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An Efficient Copper-mediated 1,3-Dipolar Cycloaddition of Pyrazolidinone-based Dipoles to Terminal Alkynes to Produce *N*,*N*-Bicyclic Pyrazolidinone Derivatives

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A simple dinuclear copper complex [Cu(μ-OH)(tmen)]$_2$Cl$_2$ (tmen = *N*,*N*,*N′*,*N′*-tetramethylethylenediamine) could act as an effective precatalyst for the 1,3-dipolar cycloaddition of pyrazolidinone-based dipoles to terminal alkynes to produce the corresponding *N*,*N*-bicyclic pyrazolidinone derivatives.

1,3-Dipolar cycloaddition reactions are one of the most powerful procedures for the synthesis of a variety of five-membered heterocycles in a convergent manner.[1] For example, the groups of Sharpless[2a] and Meldal[2b] have independently reported that the 1,3-dipolar cycloaddition of organic azides (as dipoles) to alkynes (as dipolarophiles) can dramatically be accelerated by the presence of copper (pre)catalysts and is totally regioselective, affording the corresponding 1,4-disubstituted-1,2,3-triazole derivatives (so-called "click reaction"). To date, many efficient copper-based (pre)catalysts have been reported for the click reaction.[2–5]

Very recently, we have also reported that the copper-substituted silicotungstate with the diazido-bridged dicopper core TBA$_4$[γ-H$_2$SiW$_{10}$O$_{36}${Cu$_2$(μ-1,1-N$_3$)$_2$}] (TBA = tetra-*n*-butylammonium) could act as an efficient homogeneous precatalyst with extremely high turnover frequency (TOF) and turnover number (TON).[5] The dicopper core plays an important role for the click reaction: Initially, the alkyne homocoupling efficiently proceeds via the Cu(II)–alkynyl intermediate {Cu$_2$(μ-C≡CR)$_2$}, followed by the formation of the corresponding diyne (as a co-product) and truly active Cu(I) species.[6] This means that *an alkyne itself can act as an efficient reducing reagent to generate the catalytically active Cu(I) species in situ and no additional reducing reagents are necessary in the case of "dicopper complexes"*.

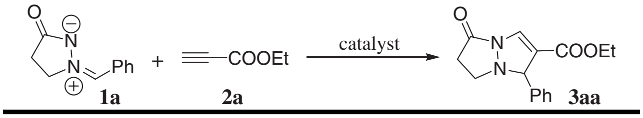
On the basis of the above-mentioned results, we found that a dinuclear copper complex [Cu(μ-OH)(tmen)]$_2$Cl$_2$ could act as an effective precatalyst for the click reaction (Figure S1).[7] In addition, we now found that the 1,3-dipolar cycloaddition of pyrazolidinone-based dipoles (azomethine imides) to terminal alkynes was efficiently promoted by [Cu(μ-OH)(tmen)]$_2$Cl$_2$ and the catalytic activity was superior to that of TBA$_4$[γ-H$_2$SiW$_{10}$O$_{36}${Cu$_2$(μ-1,1-N$_3$)$_2$}].[8]

In this paper, we mainly focused on the synthetic scope of the [Cu(μ-OH)(tmen)]$_2$Cl$_2$-mediated 1,3-dipolar cycloaddition of pyrazolidinone-based dipoles to terminal alkynes. The *N*,*N*-bicyclic pyrazolidinone derivatives produced by this reaction have a variety of applications.[9] However, *only a few catalytic systems*, for example, CuI/Cy$_2$NMe[10a,10b] and Cu(I)-exchanged zeolites,[10c] have been reported until now. Although [Cu(μ-OH)(tmen)]$_2$Cl$_2$ has been utilized as a catalyst for various functional group transformations,[11] *the [Cu(μ-OH)(tmen)]$_2$Cl$_2$-mediated 1,3-dipolar cycloaddition reactions have never been reported*.

Initially, the [Cu(μ-OH)(tmen)]$_2$Cl$_2$-mediated 1,3-dipolar cycloaddition of 1-benzylidene-3-oxo-1-pyrazolidinium-2-ide (**1a**) to ethyl propiolate (**2a**) was carried out in various solvents under Ar atmosphere (Table S1).[7] A typical procedure for the 1,3-dipolar cycloaddition is as follows: Into a glass vial were successively placed catalyst (typically 1 mol % Cu with respect to a dipole), a pyrazolidinone-based dipole (0.5 mmol), an alkyne (0.55 mmol), and a solvent (3 mL). Then, the resulting solution was stirred at 60 °C under Ar atmosphere. The yields were determined by ^{1}H NMR analyses. The products could be isolated by column chromatography on silica gel. Among the solvents examined, non- and low-polar solvents such as chloroform and toluene gave the corresponding *N*,*N*-bicyclic pyrazolidinone **3aa** in high yields. Polar tetrahydrofuran and acetonitrile gave **3aa** in moderate yields. On the other hand, protic and highly polar solvents such as methanol and *N*,*N*-dimethylformamide were poor likely because of the strong coordination to the active site(s). The hydrolytic decomposition of **1a** proceeded to some extent (ca. 4%) when the reaction was carried out in water.

Under the conditions described in Table 1,[12] the 1,3-dipolar cycloaddition of **1a** to **2a** efficiently proceeded to give the corresponding *N*,*N*-bicyclic pyrazolidinone **3aa** in the presence of [Cu(μ-OH)(tmen)]$_2$Cl$_2$ (Entry 1).[8] In this case, only the single regioisomer **3aa** could be obtained. The reaction hardly proceeded in the absence of catalysts (Entry 9). The catalytic activities of simple copper salts and complexes alone were lower than that of [Cu(μ-OH)(tmen)]$_2$Cl$_2$ (Entries 2–8).[13] Therefore, the dicopper core in [Cu(μ-OH)(tmen)]$_2$Cl$_2$ plays an important role in the present transformation.

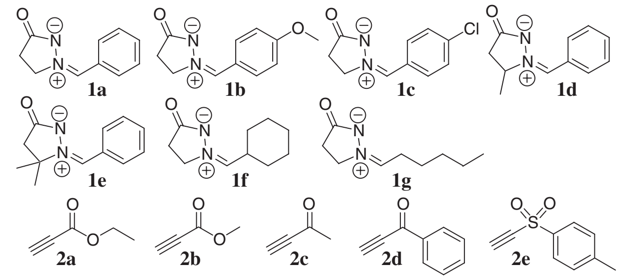
Table 1. 1,3-Dipolar cycloaddition of **1a** to **2a** with various copper-based catalysts[a]



Entry	Catalyst	Yield[b]/%
1	[Cu(μ-OH)(tmen)]$_2$Cl$_2$	49(98)[c]
2	CuSO$_4$•5H$_2$O	2
3	CuCl$_2$•2H$_2$O	4
4	Cu(ClO$_4$)$_2$•6H$_2$O	3
5	Cu(OTf)$_2$	3
6	CuCl	4
7	CuI	11
8	[Cu(CH$_3$CN)$_4$]PF$_6$	19
9	None	3

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), catalyst (Cu: 1 mol % with respect to **1a**), CD$_3$CN (3 mL), 60 °C, 1.0 h, Ar (1 atm). [b]Determined by ^{1}H NMR analysis. [c]The result obtained with CDCl$_3$.

Table 2. Scope of the $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$-mediated 1,3-dipolar cycloaddition[a]



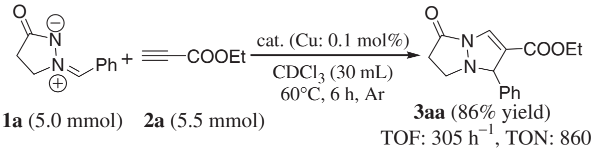
Entry	Dipole	Alkyne	Product	Time/h	Yield[b]/%
1	**1a**	**2a**	**3aa**	1.0	98
2	**1a**	**2b**	**3ab**	1.0	96
3	**1a**	**2c**	**3ac**	1.0	97
4	**1a**	**2d**	**3ad**	2.0	92
5	**1a**	**2e**	**3ae**	1.0	96
6	**1b**	**2a**	**3ba**	2.0	97
7	**1c**	**2a**	**3ca**	1.0	99
8	**1d**	**2a**	**3da**[c]	3.0	97
9	**1e**	**2a**	**3ea**	8.0	>99
10	**1f**	**2a**	**3fa**	1.0	89
11	**1g**	**2a**	**3ga**	2.5	>99

[a]Reaction conditions: Dipole (0.5 mmol), alkyne (0.55 mmol), $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ (Cu: 1 mol % with respect to dipoles), $CDCl_3$ (3 mL), 60 °C, Ar (1 atm). At the initial stage of the reaction, the alkyne homocoupling proceeded to reduce Cu(II) species in $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ ($\leq$0.9% with respect to alkynes). [b]Determined by ^1H NMR analysis. [c]*syn*/*anti* = 90/10.

As mentioned above, the alkyne homocoupling efficiently proceeded on the dicopper core in $TBA_4[\gamma\text{-}H_2SiW_{10}O_{36}\{Cu_2(\mu\text{-}1,1\text{-}N_3)_2\}]$.[6] Similarly, it was confirmed by a separate experiment that the alkyne homocoupling efficiently proceeded on the dicopper core in $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$.[6] An alkyne **2a** (100 equivalents) was added to a chloroform solution of $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ (1.7 mM), and the resulting solution was heated to 60 °C for 30 min under Ar atmosphere. Then, the UV–vis spectrum was measured. By the treatment, the absorption band at 700 nm assignable to the d–d transition of the Cu(II) species almost disappeared, and a new broad absorption band appeared around 400–500 nm. The solid-state UV–vis spectrum of $[Cu^I(C{\equiv}CPh)]_n$ shows a similar broad absorption band around 400–460 nm.[4a] Therefore, in the present $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$-mediated 1,3-dipolar cycloaddition, it is likely that the Cu(I)–acetylide species would be formed by the reaction of the in situ generated Cu(I) species with an alkyne, followed by the reaction with a pyrazolidinone-based dipole to form the corresponding *N*,*N*-bicyclic pyrazolidinone.[10]

Finally, we turned out our attention to the synthetic scope of the 1,3-dipolar cycloaddition. As shown in Table 2, various kinds of pyrazolidinone derivatives and terminal alkynes with electron-withdrawing groups could be used as dipoles and dipolarophiles, respectively, to produce the corresponding *N*,*N*-bicyclic pyrazolidinone derivatives in excellent yields. The 1,3-dipolar cycloaddition of a dipole monomethyl-substituted at the 5-position (**1d**) to **2a** showed a high *syn*-diastereoselectivity for the methyl and phenyl groups of **3da** (*syn*/*anti* = 90/10), suggesting that the addition of an alkyne (acetylide species) mainly takes place *anti* to the methyl group in **1d** (Figure S2).[7,10c]

Notably, the catalyst amount could be much reduced; in a 5 mmol-scale 1,3-dipolar cycloaddition of **1a** to **2a** using only 2.5 µmol of $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ (Cu: 0.1 mol %), the TOF (based on the initial rate) was 305 h^{-1} and the TON reached up to 860 (eq 1). These TOF and TON values were much higher than those reported for copper-based systems so far; CuI/Cy_2NMe (TOF: 1.0 h^{-1}, TON: 20).[10a,10b] and Cu(I)-exchanged zeolites (TOF: 4.5 h^{-1}, TON: 18).[10c]



(1)

1a (5.0 mmol) **2a** (5.5 mmol)

3aa (86% yield)
TOF: 305 h^{-1}, TON: 860

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7 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

8 The reaction rate for the 1,3-dipolar cycloaddition of **1a** to **2a** with $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ was 6.9 mM min^{-1} (in $CDCl_3$) and ca. 1.9 times larger than that with $TBA_4[\gamma\text{-}H_2SiW_{10}O_{36}\{Cu_2(\mu\text{-}1,1\text{-}N_3)_2\}]$ (3.6 mM min^{-1} (in CD_3CN)).

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12 The solubilities of common copper salts in chloroform were low. Although acetonitrile was not the best solvent for $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$, the reactions were carried out in acetonitrile in order to dissolve copper salts and complexes examined in Table 1.

13 It is known that bases and/or stabilizing ligands are required to generate the acetylide species in the case of common copper salts.