Organic &
Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 5254

Received 19th May 2017,
Accepted 6th June 2017

DOI: 10.1039/c7ob01235g

rsc.li/obc

Metal-free synthesis of isatin oximes *via* radical coupling reactions of oxindoles with *t*-BuONO in water†

Wen-Ting Wei, * Wen-Ming Zhu, Wei-Wei Ying, Yi Wu, Yi-Ling Huang and Hongze Liang

A metal-free method for the synthesis of isatin oximes was developed through the radical coupling reactions of oxindoles with *t*-BuONO. This protocol provides a practical and environmentally benign method for the construction of C–N bonds in water at room temperature without using any other reagents. The advantages of this strategy are its mild reaction conditions and clean procedure.

Introduction

Isatin oximes constitute the central core of a wide variety of bioactive compounds and pharmaceutical molecules that exhibit potential biological activities (Fig. 1, *e.g.*, anticonvulsant, antiviral, and anticancer).[1] On the other hand, an oxime group is a valuable synthetic building block, which can be widely used in the dehydration reaction,[2] 1,3-dipolar addition reaction,[3] and Beckmann rearrangement reaction.[4] The most common methods for obtaining an isatin oxime framework are through the base promoted condensation reaction of a carbonyl compound with hydroxylamine hydrochloride[5] and the Lewis acid catalyzed cyclization reaction of isonitrosoacetanilides.[6] However, the use of stoichiometric amounts of a hydroxylamine salt and an equal equivalent of a base or Lewis acid greatly restricts their application in organic chemistry. Therefore, a green and highly efficient method is still required.

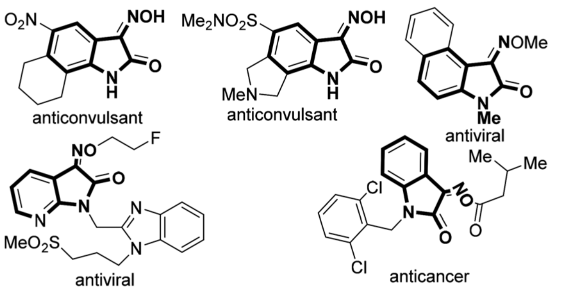
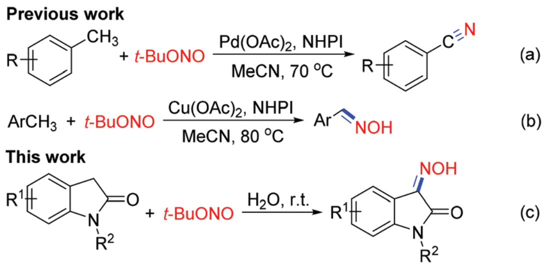


Fig. 1 Representative bioactive compounds or drugs containing isatin oximes.

Recently, methods have been developed to build complex molecules *via* a radical coupling reaction between two inactivated C–H bonds.[7] Compared with traditional coupling reactions, this protocol avoids the pre-functionalization of C–H bonds, thus exhibiting step and atom economy. In this regard, the construction of the C–N bond has been attracting increasing interest due to its ubiquitous presence in pharmaceutical and materials science.[8] One efficient example was reported by Wang and co-workers, who documented a palladium-catalyzed direct conversion of methyl arenes into aromatic nitriles (Scheme 1a).[9] In 2015, Lu and co-workers reported a radical coupling reaction to construct the C–N bonds by the use of $Cu(OAc)_2$ as a catalyst and *N*-hydroxyphthalimide (NHPI) as an additive at 80 °C (Scheme 1b).[10] However, both of the protocols require the use of a metal catalyst and an external oxidant, as well as elevated temperature to promote the reaction.



Scheme 1 C–N bond formation using *t*-BuONO as a partner *via* radical coupling reactions.

Hence, from the environmental point of view, establishing a green and simple route to isatin oxime synthesis through the radical coupling reaction has attracted increasing attention.[11] Moreover, the use of water as the reaction medium for the radical coupling reaction, especially without the addition of any metal catalysts and external oxidants at room temperature,

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School of Materials Science and Chemical Engineering, Ningbo University, Ningbo 315211, China. E-mail: weiwenting@nbu.edu.cn; Fax: +86(0574)87600784

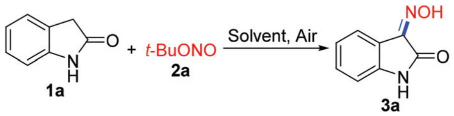
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ob01235g

is still a challenge. All of these pioneering studies encouraged us to explore a clean and efficient methodology for the synthesis of isatin oximes. As a continuing interest in radical coupling reactions,[12] we present our preliminary experimental results of a metal-free synthesis of isatin oximes *via* radical coupling reactions of oxindoles with *t*-BuONO in water at room temperature (Scheme 1c).

Results and discussion

To verify our hypothesis, the reaction of oxindole **1a** and *t*-BuONO **2a** was chosen as a model reaction to optimize the conditions by using diverse solvents and the results are summarized in Table 1. The coupling product **3a** was only produced in 5% isolated yield when the reaction was carried out in 1,4-dioxane at room temperature for 18 h (entry 1). Therefore, a preliminary study was implemented with the aim of searching an appropriate solvent to promote the reaction between **1a** and **2a**. H_2O was chosen due to reports revealing its friendly applications in such radical coupling reactions. Changing the solvent to 1,4-dioxane–H_2O (1.6 mL : 0.2 mL) afforded **3a** in 37% isolated yield (entry 2). Encouraged by this result, different volume ratios of 1,4-dioxane–H_2O were evaluated for this reaction (entries 3–5): we found that the yield of **3a** increased along with the increased loading of H_2O. When H_2O was used as the sole solvent, the yield of **3a** rose to 96%. Screening the loading of *t*-BuONO revealed that the amount of *t*-BuONO affected the reaction, and the reaction with 4.0 equiv. of *t*-BuONO was revealed as the most effective loading (entries 5–7). Moreover, no further improvement was observed at higher temperature (40 °C, entry 8). It is noteworthy that a good yield is still achieved by using the 1 gram scale of **1a** by prolonging the reaction time to 48 h (entry 9). Thus, based on the above experiments, we determined the optimized conditions to be **1a** (0.3 mmol), *t*-BuONO (4.0 equiv.), and H_2O (2 mL) at room temperature in air for 18 h.

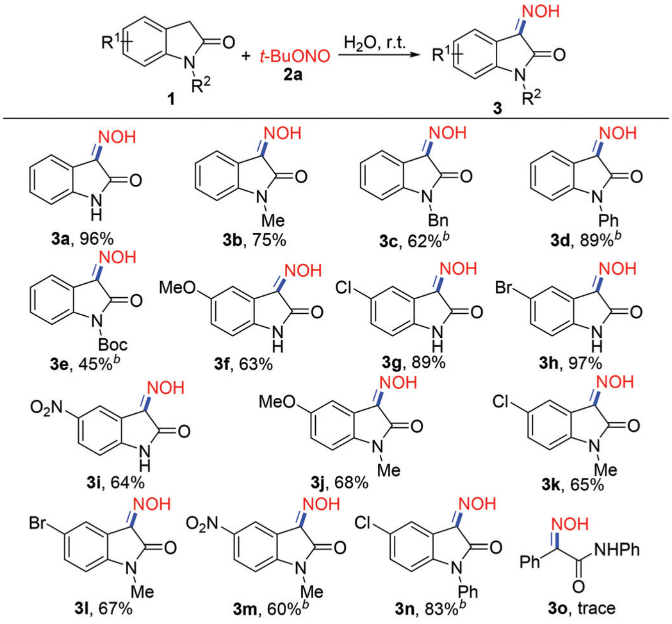
Table 1 Optimization of reaction conditions[a]



Entry	Solvent (mL)	Yield (%)
1	1,4-Dioxane (2.0)	5
2	1,4-Dioxane (1.6)–H_2O (0.2)	37
3	1,4-Dioxane (1.6)–H_2O (0.4)	53
4	1,4-Dioxane (1.6)–H_2O (0.8)	58
5	H_2O (2.0)	96
6[b]	H_2O (2.0)	71
7[c]	H_2O (2.0)	95
8[d]	H_2O (2.0)	97
9[e]	H_2O (2.0)	89

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 mmol) and solvent in air at r.t. for 18 h. [b] **2a** (3.0 equiv.). [c] **2a** (5.0 equiv.). [d] At 40 °C. [e] **1a** (7.52 mmol, 1 g) for 48 h.

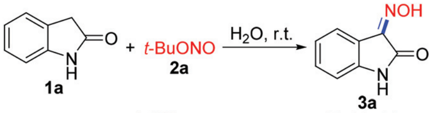
Table 2 Examples of radical coupling reactions[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (1.2 mmol) and H_2O (2 mL) in air at r.t. for 18 h. [b] 0.2 mL of 1,4-dioxane was added.

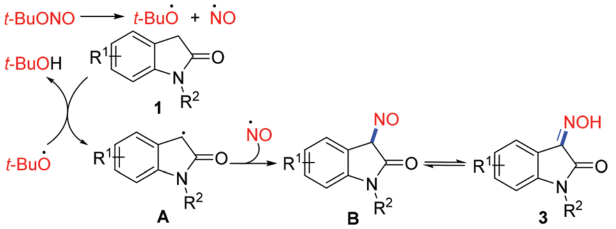
Having optimized the reaction conditions, we next investigated the scope of the radical coupling reaction by different oxindoles with *t*-BuONO **2a**. As shown in Table 2, a variety of oxindoles, bearing both electron-rich substituents (R = Me, Bn, Ph) and electron-poor substituents (R = Boc) at the *N*-substituted position, reacted smoothly with **2a**, affording the corresponding isatins **3b–3e** in good to excellent yields. The unprotected oxindole gave the desired product **3a** in 96% yield. Notably, *N*-Me, *N*-Bn and *N*-Ph substituents can be tolerated in this radical coupling reaction (products **3b–3d**), giving the corresponding products in 75%, 62%, and 89% yields respectively. Moreover, the *N*-Boc substituted substrate was also reacted effectively with **2a** to give the corresponding product **3e** in 45% yield. We then turned our attention to an aryl moiety, as shown in Table 1, and a range of oxindoles, with both electron-donating groups and electron-withdrawing groups on an aryl ring, were viable in this transformation. The aryl ring with an electron-donating group (**3f**) displayed a lower reactivity than those bearing electron-withdrawing groups (**3g**, **3h** and **3i**). Notably, Cl and Br substituents can be tolerated in the radical coupling reaction, thereby facilitating additional modifications at the halogenated positions. To our delight, this method was successfully applied to multiple oxindoles, and these substrates were smoothly converted to the corresponding isatins **3j–3n** in moderate yields. Unfortunately, the substrate *N*,2-diphenylacetamide was not suitable for the radical coupling reaction under the current conditions.

As shown in Scheme 2, two radical inhibitors (4.0 equiv.), including 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and 2,6-di-*tert*-butyl-4-methyl phenol (BHT), were added to the radical



Additive	Yield of 3a
TEMPO (4.0 equiv)	0%
BHT (4.0 equiv)	trace

Scheme 2 Control experiments.



Scheme 3 Plausible mechanism.

coupling reaction, resulting in no conversion of oxindole **1a**. These results suggest that the current reaction includes a radical process.

Based on the above-mentioned control experiments and previous mechanistic studies,[9,10,13,14] a possible reaction pathway has been proposed in Scheme 3. Initially, *t*-BuONO is split into the *t*-BuO radical and NO radical.[13] Subsequently, the *t*-BuO radical abstracted a hydrogen atom from the oxindole **1** to generate the *t*-BuOH and oxindole radical **A**.[9] Finally, the radical (radical **A**)–radical (NO radical) coupling reaction occurred to furnish intermediate **B** which was followed by the isomerization to afford the final product isatin oxime **3**.[10]

Conclusions

In conclusion, we have developed a simple and metal-free synthesis method for the conversion of oxindoles into isatin oximes. This radical coupling reaction provides a green and clean procedure for the construction of C–N bonds. Most importantly, the use of *t*-BuONO as a nitrogen source, and H_2O as the solvent makes this new transformation sustainable and practical. Further studies on the development of radical coupling reactions are currently underway in our laboratory.

Experimental

Typical experimental procedure for the radical coupling reaction

To a Schlenk tube were added oxindole **1** (0.3 mmol), *t*-BuONO **2a** (1.2 mmol) and H_2O (2 mL). Then the tube was stirred at room temperature in air for the indicated time until complete consumption of starting materials as monitored by TLC analysis. After the reaction was complete, the solution was diluted with ethyl acetate and washed with brine. The organic layer was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After the removal of sodium sulfate through filtration, 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 the research funds of NBU (No. ZX2016000706), the Foundation of Ningbo University (No. XYL17009), and the K. C. Wong Magna Fund in Ningbo University.

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