IBX-promoted oxidation reaction. Subsequently, the aldehyde group of **3** was activated by acid to undergo intramolecular Friedel–Crafts cyclization to give alcohol **4**. Finally, the desired isatin **2** was obtained after **4** was oxidized by IBA and/or air.



Scheme 4 A proposed mechanism accounting for the formation of isatins.

Conclusions

In summary, an efficient and IBX-promoted divergent synthesis of isatins and α-formyl amides from α-hydroxy amides under different temperature conditions has been developed. Isatins was obtained from α-hydroxy amides in good to excellent yields at 100 °C, while decrease of temperature to 25 °C leads to α-formyl amides as the major product. These two methods feature operational simplicity, good functional group tolerance and metal-free reaction conditions. And further studies for the utilization of these products are ongoing in our laboratory.

Acknowledgements

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