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Efficient Synthesis of *N*-Alkylated α,β-Unsaturated Ketonitrones via Cu-Catalyzed Rearrangement

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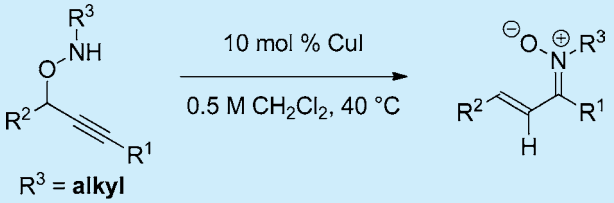
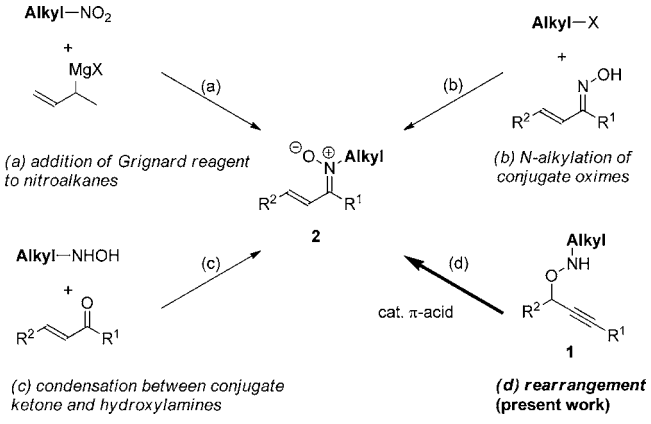
Supporting Information

ABSTRACT: *N*-Alkylated unsaturated ketonitrones were efficiently synthesized from propargyloxyamines using Cu catalysts. Mechanistic studies suggest that the rearrangement reaction proceeds via Cu-catalyzed intramolecular hydroamination, followed by thermally induced electrocyclic ring opening.



The nitrone functional group has often served as a fundamental element in heterocyclic synthesis, and in particular, α,β-unsaturated ketonitrones have recently gained attention as useful building blocks in the synthesis of highly elaborate molecules.[1] Accordingly, efficient preparations of such conjugated nitrone molecules are essential for their synthetic utility. Although *N*-arylated ketonitrones can be efficiently prepared by various approaches,[1a,2] *N*-alkylated α,β-unsaturated ketonitrones **2** have remained elusive from the synthetic point of view and are available only through a very limited number of synthetic methodologies (Scheme 1). For example, the reaction of

Scheme 1. Synthesis of *N*-Alkylated α,β-Unsaturated Ketonitrones



nitroalkanes with methallyl Grignard reagents is limited in terms of functional group tolerance (type a),[3] while the *N*-alkylation of the corresponding oximes inevitably competes with *O*-alkylation (type b).[4] Condensation reactions between α,β-unsaturated ketones and hydroxylamines are highly dependent on the stability of the conjugated ketone due to the fact that the condensation process is reversible (type c).[5,6] Overall, it remains a challenge to develop a general method for the synthesis of *N*-alkylated α,β-unsaturated ketonitrones that (i) can accommodate a wide scope of substituents, (ii) is highly tolerant of various functional groups, and (iii) can be carried out under mild reaction conditions. We envisioned an entirely different approach, in which the *N*-alkylated α,β-unsaturated ketonitrones are prepared via π-acidic metal-catalyzed 2,3-rearrangement from propargyloxyamines **1** (type d). Specifically, we have recently demonstrated that a π-acidic metal-catalyzed reaction of *O*-propargylic oxime proceeds via 2,3-rearrangement involving C−N bond formation and C−O bond cleavage,[7] and accordingly, we can expect that propargyloxyamines **1** can undergo such a cascade reaction involving C−N bond formation followed by C−O bond cleavage by the action of the π-acidic metal catalysts,[8] leading to targeted molecule **2**. Herein, we report on the Cu-catalyzed reactions of propargyloxyamines **1** to afford *N*-alkylated ketonitrones **2** in good to excellent yields.

Initially, propargyloxyamine **1a** was treated with catalytic amounts of CuI (10 mol %) in CH_2Cl_2 at 40 °C for 4 h to afford the corresponding ketonitrone **2a** in 96% isolated yield (Table 1, entry 1). CuBr and CuCl were also effective catalysts (entries 2 and 3, respectively), while $CuCl_2$ resulted in a lower yield (entry 4). Other metal salts such as AuCl, $PtCl_2$, and $PdCl_2$ also exhibited catalytic activities for the present reaction, albeit with lower yields (entries 5−7). As a note, the use of a Brønsted acid such as *p*-toluenesulfonic acid was ineffective (entry 8). In the absence of metal catalysts, the reaction did proceed, albeit sluggishly, to afford the desired product in a low yield, involving partial decomposition of **1a** (entry 9). Although the present reaction was effective in various solvents, CH_2Cl_2 was selected over CH_3CN, THF, and toluene as the optimal solvent due to the high solubility of ketonitrone product **2a** (see Supporting Information).

The Cu-catalyzed reaction of **1a** was carried out in $CDCl_3$ (as the solvent) at 30 °C and monitored by ^1H NMR. As shown

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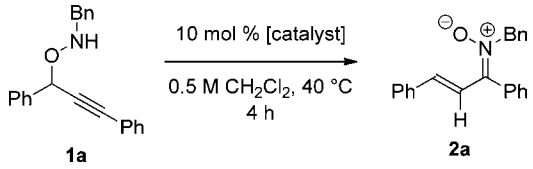
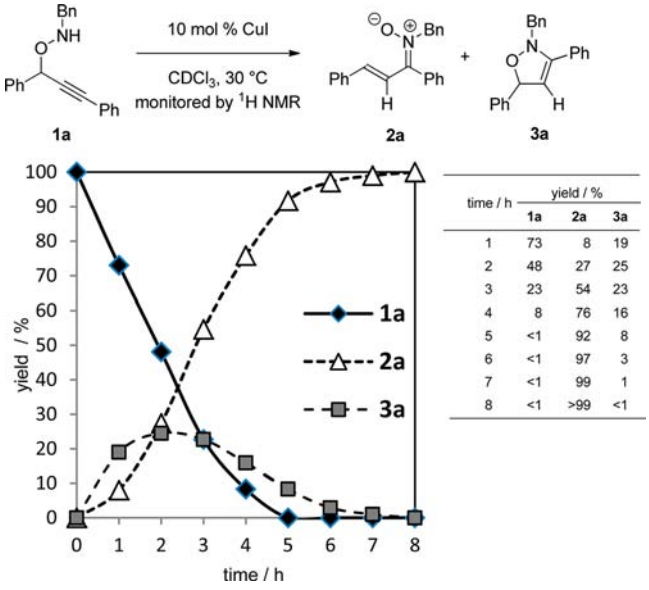
Table 1. Optimization of Reaction Conditions



entry	catalyst	yield (%)[a]
1	CuI	97 (96)
2	CuBr	97 (96)
3	CuCl	96 (97)
4	$CuCl_2$	71
5	AuCl	89
6	$PtCl_2$	72
7	$PdCl_2$	88
8	$TsOH·H_2O$	13[b]
9	none	29[c]

[a]Yields were determined by ^{1}H NMR using 1,3-benzodioxole as an internal standard. Isolated yields in parentheses. [b]64% of **1a** was recovered. [c]60% of **1a** was recovered.



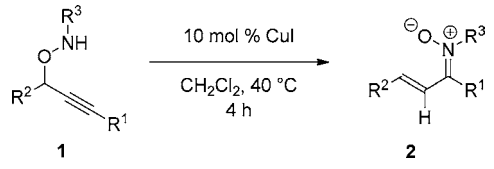
time / h	yield / % 1a	2a	3a
1	73	8	19
2	48	27	25
3	23	54	23
4	8	76	16
5	<1	92	8
6	<1	97	3
7	<1	99	1
8	<1	>99	<1

Figure 1. Reaction progress of Cu-catalyzed reaction of **1a** in $CDCl_3$ at 30 °C.

in Figure 1, the transient formation of 3-isoxazoline **3a** is evident during the quantitative transformation from **1a** to **2a**, suggesting that **3a** is a reactive intermediate for the present reaction. Moreover, because **3a** is converted to **2a** in the absence of copper catalysts,[9] the present reaction does *not* proceed via direct 2,3-rearrangement, but rather through a cascade process involving Cu-catalyzed intramolecular hydroamination[10] followed by thermally induced ring opening.[11]

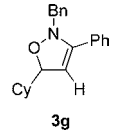
Based on the optimized reaction conditions (Table 1, entry 1), reactions were carried out using various substrates **1**, as summarized in Table 2. Despite the differences in the electronic characteristics, substrates **1b** and **1c**, which possess an aromatic ring at the alkyne terminus (R^1), afforded the corresponding products **2b** and **2c** in excellent yields (entries 1 and 2). Substitution at the R^1 position with an alkyl group did not affect the reaction (entry 3). Although electronic effects due to the aryl substituent on the propargylic position (R^2) were insignificant (entries 4 and 5), an alkyl subtituent at the propargylic position

Table 2. Cu-Catalyzed Reaction of 1b–l[a]



	1	R^1	R^2	R^3	2	yield (%)[b]
1	**1b**	*p*-$MeOC_6H_4$	Ph	Bn	**2b**	91
2	**1c**	*p*-$F_3CC_6H_4$	Ph	Bn	**2c**	91
3	**1d**	Cy	Ph	Bn	**2d**	72
4	**1e**	Ph	*p*-$MeOC_6H_4$	Bn	**2e**	81
5	**1f**	Ph	*p*-$F_3CC_6H_4$	Bn	**2f**	86
6	**1g**	Ph	Cy	Bn	–[c]	–
7	**1h**	Ph	Ph	*p*-$MeOC_6H_4CH_2$	**2h**	99
8	**1i**	Ph	Ph	*p*-$F_3CC_6H_4CH_2$	**2i**	93
9	**1j**	Ph	Ph	*p*-$O_2NC_6H_4CH_2$	**2j**	86
10	**1k**	Ph	Ph	$CyCH_2$	**2k**	94
11	**1l**	Ph	Ph	Cy	**2l**	81

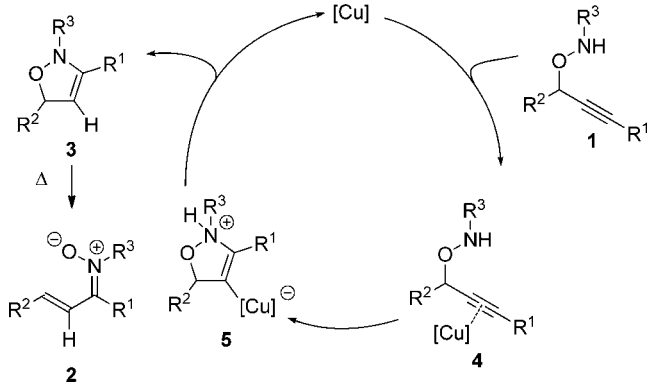
[a]The reactions of **1** (0.4 mmol) was carried out in the presence of CuI (10 mol %) in CH_2Cl_2 (0.8 mL) at 40 °C for 4 h. [b]Isolated yield. [c]The corresponding isoxazoline **3g** was obtained in 83% yield.



(R^2) resulted in the formation of 3-isoxazoline **3g** in good yield (entry 6). In regards to the substituent on the nitrogen atom (R^3), the reaction was tolerant toward various benzyl groups (entries 7–9), even a bulky substituent such as a cyclohexyl group (entry 11). Structure determination of the final products was carried out by spectroscopic analysis including ^{1}H NMR, IR, and HRMS. Moreover, the structure of **2j** was unambiguously determined by X-ray crystallographic analysis (see Supporting Information).

A plausible mechanism is illustrated in Scheme 2. First, the π-acidic Cu catalyst coordinates to the alkyne moiety of substrate

Scheme 2. A Plausible Mechanism



1 to form π-complex **4**. Nucleophilic attack of the nitrogen atom onto the electrophilically activated C–C triple bond occurs in a 5-endo manner, leading to the cyclized Cu-vinyl intermediate **5**. Subsequent protodemetalation gives 3-isoxazoline **3** while regenerating the Cu catalyst. An aryl substituent at the propargylic

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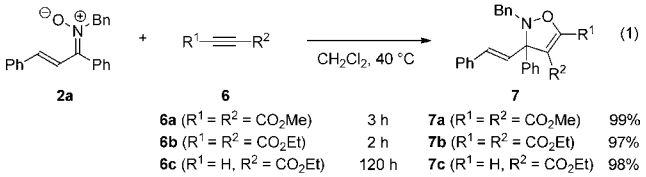
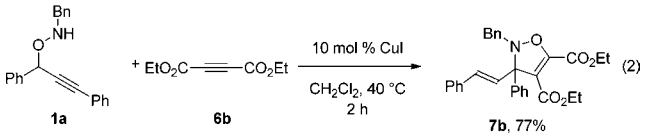
position would encourage the electrocyclic ring opening to afford α,β-unsaturated ketonitrone **2**. Thus, the present transformation can be regarded as a cascade process via Cu-catalyzed hydroamination and thermal 6π electrocyclic ring opening. As a note, the reactivity of 3-isoxazolin-4-yl metal intermediate **5** (and its proton isomer[1a]) is highly influenced by the substituent on the nitrogen atom. When the substituent is an electon-withdrawing sulfonyl or acyl group, rapid protodemetalation takes place due to their high acidity, leading to stable 3-isoxazoline **3**.[10] It is also known that an aryl or alkenyl substituent at the R^3-position facilitates the cleavage of the N−O bond due to the carbene formation or via a concerted manner.[1a,12] In the present research, we demonstrated that an alkyl substituent at the R^3-position facilitates not only the protodemetalation step due to the high basicity at the enamine moiety but also the ring opening of isoxazoline **3** due to electronic contributions from the electron-rich nitrogen atom.

Subsequently, ketonitrone **2** was shown to undergo [3 + 2] cycloaddition reactions with electron-deficient alkynes **6** (eq 1).





Specifically, the reaction with dimethyl acetylenedicarboxylate **6a** (1.5 equiv) afforded the corresponding 2-isoxazoline **7a** in 97% yield, whereas the reaction with ethyl propiolate **6c** afforded a single regioisomer **7c**. Moreover, the one-pot reaction of **1a** and **6** in the presence of a Cu catalyst afforded **7b** in good yield (eq 2).

In conclusion, we have successfully developed an entirely novel and efficient approach to the preparation of *N*-alkylated α,β-unsaturated ketonitrones. Further mechanistic studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products **2**, **3**, and **7**. 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 ratio between **2a** and **3a** was changed from 26:74 to 78:22 for 30 min in $CDCl_3$ at 40 °C, regardless of whether the Cu catalyst was present or absent.

(10) π-Acidic metal-catalyzed cyclization of propargyloxyamides: (a) Yeom, H.-S.; Lee, E.-S.; Shin, S. *Synlett* **2007**, 2292. (b) Knight, D. W.; Proctor, A. J.; Clough, J. M. *Synlett* **2010**, 628.

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