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Copper-Catalyzed Oxyazidation of Unactivated Alkenes: A Facile Synthesis of Isoxazolines Featuring an Azido Substituent

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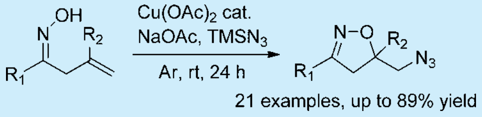
Supporting Information

ABSTRACT: A novel and efficient $\mathrm{Cu(OAc)_2}$-catalyzed oxyazidation of unactivated alkenes was developed. The reactions are easy to conduct, occur under mild conditions, and form azido-substituted isoxazolines in good yields.



21 examples, up to 89% yield

Organic azides are important intermediates and building blocks that can be easily converted to N-containing structural motifs, especially pharmaceutically important heterocycles.[1] The Cu-catalyzed cycloaddition of azide and alkyne (Huisgen 1,3-dipolar cycloaddition[2]) has been intensively studied in the past decade and broadly used in polymer synthesis,[3] peptide chemistry,[4] material science,[5] and drug discovery.[6] Many azido-substituted compounds show interesting biological activities.[7] More interestingly, organic azides are used as photoaffinity labeling agents for biomolecules.[8]

A traditional method for the preparation of organic azides is the Sandmeyer reaction, which suffers from the formation of equal amounts of potentially hazardous byproducts.[9] In the past years, Cu-catalyzed cross coupling reactions of aromatic halides or boronic acids with azide reagents ($\mathrm{TfN_3}$, $\mathrm{NaN_3}$, or $\mathrm{TMSN_3}$ ($\mathrm{Me_3SiN_3}$)) have been well documented.[10] Recently, a more economical and efficient method for the synthesis of aryl azides has been developed by a transition-metal-catalyzed C−H azidation. In the reactions, the hypervalent iodine reagents or peroxides were essentially required.[11] Aliphatic azides are usually obtained via substitutions of alkyl halides by inorganic azides,[12] transition-metal-catalyzed hydroazidation of alkenes,[13] radical azidation,[14] and electrophilic substitution with azido iodine(III) reagents.[15]

Difunctionalization of unactivated alkenes attracts more and more attention in organic synthesis. Compared with previously reported reactions between alkenes and azide reagents, difunctionalization of an alkene with an azido group and another functional group has not been well explored.[16] In 2010, Chemler and co-workers reported a stoichiometric copper(II)-promoted intramolecular azidoamination and oxyazidation of alkenes.[17a,b] Very recently, Zhang and Studer disclosed a radical oxyazidation of alkenes. In the reaction, a freshly prepared TEMPONa solution was used as the radical precursor, which needs to be injected to the system via a syringe pump. The separately prepared azido iodine(III) reagent is also essentially required to facilitate the transformation.[17c]

Arxime radical was isolated 50 years ago, whereas its applications in organic synthesis are very few.[18] We envisioned that a proper catalyst could promote the formation of oxime radical, which could add to an alkene and subsequently be trapped by a suitable azido radical reagent. In this way, the oxyazidation of alkene could be achieved in an alkene difunctionalization. Isoxazolines are an important class of heterocycles found in several biologically active agents and versatile intermediates in organic synthesis. Importantly, by using the above-mentioned oxyazidation protocol, isoxazolines featuring an azido substituent can be easily synthesized through oxime radical intramolecular alkene cyclization and an azido-trapping pathway. As part of our research interests on copper-catalyzed synthesis of heterocycles,[19] we disclose here a novel Cu(II)-catalyzed oxyazidation of unactivated alkenes for the synthesis of azido-substituted isoxazolines. Notably, in our system, the more reliable and commercially available $\mathrm{TMSN_3}$ is employed as the azide reagent, which avoids the preparation of the azido iodine(III) reagents as a separate process. Moreover, neither hypervalent iodine(III) reagents nor other oxidants were required in the reaction. We found that inorganic bases, such as NaOAc and $\mathrm{Na_2CO_3}$, are able to promote the formation of oxime radical. By using this method, the oxime radicals were very efficiently generated and subsequently added to alkenes at room temperature, which provide a simple and mild method for oxime radical generation and could be further applied in the synthetic application of oxime radicals.

At the beginning, we chose oxime **1a** as substrate, 1.5 equiv of $\mathrm{TMSN_3}$ as azide reagent, and 20 mol % of $\mathrm{Cu(OTf)_2}$ as catalyst. The reaction was carried out in dry DMF under an argon atmosphere at room temperature. After 24 h, only 10% of the desired oxyazidation product **3a** was obtained (Table 1, entry 1). To our delight, the basic additives dramatically increased the product's yield. A stoichiometric amount of NaOAc, $\mathrm{K_2CO_3}$, or $\mathrm{Cs_2CO_3}$ gave quantitative conversions in which use of NaOAc led to the cleanest reaction with 83% isolated yield (entries 2−4).[20] We then tested the catalytic activities of other copper salts, such as $\mathrm{Cu(OAc)_2}$, $\mathrm{CuCl_2{\cdot}2H_2O}$, CuI, CuBr, and CuCl. The results indicated that all Cu salts were effective for this transformation regardless of the different

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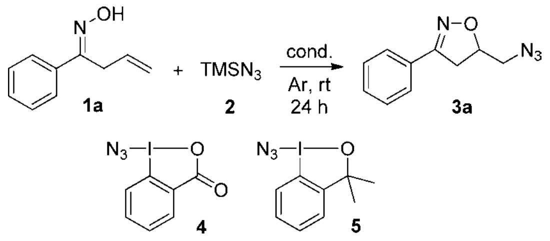
Table 1. Optimization of Reaction Conditions[a]

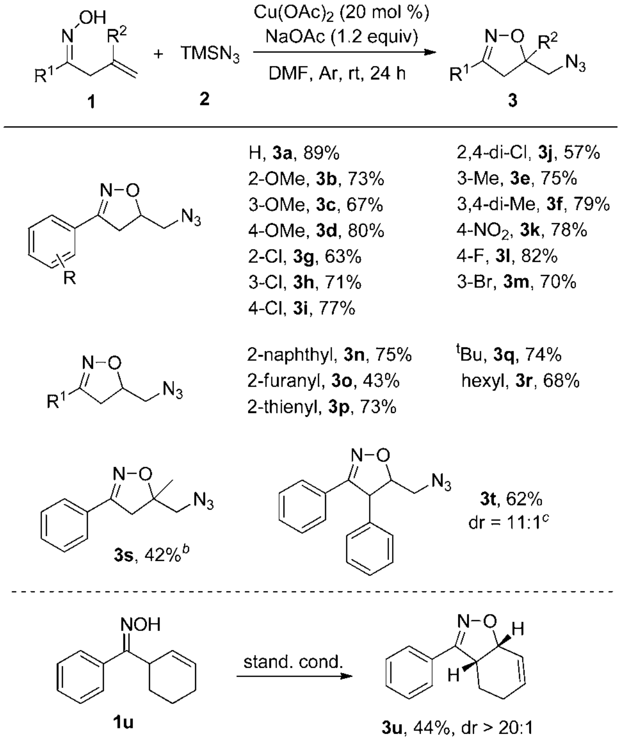


entry	catalyst	additive	solvent	yield[b] (%)
1	Cu(OTf)$_2$		DMF	10
2	Cu(OTf)$_2$	NaOAc	DMF	83
3	Cu(OTf)$_2$	K$_2$CO$_3$	DMF	71
4	Cu(OTf)$_2$	Cs$_2$CO$_3$	DMF	76
5	Cu(OAc)$_2$	NaOAc	DMF	89
6[c]	Cu(OAc)$_2$	NaOAc	DMF	51
7[d]	Cu(OAc)$_2$	NaOAc	CH$_3$CN	70
8	Cu(OAc)$_2$	NaOAc	THF	19
9	Cu(OAc)$_2$	NaOAc	CHCl$_3$	10
10	Cu(OAc)$_2$	NaOAc	toluene	trace
11[e]	Cu(OAc)$_2$	NaOAc	DMF	79
12[f]	Cu(OAc)$_2$	NaOAc	DMF	70
13		NaOAc	DMF	trace
14[g]	Cu(OAc)$_2$	NaOAc	DMF	90
15[h]	Cu(OAc)$_2$	NaOAc	DMF	75

[a] All reactions were carried out by using **1** (0.2 mmol), compound **2** (1.5 equiv), anhydrous basic additive (1.2 equiv), catalyst (20 mol %), and solvent (2 mL) under argon and stirred at room temperature for 24 h, except as noted. [b] Isolated yield. [c] 0.2 equiv of NaOAc, 50 °C. [d] Dry solvents were used in all cases. [e] 22 mol % of 2,2′-bipyridine was used. [f] 22 mol % of 1,10-phenanthroline was used. [g] 1.5 equiv of **4**, 0.5 h. [h] 1.5 equiv of **5**, 0.5 h.

valencies of the metal catalysts (see the Supporting Information). The highest yield was obtained when 20 mol % of Cu(OAc)$_2$ was employed (entry 5). Although a catalytic amount of NaOAc can promote the reaction by raising the temperature to 50 °C, the yield was low (51%, entry 6). The yield heavily relied on the choice of solvent: CH$_3$CN, THF, or CHCl$_3$ provided moderate to low yield whereas toluene only gave a trace amount of the oxyazidation product (entries 7−10). The use of ligands, namely 2,2′-bipyridine and 1,10-phenanthroline, deteriorated the reaction (entries 11 and 12). It should be noted that the reaction did not occur in the absence of Cu(OAc)$_2$, which revealed that the copper catalyst was crucial to this transformation (entry 13). Other transition-metal catalysts were examined: FeCl$_3$, Yb(OTf)$_3$, and Al(OTf)$_3$ led to lower yield; Ni(OAc)$_2$·4H$_2$O, Zn(OTf)$_2$, Sc(OTf)$_3$, or In(OTf)$_3$ were completely ineffective in this reaction (see the Supporting Information). Finally, azido iodine(III) reagents **4** and **5** were also tested in this reaction.[21] To our astonishment, the reaction was complete within 30 min and gave the desired product with 90% and 75% yield, respectively (entries 14 and 15).

Scheme 1. Substrate Scope Study[a]

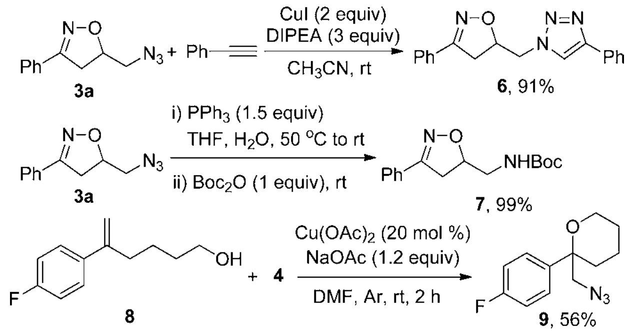


[a] All reactions were carried out by using 0.2 mmol of **1**, 1.5 equiv of **2**, and 2 mL of DMF. Yields refer to isolated yields. [b] 80 °C, 2 h. [c] relative configuration was not assigned.

Although the yield was quite good by using **4** (Table 1, entry 14),[22] considering the availability of the azide reagents, we finally chose entry 5 as the optimal conditions for the substrate scope investigations (Scheme 1). The oximes with an electron-donating substituent at the *o*-, *m*-, or *p*-position on the aryl ring underwent the oxyazidation smoothly and provided the desired products with good yields (**3b−d**). The monomethyl- or dimethyl-substituted substrates efficiently proceeded to form **3e** (75%) and **3f** (79%), respectively. The 2-, 3-, 4-, and 2,4-dichlorophenyl substituted oximes were suitable and exhibited good reactivities (**3g−j**). The substrates with other types of electron-withdrawing substituents, such as −NO$_2$ and −F, also reacted well under standard conditions (**3k** and **3l**). Copper was reported as an effective catalyst for the cross coupling of aryl bromide with an azide reagent under basic conditions.[10b] Interestingly, we noticed that 3-bromophenyl oxime reacted with TMSN$_3$ efficiently and formed **3m** (70%) with the highly reactive bromo substituent untouched under such copper catalytic conditions, which render the azidation products good opportunities for further transformations, e.g., transition-metal-catalyzed functionalization of the C−Br bond. The oxime bearing a naphthyl group was a compatible substrate and gave the product in good yield (**3n**). The azidation with heteroarene-substituted oximes were achieved, furnishing the corresponding biheteroarenes in moderate to good yields (**3o** and **3p**), respectively. We were pleased to find that under the stated conditions the aliphatic oximes provided good conversion to the desired products as well (**3q** and **3r**). Then the present method was successfully applied to construct an azido-substituted isoxazoline containing a quaternary carbon center (**3s**). In addition, the reaction gave **3t** with a moderate diastereselectivity (dr = 11:1).[23] Interestingly, **3u** was formed under standard conditions instead of azido-substituted isoxazolines.

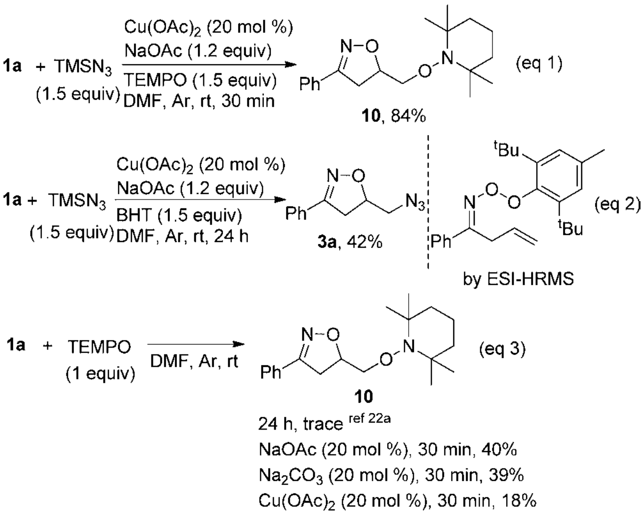
Organic azides are versatile intermediates and building blocks in organic synthesis. Considering the abundance of isoxazoline in biologically active agents, the synthetic utility of the oxyazidation product was further demonstrated for the synthesis of isoxazoline analogues. Under the typical click reaction conditions, **3a** was treated with phenylacetylene in the presence of CuI to give the corresponding triazole **6** in 91% yield (Scheme 2). Compound **3a** could easily convert to **7** through a Staudinger reduction and in situ protection sequence with excellent yield. It is worth noting that under slightly modified conditions with the azido iodine(III) reagent **4**, the alcohol **8** was readily cyclized to give the corresponding oxyazidation product **9** in moderate yield.[7b]

Scheme 2. Synthetic Utility of Current Method



To shed light on the reaction mechanism, several experiments were conducted (Scheme 3). When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 1.5 equiv) was added to the reaction under standard conditions, the oxyazidation reaction was completely shut down and gave the TEMPO-trapped product **10** in 84% yield (eq 1). The result suggested that a radical pathway might be involved in the reaction. Using 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1.5 equiv) as additive, the yield of desired product was lowered to 42% (eq 2). Interestingly, the BHT−oxime adduct was detected by ESI-HRMS measurement of the crude reaction mixture, which indicated that the oxime radical was generated in the system and served as a radical reagent for this transformation. A careful literature survey revealed that the generation of oxime radicals usually requires a radical initiator (e.g., TEMPO), oxidant (e.g., Ag_2O, DEAD), or photolyzing.[24] However, in our reaction, none of these factors were introduced to the system, except for a copper catalyst and basic additive. To probe the possibility for the generation of oxime radical by Cu(II) salt and/or NaOAc, we performed several reactions (eq 3). Han and co-workers reported that a stoichiometric amount of TEMPO can serve as an initiator and trapping reagent for the oxime radical cyclization. In the reaction, a relatively long time (48 h) and high temperature (80 °C) were essentially required.[24a] According to Han's report, we carried out a reaction by using oxime **1a** and TEMPO (1 equiv) as the substrates. After 24 h at rt, no reaction occurred, suggesting that the oxime radical is not able to form at low temperature by this procedure. We then tested the activities of the copper catalyst and basic additives for this transformation. To our delight, a catalytic amount of NaOAc (20 mol %) promoted the reaction very efficiently and gave the cyclization product in 40% yield after 30 min. The moderate outcome might be attributed to the formation of TEMPO-H, which was detected by the ESI-HRMS study of the reaction mixture.[25] The control experiments proved that both Na_2CO_3 and $Cu(OAc)_2$ are effective for this reaction and gave the desired product in 39% and 18% yield, respectively. Although the mechanism of the oxyazidation reaction is not completely clear yet, the experimental results indicated that, in the reaction, the basic additive served as a catalyst for the generation of oxime radical,[26] whereas $Cu(OAc)_2$ catalyzed the formation of azido radical[11c] (for a detailed discussion, see the Supporting Information).

Scheme 3. Mechanistic Studies



In conclusion, we have developed a novel process for the intramolecular radical oxyazidation of alkenes. The reactions are easy to conduct, occur under mild conditions, and form the azido-substituted isoxazolines in good yields. In the transformation, the cheap and commercially available $TMSN_3$ is employed as the azide reagent instead of the widely used azido iodine(III) reagents (or the combination of organic azides and hypervalent iodine reagents).[11,17c] The preliminary mechanistic study demonstrates that the inorganic base, such as NaOAc and Na_2CO_3, can efficiently catalyze the formation of oxime radicals. The process is an important complement to the previously reported methods for oxime radical generation, which is effective for both alkene radical oxyazidation and alkene radical dioxygenation. The synthetic utility of the current method is demonstrated with a couple of synthetically useful transformations. Further studies for a clearer understanding of the reaction mechanism and the asymmetric version of the reaction are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and NMR spectra. 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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