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Sodium Iodide/Hydrogen Peroxide-Mediated Oxidation/Lactonization for the Construction of Spirocyclic Oxindole-Lactones

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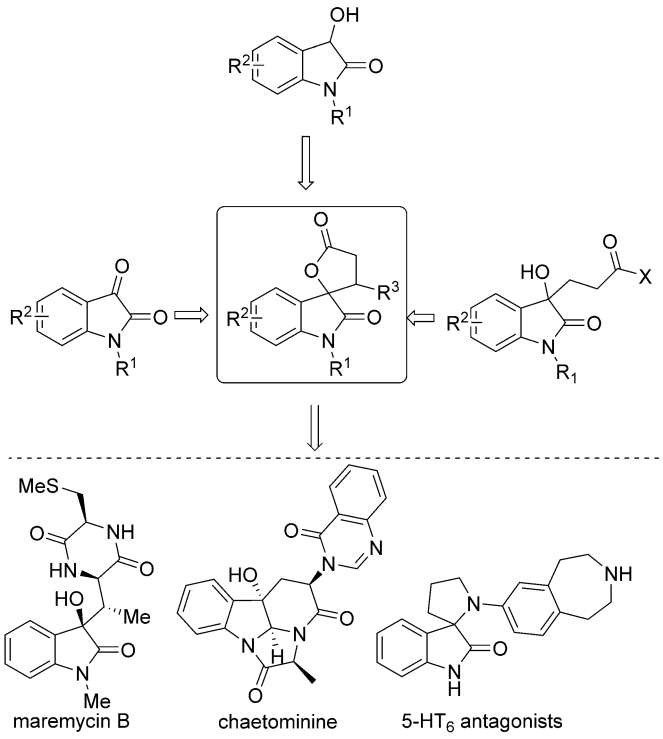
Abstract: The sodium iodide/hydrogen peroxide-mediated oxidation/lactonization of indolepropionic acids was achieved, affording the corresponding spirocyclic oxindole-lactones in moderate to high yields. This metal-free procedure features mild reaction conditions, non-toxicity and easy handling, with hydrogen peroxide (H_2O_2) as a clean oxidant.

Keywords: hydrogen peroxide; indolepropionic acids; oxidation; sodium iodide; spirocyclic oxindole-lactones

3,3-Disubstituted oxindoles are frequently found in many natural products, pharmaceuticals, and biologically active compounds. Thus the synthesis of these compounds has been intensely pursued by synthetic chemists and pharmaceutical chemists.[1] Among them, spirocyclic oxindole-lactones are a family of common oxindole motifs with interesting biological activities and act as useful synthons for the synthesis of 3-hydroxyoxindole derivatives.[2] Previously reported methods mainly focused on (i) the annulations of isatins with enals or propionic acid,[3] (ii) Michael/cyclization of 3-hydroxyoxindoles,[4] and (iii) intramolecular lactonization of 3-hydroxyoxindole esters.[5] All these methods need the use of the pre-prepared isatins and 3-hydroxyoxindoles (Scheme 1). Thus the development of general and direct methods for the preparation of spirocyclic oxindole-lactones from simple substrates like indoles is of great importance.

Oxidization/lactonization of indolepropionic acids is a direct approach for the synthesis of spirocyclic oxindole-lactones.[6] However, most of the existing methods typically require the multistep procedures and the use of environmentally harmful metals like Hg, Tl, strong acids or non-ideal solvents, which hinder their practical application. Therefore, we aimed to realize a mild and metal-free strategy for the direct synthesis of spirocyclic lactones.

Recently, a simple catalytic system combining the use of an iodide salt or iodine with a terminal oxidant has been found effective in various oxidative coupling reactions.[7,8] The exploration of efficient transforma-

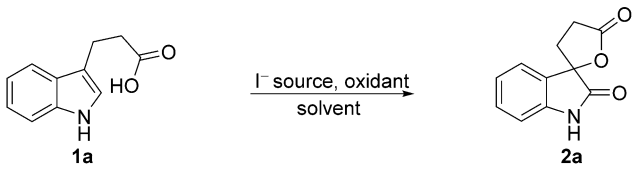


Scheme 1. Synthesis and transformation of spirocyclic oxindole-lactones.

tions by this strategy is still attractive and promising. With the continuing interest in the synthesis of spirooxindoles,[9] we herein communicate our progress in the NaI/H_2O_2-mediated oxidization/lactonization of 3-indolepropionic acids for the synthesis of spirocyclic oxindole-lactones in moderate to good yields. This method has several advantages, including being metal-free, mild reaction conditions and avoiding toxic by-products derived from the oxidant.

We started our study by using 3-indolepropionic acid **1a** as a model substrate at room temperature in CH_3CN for 12 h. To our delight, when treated with iodine (10 mol%) in the presence of H_2O_2 (2.2 equiv.), the corresponding spirocyclic oxindole-lactone **2a** could be obtained in a promising conversion of 70% (Table 1, entry 1). Encouraged by this result, further screening of other iodide sources like NaI, CuI, TBAI, NIS and KI was carried out (Table 1, entries 2–6). The conversion could be increased to 93% when using NaI (Table 1, entry 2), while TBAI and KI gave 80% and 85% conversion, respectively (Table 1, entries 4 and 6). When applying CuI and NIS as iodide source, complex mixtures were observed instead of the spirocyclic oxindole-lactone. We

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant[b] (equiv.)	Solvent	*t* [h]	Conv.[c] [%]
1	I_2	H_2O_2 (2.2)	CH_3CN	12	70
2	NaI	H_2O_2 (2.2)	CH_3CN	12	93
3	CuI	H_2O_2 (2.2)	CH_3CN	12	–
4	TBAI	H_2O_2 (2.2)	CH_3CN	12	80
5	NIS	H_2O_2 (2.2)	CH_3CN	12	–
6	KI	H_2O_2 (2.2)	CH_3CN	12	85
7	–	PIAD (2.2)	CH_3CN	12	–
8	NaI	TBHP (2.2)	CH_3CN	12	–
9	NaI	H_2O_2 (4.0)	CH_3CN	2	90
10	NaI	H_2O_2 (6.0)	CH_3CN	2	99
11	NaI	H_2O_2 (6.0)	CH_2Cl_2	2	50
12	NaI	H_2O_2 (6.0)	EtOAc	2	95
13	NaI	H_2O_2 (6.0)	toluene	2	80
14	NaI	H_2O_2 (6.0)	THF	2	10
15	NaI	H_2O_2 (6.0)	MeOH	2	40

[a] All reactions were performed with **1a** (0.10 mmol) and catalyst (10 mol%) in 1.0 mL of the solvent at room temperature.
[b] H_2O_2 is a 30% aqueous solution, TBHP is a 70% aqueous solution.
[c] Determined by ^{1}H NMR spectroscopy of the crude mixture.

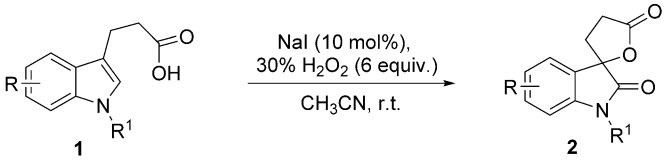
then examined other oxidants such as PIDA and TBHP, but neither of them could lead to formation of the desired product (Table 1, entries 7 and 8). Furthermore, when increasing the amount of H_2O_2 to 4.0 and 6.0 equiv., 90% and 99% conversions, respectively, were obtained in a greatly reduced reaction time of 2 h (Table 1, entries 9 and 10). At last, other solvents such as CH_2Cl_2, EtOAc, toluene, THF, MeOH were screened, but none of them gave better conversion than CH_3CN (Table 1, entries 11–15). Thus, the optimal reaction reactions were 10 mol% of NaI and 6.0 equiv. of H_2O_2 as the oxidant in CH_3CN at room temperature for 2 h (Table 1, entry 10).

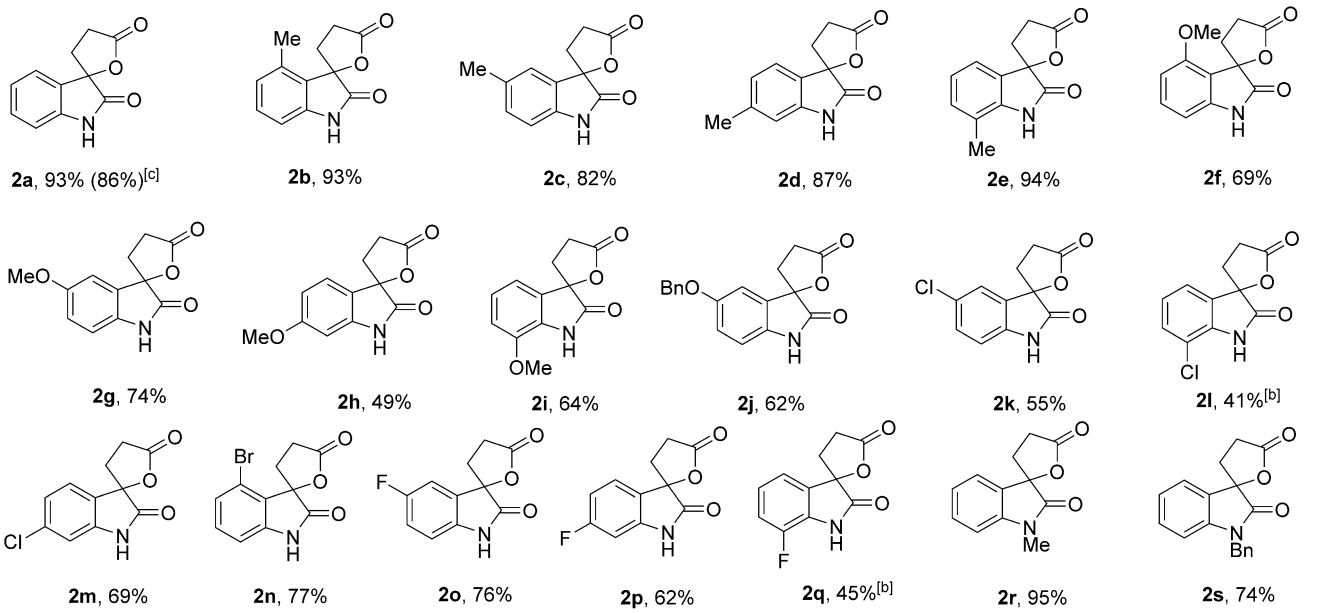
With the optimized conditions in hand, we subsequently examined the scope of this reaction by using various substituted indolepropionic acids. As shown in Table 2, all substrates containing either electron-donating or electron-withdrawing groups ran smoothly to afford the corresponding spirocyclic oxindole-lactones in moderate to good yields. Substrates with electron-donating methyl substituent on different sites worked well to afford the corresponding oxindole-lactones **2b**, **2c**, **2d** and **2e** in 82–94% yields. Compared with the methyl substituent, the methoxy or benzyloxyl substituent gave the products (**2f**–**2j**) in a slightly lower yield. Electron-withdrawing, halogen-containing indolepropionic acids were tolerated well and gave the desired products (**2k**–**2q**) in moderate yields. In addition, the N-protected indoles like 1-methyl-3-indolepropionic acid and 1-benzyl-3-indolepropionic acids could also furnish the oxindole-lactones **2r** and **2s** in 95% and 74% yields, respectively.[10] We have also tried 3-indolebutanoic acid and 2-methyl-3-indolepropionic acid. Unfortunately, the reaction did not proceed when 3-indolebutanoic acid was used, while 2-methyl-3-indolepropionic acid gave a complex mixture.

In order to demonstrate the synthetic utility of this methodology, we next prepared 3-hydroxy-2-oxindole derivatives **3** and **4** from the oxindole-lactones **2r** (Scheme 2). In the presence of ammonium hydroxide in methanol, the lactone **2r** underwent aminolysis to afford amide **3**, which could be used for the synthesis of a 5-HT6 antagonist.[11] When treated with $LiAlH_4$ in THF followed by acetic anhydride, hexahydropyrido[2,3-*b*]indole **4**, a core structure found in chaetominine,[12] could be formed in 42% overall yield from **2r** by sequential reduction/cyclization/acetylation.

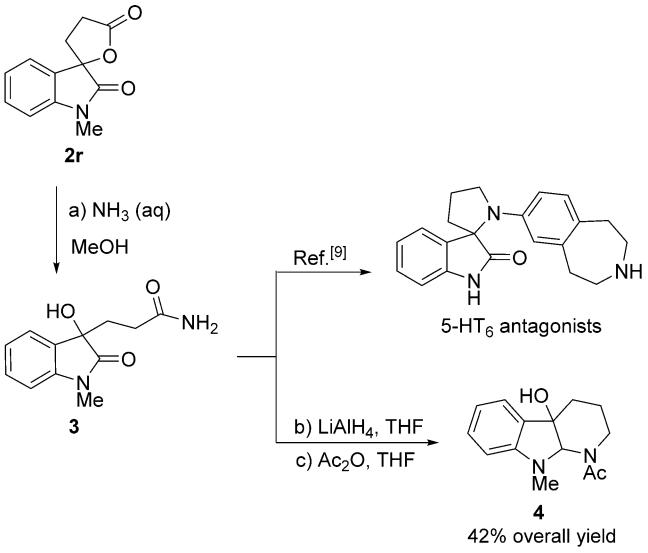
The addition of TEMPO did not hamper the reaction, showing that the reaction may not involve the radical pathway. Based on this result and the suggestion of a reviewer, we propose a plausible stepwise mechanism as shown in Scheme 3. Firstly, hypervalent iodine species $[IO]^-/[IO_2]^-$ was likely to be generated by the reaction of I^- with H_2O_2.[13] The hypervalent iodine species would then react with **1a** to form 2-iodo-3-indolepropionic acid **5**, which could be easily

Table 2. Scope of the reaction.[a]

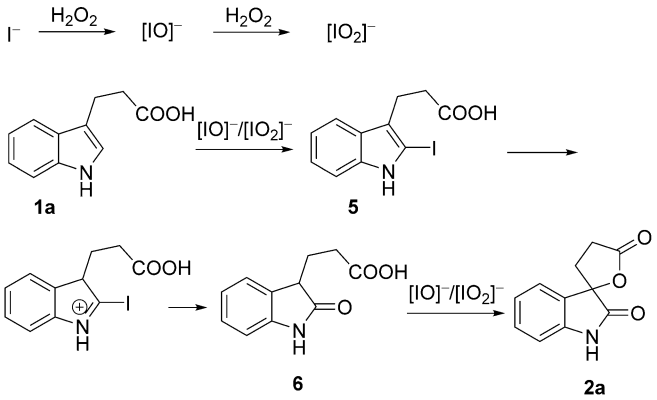




[a] Unless otherwise noted, all reactions were performed with **1** (0.10 mmol), NaI (10 mol%) and H_2O_2 (6.0 equiv.) in 1.0 mL of CH_3CN at room temperature for 2 h. The isolated yield is given in each case.
[b] This reaction was conducted at 60 °C.
[c] A scale-up experiment to 1 mmol was performed.



Scheme 2. Transformation of **2r**.



Scheme 3. Proposed mechanism.

hydrolyzed to the oxindole **6**.[14] Then, oxidation of oxindole **6** would afford the final product spirolactone **2a**.[7a]

In summary, we have developed an environmentally and economic transformation mediated by NaI/H_2O_2 for the synthesis of spirocyclic oxindole-lactones in moderate to high yield. This metal-free method can provide an efficient approach to afford 3-hydroxyoxindole derivatives, which possess potential biologically activity. Further study on the enantioselective genera-

tion of the quaternary carbon center in spirocyclic oxindole-lactones is under way in our laboratory.

Experimental Section

Typical Procedure

To a solution of 3-indolepropionic acids **1** (0.10 mmol) in CH_3CN(1.0 mL) was added NaI (10 mol%) followed by 30% H_2O_2 (6 equiv.). The reaction mixture was stirred at room temperature until completion of the reaction. After this time, the solvent was removed under vacuum and the residue was purified by flash column chromatography (petroleum ether/AcOEt) to give the pure desired product **2**.

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