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Facile Synthesis of Disubstituted Isoxazoles from Homopropargylic Alcohol via C═N Bond Formation

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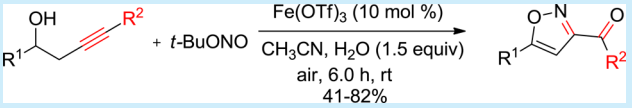
Supporting Information

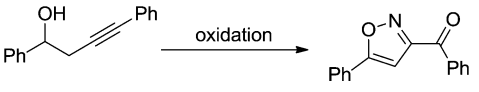
ABSTRACT: A novel iron-catalyzed aerobic oxidative reaction to synthesize disubstituted isoxazoles from homopropargylic alcohol, *t*-BuONO, and H_2O is developed. The method provides mild conditions to afford a variety of useful substituted heterocycles in an efficient and regioselective manner. The mechanism has been studied and proposed, which indicates that the transformation can be realized through construction of a C═N bond and C═O bond, C−H oxidation, and then cyclization. Moreover, this method can be enlarged to gram scale.



Isoxazole derivatives occupy an important field in organic chemistry because of their wide applications in organic synthesis pharmacy chemistry, biologically active molecules, and advanced organic materials.[1] As a consequence, the development of versatile and efficient methods for the preparation of such compounds is an important task.[2] Commonly used strategies for the formation of isoxazoles include oximation and cyclization of 1,3-dicarbonyl compounds and α,β-unsaturated compounds with hydroxylamine as the nitrogen source,[3a,b] condensation of oxime dianions,[3c−e] 1,3-dipolar cycloaddition reaction between alkynes and the primary nitro compounds or nitrile oxides.[3f−i] However, most of the above reactions often required harsh reaction conditions, showed modest regioselectivities and yield, and were neither economic nor eco-friendly. The discovery and development of new methods with easy preparation material, mild reaction conditions, and high regioselectivities for the synthesis of isoxazoles is highly desirable and challenging.[4] In 2010, Miyata's group reported a gold-catalyzed domino reaction involving cyclization and Claisen-type rearrangement of alkynyl oxime resulting isoxazoles in a regioselective and atom economic manner.[5a] In 2011, Carreira reported an unexpected cascade and rearrangement reaction to give 3,4-disubtituted isoxazoles with commercially available material.[5b] 1.3-Dipolar cycloaddition of benzoylnitromethane with phenylacetylene under green conditions has been realized by Pal's group.[5c] Although significant progress in the area has been made, synthesis of isoxazoles via constructing the C═N bond is still less exploited[4a,5d] and remains both challenging and of great value.

Difunctionalization of unactivated alkynes has gained more and more attention in organic synthesis. To continue our interest in functionalization of homopropargylic alcohol,[6] we anticipated that the alcohol would react with additional nitrogen source to produce the nitrogen-containing heterocycles. *tert*-Butyl nitrite is a safe and extensively used reagent in organic synthesis as a nitrating reagent[7a−g] or a diazo reagent to undertake Sandmeyer-type reaction;[8] however, it has rarely been reported as the nitrogen source to construct heterocycles.[7g,h] Herein, we report a novel iron-catalyzed aerobic oxidative reaction to synthesize disubstituted isoxazoles from homopropargylic alcohol, *t*-BuONO, and H_2O (Scheme 1). This method is realized via construction of a C═N bond and C═O bond in a highly regioselective difunctionalization of alkyne, C−H oxidation, and then cyclization.

Scheme 1. Our Method for Synthesis of Disubstituted Isoxazoles



Our investigation commenced with the reaction of 1,4-diphenylbut-3-yn-1-ol (**1a**) with *tert*-butyl nitrite (**2**), 10 mol % of $Zn(OTf)_2$,and 1.5 equiv of H_2O in acetonitrile (MeCN) at room temperature under air atmosphere. The disubstituted isoxazoles (**3a**) were isolated in 12% yield (Table 1, entry 1). By screening different metal salts for this cyclic transformation, including $Cu(OTf)_2$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Fe(OTf)_2$, $Fe(OTf)_3$, $FeCl_3$, and $Fe(NO_3)_3{\cdot}9H_2O$, we found that $Fe(OTf)_3$ was the most efficient and increased the yield to 81% (Table 1, entries 2−10). Next, different solvents were tested with $Fe(OTf)_3$ as the catalyst (Table 1, entries 11−14). Results revealed that the reaction was highly solvent-dependent with optimal isolated yields in acetonitrile, and the use of DCM, toluene, 1,4-dioxane, DMF proved to be ineffective to promote this transformation. Lowering the catalyst loading reduced the yield of **3a** to 67% (Table 1, entry 15). Considering that the catalyst might be hydrolyzed to produce trifluoromethanesulfonic acid, different amounts of trifluoromethanesulfonic acid were investigated and gave the product in moderate yield (Table 1, entries 16 and 17). Other NO_2 sources were tested but did not afford better yields

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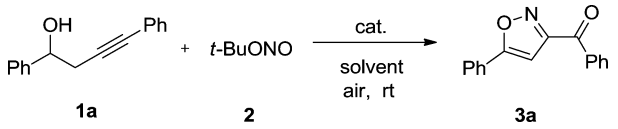
Table 1. Optimization of the Reaction Conditions[a]



1a 2 3a

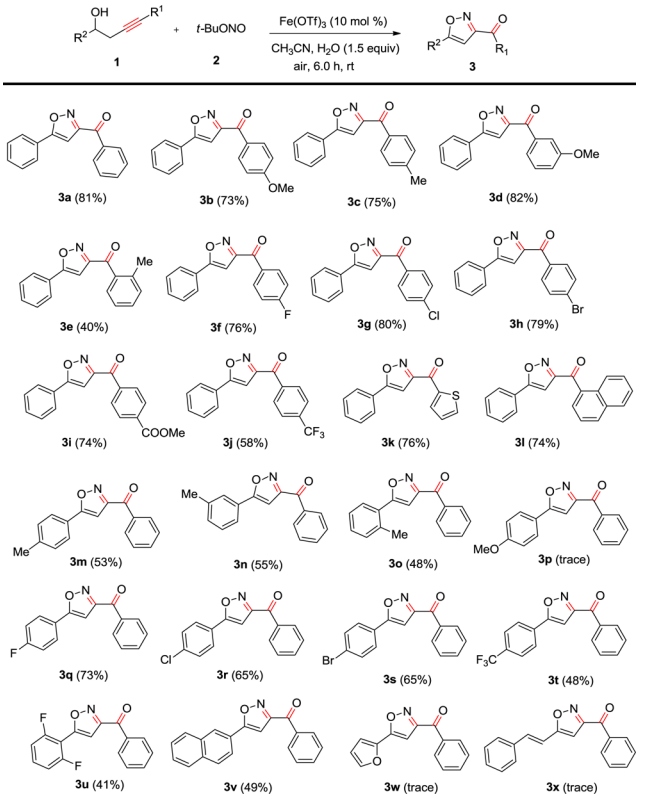
entry	cat	solvent	yield[b] (%)
1	$Zn(OTf)_2$	MeCN	12
2	$Cu(OTf)_2$	MeCN	trace
3	$Sc(OTf)_3$	MeCN	64
4	$Fe(OTf)_2$	MeCN	58
5	AgOTf	MeCN	trace
6	$Bi(OTf)_3$	MeCN	67
7	$Yb(OTf)_3$	MeCN	63
8	**$Fe(OTf)_3$**	**MeCN**	**81**
9	$FeCl_3$	MeCN	56
10	$Fe(NO_3)_3{\cdot}9H_2O$	MeCN	trace
11	$Fe(OTf)_3$	DCM	17
12	$Fe(OTf)_3$	toluene	trace
13	$Fe(OTf)_3$	dioxane	trace
14	$Fe(OTf)_3$	DMF	trace
15[c]	$Fe(OTf)_3$	MeCN	67
16[d]	HOTf	MeCN	65
17[e]	HOTf	MeCN	42
18[f]	$Fe(OTf)_3$	MeCN	18
19[g]	$Fe(OTf)_3$	MeCN	trace
20[h]	$Fe(OTf)_3$	MeCN	0
21		MeCN	0

[a]Reaction conditions: **1a** (0.2 mmol), *tert*-butyl nitrite (**2**) (0.24 mmol), catalyst (0.02 mmol), H_2O (0.3 mmol) in solvent (2.0 mL) were stirred at rt for 6.0 h under air. [b]Isolated yield. [c]Catalyst (0.01 mmol) was used. [d]Catalyst (0.10 mmol) was used. [e]Catalyst (0.05 mmol) was used. [f]$Fe(NO_3)_3{\cdot}9H_2O$ (0.24 mmol) was added instead of *t*-BuONO. [g]$AgNO_2$ (0.24 mmol) was added instead of *t*-BuONO. [h]4 Å MS (40 mg) were added instead of H_2O.

(Table 1, entries 18 and 19). The control experiment revealed that the iron catalyst and H_2O were essential for the reaction (Table 1, entries 20 and 21). Consequently, the reaction proceeded efficiently in the presence of 10 mol % of $Fe(OTf)_3$ and 1.5 equiv of H_2O in acetonitrile at room temperature.

The scope of the substrates was investigated under the optimized conditions (Scheme 2). A variety of substituted homopropargylic alcohols were found to be compatible with this tandem cyclization transformation, giving various 3,5-disubstituted isoxazoles derivatives. First, the influences of substituents on the aryl groups attached to the alkyne were tested. When homopropargyl alcohols bearing electron-donating substituents (Me, OMe) and electron-drawing substituents (F, Cl, Br, COOMe) were placed on the *para* or *meta* position, the substrates performed well and afforded the desired products in good yield (**3a**–**d**,**f**–**i**). The steric hindrance effect was obvious on the transformation reactivity. The corresponding product **3e** was obtained in a low yield when the *ortho* position was substituted with a methyl group (**1e**). Substrate **1j** containing a strong electron-withdrawing CF_3 group afforded the disubstituted isoxazoles **3j** in moderate yield. It is noteworthy that substrates with thiophene **1k** and naphthalene (**1l**) attached to the triple bond could also undergo tandem cyclization successfully, affording the desired products in 76% and 74% yield, respectively. However, when the methyl attached to the alkyne was tested, no desired product was observed. Then, a number of alcohols derived from substituted benzaldehydes were

Scheme 2. Substrate Scope of the Synthesis of Isoxazoles[a,b]



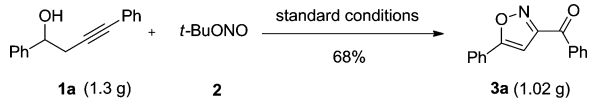
[a]Reaction conditions: **1a** (0.2 mmol), *tert*-butyl nitrite (**2**) (0.24 mmol), $Fe(OTf)_3$ (0.02 mmol), and H_2O (0.3 mmol) in solvent (2.0 mL) were stirred at rt for 6.0 h under air. [b]Isolated yield.

tested. Substrates bearing methyl substituents in the *ortho*, *meta*, or *para* position of the aryl groups provided the corresponding disubstituted isoxazoles **3m**–**o** in moderate yield. When the substrate bearing a methoxyl substituent in para position of the aryl group was examined (**1p**), the reaction system was complex and trace product was observed. Halo-substituted alcohols **1q**–**s** were tolerated in the cyclization reaction, producing the products **3q**–**s** in good yields. The structure of **3s** was determined by X-ray crystallographic analysis (see the Supporting Information).[9] This cyclization transformation protocol could be applicable to substrates **1t** and **1u** with a 4-trifluoromethyl group or 2,6-difluoro groups on the aromatic ring, giving **3t** and **3u** in moderate yield. Notably, the naphthalene group of isoxazoles **3v** was also tolerated in this transformation. Unfortunately, substrates containing the furyl or cinnamyl groups (**1w** and **1x**) were not compatible with the reaction conditions.

To expand the synthetic efficiency of this method, a gram-scale reaction of **1a** was performed under the standard conditions. The desired isoxazole **3a** was isolated in 68% yield, which means there is a potential industrial application (Scheme 3).

Next, some additional experiments were performed in order to give a better understanding of the cyclization reaction. When the reaction was stirred under the standard conditions for 10 min, we

Scheme 3. Synthetic Application: Gram-Scale Reaction



1a (1.3 g) 2 3a (1.02 g)

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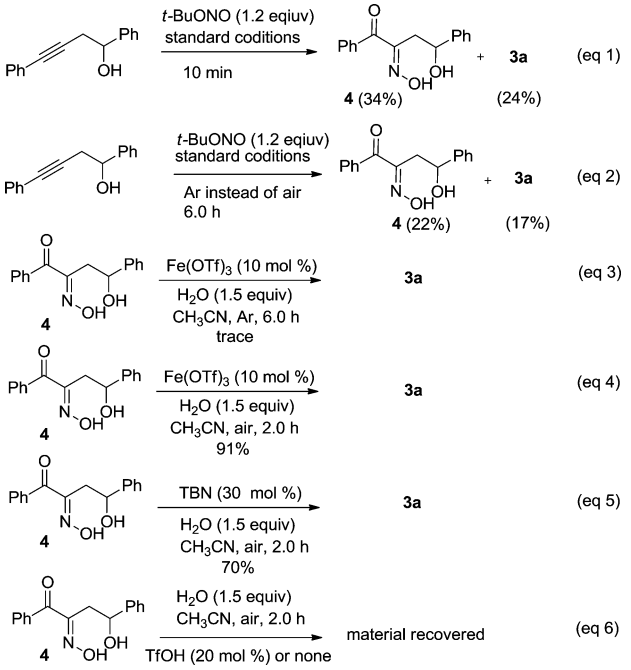
not only obtained the product **3a** in 24% yield but also isolated the oxime intermediate **4** in 34% yield (Scheme 4, eq 1). X-ray

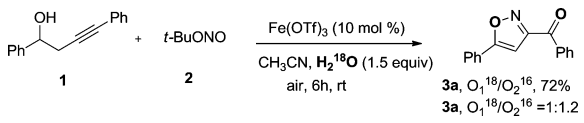
Scheme 4. Mechanistic Studies and Control Experiments



crystallographic analysis revealed that the intermediate **4** is the absolute *E*-stereoisomer, which is the favored style for the cyclization.[10] However, when the system was stirred under argon atmosphere for 6.0 h, **3a** could only be obtained in 17% yield; the intermediate **4** was also observed and isolated in 22% (Scheme 4, eq 2). When the intermediate **4** was stirred under argon atmosphere for 6 h, only trace **3a** was isolated (Scheme 4, eq 3). These observations indicated that O_2 is necessary for the conversion of the key intermediate **4** to the product. This intermediate **4** can be directly transformed into isoxazole product **3a** with $Fe(OTf)_3$ or *tert*-butyl nitrite as the catalyst in 91% and 70% yield, respectively (Scheme 4, eqs 4 and 5). However, the intermediate **4** was fully recovery without the catalyst or with trifluoromethanesulfonic acid, which can be produced by the $Fe(OTf)_3$ and H_2O, as the catalyst (Scheme 4, eq 6). It can thus be concluded that ferric catalyst or *tert*-butyl nitrite play an important role in the further transformation of intermediate **4**.

The ^{18}O-Labeled Experiment in the presence of $H_2{}^{18}O$ has been performed to understand the cyclization reaction mechanism (Scheme 5). The results showed that a mixture of

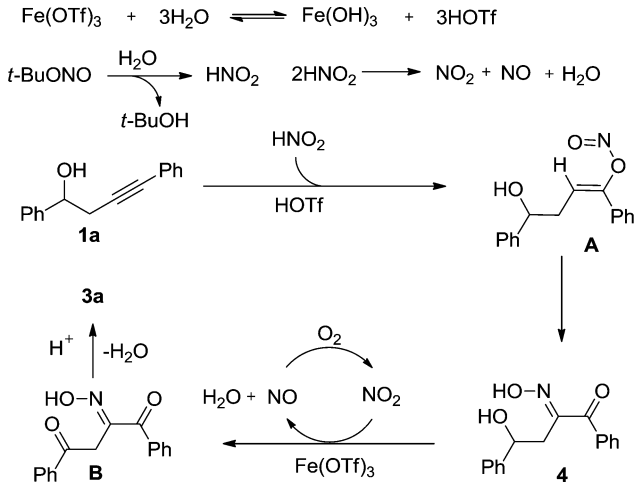
Scheme 5. ^{18}O-Labeled Experiment



mono-oxygen-atom-containing products **3a**, $O_1{}^{18}$, and **3a** were observed with a 1:1.2 ratio. This suggests that the oxygen atom of the product **3a** can be from *t*-BuONO and H_2O (for details, see the Supporting Information).

On the basis of these preliminary results and previous reports,[3a,7g,11,12] a possible mechanism is proposed (Scheme 6). Initially, addition of HNO_2, in situ generated from *t*-

Scheme 6. Proposed Mechanism



BuONO[7g,11a] and H_2O, to the triple bond of homopropargylic alcohol **1a** led to the formation of a vinyl nitrite **A**[11b] with HOTf as the catalyst, which was generated from $Fe(OTf)_3$. The intermediates **A** can easily isomerize to the acyloxime intermediates **4**.[11b] Subsequently, aerobic oxidation of the intermediates **4** produces the intermediates **B**,[12,13] which would convert to the desired isoxazole **3a** by treatment with acid.[3a]

In conclusion, we have developed a novel iron-catalyzed aerobic oxidative reaction to synthesize disubstituted isoxazoles from homopropargylic alcohol, *t*-BuONO, and H_2O under mild conditions. The reaction proceeds efficiently in a highly regioselective manner to give various disubstituted isoxazoles in moderate to excellent yields. Preliminary mechanistic studies revealed that the transformation is realized via construction of a C═N bond and C═O bond in a highly regioselective difunctionalization of alkyne, C−H oxidation, and then cyclization. To our knowledge, this is the first example employing *t*-BuONO as the nitrogen source to construct isoxazoles, thus making it an attractive reagent for synthetic purposes.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and spectroscopic data (^1H NMR and ^{13}C NMR) for the corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) The structure of **3s** was confirmed by X-ray crystallography. For details of the crystal analysis data, see the Supporting Information.

(10) The structure of **4** was confirmed by X-ray crystallography. For details of the crystal analysis data, see the Supporting Information.

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(13) When the reaction was performed under the standard conditions for 25 min, we observed another intermediate by TLC but failed to obtain the pure compound. The structure of the mixture was determined by HMRS analysis. For the details, see the Supporting Information.

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