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# Preparation of 2,4,5-Trisubstituted Oxazoles through Iodine-mediated Aerobic Oxidative Cyclization of Enaminones

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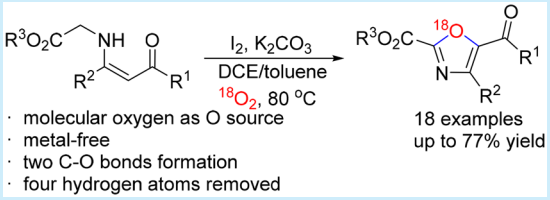
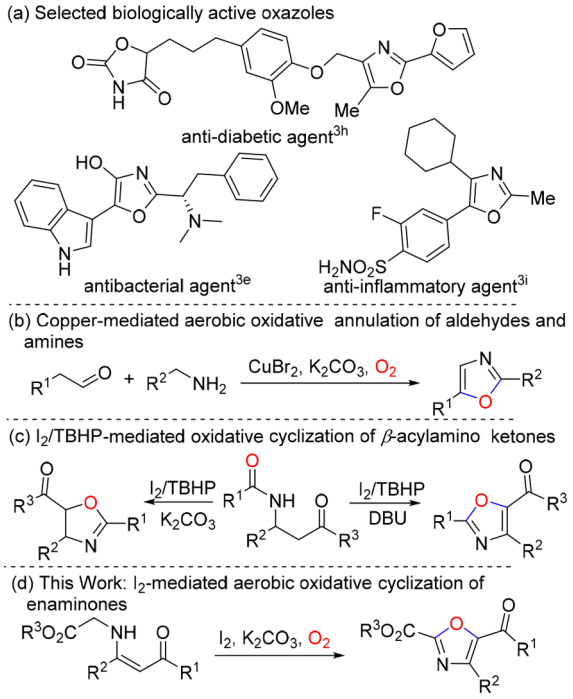
Supporting Information

**ABSTRACT:** A novel approach to trisubstituted oxazoles has been developed that is based upon an iodine-mediated aerobic oxidative cyclization of enaminone derivatives. This transition-metal-free procedure was highly efficient and involved the removal of four hydrogen atoms under mild conditions.




In recent years, oxazoles have gained considerable attention[1] since a number of oxazole-containing natural products derived from marine invertebrates and microorganisms have showed diverse and significant biological activities.[2] Additionally, oxazole moieties are frequently used as chemical blocks in the synthesis of bioactive natural products and pharmaceuticals.[3] In many cases, promising antibacterial,[3e] antidiabetic,[3h] and anti-inflammatory[3i] activities have been identified for synthetic trisubstituted-oxazoles (Scheme 1a). As a result, extensive efforts have been made to achieve the synthesis of fully substituted oxazole ring systems.

**Scheme 1. Various Procedures for Multisubstituted Oxazole Synthesis**




To date, a range of highly functionalized oxazoles has been prepared via the cyclization of acylic precursors. In particular, the cyclodehydration of α-acylamino ketones, esters, or amides promoted by Brönsted or Lewis acids (known as Robinson−Gabriel condensation)[4] is a classical strategy to synthesize oxazole derivatives. Transition-metal-catalyzed[5] or iodine-mediated[6] cyclization reactions of enamides have also been widely developed for the synthesis of multisubstituted-oxazoles. For example, in 2012, Jiao and co-workers developed a good method for the synthesis of 2,5-disubstituted oxazoles from aldehydes and amines through copper-mediated aerobic oxidative dehydrogenative annulation (Scheme 1b).[7] In 2015, Gao and co-workers reported an elegant method for the synthesis of 2,4,5-trisubstituted-oxazoles and oxazolines through $I_2$-catalyzed C−O bond formation/dehydrogenation from β-acylamino ketones (Scheme 1c).[8] However, most of the aforementioned strategies do have some disadvantages such as the use of a strong Brönsted acid or stoichiometric amounts of oxidants, and in some cases, transition-metal catalysts are a requirement. In response to these challenges, practical and efficient approaches to the synthesis of highly functionalized oxazoles under mild reaction conditions still remain desirable.

As part of our effort in the transformation of enaminones toward nitrogen-containing heterocycles,[9] we herein present a practical and efficient approach for the synthesis of 2,4,5-trisubstituted oxazole derivatives from enaminones by iodine-mediated aerobic dehydrogenative annulation. In this transformation, four hydrogen atoms are efficiently removed under transition-metal-free conditions. Moreover, molecular oxygen serves as the oxidant[10] for construction of those *O*-containing heterocycles, which is advantageous due to its abundance.

An initial survey of reaction conditions was studied with *N*-(3-oxo-1,3-diphenylprop-1-en-1-yl)-glycine ethyl ester **1a** as substrate using iodine as the additive and $K_2CO_3$ as the base at 80 °C in DCE under air atmosphere (Table 1). To our delight,

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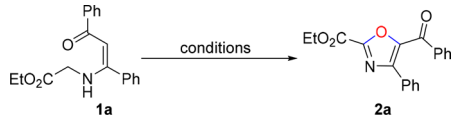
**Table 1. Screening of the Reaction Conditions**[a]



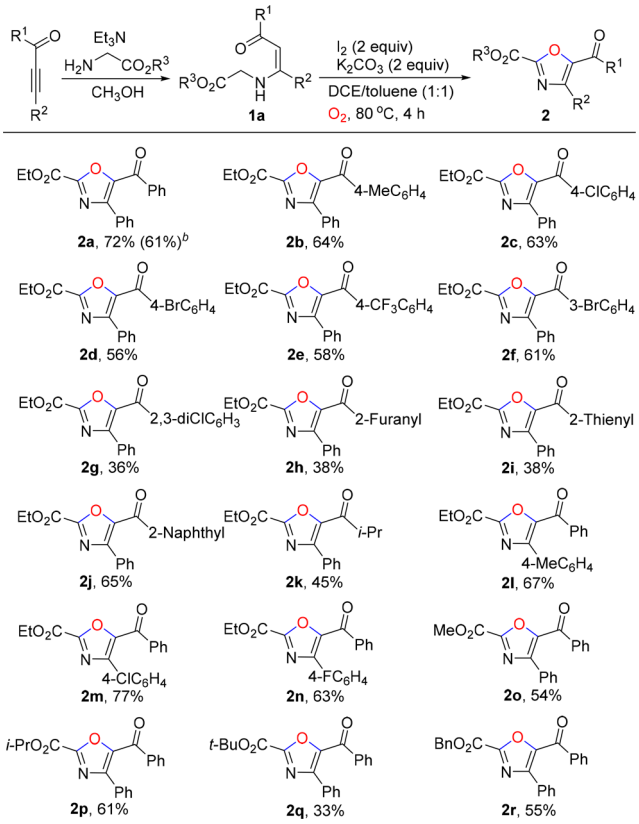

| entry | solvent | base | additive | atm. | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | DCE | $K_2CO_3$ | $I_2$ | air | 52 |
| 2 | toluene | $K_2CO_3$ | $I_2$ | air | 42 |
| 3 | MeCN | $K_2CO_3$ | $I_2$ | air | 7 |
| 4 | DMSO | $K_2CO_3$ | $I_2$ | air | n.d. |
| 5 | DCE | $Cs_2CO_3$ | $I_2$ | air | 16 |
| 6 | DCE | KOH | $I_2$ | air | n.d. |
| 7 | DCE | $K_2CO_3$ | NIS | air | 12 |
| 8 | DCE | $K_2CO_3$ | PIDA | air | n.d. |
| 9 | DCE | $K_2CO_3$ | $I_2$ | $O_2$ | 59 |
| 10 | DCE | $K_2CO_3$ | $I_2$ | $N_2$ | 6 |
| 11 | DCE/toluene | $K_2CO_3$ | $I_2$ | $O_2$ | 76(72) |
| 12[c] | DCE/toluene | $K_2CO_3$ | $I_2$ | $O_2$ | 61 |
| 13[d] | DCE/toluene | $K_2CO_3$ | $I_2$ | $O_2$ | 67 |

[a]Reaction conditions: **1a** (0.2 mmol), base (0.4 mmol), additive (0.4 mmol), and solvent (2 mL) at 80 °C for 4 h. [b]Yields were determined by GC analysis with dodecane as internal standard. Isolated yields in parentheses. [c]3 equiv of $K_2CO_3$ was used. [d]1.5 equiv of $I_2$ was used. n.d. = not detected.

the desired oxazole product **2a** was obtained in 52% GC yield (entry 1). Then, different solvents were screened, among which DCE gave the best result (entries 1−4). Although other bases were examined ($Cs_2CO_3$, KOH, entries 5 and 6), the use of 2 equiv of $K_2CO_3$ was found to be optimal (entry 1). The choice of the additive played a crucial role; the reaction with NIS gave a poor yield of **2a** (12%, entry 7). However, when PIDA ((diacetoxyiodo)benzene) was used, no oxazole was detected at all (entry 8). It is noteworthy that the yield of **2a** was improved to 59% when the reaction was carried out under an oxygen atmosphere (entry 9). In contrast, the reaction did not proceed well under a nitrogen atmosphere (entry 10). It was found that the cosolvent system of 1:1 DCE/toluene delivered a better yield of **2a** (entry 11). However, by increasing the loading of $K_2CO_3$ to 3 equiv or decreasing the loading of $I_2$ to 1.5 equiv, the yield was decreased to 61% and 67%, respectively (entries 12 and 13). Finally, the optimized reaction conditions were assigned as entry 11.

Under the optimized reaction conditions, the scope of enaminones **1** was studied (Scheme 2). The structure of **2a** was confirmed by single-crystal X-ray crystallography. First, the substituents on the aroyl moiety of enaminones were examined, and the substrates with electron-donating groups (**2b**) and electron-withdrawing groups (**2e**) were all suitable for this reaction system, affording the corresponding products in 64% and 58% yields, respectively. Substrates with halogen substituents were well tolerated, giving the corresponding products in moderate yields (**2c**, **2d**), which could be used for further transformations. The significant influence of steric hindrance on this reaction was observed (**2g**, yield 36%). Other representative aromatic substrates, such as furanyl, thienyl, and naphthyl groups, were also tolerated (**2h**−**2j**). In addition, when $R^1$ was replaced by an isopropyl group, the desired oxazole **2k** was obtained in 45% yield. Then, the aromatic rings of $R^2$ with *para*-methyl group gave a 67% yield of **2l**. When $R^2$ was replaced by a *p*-chlorophenyl group, it gave a better yield than *p*-fluorophenyl group (**2m**, **2n**). Next, substrates with

**Scheme 2. Scope of Substrates To Form 2**[a,b]

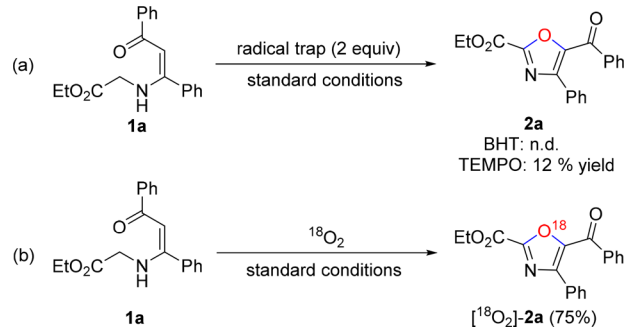



[a]Reaction conditions: **1** (0.2 mmol), $I_2$ (0.4 mmol), and $K_2CO_3$ (0.4 mmol) in 2 mL of DCE/toluene (1:1) at 80 °C under $O_2$ for 4 h. Isolated yields. [b]Reaction performed with 1 mmol scale of **1a** (see Supporting Information for details).

different substituted glycine esters were tested and gave the desired oxazole derivatives **2o**−**2r**, in 54%, 61%, 33%, and 55% yields, respectively.

To gain some insight into the mechanism of this transformation, several control experiments were carried out under the standard conditions as shown in Scheme 3. When an

**Scheme 3. Control Experiments**




equimolar amount of the free-radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) or TEMPO (2,2,6,6-tetramethyl-piperidinooxy) was added to these reaction mixtures, the product yields were significantly lowered (Scheme 3a), indicating that a radical pathway might be involved in this transformation. As shown in Table 1, entry 10, only a 6% yield was observed under a $N_2$ atmosphere. In contrast, the isotope-labeling experiment



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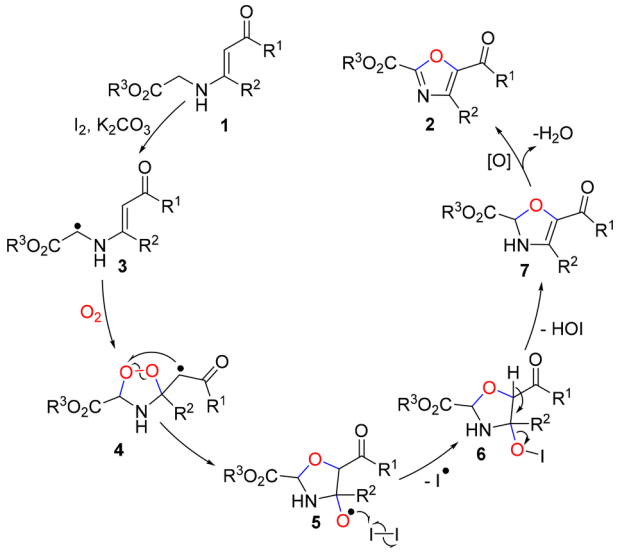
using an $^{18}O_2$ atmosphere gave $^{18}O$-labeled product [$^{18}O$]-**2a** in 75% yield under the standard conditions (Scheme 3b). The above results indicate that the oxygen atom of the oxazole product was derived from molecular oxygen.

On the basis of the experimental results and literature reports, our proposed mechanism for this oxazole formation reaction is shown in Scheme 4. Under basic conditions, the

**Scheme 4. Possible Reaction Mechanism**




relatively active C−H of glycine ester in enaminones **1** is thought to be oxidized by molecular iodine to give radical intermediate **3**,[11] which is then trapped by dioxygen to form radical intermediate **4**. Subsequently, isomerization of the radical **4** would afford the radical **5**, which could react with $I_2$ to produce intermediate **6**. HOI could then be released from intermediate **6** to deliver **7**, which is oxidized under the oxygen atmosphere, to provide the desired oxazole product **2**.

In summary, we have developed a new protocol for the synthesis of 2,4,5-trisubstituted oxazoles based upon an iodine-mediated aerobic dehydrogenative cyclization reaction between enaminone derivatives and molecular oxygen. The removal of four hydrogen atoms and the formation of two new C−O bonds is involved in this procedure. In this aerobic oxidation reaction, the use of molecular oxygen as the oxygen source of the oxazole core makes this process environmentally friendly and atom economical. Owing to the mild reaction conditions and good functional group tolerance, this method could have potential application in the synthesis oxazole-containing natural products.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00376.

General experimental procedures, characterization data, $^1H$ and $^{13}C$ NMR spectra of new compounds, and X-ray data for **2a** (PDF)

### Accession Codes

CCDC 1486793 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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