Cascade Reactions

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Copper Nitrate Mediated Regioselective [2+2+1] Cyclization of Alkynes with Alkenes: A Cascade Approach to Δ^2-Isoxazolines**

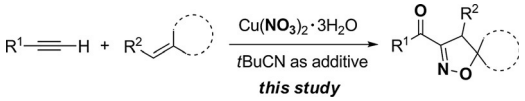
*Mingchun Gao, Yingying Li, Yuansheng Gan, and Bin Xu**

Abstract: *An efficient method for the regioselective synthesis of pharmacologically relevant polysubstituted Δ^2-isoxazolines is based on the copper-mediated direct transformation of simple terminal alkynes and alkenes. The overall process involves the formation of four chemical bonds with inexpensive and readily available copper nitrate trihydrate as a novel precursor of nitrile oxides. The reaction can be easily handled and proceeds under mild conditions.*

Copper nitrate and other nitrate salts are ubiquitous reactants in nitration reactions owing to their many advantages, such as inexpensiveness, stability, hypotoxicity, and ease of handling, compared with nitric acid or nitrite salts.[1] Among those nitration reactions, most of them proceed via nitrogen dioxide radicals or via the nucleophilic attack of alkenes or aryl rings at a cationic intermediate.[2] Although copper nitrate has been disclosed as an effective direct nitration reagent for arenes[3] and ketones,[4] the use of this simple and inexpensive reagent as a new and versatile nitrogen and oxygen source to replace the traditionally required agents still remains both challenging and of great value.

Δ^2-Isoxazoline derivatives represent an important class of five-membered heterocycles[5] and are frequently found in numerous biologically active molecules with antibacterial,[6a] antitubercular,[6b] siderophore,[6c] antidepressant,[6d] and β-galactosidase-inhibiting properties.[6e] Furthermore, they can also be employed as efficient chiral ligands[7] and eminent building blocks in organic synthesis as the precursors of diverse key synthetic intermediates, such as β-amino acids,[8] β-hydroxy ketones,[9] β-hydroxy nitriles,[10] and γ-amino alcohols.[11] Therefore, the development of convenient methods for the synthesis of Δ^2-isoxazoline scaffolds has invoked ever-growing synthetic efforts over the last decades.[12] Generally, Δ^2-isoxazolines are prepared by 1,3-dipolar cycloaddition reactions of olefins and nitrile oxides, which are commonly generated in situ from substituted oximes[13] or nitro compounds[4,14] in the presence of various additives. Although these methods are often effective, some of them suffer from a limited scope of starting materials, need harsh reaction conditions, or require that the substrates are employed as the solvent. Thus, the development of methods for the efficient synthesis of Δ^2-isoxazolines from readily available starting materials continues to be an active and rewarding research area.

Alkynes have been widely used in cross-coupling reactions, such as the Sonogashira reaction, and for the construction of various heterocycles.[15] Owing to their significance and wide application in organic synthesis, the exploration of new types of transformations with alkynes has attracted considerable attention.[16] Recently, an elegant procedure for the direct transformation of alkynes into nitriles was developed by Jiao and co-workers and involved a Ag-catalyzed nitrogenation reaction by C≡C bond cleavage.[17] Herein, we report a novel copper nitrate trihydrate mediated cascade reaction from simple terminal alkynes and alkenes that provides polysubstituted Δ^2-isoxazolines in high yields through a regioselective [2+2+1] cyclization under mild conditions (Scheme 1). The significance of this transformation is threefold: 1) It is the first example of a copper-mediated direct transformation of simple terminal alkynes and alkenes into pharmacologically relevant Δ^2-isoxazolines. 2) Compared with the traditional activation of alkynes by noble metals,[16a,c] a readily available copper nitrate trihydrate reactant is employed for the transformation of simple alkynes, and reported to act as a precursor of the crucial nitrile oxide dipole for the first time. 3) The valuable mechanistic insights that were obtained along the way may promote the discovery



Scheme 1. Copper nitrate mediated synthesis of Δ^2-isoxazolines.

[*] M. Gao, Y. Li, Y. Gan, Prof. Dr. B. Xu
School of Materials Science and Engineering
Department of Chemistry, Innovative Drug Research Center
Shanghai University
Shanghai 200444 (China)
E-mail: xubin@shu.edu.cn
Homepage: http://www.xubin.shu.edu.cn
Prof. Dr. B. Xu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
Shanghai 200032 (China)
and
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry
East China Normal University
Shanghai 200062 (China)

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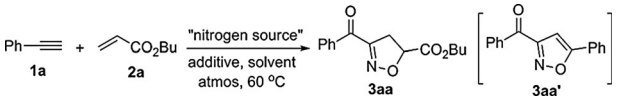
of other new types of cascade reactions for the construction of bioactive N-containing heterocycles.

We started our investigation by exploring the reaction of phenylacetylene (**1a**) with *n*-butyl acrylate (**2a**) in the presence of copper nitrate trihydrate in acetonitrile at 60 °C under nitrogen atmosphere. Intriguingly, isoxazoline **3aa** was formed in 34 % yield along with phenyl(5-phenylisoxazol-3-yl)methanone (**3aa′**, 15 % yield) as a side product (Table 1, entry 1). By switching the solvent from acetonitrile to benzonitrile, the yield was increased to 67 % (entry 2), whereas other solvents provided only trace amounts of **3aa** with unexpected 1,4-diphenylbuta-1,3-diyne as the major product by the homocoupling of **1a** (entries 3–6). An extensive screening of nitrogen sources (entries 7–11), ligands (entries 12–16),[18] temperature (entries 17 and 18), copper loading (entry 19), additives (entries 20 and 21), and the atmosphere (entries 22 and 23) revealed that the use of two equivalents of $Cu(NO_3)_2{\cdot}3H_2O$ in benzonitrile at 60 °C under nitrogen atmosphere using *tert*-butylnitrile (2.0 equiv) as an additive provides the most suitable conditions and afforded **3aa** in 83 % yield.

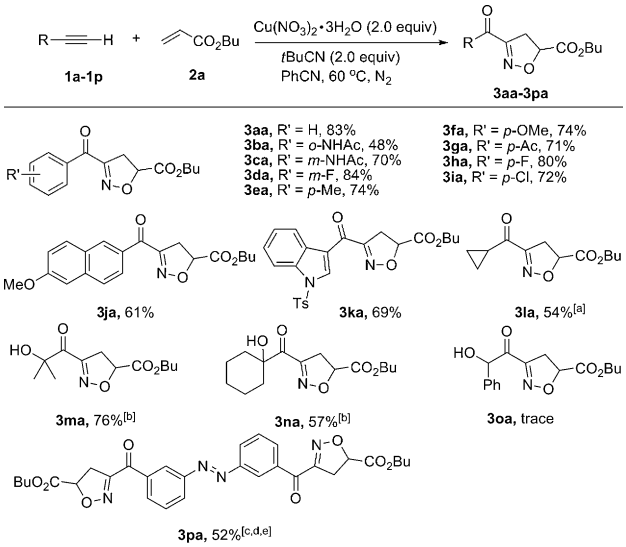
Table 1: Optimization of the reaction conditions.[a]



Entry	Nitrogen source	Solvent	Additive (*x* equiv)	Atmosphere	Yield [%][b]
1	$Cu(NO_3)_2{\cdot}3H_2O$	MeCN	–	N_2	34[c]
2	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	–	N_2	67
3	$Cu(NO_3)_2{\cdot}3H_2O$	toluene	–	N_2	< 5
4	$Cu(NO_3)_2{\cdot}3H_2O$	MeOH	–	N_2	< 5
5	$Cu(NO_3)_2{\cdot}3H_2O$	DMF	–	N_2	< 5
6	$Cu(NO_3)_2{\cdot}3H_2O$	DMSO	–	N_2	< 5
7	$Fe(NO_3)_3{\cdot}9H_2O$	PhCN	–	N_2	41
8	$Co(NO_3)_2{\cdot}6H_2O$	PhCN	–	N_2	< 5
9	KNO_3	PhCN	-	N_2	< 5
10	$Ce(NH_4)_2(NO_3)_6$	PhCN	–	N_2	< 5
11	*t*BuONO	PhCN	–	N_2	< 5
12	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	1,10-phen (2)	N_2	< 5
13	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	TMEDA (2)	N_2	< 5
14	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	1-AdCN (2)	N_2	79
15	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuNC (2)	N_2	81
16	**$Cu(NO_3)_2{\cdot}3H_2O$**	**PhCN**	***t*BuCN (2)**	N_2	**83**
17	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (2)	N_2	82[d]
18	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (2)	N_2	77[e]
19	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (2)	N_2	70[f]
20	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (1)	N_2	77
21	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (3)	N_2	77
22	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (2)	O_2	< 5
23	$Cu(NO_3)_2{\cdot}3H_2O$	PhCN	*t*BuCN (2)	air	71

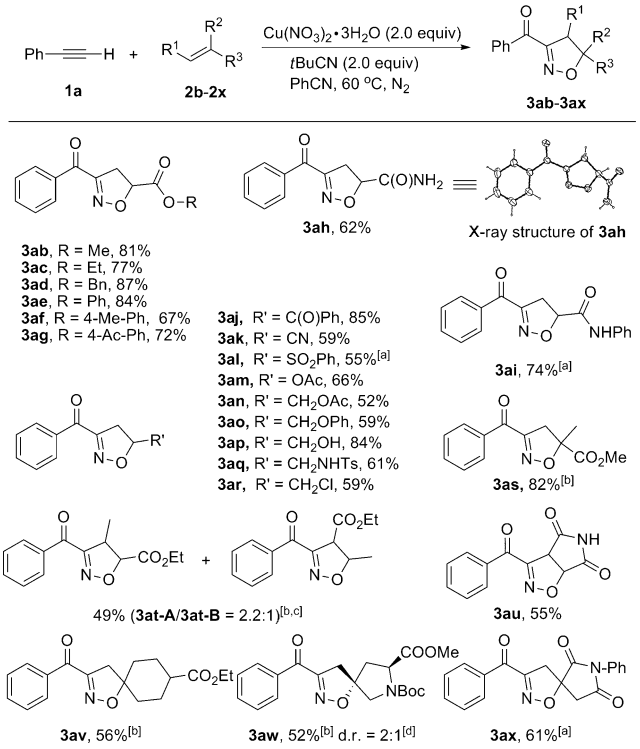
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), nitration reagent (0.6 mmol), solvent (1.5 mL), nitrogen atmosphere. [b] Yield of isolated product. [c] **3aa′** was also isolated in 15 % yield. [d] 70 °C. [e] 50 °C. [f] $Cu(NO_3)_2{\cdot}3H_2O$ (1.0 equiv) was used. 1-AdCN = 1-adamantane carbonitrile, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

With the optimized conditions in hand, various alkynes with different substituents were investigated for the synthesis of isoxazolines. As illustrated in Scheme 2, a wide variety of substitution patterns and functional groups were tolerated. Substrates bearing different functional groups on the aryl ring, such as acetamide (**3ba** and **3ca**), halide (**3da**, **3ha**, and **3ia**), alkyl (**3ea**), alkoxy (**3fa**), or acetyl (**3ga**) moieties, were compatible with this reaction and provided the corresponding products in moderate to good yields, regardless of their different electronic properties and substitution patterns. The reaction was not limited to simple benzene-based aryl alkynes, as naphthyl- or heterocycle-substituted alkynes also gave the desired products in good yields (**3ja** and **3ka**). Notably, reactions of alkynes with cyclopropyl (**3la**) or tertiary alcohol (**3ma** and **3na**) substituents proceeded smoothly and afforded the corresponding products in moderate to good yields. However, a substrate with a secondary alcohol moiety gave no product under the optimized conditions (**3oa**), which may be due to the oxidation of the hydroxy group during the reaction. To our delight, a dimeric product (**3pa**) was successfully isolated from the reaction of (*E*)-1,2-bis(3-ethynylphenyl)diazene; **3pa** is a symmetric azo compound with carbonyl linkers and a potential dye.



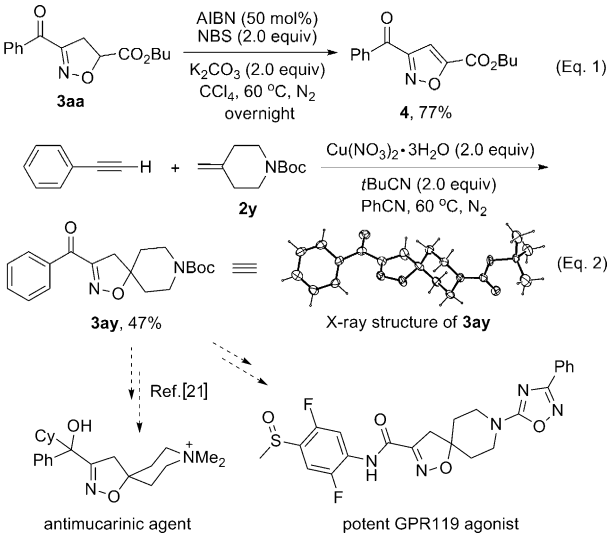
Scheme 2. Alkyne substrate scope. Reaction conditions: **1a–1p** (0.3 mmol), **2a** (0.45 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv), *t*BuCN (2.0 equiv), PhCN (1.5 mL), 1–4 h, N_2 atmosphere, 60 °C. Yields of isolated products are given. [a] **2a** (4.0 equiv). [b] 26 h. [c] **2a** (3.0 equiv). [d] $Cu(NO_3)_2{\cdot}3H_2O$ (4.0 equiv). [e] *t*BuCN (4.0 equiv).

To further explore the scope and generality of this method, we next used various alkenes as the coupling partners for this cascade reaction under the optimized conditions (Scheme 3). Alkyl and aryl acrylates provided the corresponding products in high yields with good regioselectivities (**3ab–3ag**), regardless of the electron-donating or -withdrawing properties of the aryl ring. A substrate bearing an amide group also afforded the desired product in good yield (**3ah**), and the free $-C(O)NH_2$ group remained untouched in the reaction. The identity of product **3ah** was determined by NMR spectroscopy and further confirmed by X-ray crystallography.[19] Moreover, *N*-substituted acrylamide, acryl ketone, acrylonitrile, and phenyl vinyl sulfone substrates could also be employed in this transformation and afforded



Scheme 3. Alkene substrate scope. Reaction conditions: **1a** (0.3 mmol), **2b–2x** (1.5 equiv), $Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv), *t*BuCN (2.0 equiv), PhCN (1.5 mL), 1–2 h, N_2 atmosphere, 60°C. Yields of isolated products are given. [a] Alkene (1.0 equiv). [b] $Cu(NO_3)_2{\cdot}3H_2O$ (4.0 equiv). [c] Alkene (4.0 equiv). [d] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. Bn = benzyl, Ts = *para*-toluenesulfonyl.

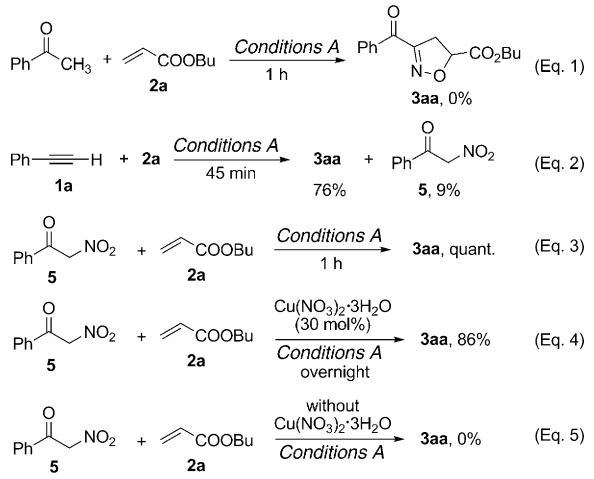
the corresponding products in good yields (**3ai–3al**). To determine the effect of the electronic properties of the alkene on the cascade process, a series of electron-rich alkenes, such as vinyl acetate (**2m**), and substrates with various allylic substituents (**2n–2r**), including protected (**2n** and **2o**) and unprotected allylic alcohols (**2p**), were investigated and afforded the desired products in good yields (**3am–3ar**). For disubstituted acrylates, the regioselectivity of the isoxazoline formation arises from the contribution of the dominant next lowest unoccupied molecular orbital (NLUMO) of the 1,3-dipole generated in situ from phenylacetylene during the reaction with the alkene dipolarophiles,[14a] so that the oxygen atom is attached to the sterically most hindered carbon atom of the alkene (**3as** and **3at**). For example, excellent regioselectivity could be achieved with 1,1-disubstituted ethyl methacrylate (**2s**), and a good regioselectivity (**3at-A/3at-B** 2.2:1) was observed for 1,2-disubstituted (*E*)-ethyl but-2-enoate (**2t**). Furthermore, bicyclic (**3au**) and spiro (**3av–3ax**) compounds could be obtained smoothly, which further illustrates the broad substrate scope and product diversity. It should be noted that both six- and five-membered (hetero)-cycles could be embedded in the final spiro products, and the chiral center in the starting material was not affected during the reaction (**3aw**). Compound **3aw** was formed with a diastereoselectivity of approximately 2:1 as determined by ^{1}H NMR spectroscopy, which indicates that this transformation could be performed in a diastereoselective way upon further optimization.



Scheme 4. Synthetic applications. AIBN = azobis(isobutyronitrile), NBS = *N*-bromosuccinimide.

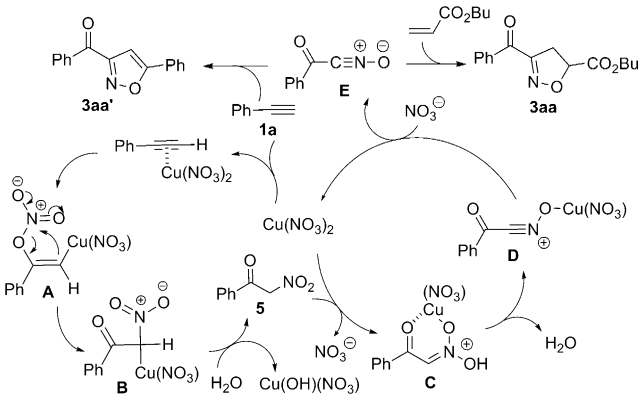
To illustrate the synthetic utility of our method, we studied further transformations of our products (Scheme 4). Isoxazoline **3aa** could be directly transformed into the corresponding oxidized isoxazole **4** by treatment with AIBN/NBS in the presence of K_2CO_3. The scaffold of **4** has been shown to be a privileged structure in medicinal chemistry and can be found in many marketed drugs [Eq. (1)]. Notably, spiro product **3ay** could be synthesized smoothly from *tert*-butyl 4-methylenepiperidine-1-carboxylate (**2y**),[19] and is a close analogue of the potent GPR119 agonist, a new antidiabetic target,[20] and a potential precursor to an antimuscarinic agent, which was previously synthesized through a longer process and in lower overall yield [Eq. (2)].[21]

To gain insight into possible intermediates and the pathway of this reaction, several control experiments were carried out (Scheme 5). The desired product was not obtained when acetophenone was used instead of phenylacetylene under the optimized conditions, which suggests that acetophenone is not a key intermediate of this reaction [Eq. (1)]. When the reaction time was reduced to 45 min under conditions A, 2-nitro-1-phenylethanone **5** could be isolated in 9% yield together with isoxazoline **3aa** in 76% yield [Eq. (2)]. The in situ generated intermediate **5** could be consumed completely through a fast transformation into **3aa** by prolonging the reaction time. Isolated nitro compound **5** could further be transformed into **3aa** in almost quantitative yield under conditions A [Eq. (3)], which indicates that this cyclization reaction may mainly proceed via intermediate **5** to afford isoxazoline **3aa**. However, a high yield of **3aa** could still be achieved in the presence of 30 mol% of copper nitrate [Eq. (4)], whereas no reaction was observed in the absence of the copper salt [Eq. (5)]. These results imply that the presence of catalytic amounts of the copper salt is crucial for this transformation. Furthermore, the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger had no significant effect on this reaction so that a radical mechanism could be ruled out.



Scheme 5. Preliminary mechanistic studies. Conditions A: $Cu(NO_3)_2{\cdot}3H_2O$ (2.0 equiv), *t*BuCN (2.0 equiv), PhCN, 60 °C, N_2.

Although the details of the reaction pathway remain to be clarified, a plausible mechanism for this reaction was proposed on the basis of the above results (Scheme 6).



Scheme 6. Proposed mechanism for the synthesis of **3a** from **1a** (ligands are omitted for clarity).

Initially, copper nitrate coordinates to the C≡C bond, which is followed by an insertion reaction to *cis* adduct **A**. Sequential transfer of the nitro group and hydrolysis via complex **B** lead to key intermediate **5**. Subsequently, α-nitroketone **5** is presumably converted into intermediate **C** with the assistance of catalytic amounts of copper nitrate, which then affords copper salt **D** in a dehydration reaction. Cleavage of the Cu–O bond in compound **D** in the presence of free nitrate ions leads to the formation of the crucial nitrile oxide **E** and regenerates copper nitrate. Finally, isoxazoline product **3aa** was afforded by a 1,3-dipolar cycloaddition reaction of nitrile oxide **E** with *n*-butyl acrylate. Meanwhile, the undesired formation of side product **3aa′** could also be explained by the cycloaddition of in situ generated nitrile oxide **E** with another equivalent of phenylacetylene.

In summary, we have developed a direct transformation of alkynes into polysubstituted Δ^2-isoxazolines through a cascade reaction with copper nitrate participation; four chemical bonds are thus formed under mild conditions. This convenient and practical method can be applied to the regioselective construction of pharmacologically interesting Δ^2-isoxazolines in moderate to good yields and features a wide substrate scope, good functional group tolerance, and high modularity. Simple and commercially available copper nitrate trihydrate was employed to mediate the transformation of alkynes and as a novel precursor of nitrile oxides from alkynes. Further applications of this reaction are currently studied in our laboratory.

Experimental Section

1a (33.0 μL, 0.3 mmol), **2a** (65.0 μL, 0.45 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (145.0 mg, 0.6 mmol), *t*BuCN (66.0 μL, 0.6 mmol), and PhCN (1.5 mL) were added to a Schlenk tube. The mixture was stirred at 60 °C for one hour under N_2 atmosphere, and the reaction was monitored by TLC. Upon completion of the reaction, the solution was cooled down to room temperature, quenched with water, and extracted with ethyl acetate (3×10 mL); the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1) to give **3aa** (68.3 mg, 83 %) as a pale-yellow oil.

Keywords: alkenes · alkynes · cascade reactions · copper · isoxazolines

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