

TBHP/I₂-Mediated Domino Oxidative
Cyclization for One-Pot Synthesis of
Polysubstituted Oxazoles

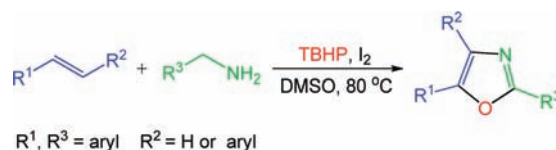
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ABSTRACT



A facile type of one-pot, transition-metal-free domino process was developed for the synthesis of oxazoles. Thus, a variety of polysubstituted oxazoles were easily synthesized via *t*-BuOOH/I₂-mediated domino oxidative cyclization from readily available starting materials under mild conditions.

Oxazole is a fundamental class of five-membered heterocycles, which directly stimulated more and more interest in both the industrial and academic fields over the past decades.¹ The 1,3-oxazole substructure is generally considered as the indispensable chemical block in organic synthesis² and the significant pharmacophore of many natural products,³ which are very important antifungal medicines containing three oxazole rings such as ulapualide A.⁴ Generally oxazole derivatives are synthesized by three typical synthetic methods including cyclization of acyclic precursors,⁵ oxidation of oxazolines,⁶ and the coupling of the prefunctionalized oxazoles with other organometallic reagents.⁷ Cyclization of acyclic precursors to access prefunctionalized oxazoles from readily available materials has attracted intensive attention.⁸

Despite primordial importance in synthetic chemistry, these methods face the limitation of inaccessible starting materials and the utilization of the toxic transition-metal catalysts.⁹ Hence, development of a more eco-friendly procedure for acquisition of oxazole derivatives from easily available starting materials still represents a continuing challenge.

Domino strategy has been extensively investigated and widely examined for the synthesis of organic compounds in modern synthetic chemistry due to its great usefulness.¹⁰ Recently, our group has reported a series of domino processes

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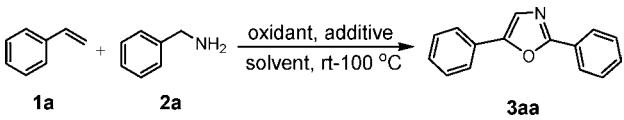
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for synthesis of heterocycle compounds.¹¹ In this communication, we present a novel synthetic method for preparation of polysubstituted oxazoles from olefins and benzylic amines with a transition-metal-free reaction. The method includes three principal procedures: the consecutive halogenation and oxidation of olefins and then functionalization of the sp³ C–H bond adjacent to the nitrogen atom.

To initiate our study, we have optimized the reaction conditions for the formation of oxazole with styrene (**1a**) and benzylamine (**2a**) as substrates (Table 1). Various oxidants were

Table 1. Optimization of Reaction Conditions^{a,b}



entry	oxidant	additive	solvent	temp (°C)	yield (%) ^c
1	DDQ	I ₂	DMSO	60	21
2	TBHP	I ₂	DMSO	60	72
3	IBX	I ₂	DMSO	60	75
4	O ₂ (1 atm)	I ₂	DMSO	60	44
5	PhI(OAc) ₂	I ₂	DMSO	60	8
6	TBHP	ICl	DMSO	60	15
7	TBHP	NBS	DMSO	60	32
8	TBHP	NIS	DMSO	60	69
9	TBHP	I ₂	DMF	60	55
10	TBHP	I ₂	toluene	60	32
11	TBHP	I ₂	THF	60	28
12	TBHP	I ₂	1,4-dioxane	60	<5
13	TBHP	I ₂	DMSO	rt	23
14	TBHP	I ₂	DMSO	80	85
15 ^d	TBHP	I ₂	DMSO	100	84
16 ^e	TBHP	I ₂	DMSO	80	91

^a Reaction was carried out with 0.5 mmol of **1a**, 2.0 equiv of **2a**, 1.2 equiv of additive, 1.5 equiv of oxidant, 3 mL of solvent, 12 h. ^b IBX = 2-iodoxybenzoic acid. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone. TBHP = *tert*-butyl hydroperoxide. ^c Determined by GC. ^d 2.5 equiv of **2a** was used. ^e 2.5 equiv of **2a** was added in two portions.

first examined. In a typical procedure, a mixture of **1a** (0.5 mmol, 1 equiv), **2a** (2 equiv), oxidant (1.5 equiv), and I₂ (1.2 equiv) in 3 mL of DMSO was stirred for 12 h at 60 °C. After completion of the reaction (monitored by TLC), **3aa** was detected in 21%, 72%, 75%, 44%, and 8% yields by GC when 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), *t*-BuOOH (TBHP), 2-iodoxybenzoic acid (IBX), O₂ (1 atm), and PhI(OAc)₂ were used as the oxidant, respectively (Table 1, entries 1–5). Obviously, IBX was the relatively efficient oxidant. Considering the economical and environmental impact, we chose TBHP as the suitable oxidant. We used several different additives such as ICl, NBS, and NIS in this reaction system

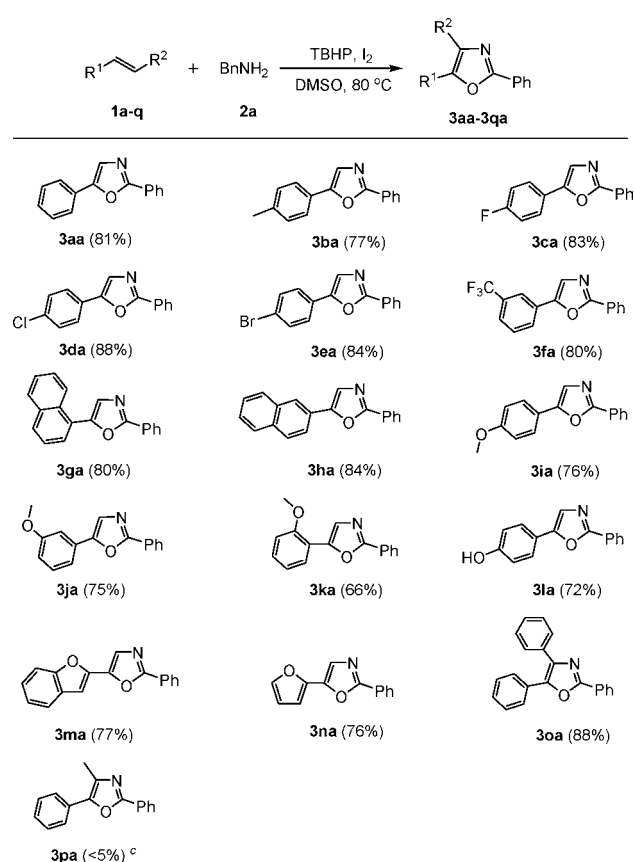
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(Table 1, entries 6–8) and found that 1,5-diphenyl oxazole was obtained in moderate yield with NIS as the additive. Among various solvents (entries 9–12 of Table 1), DMSO was the most effective media for this oxidative cyclization process, while 80 °C was found as the optimal temperature (Table 1, entries 13–15). Owing to the fact that the benzylamine tended to be oxidized to phenylaldehyde in this reaction system,¹² the addition of excess benzylamine (2.5 equiv) in two portions was necessary, which increased the yield of the desired product up to 91% (Table 1, entry 16).

Under the optimized reaction conditions, i.e., aryl alkenes (0.5 mmol), benzylamine derivatives (2.5 equiv in two portions), TBHP (1.5 equiv) as the suitable oxidant, I₂ (1.2 equiv) as the additive, and DMSO (3 mL) as the solvent, the scope of a one-pot synthesis of polysubstituted oxazoles was explored by using a series of terminal aryl alkenes and benzylamine as the substrates (Scheme 1, **3aa–3na**). Pleas-

Scheme 1. Scope of Aryl Alkenes^{a,b}



^a Reaction conditions: aryl alkenes (0.5 mmol, 1 equiv), benzylamine (2.5 equiv, being added in two portions), TBHP (1.5 equiv), I₂ (1.2 equiv), DMSO (3 mL). ^b Isolated yield was given in parentheses. ^c (*E*)-Prop-1-enylbenzene was used as the substrate.

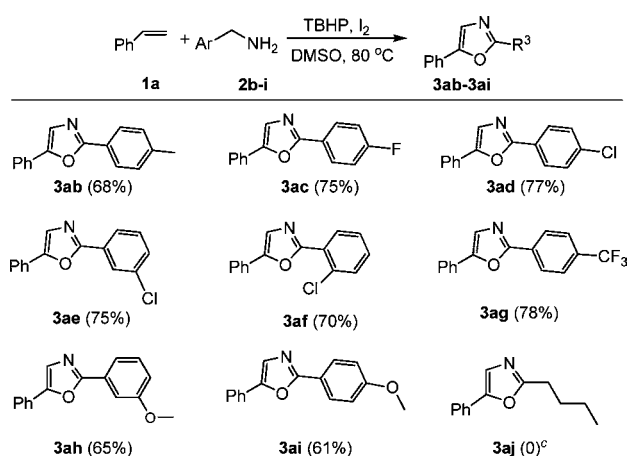
ingly, all of the olefins, regardless of their electronic or steric properties, proceeded smoothly in good yields to afford the expected 1,5-diaryl oxazoles (66–88%). Generally, higher

(12) Around half of benzylamine was oxidized to benzaldehyde detected by GC-MS.

yields were obtained with electron-withdrawing substituents on the aromatic ring. The corresponding products were also obtained in good yields with terminal heterocyclic alkenes as the substrates (Scheme 1, **3ma** and **3na**). When (*E*)-1,2-diphenylethene was employed as the substrate, the corresponding 2,4,5-trisubstitution product was isolated in good yield (Scheme 1, **3oa**), which indicated that 2,5-diaryl oxazoles or 2,4,5-triaryl oxazoles could be conveniently and electively synthesized by using different olefin substrates. However, (*E*)-prop-1-enylbenzene almost failed to yield the desired product (Scheme 1, **3pa**),¹³ due to the discrepancy of reactivity of the relevant positions.

Furthermore, various benzylamine derivatives were employed to probe the scope of the reaction substrates. As shown in Scheme 2, the electron-rich group on the aromatic

Scheme 2. Scope of Benzylamine Derivatives^{a,b}



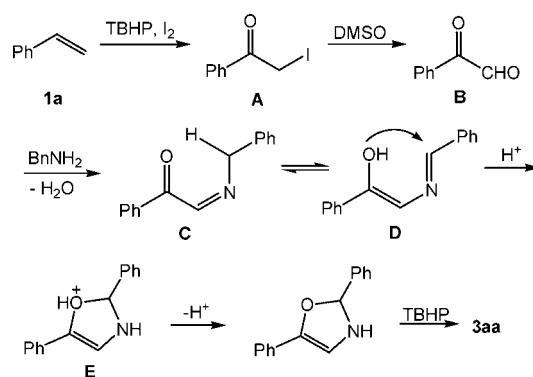
^a Reaction condition: **1a** (0.5 mmol), **2** (2.5 equiv, added in two portions), TBHP (1.5 equiv), I₂ (1.2 equiv), DMSO (3 mL). ^b Isolated yield. ^c *n*-BuNH₂ was used as the substrate.

ring was unfavorable for the formation of oxazoles, while the electron-deficient substituents increased the reaction yields (Scheme 2, **3ab-3ai**). It is worthy to note that there is a slight influence when substituents are presented on the para, meta, and ortho positions of the benzylamine such as **2d**, **2e**, or **2f**. However, the desired product was not detected with *n*-BuNH₂ as the substrate (Scheme 2, **3aj**).

A plausible mechanism of the present reaction could be described as follows (Scheme 3): TBHP/I₂-mediated oxidation of **1a** formed **A**,¹⁴ and **A** was conveniently converted to **B** in the media of DMSO via Kornblum oxidation.¹⁵

(13) Aliphatic alkenes, such as 1-octene and methyl acrylate, could not give the corresponding products as well.

Scheme 3. Plausible Reaction Mechanism



Subsequently, **C** or its enolizational isomer **D** was formed after the addition of benzylamine, then **E** was obtained undergoing intramolecular nucleophilic addition of **D**. Consequently, **E** collapsed into the final product (**3aa**) by deprotonation and oxidation.¹⁶

In conclusion, a new type of one-pot, transition-metal-free domino process through a TBHP/I₂-mediated oxidative cyclization from easily available aryl alkenes and benzylic amines was developed for the synthesis of polysubstituted oxazoles. It is worthwhile for synthetic chemistry and medical chemistry because oxazoles are useful synthetic intermediates for bioactive compounds. Further studies for the scope and the mechanism of this reaction are in progress.

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Supporting Information Available: Experimental procedure and characterization of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) When the mixture of styrene **1a** (1 equiv), TBHP (1 equiv), and iodine (1 equiv) in dichloromethane was stirred at room temperature for 4 h, compound **A** was obtained in 92% yield.

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(16) Reaction of **B** and **2a** under the reaction conditions as **1a** and **2a** afforded the desired product (**3aa**) in high yield (94%).