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Copper-Catalyzed Rearrangement of (*Z*)-Propynal Hydrazones via N−N Bond Cleavage

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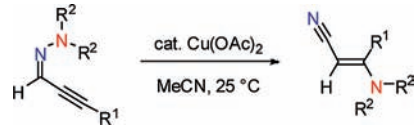
ABSTRACT



Propynal hydrazones are successfully converted to the corresponding 3-aminoacrylonitriles in the presence of copper catalysts in good to high yields. As an example, (*Z*)-*N*-(hex-2-ynylidene)morpholin-4-amine reacted in the presence of 10 mol % $Cu(OAc)_2$ in acetonitrile at 25 °C to afford (*E*)-3-morpholinohex-2-enenitrile ((*E*)-2 h) in 77% yield via C−N bond formation and subsequent *β*-elimination involving cleavage of N−N and C−H bonds.

π-Acidic metal-catalyzed reactions have gained prominence in organic synthesis because they efficiently construct highly elaborate molecules under mild reaction conditions.[1] These transformations often involve cleavage of various *σ* bonds such as carbon−hydrogen (C−H), heteroatom−hydrogen (N−H, O−H), carbon−carbon (C−C), carbon−heteroatom (C−O,[2] C−S,[3] and C−N[4]), and heteroatom−heteroatom bonds (N−O[5] and S−O[6]), proceeding without loss of any atoms in the substrate. To the best of our knowledge, however, *π*-acid metal-catalyzed reactions via N−N bond cleavage have rarely been investigated to date, except for the cyclization of alkynyl azides, in which two of three nitrogen atoms of the azido group are entirely eliminated from the starting material as N_2 gas after N−N bond cleavage.[7] We envisioned that N−N bond cleavage of alkynyl hydrazones using a *π*-acidic metal catalyst would

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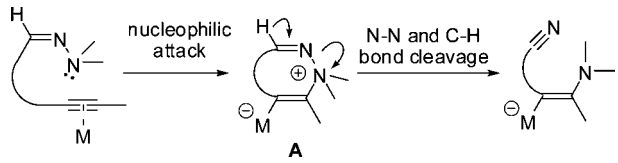
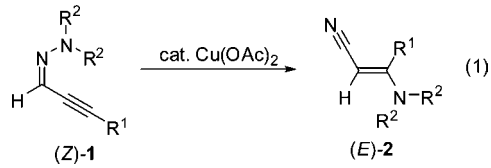
lead to formation of enamine and nitrile groups without loss of nitrogen atoms (Scheme 1).[8] It was anticipated that the

Scheme 1

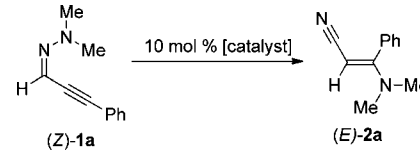


reaction would proceed via nucleophilic attack by the hydrazone sp^3 nitrogen atom onto the alkyne moiety, which would have enhanced electrophilicity due to activation by the π-acidic metal catalyst, followed by β-elimination involving cleavage of the N−N and C−H bonds in the resulting cyclized intermediate **A**.[9] Herein, we report that copper-catalyzed rearrangement of (*Z*)-propynal hydrazones (*Z*)-**1** proceeds via N−N bond cleavage, affording the corresponding β-aminoacrylonitriles **2** in good to high yields (eq 1).[10]



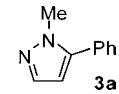
Catalysts were initially screened using (*Z*)-3-phenyl-2-propynal dimethylhydrazone (*Z*)-**1a**, as summarized in Table 1. $Cu(OAc)_2$ showed good catalytic activity in toluene at 100 °C, affording (*E*)-**2a** in 73% yield (entry 1). The acetate counteranion was shown to play an important role in the present reaction because the reaction using monovalent CuOAc as a catalyst gave (*E*)-**2a** in good yield, while other cupric salts, such as $Cu(acac)_2$ and $CuSO_4$, and cuprous salts such as CuCl and CuBr, resulted in a prolonged reaction time and a low chemical yield (entries 2−7). The formation of a considerable amount (20%) of the pyrazole **3a** as byproduct (entry 7) was observed in the reaction using CuI as catalyst. Cationic platinum and gold complexes showed lower catalytic activities (entries 8 and 9). The use of a Brønsted acid such as AcOH and TsOH afforded the desired product in low yields due to unfavorable isomerization of the substrate to the *E* isomer (entries 10 and 11). The reaction was effectively accelerated by the use of polar solvents (entries 12−17). In particular, the reaction in acetonitrile proceeded within 30 min even at 25 °C, affording (*E*)-**2a** in

Table 1. Development of Reaction Conditions



entry	catalyst	solvent	temp/°C	time/h	yield[a]/%
1	$Cu(OAc)_2$	toluene	100	16	73
2	$Cu(acac)_2$	toluene	100	72	24
3	$CuSO_4$	toluene	100	48	20
4	CuOAc	toluene	100	18	72
5	CuCl	toluene	100	36	18
6	CuBr	toluene	100	36	34
7	CuI	toluene	100	36	39[b]
8	$PtCl_2(PPh_3)_2$ + AgOTf	toluene	100	48	68
9	$AuCl(PPh_3)$ + AgOTf	toluene	100	24	50
10	AcOH	toluene	100	24	37[c]
11	TsOH	toluene	100	4	7[d]
12	$Cu(OAc)_2$	MeCN	100	0.25	83
13	$Cu(OAc)_2$	MeOH	100	0.5	70
14	$Cu(OAc)_2$	DMF	100	0.25	75
15	$Cu(OAc)_2$	THF	100	3	85
16	$Cu(OAc)_2$	CH_2Cl_2	100	0.5	76
17	$Cu(OAc)_2$	MeCN	25	0.5	83 (77)

[a] The yield was determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. Isolated yield in parentheses. [b] 1-Methyl-5-phenyl-1*H*-pyrazole **3a** was obtained (20%) as a byproduct. [c] 27% of (*E*)-**1a** was obtained. [d] 81% of (*E*)-**1a** was obtained.



77% isolated yield (entry 17). The *E*-isomer (*E*)-**1a** did not react even at 130 °C.

The optimal reaction conditions (Table 1, entry 17) were applied to various substrates (*Z*)-**1** as summarized in Table 2. When (*Z*)-**1b** having a morpholino group on the sp^2 nitrogen atom was reacted, only (*Z*)-**2b** was observed in the crude product by ^1H NMR and the *Z* isomer was readily isomerized to the *E* isomer ((*E*)-**2b**) during purification using silica gel column chromatography, however, with a significant decrease in the isolated yield (entry 1).[11] It was found that treatment of the crude product with 5 equiv of acetic acid in order to isomerize the *Z* product to the *E* isomer prior to purification resulted in improvement of the isolated yield (entry 2). An *N*-pyrrolidinyl group in the hydrazone moiety showed similar reactivity as the morpholino group, while the reaction of (*Z*)-**1d** bearing an *N*-methylanilino group required 130 °C due to the lower nucleophilicity of the methylanilino group (entries 3 and 4). The reaction of (*Z*)-**1f** with the electron-withdrawing *p*-(trifluoromethyl)phenyl group at the alkyne terminus (R^1) was slower than that having an electron-donating anisyl group (entries 5 and 6). The substrate (*Z*)-**1h** having a normal alkyl group at R^1 was readily converted to (*E*)-**2h** without treatment with AcOH (entry 8). The cyclohexenyl group at the alkynyl terminus was also tolerated under the reaction conditions (entry 9).

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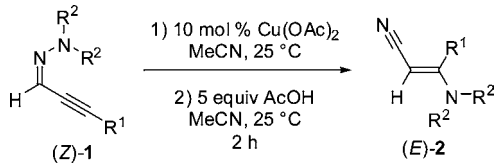
(10) Condensation of propynals with hydrazones generally afforded (*Z*)-**1** as a major product. For example, the reaction of 3-phenylpropynal with 4-aminomorpholine afforded an approximately 1.4:1 mixture of *Z*/*E* isomers of **1b** that was readily separated by silica gel column chromatography. See the Supporting Information.
(11) (*Z*)-**2b** was obtained in 97% yield as determined by NMR of the crude mixture following the copper-catalyzed reaction.

Table 2. Cu-Catalyzed Reaction of (*Z*)-**1b**−**j**[a,b]



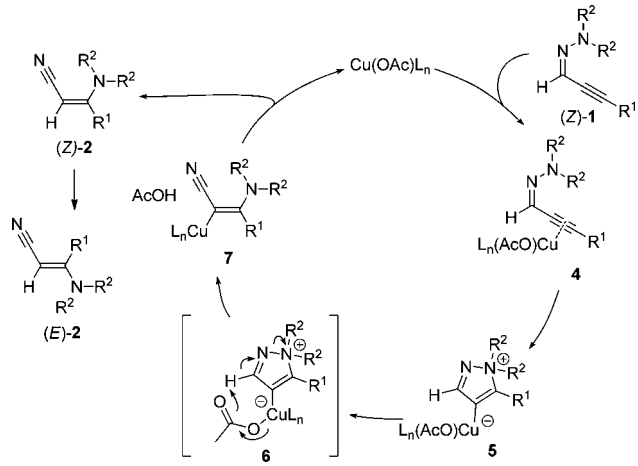
entry	**1**	R^1	NR^2_2	time/h	**2**	yield[c]/%
1[d]	**1b**	Ph	morpholino	1	**2b**	75
2	**1b**	Ph	morpholino	1	**2b**	88
3	**1c**	Ph	piperidinyl	0.5	**2c**	83
4[d,e,f]	**1d**	Ph	NMePh	3	**2d**	45
5	**1e**	*p*-MeO-C_6H_4	morpholino	1.5	**2e**	78
6	**1f**	*p*-F_3C−C_6H_4	morpholino	8	**2f**	83
7	**1g**	2-naphthyl	morpholino	2.5	**2g**	89
8[d]	**1h**	*n*-Pr	morpholino	6	**2h**	77
9	**1i**	1-cyclohexenyl	morpholino	3	**2i**	83
10	**1j**	H	piperidinyl	24	**2j**	65[g]

[a] The reaction of (*Z*)-**1** (0.25 mmol) was carried out in the presence of 10 mol % of $Cu(OAc)_2$ in acetonitrile at 25 °C. [b] After the Cu-catalyzed reaction, the crude mixture was treated with 5 equiv of acetic acid in acetonitrile at 25 °C for 2 h. [c] Isolated yield. [d] Without treatment with acetic acid. [e] At 130 °C. [f] 49% of (*E*)-**1d** was obtained as a byproduct. [g] 18% of (*Z*)-**1j** was recovered.

Furthermore, the terminal alkyne (*Z*)-**1j** was converted to (*E*)-**2j** in 65% yield, but 18% of (*Z*)-**1j** was recovered (entry 10).

As illustrated in Scheme 2, a plausible mechanism for the reaction of (*Z*)-**1** can be explained as follows. First, coordination of the π-acidic copper catalyst to the carbon−carbon triple bond leads to π-complex **4**. Next, nucleophilic attack by the sp^3 nitrogen atom of the hydrazone group onto the electrophilically activated alkyne moiety gives the cyclized intermediate **5**. β-Elimination involving cleavage of N−N and C−H bonds leads to formation of nitrile and enamine groups. Protodemetalation then gives (*Z*)-**2**, which isomerizes to the *E* isomer under the reaction conditions or by treatment with acetic acid. The efficiency of the *Z*/*E* isomerization depends on the bulkiness of both the amino group (NR^2_2) in the hydrazone moiety and the substituent at the alkyne terminus (R^1). Formation of **3a** as a byproduct (Table 1, entry 7) suggests that the present reaction proceeds through formation of the pyrazolium species **5** as a reactive intermediate. The acetate anion on the copper catalyst may act as an intramolecular base, facilitating the C−H bond cleavage from **5** to **7**, as indicated in **6**.

Scheme 2. Plausible Mechanism



In conclusion, we have developed a catalytic rearrangement of propynal hydrazones. The present reaction proceeds under mild reaction conditions and thus this methodology is useful for synthesizing β-aminoacrylonitriles in an efficient manner.

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Supporting Information Available: Experimental procedures and characterization of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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