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**Title:** Metal-Free Nitration of the C(sp<sup>3</sup>)-H Bonds of 2-Oxindoles through Radical Coupling Reaction at Room Temperature

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.201700870

**Link to VoR:** <http://dx.doi.org/10.1002/adsc.201700870>

DOI: 10.1002/adsc.200((will be filled in by the editorial staff))

# Metal-Free Nitration of the C(sp<sup>3</sup>)-H Bonds of 2-Oxindoles through Radical Coupling Reaction at Room Temperature

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200#####>. ((Please delete if not appropriate))

**Abstract.** A metal-free nitration of the C(sp<sup>3</sup>)-H bonds of 2-oxindoles with *t*-BuONO through radical coupling reaction at room temperature has been developed. Using *t*-BuONO both as a nitrating reagent and as an oxidant, to couple with the C(sp<sup>3</sup>)-H bonds of 2-oxindoles, thus forming a new C-N bond without using any other reagents. This reaction provides a green and straightforward approach to some useful 3-nitro-2-oxindoles in moderate to good yields.

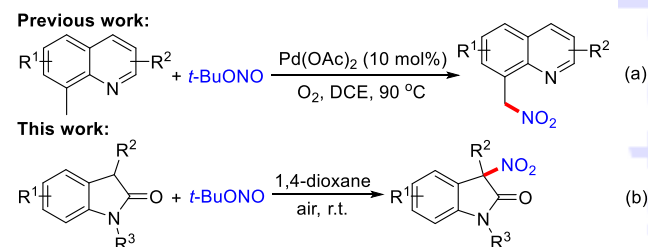
**Keywords:** metal-free; nitration; 2-oxindoles; *t*-BuONO; radical coupling reaction

3,3-Disubstituted oxindoles have been found in a variety of biologically active molecules as well as in pharmaceutical compounds.<sup>[1]</sup> Therefore, considerable research efforts have been devoted to synthesize such compounds. Traditionally, the 3,3-disubstituted oxindole scaffolds were prepared by condensation of anilines with carbonyl compounds.<sup>[2]</sup> More recently, the methods through difunctionalization of *N*-aryl acrylamides<sup>[3]</sup> and coupling of oxindoles with nucleophiles or radical reagents<sup>[4]</sup> provide an alternative to access these compounds. However, many of these methods require the use of transition-metal catalysts or bases, which greatly restrict their application in organic synthetic chemistry. Hence, the development of a green and convenient protocol for the construction of 3,3-disubstituted oxindoles is still required.

Nitration of C(sp<sup>3</sup>)-H bonds has long been a challenging topic in organic synthesis, especially employing nitro radical process.<sup>[5]</sup> One example was reported by Liu and co-workers, who documented a Ag(I)-mediated direct nitration of the quinoxaline tertiary C-H bond at 110 °C in the presence of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> using AgNO<sub>2</sub> as a nitro source.<sup>[6]</sup> Very recently, Zhang and co-workers reported a Cu(II)-assisted nitration of cyclic ketones with ceric ammonium nitrate at 80 °C.<sup>[7]</sup> To the best of our knowledge, there is only one reported example concerning the nitration of C(sp<sup>3</sup>)-H bonds through radical reaction using non-metallic nitrating reagent. In 2015, a wonderful work from Liu's group who developed a Pd(II)-catalyzed

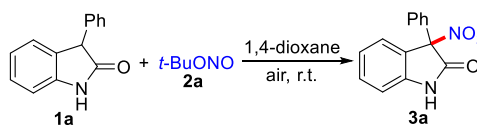
nitration of 8-methylquinolines with *t*-BuONO at 90 °C (Scheme 1a).<sup>[8]</sup> However, all of the methods suffer from the cost of the transition-metal catalytic systems as well as consuming too much energy.

Therefore, from the green chemistry point of view, the development of a metal-free nitration of C(sp<sup>3</sup>)-H bonds through radical coupling reaction at room temperature is essential. In addition, remarkable progress has been made in nitration using *t*-BuONO as a nitrating reagent due to its low toxicity, low cost, and ease of handling.<sup>[9]</sup> As a continuing interest in radical coupling reaction,<sup>[10]</sup> we present a metal-free nitration of the C(sp<sup>3</sup>)-H bonds of 2-oxindoles with *t*-BuONO through radical coupling reaction at room temperature (Scheme 1b).



**Scheme 1.** Nitration of C(sp<sup>3</sup>)-H Bonds with *t*-BuONO

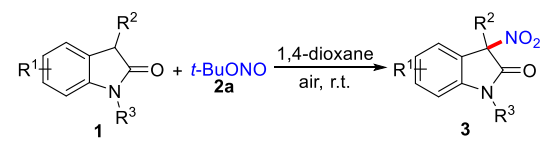
Our initial study focused on the radical coupling reaction between 3-phenylindolin-2-one (**1a**) with *t*-BuONO (**2a**) (Table 1). The results showed that the yield of the desired product **3a** relied on the amount of *t*-BuONO and solvents, and the highest yield was isolated by the use of 2 equiv *t*-BuONO in 1,4-dioxane at room temperature (92%; entry 1). Some solvents, including THF, MeCN, PhCl and EtOAc, were evaluated in the presence of 2 equiv *t*-BuONO, and found to be less effective than 1,4-dioxane (entry 1 vs. entries 2-5). Subsequently, the reaction conditions were further investigated, the amount of *t*-BuONO affected the reaction: a decrease in the loading of *t*-BuONO to 1.5 equiv was not beneficial to the formation of product **3a** (entry 6), whereas an

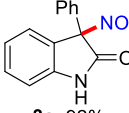
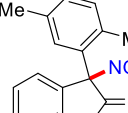
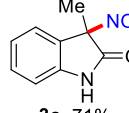
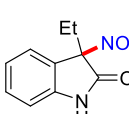
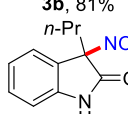
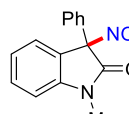
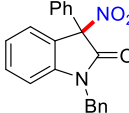
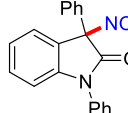
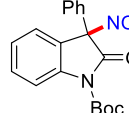
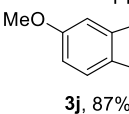
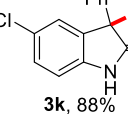
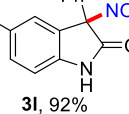
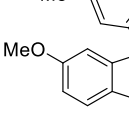
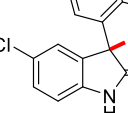
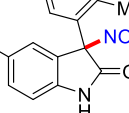
**Table 1.** Screening of optimal reaction conditions<sup>a)</sup>


Entry	Variation from the standard conditions	Isolated yield (%)
1	none	92
2	THF instead of 1,4-dioxane	80
3	MeCN instead of 1,4-dioxane	84
4	PhCl instead of 1,4-dioxane	79
5	EtOAc instead of 1,4-dioxane	87
6	1.5 equiv <i>t</i> -BuONO instead of 2 equiv <i>t</i> -BuONO	72
7	3 equiv <i>t</i> -BuONO instead of 2 equiv <i>t</i> -BuONO	92
8	at 40 °C	92

<sup>a)</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv) and 1,4-dioxane (2 mL) at r.t. in air for 12 h.

increase in the loading of *t*-BuONO to 3 equiv only resulted in identical result to that of 2 equiv *t*-BuONO (entry 7). A higher temperature (40 °C) did

**Table 2.** Nitration of 2-oxindoles with *t*-BuONO<sup>a)</sup>


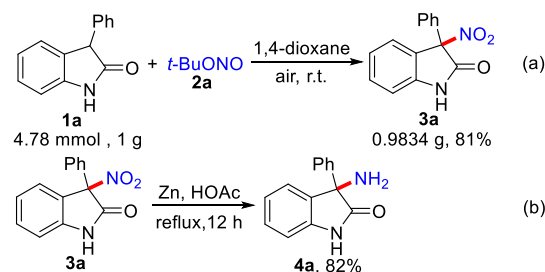
		
		
		
		
		

<sup>a)</sup> Reaction conditions: **1** (0.2 mmol), **2a** (2 equiv) and 1,4-dioxane (2 mL) at r.t. in air for 12 h.

not improve the yield compared with the result at room temperature (entry 8). Therefore, the combinations listed in entry 1 were the optimal reaction conditions for this radical coupling reaction.

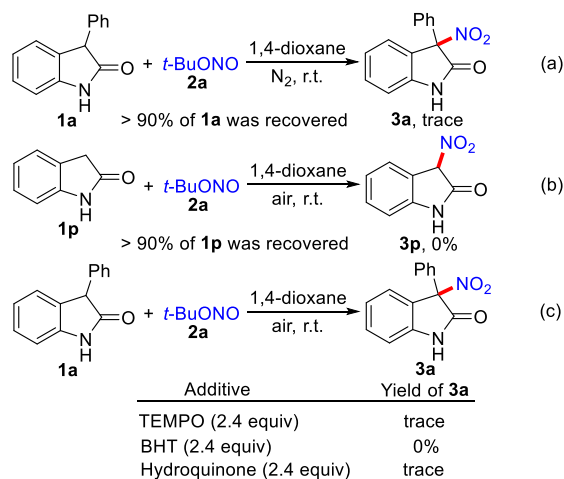
With the optimized conditions in hand, the generality of the nitration of 2-oxindoles was explored, and the results are listed in Table 2. A variety of 3-aryl-2-oxindoles and 3-alkyl-2-oxindoles underwent nitration with *t*-BuONO to furnish the desired products **3a–3e** in good to excellent yields. 2-Oxindoles with a Ph group and a 2,5-dimethylphenyl group at the C3-position, reacted with *t*-BuONO to generate the corresponding products **3a** and **3b** in 92% and 81% yields, respectively. Meanwhile, 2-oxindoles bearing an alkyl group, such as Me, Et, and *n*-Pr, generated the desired products **3c–3e** in 71–41% yields. Several *N*-substituted-2-oxindoles, bearing both electron-rich substituents (Me, Bn, Ph) and electron-poor substituent (Boc) gave good results, forming the corresponding radical coupling products **3f–3i** in 82–40% yields. We then turned our attention to aryl moiety of 2-oxindoles, as shown in Table 2, a range of 2-oxindoles, with both electron-donating group and electron-withdrawing groups on aryl ring, were viable in the radical coupling reaction. Notably, Cl and Br substituents were also well tolerated, thereby facilitating possible additional modifications at the halogenated positions. Extensive screening revealed that 2-oxindoles **1m–1o** were tolerated well, giving the corresponding products **3m–3p** in 76%, 90%, and 88% yields, respectively.

As shown in Scheme 2a, 81% yield of nitration product **3a** was obtained on the gram scale under the optimal conditions. In addition, the reduction of **3a** to 3-amino-3-phenylindolin-2-one **4a** was achieved (Scheme 2b). Thus, **3a** could be selectively reduced to **4a** in 82% yield by using the modified methods.<sup>[11]</sup>

**Scheme 2.** Synthesis Application: Scale-up Experiments and Reduction Reaction.

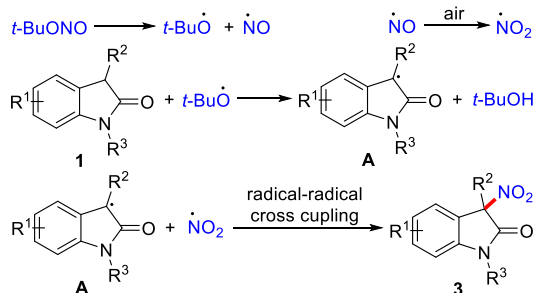
As shown in scheme 3a, when the reaction was carried out in nitrogen, the desired product **3a** was not obtained. Meanwhile, we screened other substrate for this nitration reaction. Unfortunately, **1p** was not a suitable substrate for this reaction, probably due to the instability of secondary

carbocation (Scheme 3b). When 2,2,6,6-tetramethylpiperidinoxy (TEMPO), 2,6-di-*tert*-butyl-4-methyl phenol (BHT), and hydroquinone were added under the optimal reaction conditions, the desired nitration was obviously suppressed, which indicate that a radical process might be involved in the current transformation (Scheme 3c).



**Scheme 3.** Control Experiments.

The mechanism for the metal-free nitration of the C(sp<sup>3</sup>)-H bonds of 2-oxindoles with *t*-BuONO was proposed on the basis of present results and previous reports (Scheme 4).<sup>[7,12-14]</sup> Initially, NO radical and *t*-BuO radical were directly generated from *t*-BuONO.<sup>[12]</sup> The NO radical was then converted to NO<sub>2</sub> radical under aerobic conditions.<sup>[7,13]</sup> Subsequently, the *t*-BuO radical rapidly reacted with 2-oxindole **1** to generate alkyl radical **A**.<sup>[14]</sup> Finally, the radical coupling reaction between alkyl radical **A** and NO<sub>2</sub> radical afford the desired product **3**.



**Scheme 4.** Possible Mechanism.

In summary, we have demonstrated the first example of metal-free nitration of C(sp<sup>3</sup>)-H bonds with *t*-BuONO through radical coupling reaction. In this process, *t*-BuONO was used as a nitrating reagent which coupled with the five-membered ring scaffold at room temperature without using a metal catalyst or a base. This method provides a green and efficient

route to 3-nitro-2-oxindoles, and exhibits a broad substrate scope with good functional group tolerance. Additionally, the radical process was revealed by radical-trapping experiments. Further studies on the development of radical coupling reaction using more complex molecules are currently underway in our laboratory.

## Experimental Section

### Typical Experimental Procedure for the the Radical Coupling Reaction:

To a Schlenk tube were added 2-oxindoles **1** (0.2 mmol), *t*-BuONO **2a** (0.4 mmol) and 1,4-dioxane (2 mL). Then the tube was stirred at room temperature under air for the indicated time until complete consumption of starting material as monitored by TLC analysis. After the reaction was finished, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (hexane/ethyl acetate) to afford the desired products **3**.

## Acknowledgements

This research is sponsored by research funds of NBU (No. ZX2016000706), foundation of Ningbo University (No. XYL17009), and the K. C. Wong Magna Fund in Ningbo University.

## References

- [1] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8445; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) B. Trost, M. Brennan, *Synthesis* **2009**, 3003; c) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381; d) S. Denoyelle, T. Chen, H. Yang, L. Chen, Y. Zhang, J. A. Halperin, B. H. Aktas, M. Chorev, *Eur. J. Med. Chem.* **2013**, *69*, 537; e) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; f) K. Ohmatsu, Y. Ando, T. Ooi, *J. Am. Chem. Soc.* **2013**, *135*, 18706; g) R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, *Synthesis* **2015**, 1195.
- [2] a) P.-B. Zhao, B.-B. Zhao, Y. Li, W.-T. Gao, *Chin. J. Org. Chem.* **2014**, *34*, 126; b) W. M. Bryant, G. F. Huhn, J. H. Jensen, M. E. Pierce, C. Stammach, *Synth. Commun.* **1993**, *23*, 1617; c) P. Hewawasam, N. A. Meanwell, *Tetrahedron Lett.* **1994**, *35*, 7303.
- [3] a) T. Wu, X. Mu, G. Liu, *Angew. Chem.* **2011**, *123*, 12786; *Angew. Chem. Int. Ed.* **2011**, *50*, 12578; b) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie, J.-H. Li, *Angew. Chem.* **2013**, *125*, 3726; *Angew. Chem. Int. Ed.* **2013**, *52*, 3638; c) H. Wang, L.-N. Guo, X.-H. Duan, *Org. Lett.* **2013**, *15*, 5254; d) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng, J.-H. Li, *Chem. Sci.* **2013**, *4*, 2690.

- [4] a) H.-Y. Huang, L. Cheng, J.-J. Liu, D. Wang, L. Liu, C.-J. Li, *J. Org. Chem.* **2017**, *82*, 2656; b) C. D. Prasad, M. Sattar, S. Kumar, *Org. Lett.* **2017**, *19*, 774; c) F. T. K. Hendrik, F. G. G. Alexander, C. D. Douglas, M. S. Brian, *Org. Lett.* **2017**, *19*, 988; d) M. Liu, S. Qiu, Y. Ye, G. Yin, *Tetrahedron Lett.* **2016**, *57*, 5856; e) M. Sattar, V. Rathore, C. D. Prasad, S. Kumar, *Chem. Asian J.* **2017**, *12*, 734; f) M. B. Chaudhari, G. S. Bisht, P. Kumari, B. Gnanaprakasam, *Org. Biomol. Chem.* **2016**, *14*, 9215; g) M. Zhou, K. En, Y. Hu, Y. Xu, H. C. Shen, X. Qian, *RSC Adv.* **2017**, *7*, 3741.
- [5] a) Y. G. Lin, W. G. Kong, Q. L. Song, *Org. Lett.* **2016**, *18*, 3702; b) Y.-Y. Liu, X.-H. Yang, R.-J. Song, S. L. Luo, J.-H. Li, *Nat. Commun.* **2017**, *8*, 14720; c) Y. Yang, R.-J. Song, X.-H. Ouyang, C.-Y. Wang, J.-H. Li, S. L. Luo, *Angew. Chem.* **2017**, *129*, 8024; *Angew. Chem. Int. Ed.* **2017**, *56*, 7916.
- [6] D. Wu, J. Zhang, J. Cui, W. Zhang, Y. Liu, *Chem. Commun.* **2014**, *50*, 10857.
- [7] Z.-Q. Zhang, T. Chen, F.-M. Zhang, *Org. Lett.* **2017**, *19*, 1124.
- [8] W. Zhang, S. Ren, J. Zhang, Y. Liu, *J. Org. Chem.* **2015**, *80*, 5973.
- [9] a) X.-F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Commun.* **2011**, *47*, 12462; b) Q. Cao, J. D. Liu, L. Yu, Q. W. Gui, X. Chen, Z. Tan, *Synth. Commun.* **2015**, *45*, 2181; c) X.-H. Yang, R.-J. Song, J.-H. Li, *Adv. Synth. Catal.* **2015**, *357*, 3849; d) Y. Liu, J.-L. Zhang, R.-J. Song, P.-C. Qian, J.-H. Li, *Angew. Chem.* **2014**, *126*, 9163; *Angew. Chem. Int. Ed.* **2014**, *53*, 9017.
- [10] a) W.-T. Wei, W.-M. Zhu, W.-W. Ying, Y. Wu, Y.-L. Huang, H. Z. Liang, *Org. Biomol. Chem.* **2017**, *15*, 5254; b) W.-T. Wei, W.-M. Zhu, W. D. Liang, Y. Wu, H.-Y. Huang, Y.-L. Huang, J. F. Luo, H. Z. Liang, *Synlett* **2017**, Doi: 10.1055/s-0036-1589038; c) W.-T. Wei, W.-M. Zhu, Y. Wu, Y.-L. Huang, H. Z. Liang, *Chin. J. Org. Chem.* **2017**, Doi: 10.6023/cjoc201703039.
- [11] X. Yang, F. D. Toste, *J. Am. Chem. Soc.* **2015**, *137*, 3205.
- [12] a) X.-X. Peng, Y.-J. Deng, X.-L. Yang, L. Zhang, W. Yu, B. Han, *Org. Lett.* **2014**, *16*, 4650; b) M. Hu, B. Liu, X.-H. Ouyang, R.-J. Song, J.-H. Li, *Adv. Synth. Catal.* **2015**, *357*, 3332.
- [13] a) G.-B. Deng, J.-L. Zhang, Y.-Y. Liu, B. Liu, X.-H. Yang, J.-H. Li, *Chem. Commun.* **2015**, *51*, 1886; b) S. Maity, T. Naveen, U. Sharma, D. Maiti, *Org. Lett.* **2013**, *15*, 3384.
- [14] a) X.-L. Chen, Y. Li, M.-H. Wu, H.-B. Guo, L.-Q. Jiang, J. Wang, S.-F. Sun, *RSC Adv.* **2016**, *6*, 102023; b) H. Hashemi, D. Saberi, S. Poorsadeghic, K. Niknam, *RSC Adv.* **2017**, *7*, 7619.

## FULL PAPER

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