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# Copper-Catalyzed Cascade Transformation of *O*-Propargylic Oximes with Sulfonyl Azides to *α,β*-Unsaturated *N*-Acylamidines

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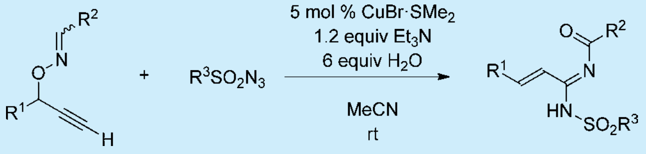
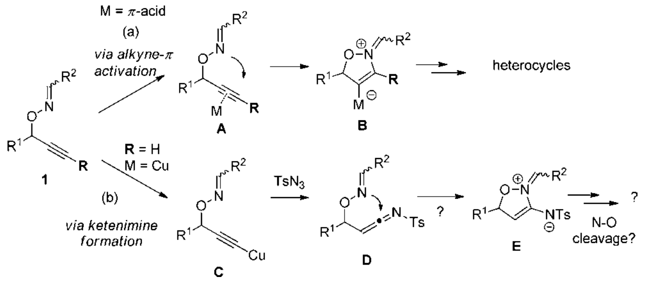
*Supporting Information*

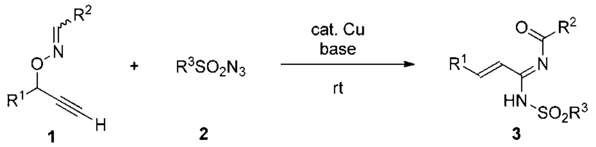
**ABSTRACT:** Copper-catalyzed cascade transformations of *O*-propargylic oximes and sulfonyl azides were carried out to efficiently afford *α,β*-unsaturated *N*-acylamidines. The reaction involved the intramolecular attack of the oxime group to the ketenimine moiety that was generated in situ, followed by the cleavage of the N−O bond.



### Scheme 1. Cascade Reaction of *O*-Propargylic Oximes



Alkynes that are tethered to nucleophilic functional groups are often utilized as substrates for metal-catalyzed cascade transformations.[1] Because the process allows for the construction of useful molecular skeletons in a single operation, various alkynyl substrates have been developed,[2] including the unique *O*-propargylic oximes **1** (Scheme 1).[3,4] Typically, the reactions are initiated by the coordination of a metal catalyst onto the carbon−carbon triple bond to form metal *π*-complex **A**. Immediately upon formation, the electrophilically activated alkyne moiety is subjected to an intramolecular nucleophilic attack by the nearby oxime nitrogen atom to form vinylmetal intermediate **B** (Scheme 1, path a), which undergoes not only an intramolecular skeletal rearrangement[3] but also an intermolecular cascade reaction[4] to effectively provide a variety of heterocyclic compounds. In our continued investigations to expand the scope of the *O*-propargylic oximes, an alternative cascade process was proposed that employs a terminal alkyne moiety (R = H, path b); specifically, the initial step of the terminal alkynyl propargylic oximes, in the presence of sulfonyl azide and copper catalysts, would favor the formation of the corresponding ketenimine via metal acetylide intermediate **C**, according to the pioneering works by Chang and Fokin.[5] Subsequently, ketenimine **D** would be subjected to an intramolecular nucleophilic attack by the pendant oxime group.[6] Most likely, cyclized intermediate **E** would undergo cleavage of its N−O bond resulting in the preferred transformation.[7] Herein, we report on the copper-catalyzed reactions between *O*-propargylic aldoximes **1** and sulfonyl azides **2** to afford *α,β*-unsaturated amidines **3** in good to high yields (eq 1).[6f−h,8,9]



(1)

To begin our investigations, the reaction conditions (summarized in Table 1) were optimized using *p*-nitrobenzaldoxime **1a** and tosyl azide **2a**. In the presence of CuCl (0.5 M) in acetonitrile, the reaction was carried out at rt (ca. 25 °C) for 1 h to afford **3a** in 51% yield (entry 1). Other copper salts such as CuBr, CuBr·SMe$_2$, CuI, and CuCl$_2$ exhibited similar catalytic activities (entries 2−5). For subsequent reactions, CuBr·SMe$_2$ was employed as a catalyst due to its high stability (entry 3). Among the reaction solvents, acceptable results were only obtained using acetonitrile; in contrast, other solvents such as DMSO, THF, toluene, and CH$_2$Cl$_2$ resulted in the rapid (<20 min) decomposition of **1a** (entries 6−9). As a note, the use of bases such as *i*-Pr$_2$EtN, pyridine, and K$_2$CO$_3$ were ineffective (see the Supporting Information). Lower reaction temperature (−10 °C) gave acceptable results (entry 10). Surprisingly, the addition of a proton source such as water or acetic acid improved the mass balance while also offering the ease of handling (entries 11−13); specifically, the reaction in the presence of 6 equiv of water afforded the desired product with an isolated yield of 71% (entry 12). Furthermore, under the optimized reaction conditions, amide byproducts that may form via reactions of

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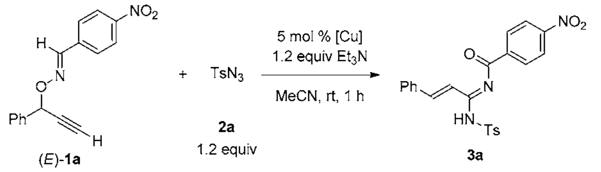
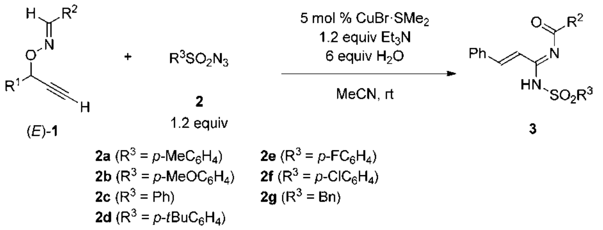
### Table 1. Optimization of Reaction Conditions



| entry | catalyst | solvent | additive | yield[a] (%) |
|---|---|---|---|---|
| 1 | CuCl | MeCN | | 51 |
| 2 | CuBr | MeCN | | 53 |
| 3 | CuBr·SMe$_2$ | MeCN | | 53 |
| 4 | CuI | MeCN | | 49 |
| 5 | CuCl$_2$ | MeCN | | 53 |
| 6[b] | CuBr·SMe$_2$ | DMSO | | 7 |
| 7[b] | CuBr·SMe$_2$ | THF | | 21 |
| 8[b] | CuBr·SMe$_2$ | $CH_2Cl_2$ | | 7 |
| 9[b] | CuBr·SMe$_2$ | toluene | | 7 |
| 10[c] | CuBr·SMe$_2$ | MeCN | | 77 |
| 11 | CuBr·SMe$_2$ | MeCN | $H_2O$ (2)[d] | 65 |
| 12 | CuBr·SMe$_2$ | MeCN | $H_2O$ (6)[d] | 76 (71)[e] |
| 13 | CuBr·SMe$_2$ | MeCN | AcOH (1)[d] | 59 |

[a] Yields were determined by $^1$H NMR using $CH_2Br_2$ as an internal standard. [b] 20 min. [c] −10 °C. [d] The equivalent of the additive. [e] Isolated yields are shown in parentheses.

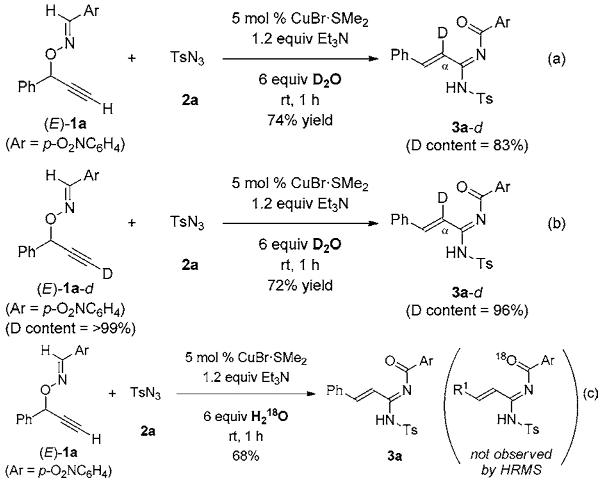
### Table 2. Cu-Catalyzed Reaction of *O*-Propargylic Oxime 1 and Sulfonazide 2[a]



| | **1** | R$^1$ | R$^2$ | **2** | time (h) | **3** | yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2b** | 1 | **3b** | 72 |
| 2 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2a** | 1 | **3a** | 71 |
| 3 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2c** | 1 | **3c** | 71 |
| 4 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2d** | 1 | **3d** | 66 |
| 5 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2e** | 1 | **3e** | 67 |
| 6 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2f** | 0.25 | **3f** | 61 |
| 7 | **1a** | Ph | *p*-$O_2NC_6H_4$ | **2g** | 1 | **3g** | 20 |
| 8 | **1b** | Ph | *p*-$F_3CC_6H_4$ | **2a** | 1 | **3h** | 60 |
| 9 | **1c** | Ph | *p*-$ClC_6H_4$ | **2a** | 1 | **3i** | 58 |
| 10 | **1d** | Ph | Ph | **2a** | 0.25 | **3j** | 41 |
| 11[c] | **1d** | Ph | Ph | **2a** | 1 | **3j** | 60 |
| 12 | **1e** | Ph | *p*-$MeOC_6H_4$ | **2a** | 0.5 | **3k** | 23 |
| 13 | **1f** | Ph | *p*-$Me_2NC_6H_4$ | **2a** | 0.25 | | <1[d] |
| 14 | **1g**[e] | Ph | $CO_2Et$ | **2a** | 1 | | <1[d] |
| 15 | **1a**[f] | Ph | *p*-$O_2NC_6H_4$ | **2a** | 1 | **3a** | 56 |
| 16 | **1h** | *p*-$MeOC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 1 | **3l** | 53 |
| 17 | **1i** | *p*-$MeC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 1 | **3m** | 70 |
| 18 | **1j** | *o*-$MeC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 1 | **3n** | 63 |
| 19 | **1k** | *p*-$FC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 2 | **3o** | 72 |
| 20 | **1l** | *p*-$ClC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 2 | **3p** | 75 |
| 21 | **1m** | *p*-$F_3CC_6H_4$ | *p*-$O_2NC_6H_4$ | **2a** | 0.25 | **3q** | 62 |
| 22 | **1n** | *n*Pr | *p*-$O_2NC_6H_4$ | **2a** | 4 | **3r** | 34 |
| 23 | **1o** | Cy | *p*-$O_2NC_6H_4$ | **2a** | 0.5 | **3s** | 53 |

[a] The reactions of **1** (0.2 mmol) and **2** (0.24 mmol) were carried out in the presence of CuBr·SMe$_2$ (5 mol %), $Et_3N$ (1.2 equiv), and water (6 equiv) in acetonitrile (0.4 mL) at rt for 1 h. [b] Isolated yield. [c] The reaction was carried out in the absence of water at −10 °C. [d] Decomposition of **1**. [e] (*E*)-**1e**/(*Z*)-**1e** = 85/15. [f] (*Z*)-**1a** isomer was used.

### Scheme 2. Labeling Experiments



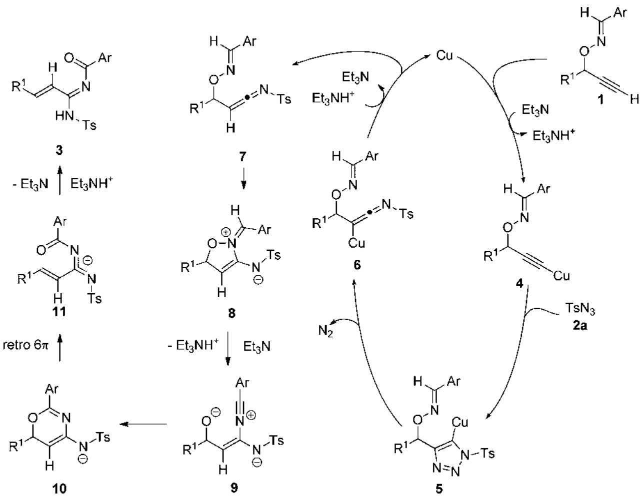
ketenimine under aqueous conditions were not detected (entry 12).[5b]

Next, using the optimized reaction conditions (Table 1, entry 12), substitution effects of substrates **1** and **2** were investigated, as summarized in Table 2. Among the R$^3$ groups of sulfonyl azides **2**, substituents possessing an electron-rich aromatic ring gave the desired product **3** in higher yields than those with an electron-poor ring (entries 1−6). However, benzylsulfonyl azide **2g** was not a very effective substrate (entry 7). Substitution by a strong electron-withdrawing group resulted in the rapid consumption of the starting material (entry 6). Among the R$^2$ groups of oxime **1**, which may serve as a potential protecting group for *α*,*β*-unsaturated amidine **3**, aryl groups possessing a strong electron-withdrawing group such as nitro, trifluoromethyl, or chloro at the *para*-position gave the desired product in high yields (entries 2, 8, and 9). In contrast, subsitutution by an electron-rich aryl group was less efficient (entries 12 and 13); the substrate **1f** having a *p*-dimethylamino group at R$^2$ was rapidly decomposed under the reaction conditions (entry 13). However, glyoxylate oxime **1g** did not afford the desired product (entry 14). The chemical yield of **3f** was inproved by carrying out the reaction in the absence of water at −10 °C (entry 11). It is noteworthy that both of the *E*- and *Z*-isomers of oxime **1a** were converted into the identical product **3a** in good yields (entries 2 and 15). Next, substituent effects at the propargylic position were investigated (entries 16−23). Substrates with various aryl substituents, including that with an *ortho*-substituent (entry 18), were effectively converted into the desired products (entries 16−21). Alkyl substituents were also effective, albeit with lower yields (entries 22 and 23).

To understand the role of added water, reactions using labeled water were carried out (Scheme 2). In the presence of deuterated water, the reaction of (*E*)-**1a** and tosyl azide afforded **3a**-*d* in 74% yield (Scheme 2a), in which the deuterium content at the *α*-position of the conjugate amidine moiety was 83%. Moreover, the deuterium content was increased by employed (*E*)-**1a**-*d*, of which the alkyne terminus was deuterated (Scheme 2b). In contrast, in the presence of $^{18}$O-labeled water, the resulting product **3a** did not incorporate the $^{18}$O-label (confirmed using HRMS), which suggests that the carbonyl oxygen of **3a** is derived from the oxime oxygen of (*E*)-**1a** (Scheme 2c).

A plausible mechanism for the reaction of **1** and tosyl azide **2a** is illustrated in Scheme 3. According to a report by Ahlquist, Fokin, and Chang,[5e] the reaction is initiated by the formation of copper acetylide **4**, followed by the [3 + 2] cycloaddition with tosyl azide **2a**.[10] Denitrogenative ring opening involving the migration of the copper atom followed by protodemetalation affords the oxime-tethered ketenimine species **7**. Nucleophilic attack by the oxime nitrogen atom onto the ketenimine C═N bond forms zwitterionic intermediate **8** that would undergo a base-promoted E2-elimination along with the cleavage of the N−O bond to give nitrilium species **9**.[7] Subsequent intramolecular attack of the oxygen anion to the nitrilium moiety gives 6*H*-1,3-oxazine intermediate **10**.[11] Retro 6π-electrocyclization of the oxazine **10** would take place leading to the conjugate base **11**, which is highly stabilized by the sulfonyl and aroyl groups.[12] Finally, protonation of **11** from the triethylammonium gives the product **3**. Presumably, the presence of water facilitates the protodemetalation process from **6** to **7**, thus avoiding decomposition via undesirable reaction pathways. Triethylamine is involved not only during the generation of copper acetylide **4** but also during the elimination process from alkoxyarylideneammonium **8** to nitrilium **9**.[7] Moreover, it is likely that the elimination of a proton for intermediate **8** is facilitated by a strong electron-withdrawing group at the arylidene moiety (Ar). Unfortunately, it remains unclear whether the copper catalyst serves to accelerate the transformation of ketenimine **7** to product **3**. Further mechanistic investigations are currently underway in our laboratory.

**Scheme 3. Plausible Mechanism**



In conclusion, we have developed an efficient scheme for the synthesis of α,β-unsaturated amidines under mild reaction conditions. Bacause amidines are often found in biologically active compounds,[9] the present method is highly useful for synthesizing a new class of amidine derivatives.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization of the products **3**. 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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