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TBHP mediated substrate controlled oxidative dearomatization of indoles to C2/C3-quaternary indolinones

Jagatheeswaran Kothandapani,[a] Singarajanahalli Mundarinti Krishna Reddy,[a] Subbiah Thamotharan,[b] Shankar Madan Kumar,[c] Kullaiah Byrappa[d] and Subramaniapillai Selva Ganesan*[a]

Dedication ((optional))

Abstract: Oxidative dearomatization of indoles with 70% aqueous *t*-butylhydroperoxide (TBHP) in the absence of any metal salts/organic solvents gave the corresponding C2/C3-quaternary indolinones under open-air reaction conditions. The nature of substituent on the indole nitrogen dictates the type of product formed in these reactions. Free (NH)-indoles gave C2-quaternary indolinone derivatives whilst (NR)-indoles yielded C3-quaternary indolinones as the major product. Moreover, the addition of excess amount of TBHP also facilitated the one-pot transformation of (NR)-indoles to the corresponding isatin derivatives.

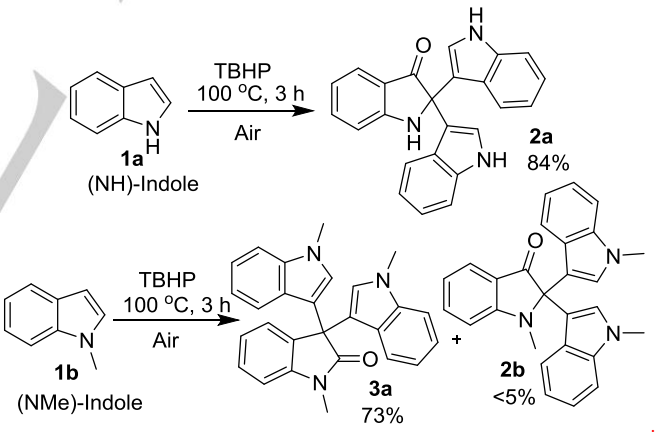
Introduction

Indole and its derivatives are considered as one of the privileged structural motifs present in several biologically relevant molecules.[1-5] Oxidative dearomatization reaction of indole leads to the formation of a diverse class of products such as 2/3-oxoindoles, indirubin, indigo, isatin and indoline derivatives.[6] Among them, the transformation of indoles to C2/C3-quaternary indolinone derivatives is synthetically quite valuable since it converts structurally simpler, planar indole skeleton to a complex three-dimensional architecture. In addition to their structural elegance, they are also highly biologically relevant molecules. Kobayashi *et al*., isolated trisindoline, a C3-quaternary indolinone derivative from the culture of *Vibrio* spp.[7] Kim and co-workers identified that trisindoline derivatives inhibited the growth of both parental and multidrug-resistant uterine sarcoma and colorectal adenocarcinoma cell lines.[8] In spite of such biological significance, only limited number of reports are available for the one-pot transformation of indole to the corresponding C2/C3-quaternary indolinone derivatives.

Guchhait *et al*., reported expensive $PdCl_2$/TBHP/MnO_2 reagent system[9] to convert free (NH)–indoles to the corresponding C2-quaternary indolinone derivatives. Liu and co-workers reported the TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) mediated synthesis of C2-quaternary indolinones from free (NH)-indoles.[10] However, the reaction required three days for completion. Ceric ammonium nitrate on silica gel also has the ability to convert *N*-methylindole to the corresponding C2-quaternary indolinone derivative, albeit in very poor yields.[11] It was previously reported that atmospheric air itself is sufficient for the oxidative dimerization of oxindole derivatives.[6] Hence, it is of interest to study the *t*-butylhydroperoxide (TBHP) assisted one-pot transformation of indole to the corresponding C2/C3-quaternary indolinone derivatives under open-air reaction conditions.

Results and discussion

During the course of our investigation, we have identified the excellent potential of 70% aqueous TBHP reagent to perform oxidative dearomatization of indoles. Interestingly, the reaction proceeds in the absence of any organic solvents and metal salts. (Scheme **1**).



Scheme 1. TBHP assisted syntheses of C2/C3-quaternary indolinones

To our surprise, free (NH)-indole **1a** gave the corresponding C2-quaternary indolinone derivative **2a** whilst (NMe)-indole **1b** yielded the corresponding C3-quaternary indolinone derivative **3a** as the major product. Along with **3a**, the minor product **2b** was also formed in the reaction medium. The formation of the major products **2a** and **3a** can be explained as given below.

TBHP mediated C3-oxygenation of free (NH)-indole could result in the *in situ* formation of indolones.[12] Further, two successive nucleophilic addition of free (NH)-indole onto the indolones transform them into a structurally complex C2-quaternary indolinone derivative **2a**. Unlike C3-oxygenation, C2-oxygenation of *N*-methylindole is quite intriguing. It was

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previously reported in the literature that TBHP/I_2 reagent system facilitated the C2-oxygenation of (NMe)-indoles through 3-iodo iminium intermediate which eventually yielded isatin as the final product.[13] However, during our investigation with TBHP in the absence of I_2, the formation of C3-quaternary indolinone **3a** was observed instead of isatin derivative. We surmise that in the absence of iodine, the nucleophilicity of C3-position of (NMe)-indole is retained and hence the product **3a** was formed in appreciable yields. Also, a careful review of literature revealed that TEMPO in the presence of $AgNO_3$/Brønsted acid in pyridine solvent gave C3-quaternary indolinone derivative **3** as a minor product.[14] In a similar manner, organic peroxide mediated C2-H oxygenation of indoles in presence of $PdCl_2$ and MnO_2 was reported earlier.[9] However, in both cases, free (NH)-indole was used as a substrate. Apart from these methods, C3-quaternary indolinones **3** can also be prepared by the nucleophilic addition of indole on to isatin derivatives.[15-17]

In order to maximize the yield of products **2a** and **3a**, the reaction conditions such as solvents, temperature, time, molar ratio of reagent, and nature of additives were optimized. The results obtained from the optimization studies are given in Table **1**.

Table 1. Optimization of reaction conditions[a]

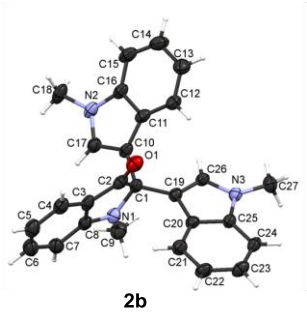
S. No	**2a** or **3a**	Additive	Solvent (mL)	Temp (^oC)	Time (h)	Yield (%)[b]
1	2a	---	H_2O (3)	Reflux	3	53
2	2a	---	MeOH (3)	Reflux	3	47
3	2a	---	CH_3CN (3)	Reflux	3	34
4	2a	---	DMSO (3)	100	3	28
5	2a	---	DMF (3)	100	3	---
6	2a	---	Toluene (3)	100	3	---
7	2a	---	---[c]	80	3	79
8	2a	---	---[c]	60	3	54
9	2a	**---**	**---[c,d]**	**100**	**3**	**84[e]**
10	2a	---	---[c]	120	3	81
11	2a	---	---[c]	120	4	83
12	2a	Copper acetate	---[c]	RT	3	---
13	2a	Copper triflate	---[c]	RT	1	---
14	2a	$ZnCl_2$	---[c]	RT	12	---
15	2a	Benzoic acid	---[c]	80	3	54
16	2a	PTSA	---[c]	80	3	---
17	**3a**	**---**	**---[c]**	**100**	**3**	**73**
18	3a	---	H_2O (3)	Reflux	3	39
19	3a	---	CH_3CN (3)	Reflux	3	68
20	3a	---	DMSO (3)	100	3	---
21	3a	---	Toluene (3)	100	3	Traces
22	3a	---	MeOH (3)	Reflux	3	44
23	3a	---	DMF (3)	100	3	---

[a] Unless otherwise mentioned all the reactions were performed with 1 mmol of (NH)-indole **1a** or (NMe)-indole **1b** and 70% aqueous solution of TBHP (400 µL). [b] Yields are for the isolated products. [c] 70% aqueous solution of TBHP (400 µL) was used as reagent cum solvent. [d] Presence of unreacted starting material was observed on TLC for the reactions performed less than 3 h. Reaction performed for 4 h didn't improved the yield of the product. [e] Reaction performed with 200 µL of TBHP required 5.5 h for completion of the reaction.

Reaction performed with polar protic solvents such as water and methanol gave the corresponding product **2a** in moderate yield (Table **1**, Entries **1, 2**). A sharp decrease in the yield of **2a** was observed when the reaction was performed in polar aprotic or non-polar solvents (Entries **3-6**). Since water gave appreciable yield among the screened solvents, it is of interest to perform the reaction with only 70% aqueous TBHP medium in the absence of any externally added organic solvents or water. To our delight, we have got the product **2a** in **84%** yield (Entry **9**). The use of additives didn't alter the reaction outcome (Entries **12-16**). Under similar organic solvent-free reaction conditions, (NMe)-indole also gave the corresponding product **3a** in good yields (Entry **17**).

Under the optimized condition, we explored the scope and limitation of the TBHP mediated oxidative dearomatization reaction of indole derivatives (Table **2**). The electronic effects of the substituent on the indole ring and the nature of substituent on the indole nitrogen play a pronounced role in determining the type and yield of the product. Presence of electron donating 5-OMe group on the free (NH)-indole produced the corresponding trimer **2c** in appreciable yields. Conversely, electron withdrawing 5-cyano group drastically affected the yield of the product **2g**. The 2-methylindole gave the corresponding unsymmetrically substituted C2-quaternary indolinone product **2f** in 80% yield. It is noteworthy to mention here that the *N*-allylindole derivative gave the corresponding *N*-deallylated C2-quaternary indolinone product **2a** by C-N bond cleavage followed by C-C bond formation (Table **2,** Entry **8**). Interestingly, inductively electron withdrawing 5-bromoindole gave the corresponding C3-quaternary indolinone **2h** instead of expected C2-quaternary product. A similar reversal in product selectivity for the electron withdrawing substituents was reported earlier.[10] The products **2f** and **2b** were further confirmed by single crystal XRD studies (Figure **1**).

2f

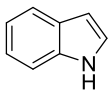
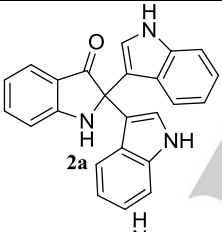
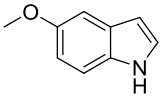
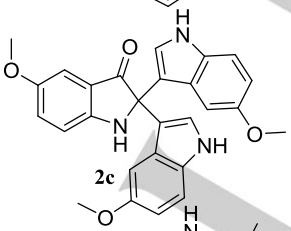
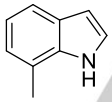
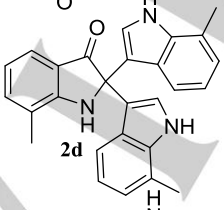
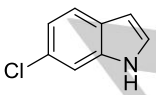
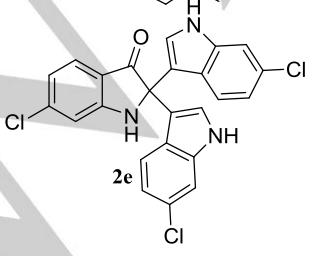
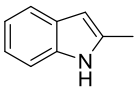
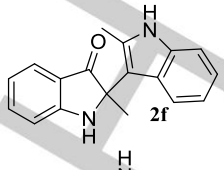
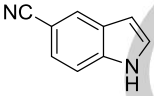
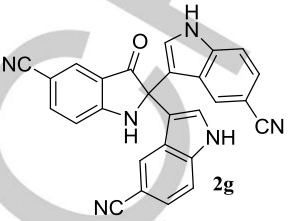
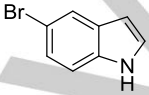
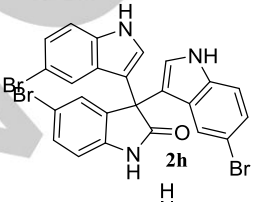
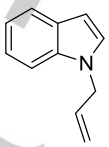
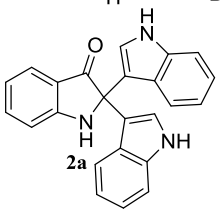
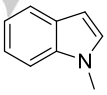
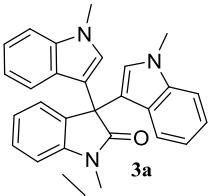
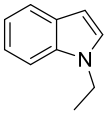
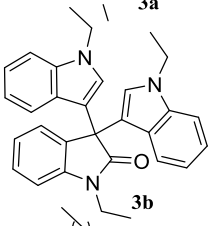
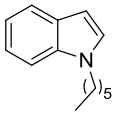
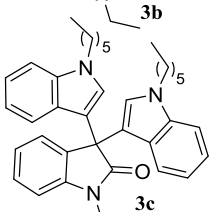
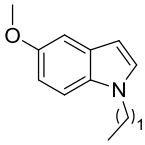
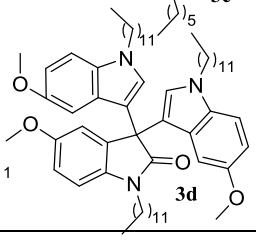


2b

Figure 1. ORTEP diagrams of compounds **2f** and **2b**[18]

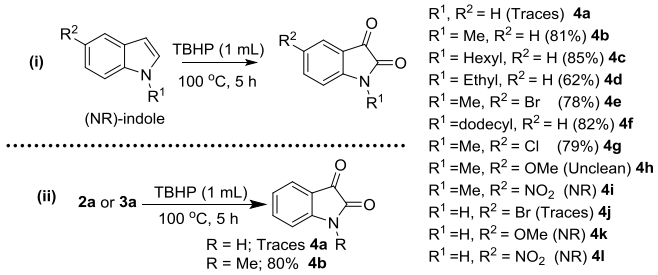
The oxidative dearomatization reaction of *N*-alkylated indole derivative was found to be general for diverse alkyl derivatives. The presence of lipophilic alkyl chain did not deter the course of reaction (**3c, 3d**). The presence of electron donating –OMe group also facilitates the formation of C3-quaternary indolinone derivative **3d** in acceptable yields. The scope of substrate is given in Table **2**.

Table 2. Substrate scope for C2/C3-quaternary indolinone derivative synthesis[a]

Entry	Indole	Product	Yield [%]
1		 **2a**	84
2		 **2c**	72
3		 **2d**	81
4		 **2e**	76
5		 **2f**	80
6		 **2g**	0
7		 **2h**	36
8		 **2a**	52
9		 **3a**	73
10		 **3b**	66
11		 **3c**	74
12		 **3d**	77

[a] Unless otherwise mentioned all the reactions were performed with 1 mmol of (NH)-indole or (NR)-indole and 70% aqueous solution of TBHP (400 µL).

MacMillan and co-workers had previously reported that the amount of oxidant in the reaction medium affected the position of oxygenation of *N*-alkylated indole derivatives.[19] Based on this report, we investigated the effect of varying the amounts of oxidant in the reaction medium. Our observations showed that increasing the quantum of TBHP oxidant from 0.4 mL to 1 mL led to the formation of corresponding isatin derivatives (Scheme **2**). Surprisingly, the reaction carried out with free (NH)-indole did not yield the expected isatin derivative.



Scheme 2. One-pot synthesis of isatin derivatives

A careful analysis of the reaction mixture (Scheme **2(i)**) revealed that the formation of trace quantities of C3-quaternary indolinone derivative **3a** along with expected isatin **4b**. The formation of **3a** was further confirmed by quenching the reaction mixture within 1 h prior to complete conversion. These observations indicate that the transformation of (NMe)-indole to isatin **4b** could progress *via* C3-quaternary indolinone intermediate **3a**. This surmise was further confirmed by performing TBHP assisted one-pot transformation of C3-quaternary indolinone **3a** to **4b** (Scheme **2(ii)**). To further substantiate the formation of **3a** in the reaction medium, the following NMR experiment was performed at different time intervals (Fig. **2**).

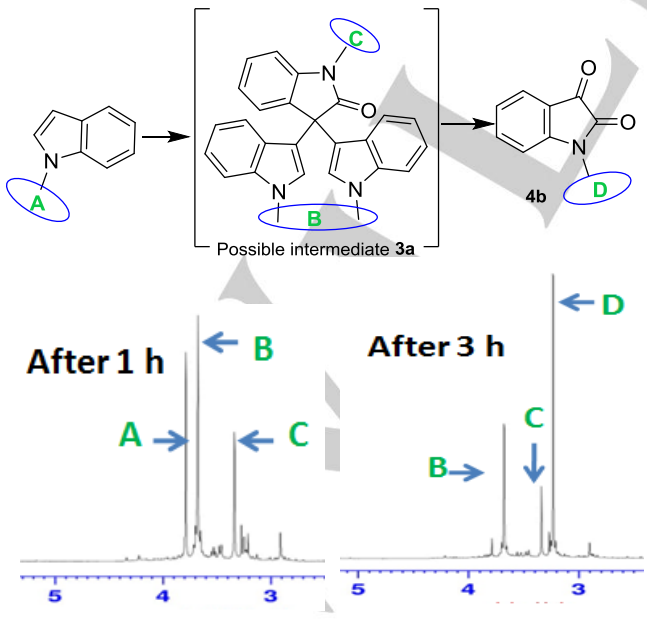
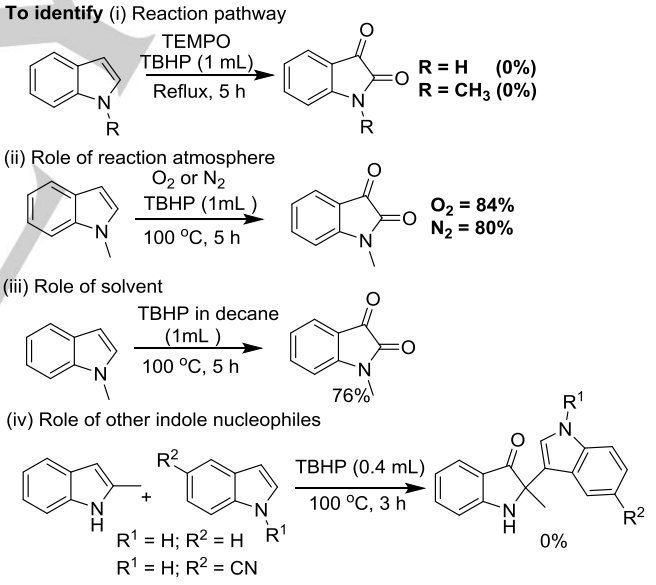


Figure 2. Variable time NMR analyses of TBHP mediated oxidation of *N*-methylindole.

The NMR studies confirmed the formation of C3-quaternary indolinone **3a** in the reaction medium. Kobayashi and co-workers stated that under oxidative reaction environment, the presence of C3 substitution in the free (NH)-indole is detrimental and it leads to the oxidative cleavage of the substrate.[12] We presume that oxidative cleavage could be one of the reasons behind the lack of formation of isatin product by the TBHP mediated oxidation of C2-quaternary indolinones **2a** (Scheme **2(ii)**). These observations imply that the substituent on indole nitrogen determines the course of the reaction.

In order to confirm whether the oxidative dearomatization of indoles proceeds *via* radical intermediate, the TBHP mediated oxidation of *N*-methylindole was performed in presence of radical quencher TEMPO (Scheme **3(i)**). The lack of formation of isatin confirms that the reaction is driven *via* a radical intermediate. The use of either nitrogen or oxygen atmosphere did not influence the yield of the product significantly (Scheme **3(ii)**). Hence, it is not required to perform the reaction under inert reaction conditions. In Scheme **3(ii)**, the use of excess amount of TBHP (1 mL) resulted in the one-pot transformation of (NMe)-indole to the corresponding isatin derivative.



Scheme 3. Mechanistic investigations

To substantiate the role of water solvent in the 70% TBHP solution in the oxidative dearomatization reaction, we have performed the reaction with TBHP solution in decane (5.0-6.0 M). The isatin product was obtained in appreciable yields (Scheme **3(iii)**). This observation indicates that the type of solvent in which TBHP is dissolved also does not play a significant role. We also carried out the oxidative dearomative cross-coupling reaction of 2-methylindole with 5-cyanoindole and indole. However, both the reaction yielded only homocoupled product **2f**

instead of expected, cross-coupled reaction product. Based on the results obtained from the control experiments, we outline a plausible mechanism for the TBHP mediated formation C2/C3-quaternary indolinone and isatin derivatives (Fig. **3**).

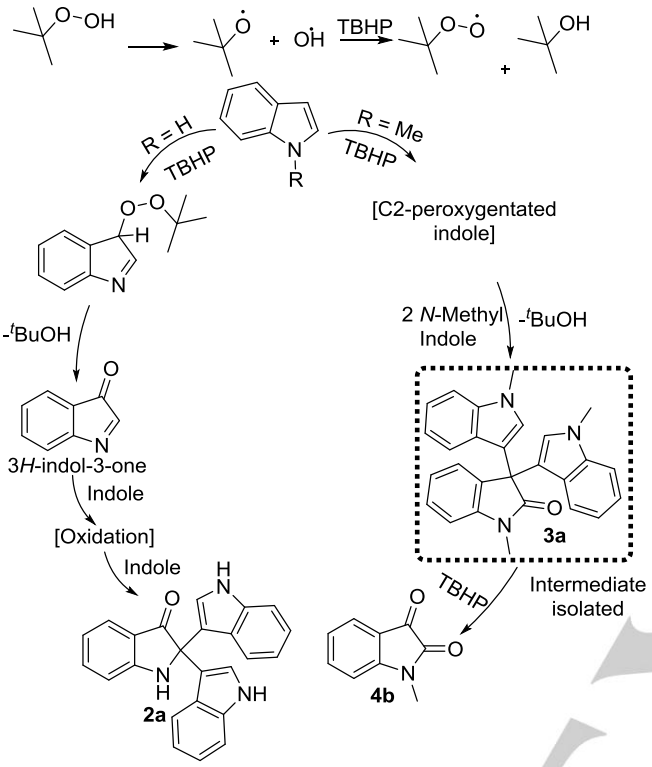


Figure 3. Plausible mechanism

The C3 peroxygenation of free (NH)-indole followed by the elimination of *t*-BuOH lead to the formation of 3*H*-indol-3-one.[12] Further, two consecutive nucleophilic addition of free (NH)-indoles on to the 3*H*-indol-3-one could have resulted in the formation of C2-quaternary indolinone **2a**. Unlike free (NH)-indoles, peroxygenation of (NMe)-indole took place at C2 carbon. The C2-peroxygenated indole on elimination of *t*-BuOH followed by the addition of two molecules of (NMe)-indole led to the formation of **3a** which on further oxidation yielded **4b**. To address the reviewers comment, C3-quaternary indolinone **3a** was synthesized separately by closely following a previously reported literature procedure.[17] **3a** on subject to the TBHP mediated oxidation reaction condition also gave the product **4b** in quantitative yields. Although, at this juncture, the reason for preferential C2 vs C3 peroxygenation is not understood completely**.**

Conclusions

Thus, we have demonstrated the metal and organic solvent free, one-pot oxidative dearomatization reaction of indole leading to the formation of biologically important diverse oxindole derivatives. The substituent effect on the indole nitrogen on the product selectivity was demonstrated using free (NH)-indole and (NR)-indole derivatives.

Experimental Section

Materials and methods:

Materials:

Substituted Indoles were purchased from Sigma Aldrich and Avra chemicals. *tert*-Butyl hydroperoxide solution 70% in H_2O and *tert*-Butyl hydroperoxide solution in decane (5.0-6.0 M) were purchased from Sigma Aldrich. Melting points were uncorrected. ^{1}H-NMR was recorded in Bruker model avance-II 300 MHz & 400 MHz and ^{13}C-NMR in 75 MHz & 100 MHz spectrometer using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as a solvent. The JEOL GCMATE II GC-MS with data system is a high resolution, Electron impact (EI) methods were used for analyzing mass of molecules. FT-IR spectrum recorded using Perkin Elmer Spectrum RX I model.

Methods:

Synthesis of Indole trimer and isatin derivatives: To a stirred mixture of indole (1 mmol) and TBHP solution 70% in H_2O (400 µL for indole trimer or 1 mL for isatin synthesis) was heated at 100 ^oC under air atmosphere for 3 or 5 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Eluent: Ethyl acetate: hexane 1:2).

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Keywords: Indole; Oxidative dearomatization; Isatin; Peroxide; Green synthesis

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[18] Cell parameters for **2f**: a = 7.1656(18) Å, b = 9.8359(19) Å, c = 10.6551(16) Å, α = 106.495(15)°, β = 95.204(17)° and γ = 93.306(18)°, Triclinic, space group: P-1, volume = 714.4(3)Å^3. CCDC-1569540. Cell parameters for **2b**: a = 8.6288(8) Å, b = 7.3358(7) Å, c = 16.8217(14) Å, α = 90.0°, β = 103.830(9)° and γ = 90.0°, Monoclinic, space group:$P2_1$, volume = 1033.93(17) Å^3. CCDC-1569565.
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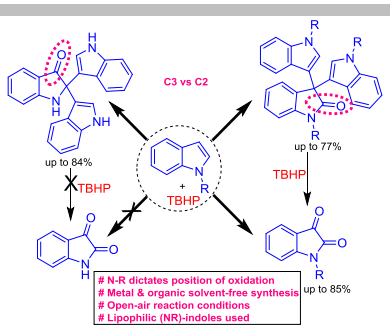

Key Topic*

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TBHP mediated substrate controlled oxidative dearomatization of indoles to C2/C3-quaternary indolinones

An efficient metal-free oxidative dearomatization reaction of indoles was reported for the synthesis of diverse C2/C3-quaternary indolinones. The nature of substituent on the indole nitrogen dictates the type of product formed in the reaction.

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