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A novel synthesis of 5-substituted isoxazoles from propargylic amines and *N*-hydroxyphthalimide

Yicheng Zhang [a,b], Wei Chen [b,*], Xueshun Jia [a,c,*]

[a] School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, PR China
[b] Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, PR China
[c] Department of Chemistry, Shanghai University, Shanghai 200444, PR China

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ABSTRACT

A mild and efficient method for the synthesis of 5-substituted isoxazoles through cyclization of propargylic amines with *N*-hydroxyphthalimide (NHPI) under metal-free conditions was developed.

Introduction

N-propargylamines are one of the most useful building blocks in chemical productions and represent as excellent synthetic intermediates for constructing many significant nitrogen-containing heterocyclic compounds.[1] Recently, *N*-propargylamines have received considerable attention as radical acceptors in developing radical initiated cyclization-aromatization cascades to synthesize 3-substituted quinolines.[2] Therefore, direct functionalization of *N*-propargylamines to introduce these molecules into complex organic compounds is important for the synthetic chemistry community.

Isoxazoles and their derivatives are privileged structural motifs, which have been widely applied in medicinal chemistry, material science, natural products, and some other fileds.[3] In the past decades, considerable efforts were focused on the synthesis of isoxazoles,[4] largely due to the fact that the functionalized isoxazoles generally exhibit analgesic,[5] antinociceptive,[6] and anticancer properties.[7] Therefore, a number of strategies for the construction of isoxazoles backbone has been reported successively, mainly including cycloaddition of ketoxime dianions or propargylic oximes[8] and [3+2] cycloaddition of alkenes/alkynes with nitrile oxides.[9] For some selected examples, Larock et al. (2005) first reported an elegant work on the synthesis of numerous highly substituted isoxazoles through the cyclization of propargylic oximes enabled by a variety of electrophiles.[8a] Then Fokin's group described a novel route to 3,4-disubstituted isoxazoles through transition-metal-catalyzed [3+2] cycloaddition.[9a] Recently, Reddy and coworkers developed a general method for the synthesis of isoxazoles from readily available propargylic ketones using $TMSN_3$ as an amino surrogate.[10] Despite significant achievement have been made in past years, most of them still necessitates transition metal catalysts, additives or harsh reaction conditions. Furthermore, it was found that only a handful of work has been reported in term of 5-substituted isoxazoles synthesis.[11] For instance, Chen and coworkers recently completed a one-pot synthesis of heterocycles from the propargyl amines, otherwise limited examples for isoxazole were presented therein.[12] Thus, the development of an alternative approach to 5-substituted isoxazoles using readily available precursors is still highly desirable.

On the other hand, it was found that *N*-hydroxyphthalimide (NHPI) as a cheap and readily available chemical has been frequently employed as a catalyst for C—H bond functionalization.[13] Recently, some studies revealed that stoichiometric amount of NHPI could be employed for the C—O bond formation in organic synthesis.[14] However, to the best of our knowledge, there is no successful example that has been reported regarding the use of NHPI for building heterocyclic compounds. Herein, we will report a rare cyclization of *N*-propargylamines with NHPI at room temperature, in which NHPI plays an important role (providing key *N*-O unit) in constructing isoxazole molecules.

* Corresponding authors at: School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, PR China (X. Jia).
E-mail address: lake688123@163.com (W. Chen).

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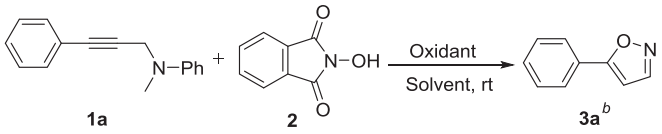
Results and discussion

In our initial experiment, propargylic amines (**1a**) and *N*-Hydroxyphthalimide (NHPI, **2**) were chosen as the model substrates to optimize the reaction conditions. To our delight, the desired product **3a** was obtained in a 44% yield when phenyliodine diacetate was used as the radical initiator in 1,2-dichloroethane (DCE) at room temperature for 12 h (Table 1, entry 1). The following optimization result showed that the oxidant used in this cyclization dramatically affected the yield of 3a. For example, the peroxides, such as *tert*-butyl hydroperoxide (TBHP), di(*tert*-butyl) peroxide (DTBP), benzoyl peroxide (BPO), *tert*-butyl peroxybenzoate (TBPB), 3-chloroperbenzoic acid (*m*-CPBA), and $K_2S_2O_8$ were found to be ineffective in promoting the model reaction, respectively (entries 2–7). Control experiments demonstrated that no product was formed in absence of oxidant (entry 8). Next, we continued the condition optimization by investigating the effect of solvent. The results indicated that EtOAc was the best reaction medium, providing **3a** in 84% yield under similar reaction conditions. It was found that the use of 1 equiv. of $PhI(OAc)_2$ led to lower yield of the product **3a**. Meanwhile, a comparable yield (82%) was obtained with 3equiv. of oxidant (entries 17 and 18). Finally, the optimized conditions were obtained from the screening of both reaction temperature and time (entry 16, Table 1).

With the optimized reaction conditions in hand, the scope of the substrates was investigated as shown in Scheme 1. First, the reaction between the substituted propargylic amines (**1**) and NHPI (**2**) were conducted under standard conditions. As expected, the transformation for the substrates bearing with substituents at the *para*-position of aromatic alkyne moiety proceeded quite smoothly, affording the desired 5-substituted isoxazoles in good yields (**3b-3k**). In addition, we found that both electron-donating groups (Me, Et, ^{i}Pr, ^{t}Bu, ^{n}Bu and MeO) and electron-withdrawing substituents (NO_2, OAc, CO_2Me and CO_2Et) within propargylamines were all well tolerated, thus electronic effects had no significant it on the yields of according products.cts.

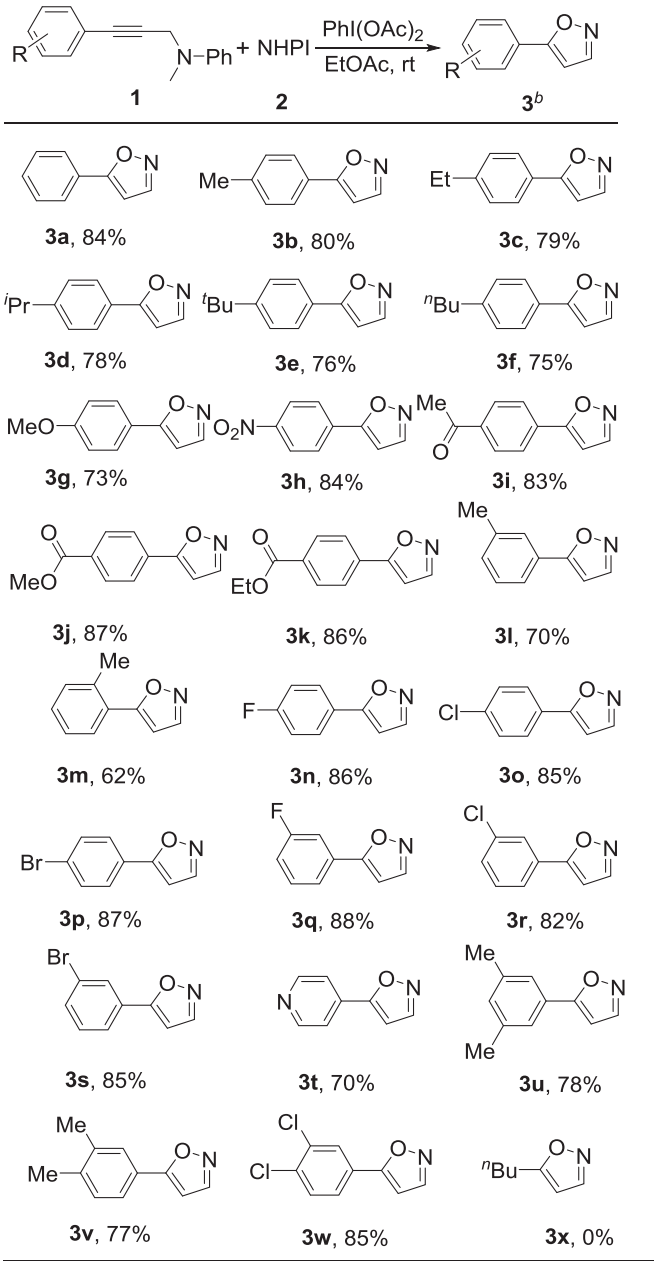
Additionally, the introduction of methyl group at the meta-position of aromatic ring in alkyne moiety could also react with NHPI to give the target product **3L**, albeit with the slightly lower yield. Furthermore, the use of substrate bearing with a methyl group at the ortho-position of aromatic ring resulted into the formation of the products **3m** in 62% yield, probably due to the steric effect. The cyclization reaction the is amenable to some *N*-methyl-*N*-propargylanilines with the halogen groups at the *para* and *meta* position (**1n-s**), which gave the corresponding products in moderate yields. Interestingly, the employment of propargylanilines

Table 1
Optimization of the reaction conditions.[a]

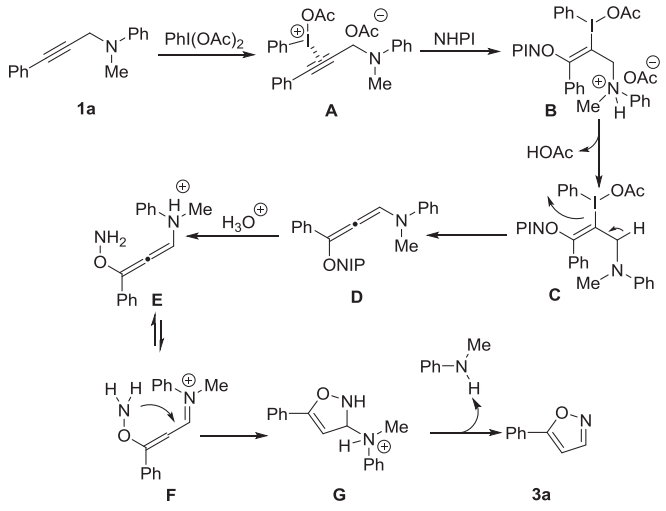


Entry	Oxidant	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$	DCE	44
2	TBHP	DCE	ND
3	DTBP	DCE	ND
4	BPO	DCE	ND
5	TBPB	DCE	ND
6	*m*-CPBA	DCE	ND
7	$K_2S_2O_8$	DCE	ND
8	–	DCE	NR
8	$PhI(OAc)_2$	CH_3CN	76
9	$PhI(OAc)_2$	THF	61
10	$PhI(OAc)_2$	MeOH	73
11	$PhI(OAc)_2$	DCM	77
12	$PhI(OAc)_2$	1,4-Dioxane	46
13	$PhI(OAc)_2$	Acetone	52
14	$PhI(OAc)_2$	Toluene	Trace
15	$PhI(OAc)_2$	DMF	Trace
16	$PhI(OAc)_2$	EtOAc	84
17[c]	$PhI(OAc)_2$	EtOAc	50
18[d]	$PhI(OAc)_2$	EtOAc	82
19[e]	$PhI(OAc)_2$	EtOAc	85
20[f]	$PhI(OAc)_2$	EtOAc	81

[a] Reaction conditions: 1a (0.2 mmol), 2 (0.3 mmol), oxidant (1.5 equiv.) in solvent (2.0 mL) at r.t. under air for 12 h.
[b] Isolated yield.
[c] $PhI(OAc)_2$ (1 equiv.) was used.
[d] $PhI(OAc)_2$ (3 equiv.) was used.
[e] At 60 °C.
[f] 6 h.



Scheme 1. The scope of *N*-methyl-*N*-propargylanilines[a], [a] Reaction conditions: 1 (0.2 mmol), 2 (0.3 mmol), $PhI(OAc)_2$ (1.5 equiv.) in EtOAc (2.0 mL) at rt. under air for 12 h. [b] Isolated yield.



Scheme 2. Proposed mechanism.

containing a 4-pyridyl group (**1t**) also reacted well with the NHPI, affording the product in 70% isolated yield. It was found that the propargylic amines with the disubstitued aromatic ring were competent substrates, which proceeded normally under the optimal conditions to generate the products in accepted yields (**3u–w**). *N*-(hept-2-yn-1-yl)-*N*-methylaniline (**1x**) was far less reactive and did not form the corresponding product **3x**.

Based on the above experimental results and previous works,[15] a possible mechanism is proposed, as shown in Scheme 2. Firstly, the interaction of propargylic amine (**1a**) with $PhI(OAc)_2$ generated the intermediate alkynyliodonium salts **A** through the electrophilic activation of the triple bond. Then Michael-type addition of NHPI to the alkynyliodonium salt **A** provided the intermediate **B**, which further underwent proton-transfer to afford intermediate **C**. A cleavage of C–I bond within **C** produced allene **D**, which is trapped and detected by High Resolution Mass Spectrometer (see ESI for details). Subsequently, the protonation of **D** delivered positively charged **E**, which can be reversibly isomerized into cationic imine intermediate **F.** Furthermore, an intermolecular cyclization of **F** produced cationic species **G**,[16] which underwent aromatization to yield the desired product **3a**,[12,17] along with the release of a *N*-methyl aniline (see ESI for details).

Conclusions

In conclusion, we have developed a simple and effective method for the synthesis of functionalized isoxazoles through a cyclization process of *N*-propargylamines and NHPI. Various substituted groups on *N*-propargylamines proceeded smoothly, and the desired isoxazoles were obtained in good yields. NHPI was used for the first time as the NO source for the synthesis of 5-substituted isoxaz oles.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.062.

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