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Synthesis of isatin derivatives under metal free conditions using hypervalent iodine

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ABSTRACT

Hypervalent iodine(III)/TEMPO-mediated C(sp^3), C(sp^2) C–H bond oxidation of different oxindole and indole derivatives to their corresponding isatin derivatives was successfully achieved with excellent yields at room temperature. This metal-free method provides a direct access to potential synthon isatin that could be applied in the total synthesis of several biologically active natural products.

Introduction

Isatins are bioactive scaffolds, possessing an indole motif with a ketone and a γ-lactam moiety with a number of interesting synthetic applications.[1] Their easy availability, high reactivity, and synthetic versatility have made them valuable synthons/building blocks of several heterocyclic frameworks of biological significance, such as SU11248 (FDA approved drug for renal cell carcinoma), spirobrassinin, convolutamydine A, SM-130686 (Fig. 1), donaxaridine, CPC-1, maremycins, arundaphine.[2] Isatin derivatives are responsible for a broad spectrum of biological properties and diverse modes of action, including antitumor,[3] anti- HIV,[4] antimalarial,[5] and antitubercular activities.[6]

Owing to its significance numerous elegant methodologies for the preparation of isatin derivatives have been reported in the literature. The most commonly adopted are metal mediated oxidations, catalytic oxidations of indoles[7] which typically have limitations with respect to selectivity, scope, yield, and functional group tolerance. Therefore, the design of general and direct strategies for the preparation of indoline-2,3-diones, particularly under metal-free, mild reaction conditions, would be highly valuable and interesting.

The modern interest in hypervalent iodine(III) reagents such as phenyliodine diacetate (PIDA), 2-iodoxybenzoic acid (IBX), PhI$(OCOCF_3)_2$ as versatile oxidizing agents has led to significant discoveries.[8] Hypervalent iodine reagents are mostly used for their broad reactivity, low toxicity, and high selectivity. Additionally, reactions with iodine involve mild and environmentally benign conditions.[9]

TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) as an environmentally benign oxidant has been widely used for oxidations by the generation of reactive oxoammonium species by employing stoichiometric oxidants, such as Br_2, NaOCl, and hypervalent iodine reagents.[10] Hypervalent iodine(III) reagents in combination with a catalytic amount of nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) have been employed in oxidations of alcohols to carbonyl compounds.[11] We envisioned the combination of phenyliodine diacetate and TEMPO as an efficient approach for C–H oxidation toward a general method for the synthesis of isatin motifs starting from 2-oxindoles.

The oxidative transformation of 2-oxindoles to isatins has been less explored as it involves C–H bond activation. However, the reported methods involve a multistep process with low selectivity and decreased yields.[12] More recently, I_2/TBHP mediated oxidation of 2-oxindole with 57% yield at 80 °C temperature has been reported.[7a]

As part of our ongoing studies to develop metal-free methodologies for bioactive scaffolds,[13] we herein describe the efficient phenyliodine diacetate/TEMPO system for C–H oxidation of 2-oxindoles to indolin 2,3 diones in moderate to excellent yields (Scheme 1).

To probe the feasibility of the reaction, we carried out the oxidation reaction in air using 2-oxindole **1a** in DCM in the presence of 0.5 equiv of PhIO and 0.5 equiv of *m*CPBA at room temperature.

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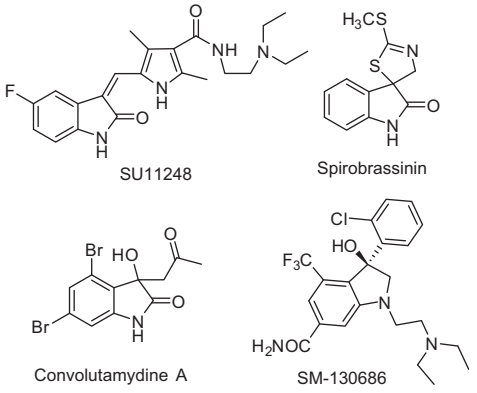
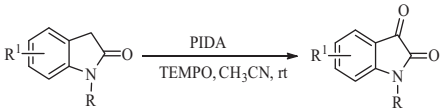


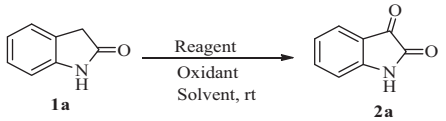
Figure 1. Representative bioactive indoline-2, 3-dione derivatives and analogues.



Scheme 1. Hypervalent iodine(III)/TEMPO catalyzed C–H oxidation of oxindoles.

The desired product was not obtained even after 48 h (Table 1, entry 1). When the reaction was mediated by other oxidant sources such as $NaIO_4$, H_2O_2, TBHP, and TEMPO they could not furnish the desired product (Table 1, entries 2–5). The desired product could be obtained in 24% yield (Table 1, entry 6) by employing PIDA as reagent and TBHP as an oxidant source. Inspired by this result mediated by hypervalent iodine(III) reagent PIDA, we screened the reaction conditions by employing various solvents with TEMPO as a terminal oxidant.

Table 1
Optimization of reaction conditions[a]



Entry	Reagent	Oxidant	Solvent	Yield[b] (%)
1	PhIO	*m*CPBA	DCM	ND
2	PhIO	$NaIO_4$	DCM	ND
3	PhIO	H_2O_2	DCM	ND
4	PhIO	TBHP	DCM	ND
5	PhIO	TEMPO	DCM	Trace
6	PIDA	TBHP	DCM	24
7	PIDA	TEMPO	DCM	45
8	PIDA	TEMPO	AcOH	40
9	PIDA	TEMPO	MeCN	94[c]
10	I_2	TEMPO	DCM	Trace
11	PhI	TEMPO	DCM	ND

[a] Reaction conditions: **1a** (0.5 mmol), reagent (0.25 mmol), and oxidant (0.25 mmol) in solvent (4 mL), at room temperature.
[b] Isolated yields.
[c] Oxidant (0.5 mmol).

To our surprise, the yield could be increased to 45%, 40%, 94% yields respectively by varying the solvents (Table 1, entries 7–9). Further screening of the reaction conditions with other solvents such as MeOH, DMSO, THF, and H_2O revealed no better results. However, when the reaction was carried out by other iodine sources such as I_2 and PhI it could not furnish the desired product (Table 1, entries 10 and 11). As the oxidation of oxindoles occurs with equimolar ratio of the oxidant, it can be considered that the environmentally benign molecular oxygen from air also acts as an additional source of oxygen as the reaction was carried out under atmospheric conditions.[14] Experimentally, when the reac-

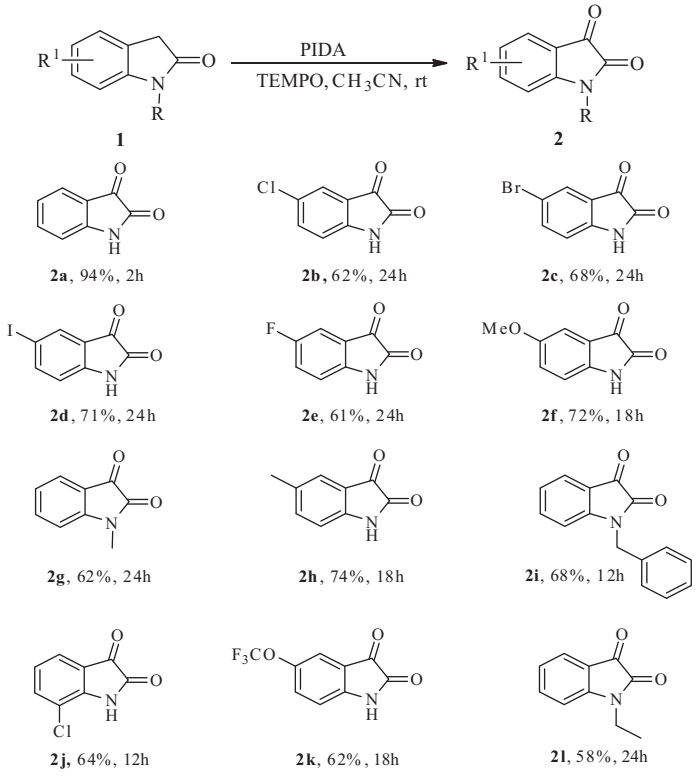


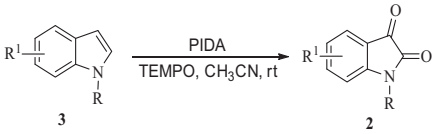
Figure 2. Synthesis of isatins by PIDA. Reaction conditions: **1** (0.5 mmol), PIDA (0.25 mmol), and TEMPO (0.5 mmol) CH_3CN (4 mL) in air at room temperature. Isolated yields are shown.

tion was carried under nitrogen atmosphere, the product formation was observed (83%, 12 h) with slight effect on the rate of reaction. Further it is also noteworthy that no product formation was observed either in the absence of TEMPO or PIDA. This clearly demonstrates that this reaction requires the interplay of both the PIDA/TEMPO and also atmospheric oxygen for completion of the cycle. Thus in conclusion PIDA/TEMPO together with atmospheric oxygen acts as the best protocol for the C–H oxidation of oxindole **1a**.

With optimal reaction conditions in hand, we next examined the generality of this method using different oxindole derivatives bearing both electron-donating (methyl, methoxy) and electron-withdrawing groups (chloro, bromo, iodo, fluoro, and trifluoromethoxy) at C-5, chloro at C-7 and substituents (methyl, benzyl, ethyl) at N-1 position. All the reactions of the substituted oxindole derivatives proceeded well to furnish the desired products in moderate to good yields as shown in Figure 2. It was observed that the unsubstituted oxindole derivative **1a** was more reactive compared to the substituted derivatives, which furnished the desired isatin **2a** in 94% yield under shorter reaction times.

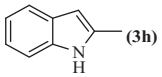
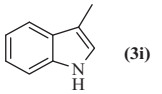
Compounds with electron donating substituents in the oxindole ring (**2f** and **2h**) gave better yields 72%, 74% than the withdrawing substituents. However, the compounds with electron withdrawing substituents in the indolinone ring (**2b**, **2c**, **2d**, **2e**, and **2k**) gave 62%, 68%, 71%, 61%, and 62%, respectively. However, there is considerable influence for C-7 substitution (**2j**) with respect to reaction rate. In case of substitution at N-1 position the yields were moderate for compounds (**2g**, **2i**, and **2l**).

Further we extended the scope of the reaction for C–H oxidation of indole derivatives in the presence of air (Scheme 2).[7a] A series of functional groups, including methyl, methoxy, fluoro, chloro, nitro, and *N*-methyl were well tolerated under the optimal reaction conditions (Table 2). Isatin **2a** could be obtained in 72% yield by direct oxidation of indole **3a** under optimized conditions. It should be noted that the reaction of **3d**, **3e**, **3g** could lead to desired products in 82%, 84%, and 81% respectively (entries 4, 5, and 7). The 5-nitroindole **3f** gave the desired product without any undesired oxidative side reaction (entry 6). However, for the electron-withdrawing substituents fluoro and chloro afforded the product in 68% and 71% yields (entries 2 and 3).



Scheme 2. C–H oxidation of indoles by hypervalent iodine(III)/TEMPO.

Table 2
Oxidation of indoles[a]

Entry	Indole **3**	Product **2**	Time (h)	Yield[b] (%)
1	R = H, R^1 = H (**3a**)	**2a**	12	72
2	R = H, R^1 = F (**3b**)	**2e**	18	68
3	R = H, R^1 = C1 (**3c**)	**2b**	18	71
4	R = H, R^1 = Me (**3d**)	**2h**	11	82
5	R = H, R^1 = OMe (**3e**)	**2f**	11	84
6	R = H, R^1 = NO_2 (**3f**)	**2m**	8	80
7	R = Me, R^1 = H (**3g**)	**2g**	15	81
8	 (**3h**)	—	24	NR
9	 (**3i**)	—	24	NR

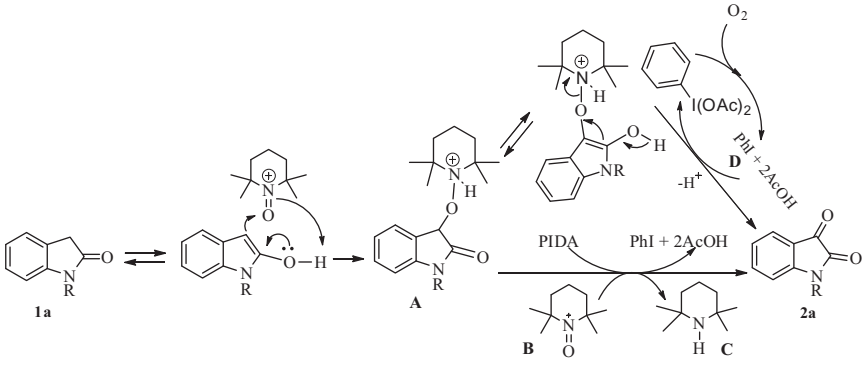
[a] Reaction conditions: **3** (0.5 mmol), PIDA (0.25 mmol) and TEMPO (0.5 mmol) in CH_3CN (4 mL), at room temperature.
[b] Isolated yields.

As expected no desired product was obtained in case of 2-methyl indole **3h** and 3-methyl indole **3i** as the methyl substituent showed significant influence on the reaction yield (Table 2, entries 8 and 9).

On the basis of the above observations and the catalytic oxidations available on the literature, a tentative mechanism to rationalize this transformation is illustrated in Scheme 3.

The hydrogen bonding of polar solvent facilitates the formation of enol tautomer **A**.[15] This formation is supported by the data (Table 1) from the solvent screening, in which low polar solvent (DCM) resulted in no reaction, whereas increasing solvent polarity (MeCN) facilitated the reaction. The increased concentration of the enol tautomer **A** likely may be due to the hydrogen bonding nature of the polar solvent. The catalytic cycle is initiated by the formation of acetic acid by phenyl iodine diacetate. The TEMPO **B** undergoes dismutation in the presence of AcOH to oxoammonium salt **D** and intermediate **C**.[16] This oxoammonium salt **D** is responsible for the selective oxidation of **1a** to **2a**. The main role of PIDA is to regenerate TEMPO, and subsequently it gets reoxidized to its initial state with molecular oxygen to complete the catalytic cycle.[17] The oxoammonium cation, which is oxidized from TEMPO, oxidizes oxindole **1a** to isatin **2a** and further it gets converted to intermediate **C**. The rearrangement of enol tautomer **A** to **2a** is clearly represented in Scheme 3.

In conclusion, we have successfully developed a convenient, simple, metal-free efficient protocol for direct synthesis of indolin-2, 3-diones[18] in moderate to good yields by using TEMPO in air as an oxidant under mild conditions. This represents a significant advancement in the area of organocatalytic C–H bond activa-



Scheme 3. Possible reaction mechanism.

tion under metal free conditions. This method has been proved to be more efficient with broad scope and high yields for C–H oxidation than the reported methods.

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Supplementary data

Supplementary data (experimental procedures, spectral/characterization data, and ^{1}HNMR and ^{13}C spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.124.

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18. *Typical procedure:* An oven-dried flask was charged with stir bar, oxindole (0.5 mmol), PIDA (0.25 mmol) in dry acetonitrile (4.0 mL). Then to the reaction mixture TEMPO (0.5 mmol) was added in presence of air and the mixture was stirred at room temperature until complete conversion takes place as indicated by TLC analysis. The resulting reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organics were dried with Na_2SO_4 and dried under vacuum to afford crude solid. Then the crude product was purified by column chromatography on silica gel.