2-Ethynylpyridine-Promoted Rapid Copper(I) Chloride Catalyzed Azide–Alkyne Cycloaddition Reaction in Water

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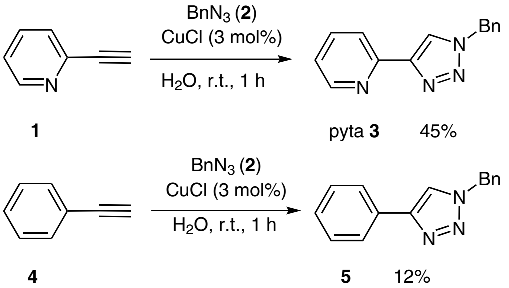
Abstract: The copper(I) chloride catalyzed reaction of azides with alkynes in water at room temperature was promoted by the addition of a catalytic amount of 2-ethynylpyridine, affording the corresponding 1,4-disubstituted 1,2,3-triazoles in good yields after a specific reaction time. The catalytic system could be successfully applied to electron-rich, electron-poor, and sterically crowded substrates. A study of the additive effect of pyridine derivatives revealed that alkynyl and 2-pyridyl groups were essential for activating the copper catalyst.

Key words: cycloaddition, azides, alkynes, copper, heterocycles

The copper-catalyzed Huisgen-type [3+2] azide–alkyne cycloaddition (CuAAC) is a well-known example of a 'click' reaction. First reported independently by the groups of Sharpless and Meldal in 2002,[1] it has emerged as a powerful and versatile tool in the fields of drug discovery, biochemistry, dendrimers, and materials and polymer science.[1f,2] In recent years, click chemistry has been applied to the synthesis of chelating components for transition-metal complexes. One example of this is the reaction of 2-ethynylpyridine with organic azides, yielding 2-pyridyl-substituted 1,2,3-triazole ligands, which resemble bipyridine ligands.[3] By combining an alkyne and an azide, a variety of electronically and sterically tunable pyridine–triazole (pyta) ligands can be prepared. The formation of complexes of these ligands with a variety of transition metals has been reported. Pyta ligands are usually prepared by CuAAC reaction using $CuSO_4$ and Na ascorbate as a catalyst. While CuI can be used in combination with diisopropylethylamine (DIPEA), where the tertiary amine is an essential additive, CuI alone was an inefficient catalyst for the CuAAC reaction.

We obtained pyta **3** in a moderate yield (45%) by the reaction of 2-ethynylpyridine (**1**) with benzylazide (**2**) in water at room temperature for one hour, using 3 mol% CuCl as the sole catalyst (Scheme 1). On the other hand, the reaction of phenylacetylene (**4**) with **2** under the same reaction conditions, gave the corresponding 1,4-disubstituted 1,2,3-triazole **5** in only 12% yield (Table 1, entry 1). It was speculated that the reaction of **1**, **2**, and CuCl might form the pyta–CuCl complex in situ, which then worked as an actual catalyst. In order to clarify this, the reaction was carried out using a combination of pyta–CuCl as a catalyst (3 mol%), and it was found that the complex did in fact catalyze the reaction, with the product formed in 47% yield (Table 1, entry 2). It is reasonable to suppose that the actual catalyst is the pyta–CuCl complex.[4] However, the product yield obtained by the reaction using a catalytic amount (3 mol%) of **1** and CuCl was much higher (96%) than that from the pyta–CuCl complex (Table 1, entry 5). This result suggests that a combination of pyta–CuCl is not likely to be the catalyst and an alternative complex form should be considered.[5] The mechanism by which the addition of **1** enhanced the catalytic activity of CuCl was of considerable interest. Pyta **3** was not observed in the reaction showing that **1** did not reacted with **2** but form complex with CuCl. Addition of large excess (20 mol%) of **1** to CuCl (3 mol%) rather spoiled the reaction to give 51% yield of **5** (Table 1, entry 6); extra **1** reacted with **2** to give pyta **3** which might form complex with CuCl. The use of less than an equimolar amount of **1** to CuCl, that is, 1 mol% of **1**, gave a low yield of **5** (Table 1, entry 7). Table 1 also summarizes the results of the CuAAC reaction with several different pyridine derivatives. The pyridinyl group or pyridine–copper complex itself appeared not to be active catalysts as the addition of pyridine and 2-methylpyridine gave only 20% and 15% yields of the product, respectively (Table 1, entries 3 and 4). The positions of the alkynyl and pyridinyl groups are likely to be essential factors for the activity of the ethynylpyridine, since 3-ethynyl and 4-ethynylpyridine were not as effective as **1** for the reaction, giving only 17% yields of the product (Table 1, entries 8 and 9). Such internal alkynylpyridine as 2-(hex-1-ynyl)pyridine moderately promoted the reaction giving 70% yield of **5** (Table 1, entry 10). It



Scheme 1 CuCl-catalyzed reaction of benzylazide with 2-ethynylpyridine and phenylacetylene

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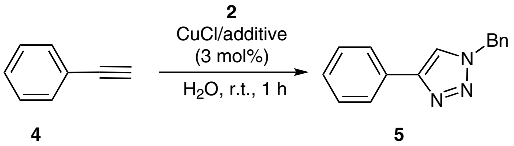
Table 1 The Additive Effect of Pyridine Derivatives in the Reaction of Phenylacetylene (**4**) with Benzylazide (**2**)[a]



Entry	Additive	Yield of **5** (%)[b]
1	none	12
2	pyta **3**	47
3	pyridine	20
4	2-methylpyridine	15
5	2-ethynylpyridine (**1**)	98 (96)[c]
6	2-ethynylpyridine (**1**)[d]	51
7	2-ethynylpyridine (**1**)[e]	47
8	3-ethynylpyridine	17
9	4-ethynylpyridine	17
10	2-(hex-1-ynyl)pyridine	70

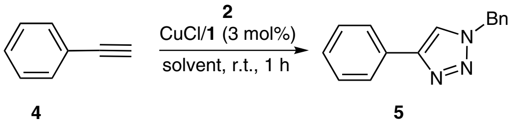
[a] Reaction conditions: **4** (1.0 mmol), **2** (1.05 mmol), CuCl (0.03 mmol, 3 mol%), additive (0.03 mmol, 3 mol%), H_2O (3.0 mL), r.t., 1 h.
[b] Determined by GC.
[c] Isolated yield is given in parenthesis.
[d] Conditions: 20 mol% of **1** and 1.25 mmol of **2** were used.
[e] Conditions: 1 mol% of **1** was used.

was envisaged that **1** might form an acetylide or alkyne complex with CuCl and work as the actual catalyst.[6]

The reaction conditions were next optimized by assessing a variety of solvents. From the results summarized in Table 2, water can be seen to be the solvent of choice, with the reaction almost complete in 30 minutes. Other solvents, such as MeOH, MeOH–H_2O (1:1), and *t*-BuOH–H_2O were found to be unsuitable, each giving low yields of the product. The reaction under neat conditions gave only 9% yield. In addition, CuBr and CuI were both found to be effective catalysts, although yields of **5** were lower than that for CuCl (Table 2, entries 7 and 8).

This new and efficient catalytic system of **1** and CuCl would be a significant breakthrough for the CuAAC reaction if the catalyst could be widely applied to alkynes and azides, including sterically crowded substrates. The scope and generality of this reaction were therefore investigated by testing the reaction between a variety of azides with alkyne **4** and a variety of alkynes with azide **2**, using the optimized experimental conditions (Table 3). Arylacetylenes bearing electron-donating (Table 3, entries 2–4) and electron-withdrawing groups (Table 3, entries 5 and 6) on the phenyl ring reacted with **2**, smoothly affording the corresponding 1,4-disubstituted 1,2,3-triazoles **5** in good yields at room temperature within 0.1–1 hour. The substitution pattern and electronic properties of the phenyl ring had little effect on the product yield, although the reaction times varied. The reaction was slower for alkyl alkynes, requiring one hour for completion, and the cyclopropyl group did not affect the reaction (Table 3, entries 7 and 8). Functional groups such as alcohols **13** and esters **14** were also tolerated (Table 3, entries 9 and 10). The reaction with **1** itself was slow and gave a low yield after one hour reaction time, which is probably because the reaction was mostly catalyzed by the lower-activity pyta–CuCl catalyst (Table 3, entries 11 and 12). Nevertheless, the reaction completed in an extended reaction time (3 h), giving almost quantitative product yield (86%). The scope of the substrates with respect to the azide was also examined. The reaction of phenylacetylene with phenylazide or 1-octylazide was extremely slow, taking 5.5–10 hours for the reaction to complete (Table 3, entries 13 and 14). Interestingly, the reaction with sterically hindered mesitylazide (2,4,6-trimethylphenylazide) completed in a shorter time (5.5 h) to give the product in 93% yield (Table 3, entry 15).[7] Encouraged by this result, the catalytic system was applied to the reaction between an alkyne and an azide that were both sterically crowded. The reaction of mesitylacetylene with mesitylazide was very slow, even when the reaction was conducted at 50 °C (Table 3, entries 16 and 17). However, when the reaction was performed at 100 °C, it almost completed in one hour to give the corresponding 1,2,3-triazole in good yield (Table 3, entry 18). The reaction between 2,6-diisopropylphenylacetylene (dipp) and 2,6-diisopropylphenylazide was also examined, and the corresponding 1,2,3-triazole was produced in 64% yield at 100 °C after 17 hours (Table 3, entry 19).[8]

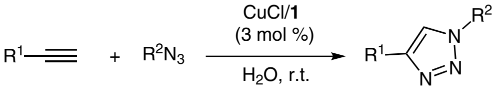
Table 2 Optimization of the Reaction[a]



Entry	Solvent	Yield of **5** (%)[b]
1	H_2O	98
2[c]	H_2O	96
3	MeOH	1
4	H_2O–MeOH (1:1)	46
5	H_2O–*t*-BuOH (1:1)	5
6	neat	9
7[d]	H_2O	91
8[e]	H_2O	85

[a] Reaction conditions: **4** (1.0 mmol), **2** (1.05 mmol), CuCl (0.03 mmol), **1** (0.03 mmol), solvent (3.0 mL), r.t., 1 h.
[b] Determined by GC.
[c] The reaction time was 0.5 h.
[d] CuBr was used.
[e] CuI was used.

Table 3 Scope of the Reaction of Azides with Alkynes[a]



Entry	R^1	R^2	Time (h)	Yield (%)[b]
1	Ph	Bn	0.5	**5**, 96[c]
2	4-MeC_6H_4	Bn	0.1	**6**, 97
3	2-MeC_6H_4	Bn	0.5	**7**, 89
4	2-MeOC_6H_4	Bn	0.25	**8**, 93
5	4-$CF_3C_6H_4$	Bn	1	**9**, 93
6	2-FC_6H_4	Bn	0.1	**10**, 94
7	*n*-C_4H_9	Bn	1	**11**, 91
8	*c*-C_3H_5	Bn	1	**12**, 89
9	CH_2OH	Bn	1.5	**13**, 83
10	CO_2Me	Bn	3	**14**, 91
11	2-pyridyl	Bn	1	**3**, 45[c]
12	2-pyridyl	Bn	3	**3**, 86
13	Ph	*n*-C_8H_{17}	5.5	**15**, 81
14	Ph	Ph	10	**16**, 94
15	Ph	Mes	5.5	**17**, 93
16	Mes	Mes	60	**18**, 89
17[d]	Mes	Mes	7	**18**, 93
18[e]	Mes	Mes	1	**18**, 91
19[e]	Dipp	Dipp	17	**19**, 64

[a] Reaction conditions: Alkyne (1.0 mmol), azide (1.05 mmol), CuCl (0.03 mmol), **1** (0.03 mmol), H_2O (3.0 mL), r.t.

[b] Isolated yield.

[c] GC yield.

[d] The reaction was carried out at 50 °C.

[e] The reaction was carried out at 100 °C.

In conclusion, this report highlights the use of a combination of 2-ethynylpyridine and CuCl as an effective catalyst for the CuAAC reaction in water and demonstrates its tolerance of various functional groups, including sterically crowded substituents on the alkynes or azides; 1,4-dipp-1,2,3-triazole can easily be prepared by using this catalyst without employing active but expensive NHC–Cu complexes.[9]

Acknowledgement

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(4) We obtained the X-ray crystal structure of pyta–CuI complex (see Supporting Information).

(5) Hohloch et al. demonstrated that the CuI complex with **5** catalyzed the reaction of phenylacetylene with benzylazide under neat conditions, but gave less than 20% yield after 100 min reaction. See: Hohloch, S.; C.-Y, Su.; Sarkar, B. *Eur. J. Inorg. Chem.* **2011**, 3067.

(6) An equimolar mixture of CuCl and **1** in MeOH (or H_2O) at r.t. overnight afforded a precipitate, which had a strong absorption at 1947 cm^{-1} in the IR spectrum attributed to the presence of a Cu acetylide complex. It has been reported that polymeric Cu acetylide complexes catalyze the CuAAC reaction ‘on water’ under microwave irradiation. See:

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(7) Yoshida and Hosoya reported that the more sterically hindered azide occasionally reacts with a specified alkyne preferentially. See: Yoshida, S.; Shiraishi, A.; Kanno, K.; Matsushita, T.; Johmoto, K.; Uekusa, H.; Hosoya, T. *Sci. Rep.* **2011**, *1*, 82.

(8) Compound **19** has previously been prepared by NHC–Cu complexes: (a) Nakamura, T.; Terashima, T.; Ogara, K.; Fukuzawa, S.-i. *Org. Lett.* **2011**, *13*, 620. (b) Huang, J.; Hong, J.-T.; Hong, S. H. *Eur. J. Org. Chem.* **2012**, 6630.

(9) **General Procedure for 2-Ethynylpyridine-Promoted Cu(I)-Catalyzed Azide–Alkyne 1,3-Dipolar Cycloaddition**
In a vial containing a magnetic stirrer bar was added CuCl (2.98 mg, 0.03 mmol), H_2O (3 mL), 2-ethynylpyridine (3.0 μL, 0.03 mmol) followed by an alkyne (1.0 mmol) and an azide (1.05 mmol) were loaded. The vial was closed with a screw cap, and the reaction mixture was stirred at specified temperature for the time specified in Table 3. The resulting solution was quenched with NH_3 solution, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and finally the solvent was removed under reduced pressure. GC–MS analysis revealed the presence of the corresponding 1,2,3-triazole. The crude product was purified by PTLC or short silica gel column (hexane–EtOAc as eluent).