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Copper-Catalyzed Oxygenation Approach to Oxazoles from Amines, Alkynes, and Molecular Oxygen

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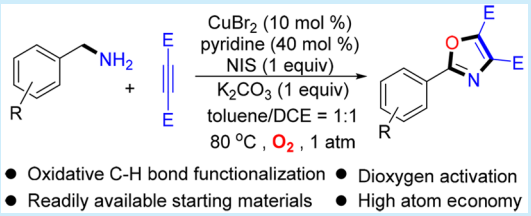
Supporting Information

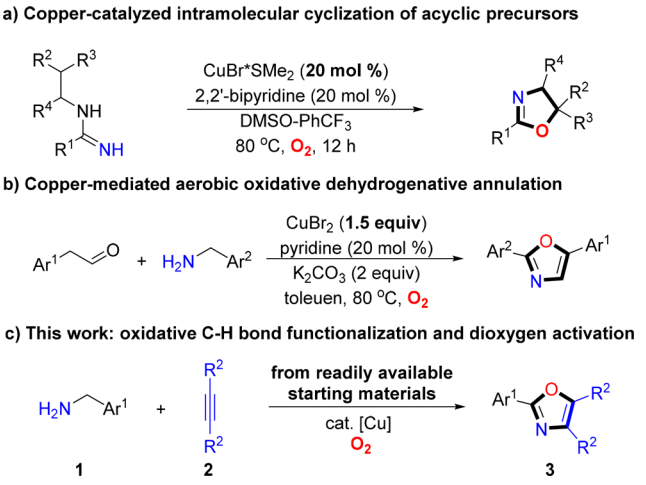
ABSTRACT: A novel and efficient oxygenation approach to trisubstituted oxazoles via a copper-catalyzed aerobic oxidative dehydrogenative annulation of amines, alkynes, and O_2 has been developed. This transformation combines dioxygen activation and oxidative C−H bond functionalization and provides a practical protocol for the preparation of oxazole derivatives, which are privileged units found in various bioactive compounds or other natural products. ^{18}O-labeling experiments were conducted to reveal that oxygenation was involved in this chemistry.



Nitrogen/oxygen-containing heterocyclic compounds show significant and extensive biological activity,[1] the synthesis of which has long been a hot and challenging topic for organic synthetic chemists. Among them, the oxazole ring is considered a privileged heterocyclic motif found in various bioactive compounds or other natural products,[2] which exhibits antibacterial, antiviral, antifungal, antineoplastic, or other properties. Consequently, a variety of approaches to oxazole derivatives have been developed, such as intramolecular[3] or intermolecular[4] cyclization, oxidative coupling,[5] oxidation of oxazolines,[6] or other developed processes.[7] Despite the significance of these reported methods, most of them suffer from low atom economy, utilization of stoichiometric amounts of transition-metal catalysts or additional oxidants, a limited substrate scope, or inaccessible starting materials. Therefore, developing efficient and practical methods for the preparation of oxazoles from readily available starting materials under mild conditions is still desirable.

Molecular oxygen is considered an ideal oxidant and oxygen source owing to its abundant, low-cost, environmentally friendly, and sustainable character.[8] Recently, copper-mediated aerobic oxidation[9,10] and oxygenation[9,11] with molecular oxygen has triggered widespread interest owing to its high efficiency and general applicability. Applying this strategy to the synthesis of oxazole derivatives, Chiba and co-workers reported an elegant approach to 2,5,5-trisubstituted dihydrooxazoles by the oxygenation of prefunctionalized *N*-alkylamidines (Scheme 1a).[3f] Our group reported a dehydrogenative annulation and oxygenation method to construct 2,5-disubstituted oxazoles from amines, aldehydes, and O_2 (Scheme 1b).[4e] Unfortunately, stoichiometric amounts of copper salt (1.5 equiv) are required for the transformation. In addition, the transformation suffers from the preparation of corresponding unstable 2-phenylacetaldehydes (Scheme 1b). To further improve this reaction system and reduce the loading of copper salt, we herein present

Scheme 1. Copper-Mediated Oxygenation Approaches to Oxazoles



a copper-catalyzed aerobic dehydrogenative annulation[12] approach to oxazoles via dioxygen activation from readily available amines, alkynes, and O_2 (Scheme 1c). The oxidative C−H bond functionalization[13] and use of O_2 as the O-source make the present transformation highly efficient and practical.

We commenced our study by performing the reaction of benzylamine **1a** with dimethyl butynedioate **2a** in the presence of stoichiometric amounts of $CuBr_2$, pyridine, and K_2CO_3 at 80 °C in toluene under an oxygen atmosphere (1 atm) (Table 1). To our delight, trisubstituted oxazole **3a** was obtained as the desired product in 28% yield (entry 1). To further improve the reactivity, we screened a series of bases, solvents, and copper

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Table 1. Examination of Reaction Conditions[a]

entry	[Cu]	base	solvent	yield (%)[b]
1[c]	$CuBr_2$	K_2CO_3 (2 equiv)	toluene	29(28)
2[c]	$CuBr_2$	Cs_2CO_3 (2 equiv)	toluene	10
3[c]	$CuBr_2$	K_3PO_3 (2 equiv)	toluene	23
4[c]	$CuBr_2$	K_2CO_3 (2 equiv)	CH_3CN	9
5[c]	$CuBr_2$	K_2CO_3 (2 equiv)	DCE	13
6[c]	$Cu(OTf)_2$	K_2CO_3 (2 equiv)	toluene	trace
7[c]	$Cu(OTf)_2$	K_2CO_3 (2 equiv)	toluene	trace
8[c]	CuI	K_2CO_3 (2 equiv)	toluene	10
9[c,d]	$CuBr_2$	K_2CO_3 (2 equiv)	toluene	9
10[e]	$CuBr_2$	K_2CO_3 (2 equiv)	toluene	10
11[e,f]	$CuBr_2$	K_2CO_3 (2 equiv)	toluene	60
12[e,f]	$CuBr_2$	K_2CO_3 (2 equiv)	toluene/DCE = 1:1	81(79)
13[e,f]	$CuBr_2$	K_2CO_3 (1 equiv)	toluene/DCE = 1:1	80(79)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), pyridide (0.08 mmol), and solvent (2 mL), stirred at 80 °C under an oxygen atmosphere for 12 h. E = CO_2Me. [b]Yield was determined by ^1H NMR analysis of the crude reaction mixture using $Cl_2CHCHCl_2$ as an internal standard. The numbers in the parentheses are isolated yields. [c][Cu] (1.5 equiv). [d]TEMPO (10 mol %, 0.02 mmol) was employed as an additive. [e]Catalytic amount of [Cu] (10 mol %) was employed. [f]NIS (1 equiv, 0.2 mmol) was employed as an additive.

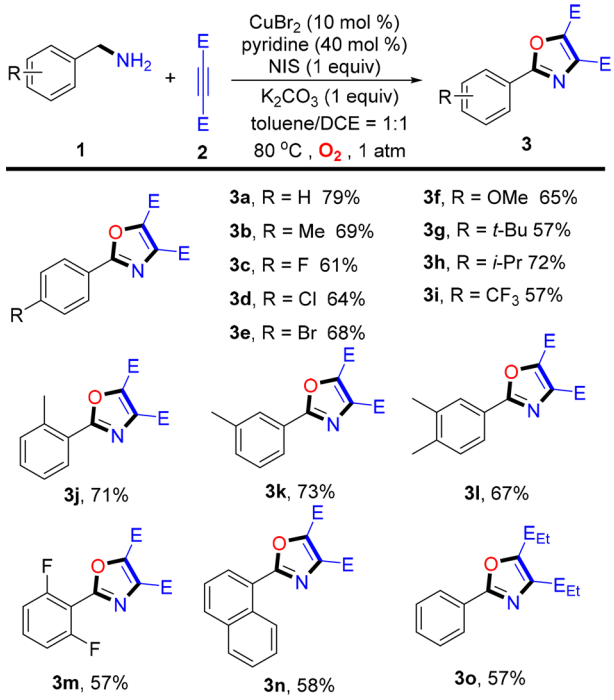
salts (entries 2−9; see Supporting Information (SI)), but the efficiency was not improved. Reducing the load of copper salt resulted in lower reactivity (entry 10). Further additive screening in the presence of catalytic amounts of $CuBr_2$ revealed that NIS played a positive role in the reactivity (entry 11). By switching the solvent from toluene to the mixture toluene/DCE (1:1), the reaction worked better and delivered **3a** in 79% yield (entry 12). In addition, several control experiments were carried out to reveal that each component in this protocol was essential for the improvement of the efficiency (see SI). After further screening of K_2CO_3 loading, **3a** was obtained in 79% yield under the optimized conditions: $CuBr_2$ (10 mol %), pyridine (40 mol %), K_2CO_3 (1 equiv), and NIS (1 equiv) in 1:1 toluene/DCE (2 mL) at 80 °C under an oxygen atmosphere (1 atm) (entry 13).

With the established annulation conditions in hand, we examined the scope of benzylamines **1** and alkynes **2** (Scheme 2). Different substituents could be connected to the aryl ring (para-, meta-, ortho-position and multisubstituted) of the benzylamine substrates. Halo-substituted benzylamines gave the desired products in moderate yields (**3c−e**, **3m**), the reserved halogen atom of which could be used for further cross-coupling reactions. The naphthyl-substituted amine could be also smoothly transformed into the desired product in moderate yield (**3n**). Moreover, diethyl but-2-ynedioate worked well to afford oxazole **3o** in 57% yield.

To further expand the substrate scope, we chose the proposed intermediate enamines **4** as substrates to explore this transformation (Scheme 3). The phenyl-substituted enamines **4** performed well and produced the desired oxazole in moderate yields (**3p−t**). In contrast, the direct reaction of the corresponding phenyl-substituted alkynes showed very low efficiency due to the slow hydroamination step. Notably, the aliphatic amines containing a long alkyl chain or other alkyl groups were also tolerated in this transformation and produced the corresponding oxazole products **3u** and **3v** successfully.

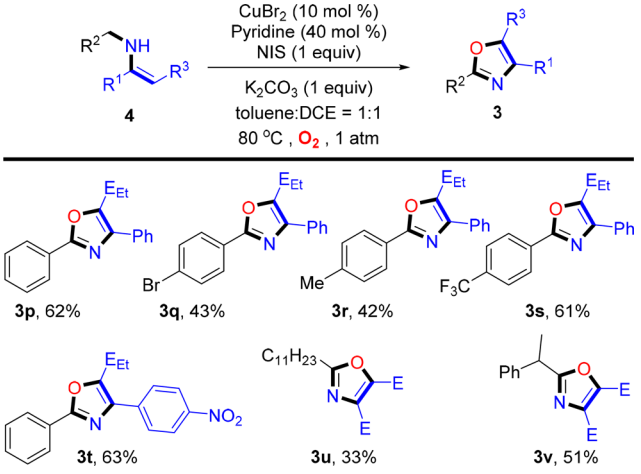
To gain further insight into this reaction mechanism, several potential substrates **4a**, **5**, and **6** were investigated under the

Scheme 2. Substrate Scope of Benzylamines and Alkynes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $CuBr_2$ (10 mol %), pyridine (40 mol %), K_2CO_3 (1 equiv), and NIS (1 equiv) in 1:1 toluene/DCE (2 mL) with stirring at 80 °C under an oxygen atmosphere (1 atm) for 12 h. Isolated yields. E = CO_2Me. E_{Et} = CO_2Et.

Scheme 3. Expansion of the Substrate Scope[a]



[a]Reaction conditions: **4a** (0.2 mmol), $CuBr_2$ (10 mol %), pyridine (40 mol %), K_2CO_3 (1 equiv), and NIS (1 equiv) in 1:1 toluene/DCE (2 mL) with stirring at 80 °C under an oxygen atmosphere (1 atm) for 12 h. Isolated yields. E = CO_2Me. E_{Et} = CO_2Et.

standard conditions (Scheme 4a−c). Only **4a** can afford the desired oxazole product. These results indicate that enamine **4a** instead of benzonitrile **5** or benzamide **6** is probably the key intermediate for this transformation. Moreover, ^{18}O-labeling experiments were conducted. As a result, the ^{18}O-labeled product [^{18}O]-**3a** was obtained in 66% yield (Scheme 4d), which demonstrates that the molecular oxygen donates the oxygen atom to the oxazole products **3**.

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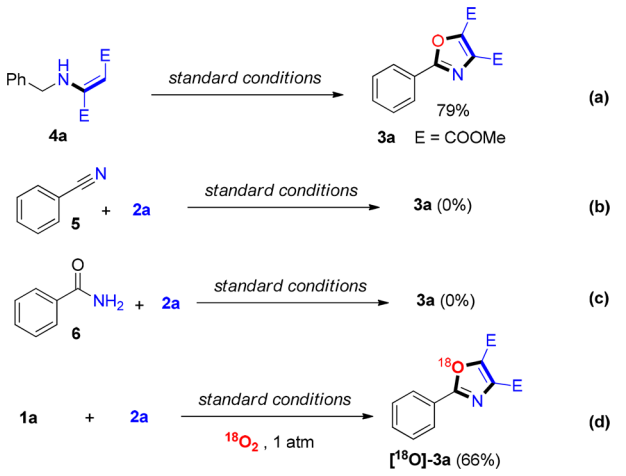
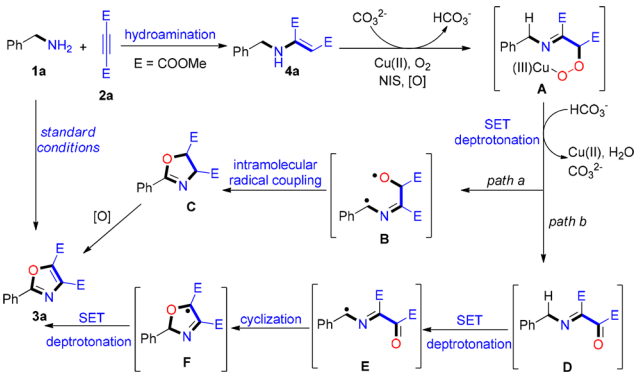
Scheme 4. Mechanistic Studies



On the basis of these experimental results and previous reports, the mechanism is proposed in Scheme 5. The

Scheme 5. Proposal Mechanism



formation of enamine intermediate **4a** is the initial step.[14] Under basic conditions, enamine **4a** is oxidized and then captures molecular oxygen to form intermediate **A**,[15] facilitated by copper salt, molecular oxygen, and NIS. Afterward, intermediate **A** undergoes a SET/deprotonation process to provide intermediate **B**,[13,16] which affords the 4,5-dihydrooxazole intermediate **C** through subsequent intramolecular radical coupling. Finally, intermediate **C** is easily oxidized to afford the desired product **3a** (Scheme 5, path a).[6e] Alternatively, intermediate **A** undergoes a SET/deprotonation process to provide intermediate **D** (pathway b), which affords intermediate **E** through a further SET/deprotonation process.[17] Then, intermediate **F** is formed through the cyclization of intermediate **E**. Finally product **3a** is produced through a further SET/deprotonation process (Scheme 5, path b).

In summary, we have developed a novel copper-catalyzed aerobic oxidative dehydrogenative annulation of amines, alkynes, and molecular oxygen for the efficient construction of trisubstituted oxazoles. Strategies of oxidative C−H bond functionalization, dioxygen activation, and aerobic oxidation make this transformation particularly practical and attractive. High atom economy, readily available starting materials, mild reaction conditions with catalytic amounts of low-cost transition-metal catalysts, and good functional group tolerance render this protocol attractive for the synthesis of oxazole-containing bioactive compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00992.

Experimental procedures, full characterization of products, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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