ORGANIC LETTERS

2012
Vol. 14, No. 1
206–209

Copper-Catalyzed Skeletal Rearrangement of *O*-Propargylic Alkylaldoximes via N−O Bond Cleavage

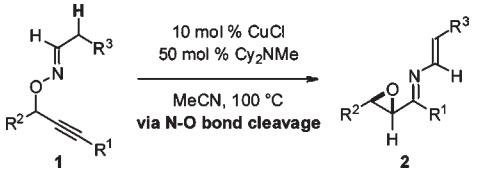
Itaru Nakamura,*[,†,‡] Tomoki Iwata,[‡] Dong Zhang,[‡] and Masahiro Terada[†,‡]

Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

itaru-n@m.tohoku.ac.jp

Received November 7, 2011

ABSTRACT



***O*-Propargylic oximes that possess a proton at the α-position of the oxime group were effectively converted to the corresponding oxiranyl *N*-alkenylimines via a 5-endo-dig cyclization followed by the cleavage of the N−O bond.**

Metal-catalyzed skeletal rearrangements have been employed in numerous elegant transformations in the construction of complex molecules, often via unique reaction mechanisms.[1] Reaction pathways of such catalytic skeletal rearrangements can be dramatically affected by substitution effects, as shown by previous investigations involving enynes and propargylic esters as substrates.[2] Recently, we have demonstrated that *O*-propargylic oximes can undergo unique skeletal rearrangements in the presence of copper catalysts.[3] As shown in Scheme 1 (path a), the key step of these transformations is the catalytic [2,3]-migration of the propargylic oxime to the *N*-allenyl nitrone via cyclic intermediate **A** involving a C−O bond cleavage. As expected, the C−O bond cleavage process is facilitated by the elimination of a stable nitrone group as the leaving group. In contrast, the elimination of a proton from the α-position of the oxime group of cyclic intermediate **A**, as shown in Scheme 1 (path b), would obstruct the C−O bond

† Research and Analytical Center for Giant Molecules.
‡ Department of Chemistry.

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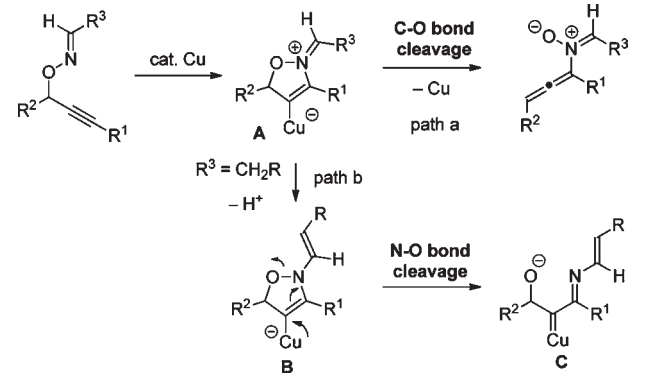
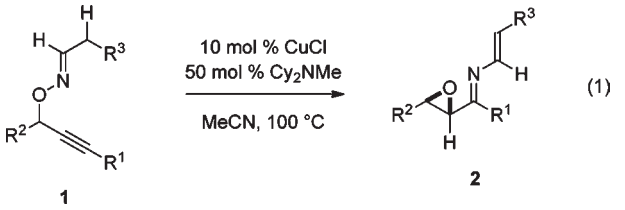
10.1021/ol203001w
Published on Web 12/14/2011

cleavage and, in turn, cause the cleavage of the N−O bond, which would be driven by the donation of electrons from the copper atom via intermediate **B**.[4−6] The resulting copper carbenoid intermediate **C** would undergo further transformations due to the highly substituted reactant. Herein, we report the copper-catalyzed skeletal rearrangements of *O*-propargylic alkylaldoximes **1** to afford the corresponding *N*-alkenyl oxiranylketimines **2** in good to excellent yields via N−O bond cleavage (eq 1).[7]

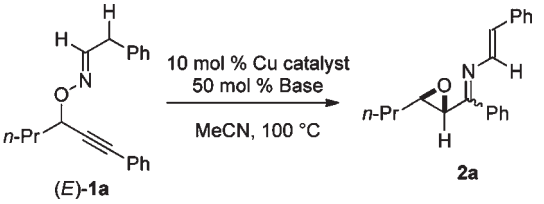
Scheme 1. Bond Cleavage in Cu-Catalyzed Skeletal Rearrangement of *O*-Propargylic Oximes





Initially, to determine the optimal conditions, the reactions were carried out using (*E*)-**1a** that was derived from phenylacetaldehyde. As shown in Table 1 (entry 1), using toluene at 100 °C, and in the presence of catalytic amounts of copper chloride, the reaction afforded the corresponding product **2a** in 39% yield (as determined by ^{1}H NMR), along with small amounts of the four-membered cyclic nitrones.[3c] The use of acetonitrile as the solvent resulted in a faster reaction, thus suppressing the formation of the undesirable byproducts (entry 2). For our reactions, the presence of a bulky base such as Cy_2NMe was effective for driving the reaction to completion within 30 min to afford **2a** in a good yield (entry 3). Similarly, but to a lesser extent, the use of a less bulky base such as iPr_2NEt afforded **2a** in an acceptable yield (entry 4). Unsurprisingly, the use of a small organic base (Et_3N, entry 5) or an inorganic base (K_2CO_3, entry 6) did not improve the reaction. The catalytic activities of copper bromide and copper iodide were similar to that of copper chloride, whereas the activities of copper acetate and cupric chloride were diminished (entries 7−10, respectively).

Table 1. Optimization of the Reaction Conditions



entry	catalyst	base	solvent	time/ h	yield/ %[a]
1	CuCl	none	toluene	24	39[b]
2	CuCl	none	MeCN	7	51
3	CuCl	Cy_2NMe	MeCN	0.5	79
4	CuCl	iPr_2NEt	MeCN	4	66
5	CuCl	Et_3N	MeCN	4	48
6	CuCl	K_2CO_3	MeCN	48	44
7	CuBr	Cy_2NMe	MeCN	0.5	76
8	CuI	Cy_2NMe	MeCN	1	74
9	CuOAc	Cy_2NMe	MeCN	1	11
10	$CuCl_2$	Cy_2NMe	MeCN	1	0

[a] The yields were determined using ^{1}H NMR, with CH_2Br_2 as an internal standard. **2a** was converted to the corresponding oxiranylketone by treatment with 1 N HCl. [b] Trace amounts of four-membered cyclic nitrones were observed.

Using the optimized reaction conditions (Table 1, entry 3), the substitution effects at the oxime moiety were investigated using various substrates, as listed in Table 2. The substrate possessing an electron-deficient aromatic ring at R^3 [(*E*)-**1b**, entry 1] exhibited a significantly faster reaction than that having an electron-rich *p*-anisyl group [(*E*)-**1d**, entry 3]. For the benzyl-substituted substrates, both *E*- and *Z*-isomers exhibited similar reactivities (entries 2 and 4, respectively). In contrast, for the alkyl-substituted substrates (and with a bulky *tert*-butyl group as the substituent at the alkyne terminus), the *Z*-isomer [(*Z*)-**1e**, entry 6] proceeded to afford **2e** in a good yield, whereas the *E*-isomer [(*E*)-**1e**, entry 5] was unreactive. Accordingly, the reaction of (*E*)-**1f**, which has a less bulky phenyl group at R^1, afforded the **2f** in a 76% yield (entry 7).

Next, the substitution effects of the *O*-propargylic group were examined using various substrates, as listed in Table 3. In all cases, the substrates possessed a *tert*-butyl moiety at either the alkyne terminus (R^1) or at the propargyl position (R^2) to ensure the stability of the product; nonetheless, the reactions were tolerant toward a wide variety of

(7) Concerning the stereochemistries of the products, the obtained products possessed only the (*E*)-configuration at the alkenyl moiety and the *trans*-isomers at the epoxy moiety. In contrast, the *E*/*Z*-isomers at the imine moiety were inseparable; in the cases where the substituent at the alkyne terminus was less bulky, both stereoisomers were observable using ^{1}H NMR spectroscopy. See footnote a of Table 1, footnote d of Table 2, and Supporting Information.

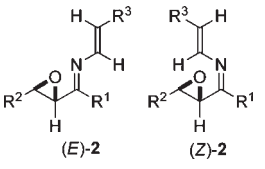
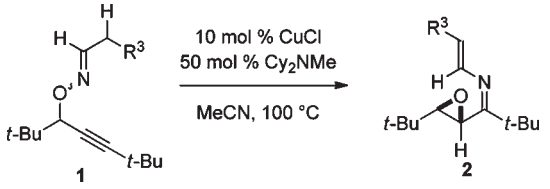


Table 2. Copper-Catalyzed Reactions of **1b**–**f**[a]



entry	1	R^3	time/ h	2	yield/ %[b,c]
1	(*E*)-**1b**	*p*-F_3C-C_6H_4	0.75	**2b**	84
2	(*E*)-**1c**	Ph	1	**2c**	87
3	(*E*)-**1d**	*p*-MeO-C_6H_4	2	**2d**	83
4	(*Z*)-**1c**	Ph	1	**2c**	87
5	(*E*)-**1e**	Et	48	**2e**	trace
6	(*Z*)-**1e**	Et	7	**2e**	71[d]
7	(*E*)-**1f**	Et	3	**2f**	76[d]

[a] The reaction of **1** (0.3 mmol) was carried out in the presence of CuCl (10 mol %) and Cy_2NMe (50 mol %) in acetonitrile (0.6 mL) at 100 °C. [b] Isolated yield. [c] *E*/*Z* ratio of the imine moiety of **2c**–**e** was 1:99. [d] NMR yield. **2e** and **2f** were unstable under the purification conditions. Thus, **2e** and **2f** were converted to the corresponding oxiranylketones by treatment with 1 N HCl.

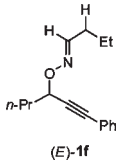
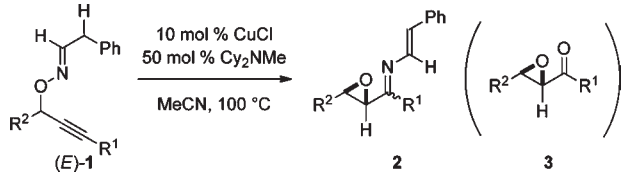


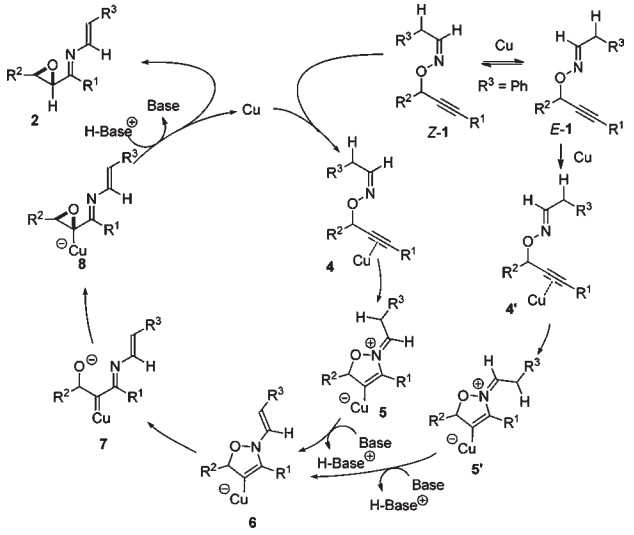
Table 3. Copper-Catalyzed Reaction of (*E*)-**1g**–**n**[a]



entry	1	R^1	R^2	time/ h	2 (3)[b,c]	yield/ %[d]
1	**1g**	*p*-$MeOC_6H_4$	*t*-Bu	0.5	**2g**	93
2	**1h**	Ph	*t*-Bu	0.75	**2h**	89
3	**1i**	*p*-$F_3CC_6H_4$	*t*-Bu	1.5	**2i**	87
4	**1j**	Cy	*t*-Bu	0.75	**2j**	85[e]
5	**1k**	*n*-Pr	*t*-Bu	0.5	(**3k**)	59
6	**1l**	*t*-Bu	*n*-Pr	0.75	(**3l**)	76
7	**1m**	*t*-Bu	Cy	0.75	**2m**	80
8	**1n**	*t*-Bu	Ph	0.75	(**3n**)	57

[a] The reaction of (*E*)-**1** (0.3 mmol) was carried out in the presence of CuCl (10 mol %) and Cy_2NMe (50 mol %) in acetonitrile (0.6 mL) at 100 °C. [b] *N*-Vinylimine **2** was converted to the corresponding ketone **4** by treatment with 1 M HCl in Et_2O at rt for 1 h. [c] The *E*/*Z* ratios of the imine moiety of **2g** (59:41), **2h** (69:31), **2i** (57:43), **2j** (26:74), and **2m** (1:99) were determined by ^1H NMR spectroscopy using $CDCl_3$ as the solvent. [d] Isolated yield. [e] **2j:3j** = 93:7.

Scheme 2. Plausible Mechanism



substituents at either position. Relative to a phenyl-type substrate (entry 2), an electron-rich aromatic ring at the alkyne terminus resulted in a faster reaction (entry 1), whereas an electron-poor *p*-trifluoromethylphenyl group caused a slow reaction (entry 3). Although substrates that possess a bulky alkyl substituent such as cyclohexyl (entry 4) or *tert*-butyl group (Table 1) at the alkyne terminus (R^1) afforded high yields, the substrate that has a relatively small normal propyl substituent [(*E*)-**1k**] resulted in a lower yield, presumably due to the instability of *N*-vinylimine **2k** under the reaction conditions (entry 5). It should be noted that the crude products of the copper-catalyzed reactions of **1a**, **1e**, **1f**, **1k**, **1l**, and **1n** included significant amounts of byproducts and, therefore, were treated with 1 N HCl after the reaction to obtain the corresponding oxiranylketones **3** in the analytically pure form.[7]

A plausible mechanism of the copper-catalyzed rearrangement reaction is illustrated in Scheme 2. First, the π-acidic copper catalyst is coordinated to the alkynyl moiety of **1** to form adducts **4** and **4′**. Next, a 5-endo-dig cyclization occurs via nucleophilic attack of the oxime nitrogen atom onto the electrophilically activated triple bond to afford vinylcopper intermediates **5** or **5′**. The proton at the α-position of the oxime group is abstracted by the base to form the common enamine intermediate **6**, which rearranges to metal-carbenoid **7** via cleavage of the N–O bond, assisted by the donation of electrons from the copper atom. The oxirane ring is then formed via nucleophilic attack of

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the oxygen anion onto the carbenoid carbon to afford product **2** following the subsequent protodemetalation step.[8−10] In the case of R^3 = phenyl, the oxime (*E*)-**1** isomerizes to its (*Z*)-isomer [(*Z*)-**1**] prior to cyclization, presumably due to the higher acidity of the α-proton (Table 2, entries 2 and 4). In contrast, in the cases of R^3 = alkyl, the reaction of an alkyl (*E*)-oxime such as (*E*)-**1e** was sluggish due to (1) steric repulsion between the substituents on the oxime group and the alkyne terminus within the cyclized intermediate **5′** and (2) lower acidity of the α proton (Table 2, entry 5). The experimental result for the reaction of (*E*)-**1f** clearly indicates that decreased steric interactions allow for the successful reaction of the (*E*)-isomer (Table 2). It is likely that Cy_2NMe serves not only as an electron-donating ligand to facilitate the donation of electrons from the copper atom during the conversion from **6** to **7**, but also as a Brønsted base to facilitate the proton transfer processes as well as to scavenge any acid components thus stabilizing the acid-sensitive product **2**.

In conclusion, we have developed an new approach in the efficient synthesis of oxiranyl imine derivatives from readily accessible starting materials. It is noteworthy that the present reaction proceeds via an intramolecular addition of an N−O bond onto an alkyne triple bond. Further investigations on its reaction mechanisms are currently underway in our laboratories.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Experimental procedures and characterization of the products **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.