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Oxidative Re-Cyclization of 1*H*-Indoles for Synthesis of 2-Indolylbenzoxazinones *via* Cleavage C2-C3 bond with AIBN Under Air

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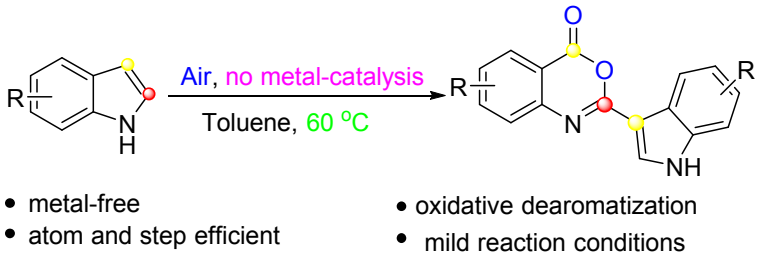


ABSTRACT

A novel and concise method for the oxidation of unprotected indole derivatives to synthesize 2-indolylbenzoxazinones in the presence of AIBN under open air has been firstly successfully demonstrated. This metal-free reaction is both atom and step efficient and is applicable to a broad scope of substrates. This new methodology provides a facile pathway for the oxidative C2-C3 bond cleavage and re-cyclization of 1*H*-indoles.

INTRODUCTION

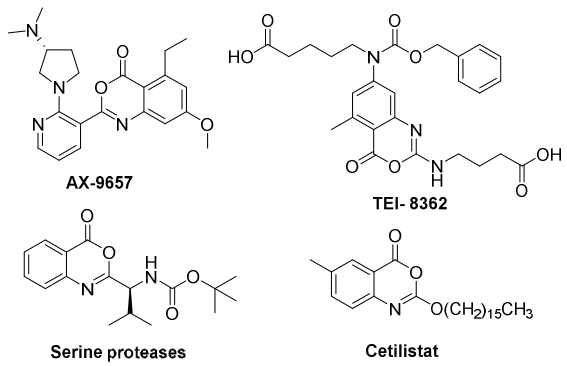


Figure 1. Structures of some bioactive 4*H*-3,1-benzoxazin-4-ones.

4*H*-3, 1-Benzoxazin-4-ones as a class has been known for more than a century. Compounds possessing this skeleton system are found in a number of physiologically and pharmaceutically

bioactive natural products with diverse bioactivities, such as HSV-1 protease inhibition, chymotrypsin inactivation, antifungal and others.[1] A few representative compounds are outlined in Figure 1.[2] Besides, benzoxazinones are useful synthetic intermediates for some pharmaceutically active compounds, [3] and they also serve as useful building blocks in organic synthesis.[4] Therefore, benzoxazinones represent a class of annulated nitrogen heterocycles that have attracted much interest from both organic and pharmaceutical chemists. In the past decade, great efforts have been devoted to these moieties and a number of synthetic methods have been reported.[5-7] Among the different methodologies developed for their preparation, [5] the most popular synthetic pathways involve the use of anthranilic acid or its derivatives, N-acylanthranilic acids, or isatonic anhydride.[6] Other synthetic methods such as oxidation of 2-substituted indoles and 2-phenylindolenin-3-ones, [4 + 2] cycloaddition of 1,2,3-benzotriazin4-ones with benzaldehydes, electrochemical cyclization of o-trichloroacetylanilides, and solid-phase synthesis were described. [7] Although alternative methodologies are known, some of them still suffer from hazardous materials or harsh reaction conditions. Hence, it is still desirable to extend known protocols for benzoxazinone synthesis.

As we all know, indoles are structural motifs prevalent in bioactive synthetic and natural products.[8] They are employed widely in medicinal chemistry, pharmacological research, and material applications.[9] Consequently, the development of efficient methodologies for the preparation and functionalization of various indole derivatives has been a subject of intense research efforts. Notably, to our knowledge, there is yet no report for direct functionalization of 1*H*-indoles to afford 2-indolylbenzoxazinones. Herein, we present a facile route for the construction of the benzoxazinone skeleton through the oxidative cleavage of 1*H*-indoles C2-C3 bond along with re-cyclization in the presence of AIBN and air.

RESULTS AND DISCUSSION

Initially, we proposed that indole could react with the toluene through the oxidative cross-coupling reaction. We chose 1*H*-indole **1a** as the model to optimize the conditions. By treating the substrate **1a** with AIBN (2.0 equiv) at 60 ^{o}C for 6 h in toluene under air, surprisingly, an unexpected product 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one **2a** was obtained in 30% yield, and the structure of **2a** was confirmed unambiguously through an X-raycrystal analysis (SI, CCDC 1496619). 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one was natural product as known as cephalandole A, showed significant cytotoxicity against human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268) cell lines.[10] Moreover, 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one was also the intermediate for some other natural alkaloids (Figure 2). This discover attracted our interest.[11] Encouraged by this result, a variety of oxidants such as O_2 , Oxone , DTBP, $PhI(OAc)_2$ and H_2O_2 were screened, but all failed to give the desired product in better results than air (entries 1−6; Table 1). Subsequently, a series of additives, including Et_3N, HOAc, PivOH, CF_3COOH, TsOH were examined. PivOH was clearly the most effective, giving **2a** in 76% yield (entries 7-11; Table 1). However, no matter we increased or decreased the amount of PivOH, no better yield was abtained (entries 12−13; Table 1). Optimization of different solvents revealed that DMF, DMSO, PhCl, and DMC were inferior to toluene in the reaction (entries 14-17; Table 1). It should be noted that lower yields of product 2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one **2a** was obtained when we changed the amount

of AIBN (entry 18; Table 1). The reaction temperature and time were also varied; 60 °C and 6 h gave the best result (entries 19–21; Table 1). Moreover, when we used TBHP, I_2, $Na_2S_2O_8$ and H_2O_2 to replace AIBN, however, we all failed to detect the desired product (entry 22; Table 1). Finally, the best result was obtained by using AIBN (2.0 equiv) in the presence of PivOH (1.0 equiv) in toulene at 60 °C under air for 6 h (entry 9; Table 1).

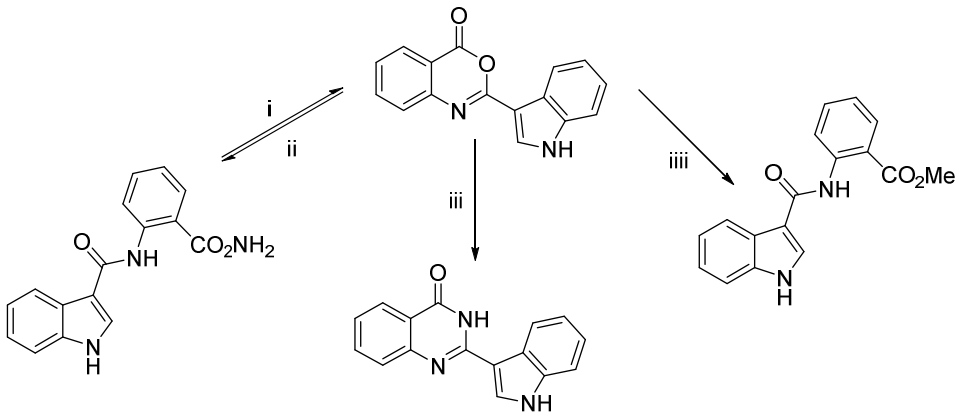
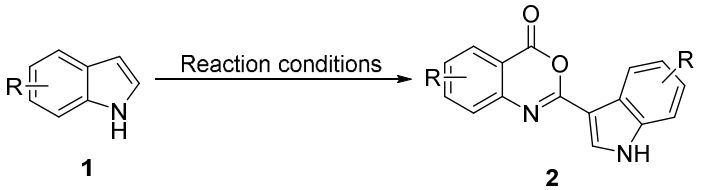


Figure 2. The applications of **2a**: (i) NH_4OAc, DMF, 70 °C, 2 h; (ii) Xylenes, p-TsOH (cat.), reflux, (Dean-Starktrap), 24 h; (iii) formamide (neat), 200 °C, 10 min, MW; (iiii) MeOH, reflux, 4 h, 99%.

Table 1. Optimization Studies [a].



1 **2**

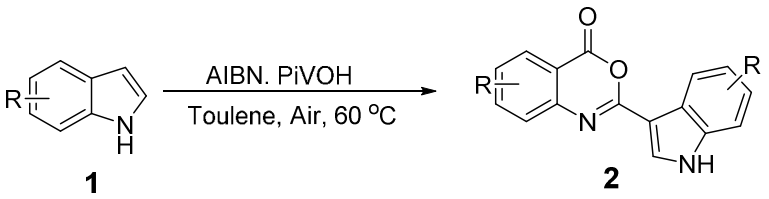
Entry	Oxidant (equiv)	Additive (equiv)	Solvent	Temp. (°C)	Yield (%)[b]
1	Air		Tol.	60	30
2	O_2		Tol.	60	15
3	Oxone		Tol.	60	16
4	DTBP		Tol.	60	20
5	PIDA		Tol.	60	24
6	H_2O_2		Tol.	60	8
7	Air	Et_3N	Tol.	60	35
8	Air	HOAc (1.0)	Tol.	60	58
9	Air	PivOH (1.0)	Tol.	60	76
10	Air	TFA (1.0)	Tol.	60	N.D.
11	Air	TsOH (1.0)	Tol.	60	N.D.
12	Air	PivOH (0.5)	Tol.	60	45
13	Air	PivOH (2.0)	Tol.	60	68

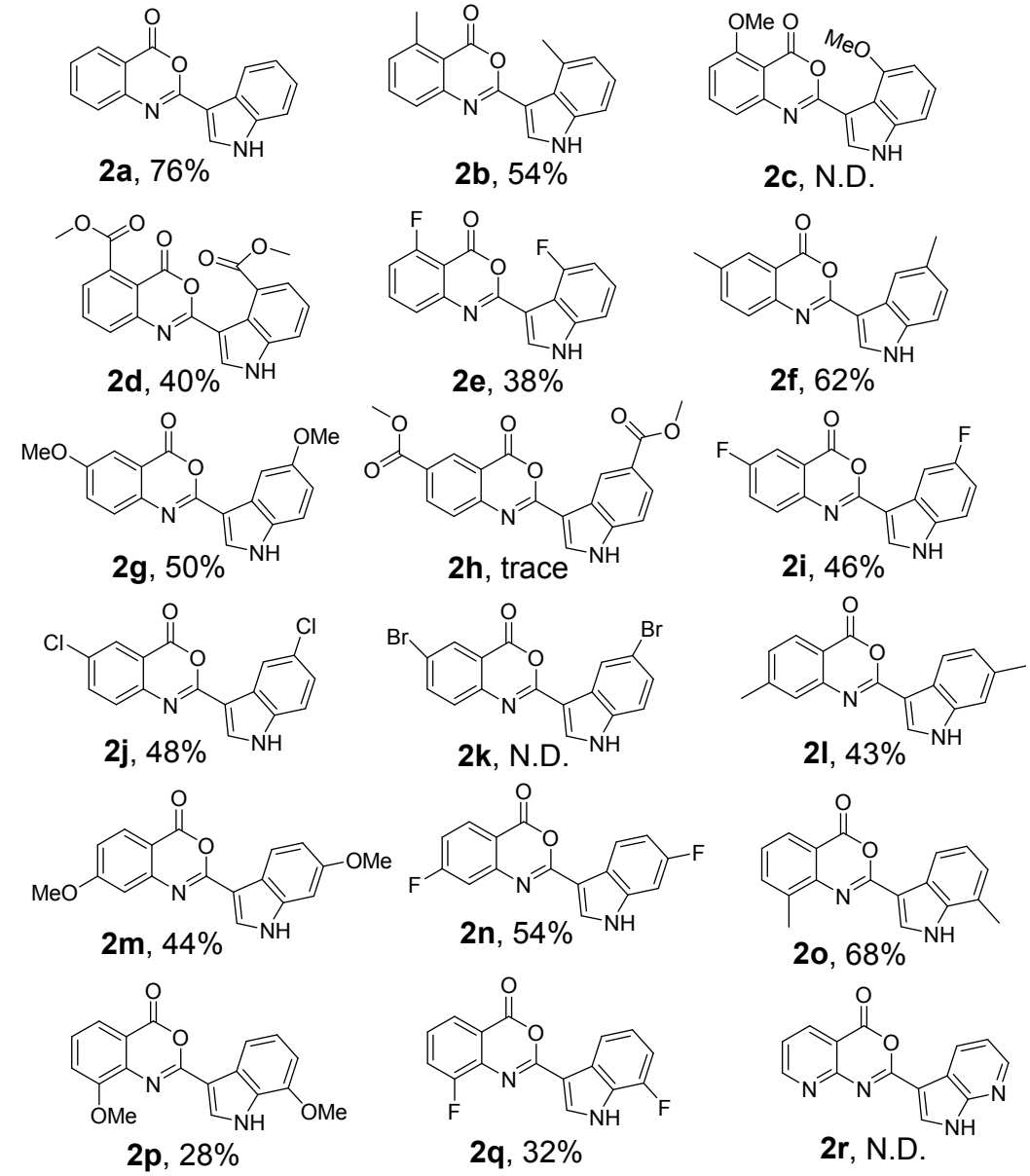
14	Air	PivOH (1.0)	DMF	60	trace
15	Air	PivOH (1.0)	DMSO	60	N.D.
16	Air	PivOH (1.0)	PhCl	60	66
17	Air	PivOH (1.0)	DMC	60	45
18	Air	PivOH (1.0)	Tol.	60	45[c],46[d]
19	Air	PivOH (1.0)	Tol.	60	46[e],64[f]
20	Air	PivOH (1.0)	Tol.	40	30[g]
21	Air	PivOH (1.0)	Tol.	80	55
22	Air	PivOH (1.0)	Tol.	60	N.D.[h]

[a] Indole **1a** (0.5 mmol), AIBN (1.0 mmol, 2.0 equiv), oxidant, additive and solvent (2 mL) at 60 °C for 6 h. [b] Yield of isolated product. [c] AIBN (0.5 mmol, 1.0 equiv). [d] AIBN (1.5 mmol, 3.0 equiv). [e] 4 h. [f] 8 h. [g] the reaction prolonged to 8h. [h] THBP (2.0 equiv), I_2 (2.0 equiv), $Na_2S_2O_8$ (2.0 equiv), H_2O_2 (2.0 equiv) instead of AIBN. AIBN = azobis(isobutyronitrile), DTBP = tert-Butyl peroxide, PIDA = Iodobenzene diacetate, TFA = trifluoroacetic acid, Tol. = toluene, TBHP = tert-Butyl hydroperoxide, HOAc = acetic acid, PivOH = Trimethylacetic acid, TsOH = 4-methylbenzenesulfonic acid, DMF = Dimethyl Formamide, DMSO = dimethylsulfoxide, DMC = Dimethyl phosphate, N.D. = no detection.

With the optimized reaction conditions established, the scope and generality of the reaction were investigated (Table 2). Delightly, a relatively broad range of indole derivatives with a substituent at C4, C5, C6, or C7 position of the indole ring were mostly successfully transformed to desired products in moderate yields. For example, indoles with a methyl at the 4-, 5-, 6- or 7-positions were examined, affording the desired products in 54%, 62%, 43% and 68%, respectively (Table 2, entries **2b**, **2f**, **2l**, **2o**). Unfortunately, we did not detect the product when a methoxy at C4 of 1*H*-indole (Table 2, entry **2c**), but the indoles with methoxy at C5, C6 and C7 positions could afford the products **2g**, **2m** and **2p** in 50 %, 44% and 28% (Table 2, entries **2g**, **2m**, **2p**). In addition, some halogen substituents (F, Cl, or Br) were tested under the optimal conditions, except the bromo group (Table 2, entry **2k**), the others could be smoothly transformed into the desired products (Table 2, entries **2e**, **2i-2j**, **2n**, **2q**). However, 7-azaindole (**1r**) failed to produce the desired product under the optimal conditions (**2r**).

Table 2. Oxidation of 1H-indoles for the synthesis of 2-indolylbenzoxazinones with AIBN[a]



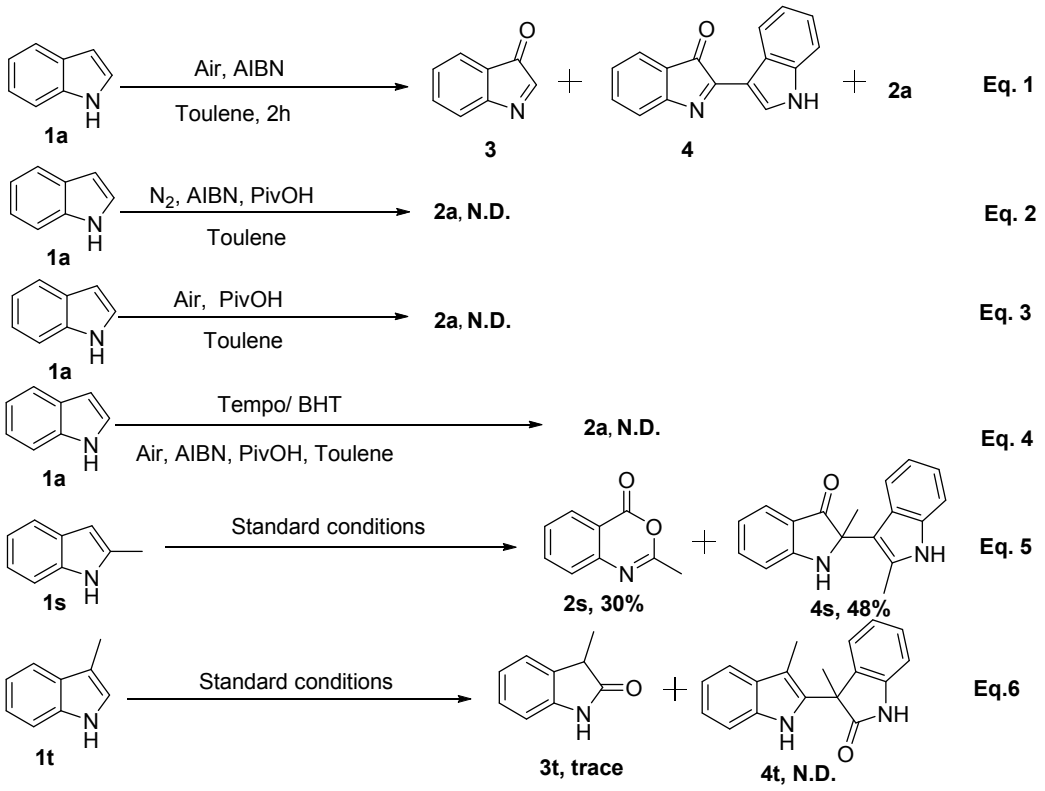


[a] Reaction conditions: **1a** (0.5 mmol), AIBN (1.0 mmol, 2.0equiv) in toluene (2 mL) at 60 °C under air for 6 h. [b] Isolated yield. N.D. = not detection.

In order to explore the reaction mechanism, some control experiments were conducted (Scheme 1). According to the results of the transformations, we proposed that the 3*H*-indol-3-ones may in fact be the crucial intermediates in the reaction. Unfortunately, under the optimized conditions, none of

the intermediates formed in isolable quantities. Therefore, we performed a control experiment in the absence of PivOH, the high resolution mass spectrum of crude mixtures (see the supporting information) withdrawn at 2 h indicated the formation of 3H-indol-3-one **3**, 1'*H*,3*H*-[2,3'-biindol]-3-one **4** (Scheme 1, Eq.1). As shown in Equation 2 and 3, we conducted the reaction in the absence of AIBN and air, respectively (Scheme 1, Eq. 2 and 3). The recations both failed to afford the product **2a.** The results indicated that AIBN and air were important factors in the conversion of **1a** to **2a**. Moreover, we added 2.0 equivalent radical-trapping reagents TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-tert-butyl-p-cresol) into the reaction system, respectively, resulting in no formation of desired products (Scheme 1, Eq.4). The results implied that the radical mechanism might be responsible for the reaction. Then, we used the substrates 2-methy-1*H*-lindole **1s** and 3-methy-1*H*-lindole **1t** to perform the reactions (Scheme 1, Eq. 5 and 6). Under the standard conditions, 2-methy-1*H*-lindole could generate 2-methyl-4H-benzo[d][1,3]oxazin-4-one **2s** in 30% and 2-methyl-2-(2-methyl-1H-indol-3-yl)indolin-3-one **4s** in 48%; however, the transformation of 3-methy-1*H*-lindole was not very positive, we just detected only a trace amount of 3-methylindolin-2-one **3t.** Consequently, the results of equations 5 and 6 could also provide an evidence for the intermediate of **4**.

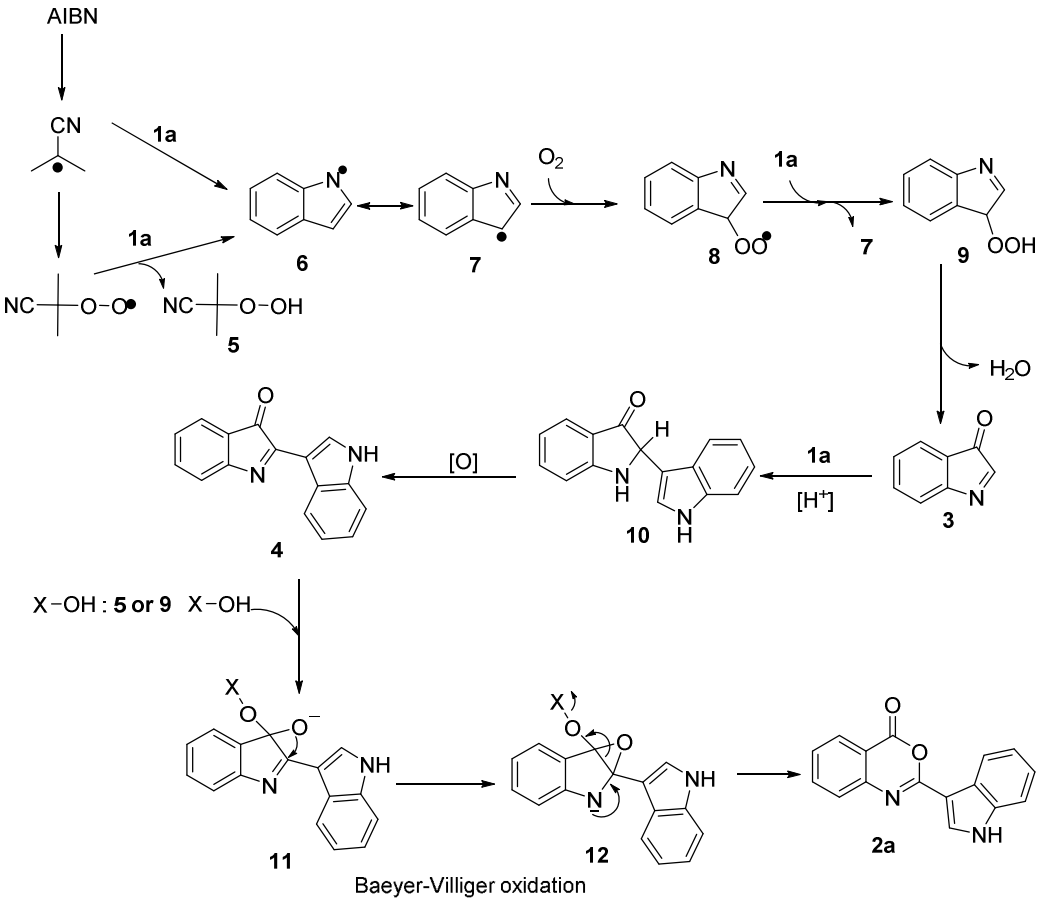
Scheme 1. Different Control Experiments



Based on the above results and literature reports,[12-26] the proposed mechanism is outlined in Scheme 2. Firstly, an initial hydrogen abstraction from the nitrogen atom of the indole ring by AIBN leads to the formation of an indolyl radical **7**. Then, in the prensence of dioxygen, the

formation of a C3-located indole hydroperoxide **8** followed by its fractionation to the intermediate 3*H*-indol-3-one **3**. Subsequently, the 1*H*-indole **1a** undergoes nucleophilic attack to **3** mediated by acid to produce another crucial intermediate **4**. Shortly afterwards, Baeyer−Villiger oxidation of **4** by **5 or 9** occurs leading to generating the product **2a** through C2-C3 bond cleavage.

Scheme 2. Plausible mechanism



CONCLUSIONS

In summary, we have developed a new, simple and practical method for the oxidative re-cyclization of 1*H*-indoles through the cleavage of C2-C3 bond to synthesize 2-indolylbenzoxazinones in the presence of AIBN under open air. This strategy features tolerance of a relatively wide range of functional groups, easily available starting materials, simple operation and mild reaction conditions. To the best of our knowledge, this is the first example of constructing benzoxazinones from easily available unprotected indole derivatives through one-pot method.

EXPERIMENTAL SECTION

General information All of the reactions were carried out in oven-dried flask. Products were

purified by flash chromatography on 200–300 mesh silica gels. Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. Unless otherwise noted, chemical shifts (δ) are reported in ppm using TMS as internal standard; ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectras were recorded in $CDCl_3$ (δ = 77.00 ppm) and *d*-DMSO (δ = 39.50 ppm). The high resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Melting points were determined on a microscopic apparatus. Copies of ^{1}H NMR and ^{13}C NMR spectra are provided. Commercially available reagents were used without further purification.

Typical Experimental Procedure for the Synthesis of 2-Indolylbenzoxazinones (2) An oven-dried tube with a magnetic stir bar was charged with the 1*H*-indole compound **1** (0.5 mmol, 1.0 equiv.), AIBN (1.0 mmol, 2.0 equiv.), PivOH (0.5 mmol, 1.0 equiv.) and toluene (2 mL). Then the reaction mixture was stirred at 60 ^{o}C under air until complete consumption of starting material as monitored by TLC. After the reaction was finished, the mixture was concentrated in vacuum, and the residues were purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford the desired product **2**.

2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (2s) [27]**,** yield 30%, 24.2 mg; brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 7.77-7.73 (m, 1H), 7.50-7.43 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 159.5, 146.3, 136.4, 128.3, 128.0, 126.2, 116.5, 21.2.

2-methyl-2-(2-methyl-1*H*-indol-3-yl)indolin-3-one (4s) [20]**,** yield 48%, 33.1 mg; yellow solid; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 10.90 (s, 1H), 7.74 (s, 1H), 7.52-7.45 (m, 2H), 7.23 (t, J = 8.0 Hz, 2H), 6.94 (dt, J_1 = 7.1 Hz, J_2 = 0.9 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.81- 6.77 (m, 1H), 6.74-6.70 (m, 1H), 2.40 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 203.9, 159.9, 137.5, 134.7, 133.0, 127.2, 124.4, 120.0, 119.4, 118.4, 117.7, 117.0, 111.8, 110.5, 108.5, 66.3, 24.4, 14.0.

2-(1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2a), yield 76%, 49.8 mg; yellow solid; m.p.: 224-226 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.12 (s, 1H), 8.43 (dd, J_1 = 6.0 Hz, J_2 = 3.2 Hz, 1H), 8.29 (d, J = 2.8 Hz, 1H), 8.10 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.90-7.86 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.29-7.25 (m, 2H) ; ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.2, 155.6, 147.6, 137.0, 136.7, 131.6, 128.0, 126.8, 126.2, 124.9, 122.9, 121.4, 121.3, 116.2, 112.5, 106.4; HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_{10}N_2O_2H^+$: 263.0815, found: 263.0819.

5-methyl-2-(4-methyl-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2b), yield 54%, 39.1 mg; yellow solid; m.p.: 222-224 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ:12.05 (s, 1H), 8.18 (d, J = 3.1 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28(d, J = 7.5Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 2.89 (s, 3H), 2.71 (s, 3H) ; ^{13}C NMR (100 MHz, *d*-DMSO) δ: 158.9, 155.5, 148.8, 141.7, 137.6, 135.7, 132.4, 131.3, 129.3, 124.1, 123.54, 123.49, 122.9, 114.4, 110.3, 108.3, 23.1, 22.2; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_2H^+$: 291.1128, found: 291.1132.

Methyl 2-(4-(methoxycarbonyl)-1*H*-indol-3-yl)-4-oxo-4*H*-benzo[*d*][1,3]oxazine-5-carboxylate (2d), yield 40%, 37.8 mg; yellow oil; ^{1}H NMR (400 MHz, CDCl3) δ: 10.12 (s, 1H), 7.94 (d, J = 3.0 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.53-7.50 (m, 2H), 7.39 (d, J = 7.4Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 4.00 (s, 3H), 3.79 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 169.0, 158.1, 155.9, 148.2, 137.4, 136.0, 134.9, 132.4, 128.0, 126.1, 125.5, 123.0, 122.9, 121.2, 115.4, 112.9, 108.2, 53.2, 52.3; HRMS: $[M+H]^+$ m/z calcd for $C_{20}H_{14}N_2O_6H^+$: 379.0925, found: 379.0931.

5-fluoro-2-(4-fluoro-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2e), yield 38 %, 28.31 mg; yellow solid; m.p.: 258-260 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ:12.46 (s, 1H), 8.36 (s, 1H), 7.89-7.84 (m, 1H), 7.37 (t, *J* = 8.5 Hz, 2H), 7.32-7.22 (m, 2H), 7.01-6.97 (m, 1H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 161.0 (d, *J* = 262.6 Hz), 155.7, 155.4 (d, *J* = 249.6 Hz), 154.9 (d, *J* = 4.8 Hz), 149.4, 139.9 (d, *J* = 10.0 Hz), 137.5 (d, *J* = 10.8 Hz) , 133.3, 123.8 (d, *J* = 7.6 Hz), 122.2 (d, *J* = 3.6 Hz) , 113.6 (d, *J* = 20.3 Hz), 112.6 (d, *J* = 19.2 Hz), 109.0 (d, *J* = 3.7Hz), 107.4 (d, *J* = 20.6Hz), 105.9 (d, *J* = 3.1Hz), 105.5 (d, *J* = 7.1Hz). HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_8F_2N_2O_2H^+$: 299.0627, found: 299.0622.

6-methyl-2-(5-methyl-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2f), yield 62%, 44.7 mg; yellow solid; m.p.: 252-254 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 11.97 (s, 1H), 8.19 (d, *J* = 2.8 Hz, 2H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.70 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, J_1 =8.2 Hz, J_2 = 1.6 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H) ; ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.3, 155.1, 145.5, 137.8, 136.6, 135.3, 131.2, 130.2, 127.4, 126.0, 125.1, 124.3, 120.9, 115.8, 112.1, 106.0, 21.4, 20.6; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_2H^+$: 291.1128, found: 291.1133.

6-methoxy-2-(5-methoxy-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2g), yield 50%, 40.2 mg; yellow solid; m.p.: 243-246 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 11.92 (d, *J* =1.6 Hz, 1H), 8.16 (d, *J* = 3.2 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.50-7.47 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.3, 157.7, 155.0, 153.9, 141.7, 131.8, 130.9, 127.9, 125.6, 125.4, 116.7, 113.137, 112.5, 108.7, 106.1, 103.4, 55.8, 55.3; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_4H^+$: 323.1026, found: 323.1029.

6-fluoro-2-(5-fluoro-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2i), yield 46%, 34.3 mg; yellow solid; m.p.: 265-268 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: :12.21 (s, 1H), 8.30 (d, *J* = 8.7 Hz,1H), 8.05 (dd, *J* = 10.0 Hz, 2.6 Hz, 1H), 7.78 (dt, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H), 7.74 (dd, J_1 = 6.5 Hz, J_2 = 1.7 Hz, 2H), 7.51 (dd, J_1 = 8.9 Hz, J_2 = 4.6 Hz, 1H), 7.11(td, J_1 = 9.2 Hz, J_2 = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.8 (d, J = 246.6 Hz), 158.5 (d, J=3.2 Hz), 158.3 (d, J=235.1 Hz), 154.7, 144.3, 133.6, 132.9, 128.9 (d, J=8.4Hz), 125.4 (d, J=11.2 Hz), 124.6 (d, J=23.9 Hz), 117.4 (d, J=8.8 Hz), 113.8 (d, J=10.0 Hz), 113.0 (d, J=24.10 Hz), 111.1 (d, J=26.2 Hz), 106.3 (d, J=4.4 Hz), 106.1 (d, J=25.0 Hz); HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_8F_2N_2O_2H^+$: 299.0627, found: 299.0632.

6-chloro-2-(5-chloro-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2j), yield 48%, 39.6 mg; yellow solid; m.p.: 248-251 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.33 (s, 1H), 8.36-8.35 (m, 2H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.91-7.88 (m, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.30-7.27 (m, 1H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 158.1, 155.4, 146.2, 136.5, 135.5, 133.2, 130.7, 128.3, 126.8, 126.3, 125.9, 123.0, 120.3, 117.7, 114.2, 106.0; HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_8Cl_2N_2O_2H^+$: 331.0036, found: 331.0043.

7-methyl-2-(6-methyl-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2l), yield 43%, 37.2 mg; yellow solid; m.p.: 246-248 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 11.97 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 3.2 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.30 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H), 7.09 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.2, 155.8, 147.7, 147.7, 137.4, 132.2, 130.9, 128.1, 127.8, 126.1, 123.12, 122.8, 121.0, 113.5, 112.2, 106.4, 21.5, 21.3; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_2H^+$: 291.1128, found: 291.1133.

7-methoxy-2-(6-methoxy-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2m), yield 44%, 35.4 mg; yellow solid; m.p.: 250-251 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 11.91 (s, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.14 (d, *J* = 2.5 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.05-7.00 (m, 2H), 6.91-6.89 (m, 1H), 3.94 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 165.9, 158.8, 156.5, 156.4, 150.1, 137.8, 130.5, 129.7, 122.0, 118.8, 115.8, 111.6, 108.8, 108.1, 106.5, 95.2, 39.1,38.9; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_4H^+$: 323.1026, found: 323.1029.

7-fluoro-2-(6-fluoro-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2n), yield 54%, 40.2 mg; yellow solid; m.p.: 278-280 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.17 (s, 1H), 8.34(dd, J_1= 8.8 Hz, J_2 = 5.6 Hz, 1H), 8.26 (d, J=2.8 Hz, 1H), 8.11 (dd, J_1 = 8.7 Hz, J_2 = 6.2 Hz, 1H), 7.42-7.39 (m, 1H), 7.32-7.26 (m, 2H), 7.10 (dt, J_1 = 9.2 Hz, J_2 = 2.4Hz, 1H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 167.0 (d, J = 254.7 Hz), 160.6, 158.2, 156.5, 150.0 (d, J=13.9 Hz), 137.0 (d, J=12.64 Hz), 132.7 (d, J=2.4 Hz), 131.1 (d, J=11.3 Hz), 122.4 (d, J=9.9 Hz), 121.5, 115.0 (d, J=23.6 Hz), 113.2 (d, J=1.8 Hz), 111.8 (d, J=22.7 Hz), 110.0 (d, J=24.1 Hz), 106.3, 98.7 (d, J=26.0 Hz); HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_8F_2N_2O_2H^+$: 299.0627, found: 299.0630.

8-methyl-2-(7-methyl-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2o), yield 68%, 49.3 mg; yellow solid; m.p.: 266-268 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.14 (s, 1H), 8.26-8.24 (m, 2H), 7.94-7.92 (m, 1H), 7.75 (d, J=6.9 Hz, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.06 (d, J=7.1 Hz, 1H), 2.62 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.6, 154.6, 145.9, 137.0, 136.5, 134.3, 130.9, 126.2, 125.5, 124.8, 123.4, 121.8, 121.7, 118.8, 115.9, 107.1, 16.9, 16.7; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_2H^+$: 291.1128, found: 291.1132.

8-methoxy-2-(7-methoxy-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2p), yield 28%, 22.5 mg; yellow solid; m.p.: 225-228 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.26 (s, 1H), 8.06-8.03 (m, 2H), 7.66 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.50-7.48 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 3.99 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 159.3, 154.4, 153.6, 146.4, 137.6, 130.1, 127.1, 126.9, 126.5, 122.2, 118.9, 117.9, 116.9, 114.0, 107.4, 103.5, 56.4, 55.3; HRMS: $[M+H]^+$ m/z calcd for $C_{18}H_{14}N_2O_4H^+$: 323.1026, found: 323.1030.

8-fluoro-2-(7-fluoro-1*H*-indol-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2q), yield 32%, 23.8 mg; yellow solid; m.p.: 276-278 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ: 12.74 (s, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.80-7.75 (m, 1H), 7.50-7.45 (m, 1H), 7.28-7.23 (m, 1H), 7.14-7.09 (m, 1H); ^{13}C NMR (100 MHz, *d*-DMSO) δ: 158.1, 158.0, 155.8, 155.4 (d, J = 251.8 Hz), 149.2 (d, J = 243.3 Hz) , 136.4 (d, J = 12.0 Hz), 132.5, 128.5 (d, J = 5.0 Hz), 127.2 (d, J = 7.6 Hz), 124.9 (d, J = 13.9 Hz), 123.7 (d, J = 3.8 Hz) , 122.3 (d, J = 13.8 Hz), 122.2, 118.3, 117.3 (d, J = 3.4 Hz), 108.0 (d, J = 15.6 Hz), 107.5; HRMS: $[M+H]^+$ m/z calcd for $C_{16}H_8F_2N_2O_2H^+$: 299.0627, found: 299.0624.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, ^{1}H/ ^{13}C NMR spectra of all products (PDF)
The high resolution mass spectrum of crude mixtures (PDF)
X-ray crystallographic data of compound **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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