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Hydrogen Peroxide Promoted Metal-Free Oxidation/Cyclization of α-Hydroxy *N*-Arylamides: A Facile One-Pot Synthesis of Isatins

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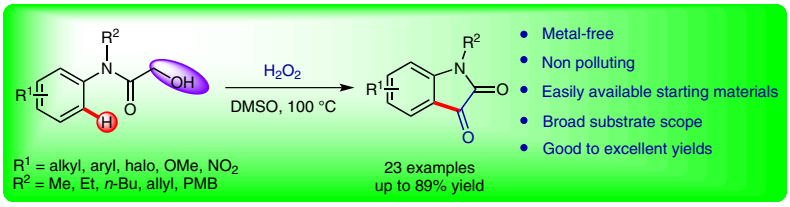

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Abstract A novel, efficient, and environmentally friendly method was developed for converting α-hydroxy *N*-arylamides into isatins (1*H*-indole-2,3-diones) by using hydrogen peroxide as oxidant. The reactions proceeded smoothly under metal-free conditions and generated the corresponding products in good to excellent yields. This method has advantages of a broad substrate scope and simple operations.

Key words hydrogen peroxide, hydroxy amides, isatins, cyclization, indoles

Isatins (1*H*-indole-2,3-diones) are common building blocks in organic synthesis. They are also frequently found in natural products that display a variety of important pharmacological and material-like properties.[1] For example, they have been developed as caspase 7 inhibitors,[2] oncolytic drugs,[3] antiparkinsonian drugs,[4] and antiepileptic drugs[5] (Figure 1). Furthermore, isatins are versatile building blocks for the synthesis of various heterocyclic compounds,[6] such as isatoic anhydrides, indoles, quinolines, or spiro-fused frameworks.[7] As a result, continual attention has been paid to the preparation of this valuable structural unit since 1840.[6–8] There are two practical approaches to their synthesis. The first is the condensation of aniline with diethyl oxomalonate (the Martinet procedure),[9] oxalyl chloride (the Stollé procedure),[10] or chloral hydrate (the Sandmeyer procedure),[11] mediated by a strong acid (often H_2SO_4) or a base. The other involves the introduction of substituents onto an existing aromatic ring.[8a,b] 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] Ilangovan and co-workers reported a molecular iodine-promoted domino synthesis of isatins from easily accessible (2-aminophenyl)acetylenes.[17] However, all these reported methods suffer from one or more drawbacks, such as the use of expensive or toxic catalysts, prolonged reaction times, tedious synthetic procedures, or low yields of product. Therefore, there is still a need to develop milder, more convenient, and more environmentally benign processes to access isatins.

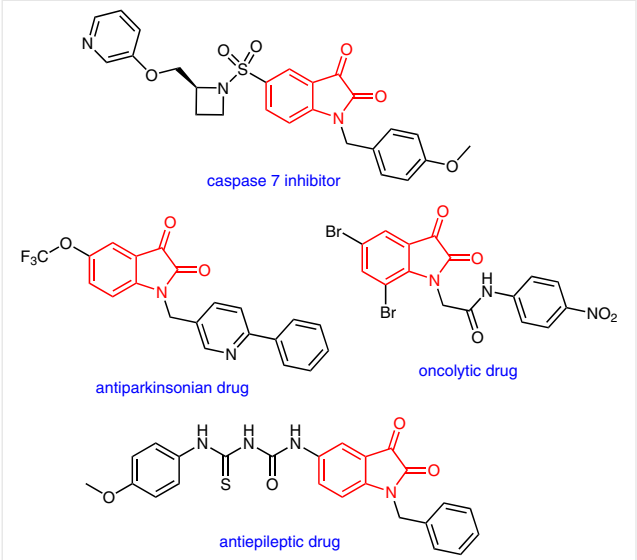
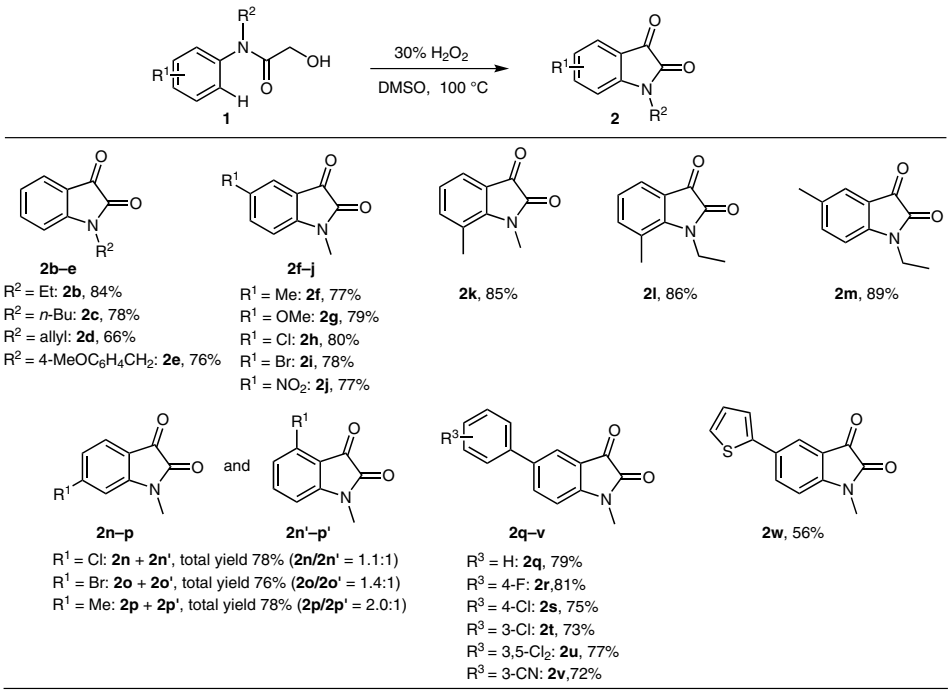


Figure 1 Biologically active molecules containing an isatin moiety

We recently reported the synthesis of isatins from α-formyl *N*-arylamides by a PCC-catalyzed intramolecular Friedel–Crafts acylation.[18] Because α-formyl *N*-arylamides are the oxidation products of α-hydroxy *N*-arylamides, we were interested in realizing the conversion of α-hydroxy *N*-arylamides into isatins in one pot. Also, hydrogen peroxide is an attractive oxidant that is widely used in laboratory-



Scheme 1 Transformation of α-hydroxy *N*-arylamides **1** into isatins **2**. *Reaction conditions*: α-hydroxy amide **1** (1.0 mmol), 30% H_2O_2 (6.0 mmol) in DMSO (2 mL) at 100 °C for 3 h under air.

scale and industrial syntheses. It is a mild oxidant and is comparatively inexpensive. From the perspective of green chemistry, the use of H_2O_2 as an oxidant is promising because water is formed as the sole byproduct.

In this study, we examined an efficient and metal-free synthesis of isatins by a H_2O_2-promoted intramolecular oxidation/cyclization reaction of α-hydroxy *N*-arylamides. To the best of our knowledge, the use of H_2O_2 in the synthesis of isatins has not been reported before.

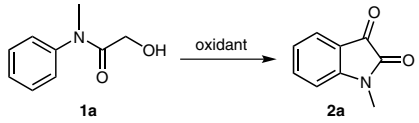
At the beginning of our investigations, we focused on the optimization of the conditions for the oxidative cyclization reaction of 2-hydroxy-*N*-methyl-*N*-phenylacetamide (**1a**) as a model substrate (Table 1). A series of peroxides promoted this reaction to give *N*-methylisatin (**2a**) in moderate to high yields (Table 1, entries 1–6), whereas $PhI(OAc)_2$, SeO_2, CrO_3, OsO_4, or PCC gave **2a** in 0–59% yield (entries 7–11). Six equivalents of H_2O_2 gave the best yield in the model reaction (entries 12 and 13). Further investigations indicated that temperature is important for this transformation, and 100 °C emerged as the best reaction temperature, whereas reactions at 50, 80, or 120 °C were less effective (entries 14–16). When the reaction was performed in various solvents, an optimal yield of 87% was obtained in DMSO (entries 12 and 17–19). The yield fell to 83% when the reaction was conducted in a sealed tube (entry 20). Therefore, H_2O_2 and DMSO, as dual oxidants, are important for the present reaction system (entries 17–19 and 21–22). The optimal reaction conditions therefore involve the α-hydroxy amide (1.0 mmol) and 30% H_2O_2 (6.0 mmol) in DMSO at 100 °C.

To evaluate the versatility of this novel method, we applied the procedure to the oxidation of a wide range of α-hydroxy *N*-arylamides (Scheme 1). Amides with electron-donating or electron-withdrawing substituents on the phenyl ring gave good to excellent yields of the desired products, indicating that the reaction is not sensitive to electronic effects. Notably, substrates with *meta*-methyl or -halo groups on the *N*-aryl ring provided mixtures of 4- and 6-substituted isatins; the 6-substituted isomers **2n**, **2o**, and **2p** were the major products in this transformation, which indicated that steric hindrance had a significant effect on this reaction. Furthermore, synthetically useful biphenyl, thienyl, and allyl substituents were tolerated in this transformation, giving **2d** and **2q**–**w** in good yields. Furthermore, a variety of functional groups such as ether, nitro, halo, cyano, and vinyl were well tolerated under the optimized reaction conditions.

Finally, in relation to the general application of this transformation, we demonstrated a gram-scale reaction of hydroxy amide **1a** that gave a good (82%) yield of the product **2a** (Scheme 2).

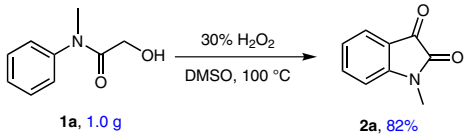
A series of control experiments were performed to explore the mechanism of this reaction (Scheme 3). When the radical scavenger TEMPO was added to the reaction mix-

Table 1 Optimization Studies for the Synthesis of Isatins[a]



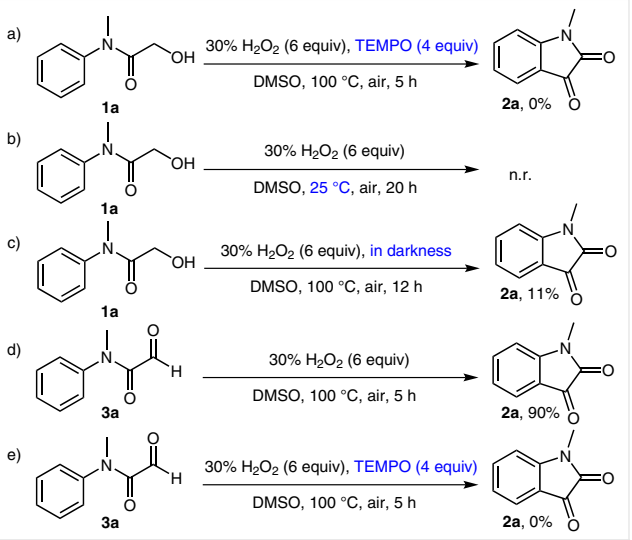
Entry	Oxidant[b] (equiv)	Solvent	Temp (°C)	Yield[c] (%)
1	H_2O_2 (2.0)	DMSO	100	72
2	TBHP (2.0)	DMSO	100	67
3	CHP (2.0)	DMSO	100	64
4	BPO (2.0)	DMSO	100	51
5	DTBP (2.0)	DMSO	100	57
6	TBPB (2.0)	DMSO	100	53
7	IBD (1.0)	DMSO	100	27
8	SeO_2 (1.0)	DMSO	100	30
9	CrO_3 (1.0)	DMSO	100	0
10	OsO_4 (1.0)	DMSO	100	11
11	PCC (1.0)	DMSO	100	59
12	H_2O_2 (4.0)	DMSO	100	81
13	H_2O_2 (6.0)	DMSO	100	89
14	H_2O_2 (6.0)	DMSO	50	41
15	H_2O_2 (6.0)	DMSO	80	74
16	H_2O_2 (6.0)	DMSO	120	51
17	H_2O_2 (6.0)	DMF	100	53
18	H_2O_2 (6.0)	1,4-dioxane	100	34
19	H_2O_2 (6.0)	toluene	100	47
20[d]	H_2O_2 (6.0)	DMSO	100	83
21	–	DMSO	100	NR[e]
22[f]	H_2O_2 (6.0)	DMSO	100	88

[a] Reaction conditions: **1a** (1 mmol), oxidant, solvent (2 mL), air, 3 h.
[b] TBHP = *tert*-butyl hydroperoxide; CHP = cumyl hydroperoxide; BPO = benzoyl peroxide; DTBP = di-*tert*-butyl peroxide; TBPB = *tert*-butyl peroxybenzoate; IBD = $PhI(OAc)_2$.
[c] Isolated yield.
[d] Sealed tube.
[e] No reaction.
[f] Under argon.



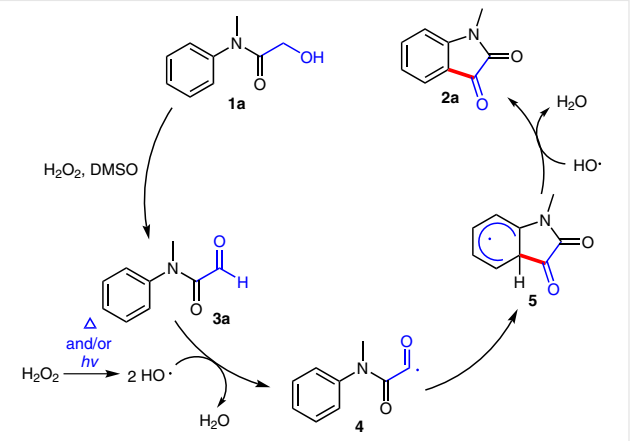
Scheme 2 Large-scale reaction

ture, no product **2a** was obtained, suggesting that the transformation might involve a radical pathway (Scheme 3, a). Also, no reaction occurred when the temperature was reduced to 25 °C (Scheme 3, b). When the reaction was conducted in darkness, only an 11% yield of **2a** was obtained (Scheme 3, c). These results imply that both a high temperature and sunlight play important roles in the radical process. Moreover, under the optimal conditions, isatin **2a** was obtained in excellent yield from the formyl amide **3a** (Scheme 3, d); this reaction also failed in the presence of TEMPO (Scheme 3, e). These results suggest that an α-formyl amide such as **3a** is an important intermediate in the synthesis of the corresponding isatin.



Scheme 3 Control experiments for the reaction mechanism

On the basis of our preliminary mechanistic investigations and some relevant publications,[19] we propose the mechanism shown in Scheme 4. Initially, α-hydroxy amide **1a** is oxidized to the α-formyl amide **3a** in the presence of H_2O_2 and DMSO. Meanwhile, hydrogen peroxide is transformed into a hydroxyl radical by the effects of heat and sunlight. The hydroxyl radical then traps the formyl hydrogen of **3a** to produce the acyl radical **4**, which is transformed into intermediate **5** by a radical aromatic substitu-



Scheme 4 A proposed mechanism for the formation of **2a**

tion reaction. Finally, the isatin **2a** is generated efficiently from intermediate **5** with the assistance of the hydroxyl radical.

In summary, a novel and efficient method for the oxidation of α-hydroxy *N*-arylamides to give isatins in the presence of H_2O_2 has been developed.[20] The utilization of cheap aqueous hydrogen peroxide as the oxidant provides a clean synthetic route, with water as the sole byproduct. In view of the wide functional-group tolerance and the mild reaction conditions, this protocol could be useful and might be widely adapted in synthetic chemistry. Further applications of this method to other substrates and detailed mechanistic investigations are in progress.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562517.

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(20) ***N*-Methylisatin (2a); Typical Procedure**
A mixture of α-hydroxy amide **1a** (152.2 mg, 1.0 mmol) and 30% aq H_2O_2 (0.68 g, 6.0 mmol, 0.61 mL) was added to DMSO (2 mL), and the mixture was stirred under air at 100 °C for 3 h. When the reaction was complete (TLC), the mixture was cooled to r.t., diluted with H_2O, and extracted with EtOAc (3 × 10 mL). The organic layer was washed with sat. brine, dried (Na_2SO_4), and evaporated to dryness. The crude residue was purified by flash chromatography [silica gel, PE–EtOAc (10:1)] to give a red solid; yield: 143.3 mg (0.89 mmol, 89%); mp 130–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 2 H), 7.15–7.11 (m, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 3.26 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 183.3, 158.1, 151.4, 138.4, 125.1, 123.8, 117.3, 109.9, 26.2. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_9H_7NNaO_2$: 184.0374; found: 184.0370.