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A simple, efficient thermally promoted protocol for Huisgen-click reaction catalyzed by $CuSO_4·5H_2O$ in water

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ABSTRACT

A thermally promoted and $CuSO_4$-catalyzed new version of the Huisgen-click reaction is presented in this Letter. Notably, this protocol was suitable not only for the reactions between organic azides and alkynes, but also for one-pot three-component reactions among alkyl halides, NaN_3, and alkynes.

It is well known that 1,2,3-triazoles have found wide applications in pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, biochemicals, polymers, and functional materials.[1] As for their preparation, the most straightforward method is perhaps the Huisgen cyclization of azide with alkyne. However, there are some drawbacks such as high reaction temperatures and lack of regioselectivity associated with this classical method. To circumvent these problems, Sharpless[2] and Meldal[3] independently discovered that Cu(I) catalysts could significantly facilitate the Huisgen cycloaddition in a regiospecific manner to give only 1,4-disubstituted triazoles. Following these pioneering works, numerous new protocols for the preparation of 1,2,3-triazole derivatives have also been developed.

So far, the copper catalysts used in Huisgen-click reaction include Cu(I) salts (usually in presence of bases and/or ligands),[4] Cu(II) salts together with a reducing agent (sodium ascorbate, metallic copper, hydrazine monohydrate, etc.),[2,5] and metallic copper.[6] Recently, protocols directly using Cu(II) salts for the Huisgen-click reaction have been reported and their mechanism has been also discussed.[7–12,6j] In 2005, Reddy and co-workers have revealed a simple protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles in water at room temperature using $Cu(OAc)_2·H_2O$ (20 mol %) as the catalyst resulting in a good yield in 20 h.[7] Recently, it was reported that $Cu(OAc)_2·H_2O$ could also accelerate the Huisgen-click reaction in alcoholic solvents in the absence of reductants. In that case, the required Cu(I) might be generated in situ via the oxidation of alcohol or homocoupling of terminal alkyne by $Cu(OAc)_2$.[8,9] Moreover, solid supported Cu(II) as recyclable and reusable catalysts in the Huisgen-click reaction have also been prepared and used. In 2007, an alginate-supported Cu(II) catalyst for the Huisgen-click reaction was reported by Reddy and coworkers.[10] In 2009, Cu(II)-Hydrotalcite was reported as an efficient heterogeneous catalyst for the Huisgen-click reaction in acetonitrile at room temperature in 6–12 h.[11] In 2011, Masuyama et al. reported hydroxyapatite-supported Cu(II) as a reusable heterogeneous catalyst with neither reducing agents nor bases for the Huisgen-click reaction in water under air at 50–70 °C.[12] Very recently, Varma and co-workers reported $CuSO_4$ on chitosan as a recyclable heterogeneous catalyst for azide-alkyne cycloaddition reactions in water at room temperature and the reaction could be finished in 4–12 h.[6j] In addition, Cu(II)-catalysts were also used for the three-component Huisgen-click reaction.[13] In all the reported Cu(II)-catalyzed Huisgen-click reactions, the reaction time is relatively longer than that of Cu(I)-catalyzed ones. Under this circumstance, we were interested in the study on how to accelerate Cu(II)-catalyzed Huisgen-click reaction while the good regioselectivity is still retained. Herein, we wish to present a thermal-promoted, simple, and efficient protocol for the Huisgen-click reaction by using $CuSO_4·5H_2O$ as the catalyst in water at 100 °C without any additives or supports.

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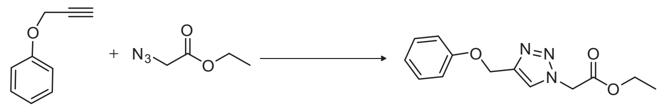
Table 1

The model reaction between propargyl phenyl ether and ethyl azidoacetate catalyzed by $CuSO_4·5H_2O$ in water



Entry	Copper source[a]	*T* (°C)	Times (min)	Yield[c] (%)
1	None	25	20 (h)	4
2	None	100	20 (h)	38
3	$CuSO_4·5H_2O$[b]	25	20 (h)	83
4	$CuSO_4·5H_2O$	40	10 (h)	84
5	$CuSO_4·5H_2O$	60	4 (h)	82
6	$CuSO_4·5H_2O$	80	70	87
7	$CuSO_4·5H_2O$	100	30	85

[a] Reaction conditions: terminal alkyne (1 mmol), Azide (1.2 mmol), $CuSO_4·5H_2O$ (1 mol %), H_2O (2 mL).

[b] $CuSO_4·5H_2O$ (20 mol %).

[c] Isolated yields.

Firstly, the reaction between propargyl phenyl ether and ethyl azidoacetate was selected as a model reaction to investigate the effect of $CuSO_4·5H_2O$ and thermal condition on the Huisgen-click reaction. As shown in Table 1, when the reaction was carried out in water in the absence of $CuSO_4·5H_2O$ at 25 °C or 100 °C for 20 h, a yield of 4% or 38% was obtained respectively. When it was run in the presence of 20 mol % $CuSO_4·5H_2O$ in water at 25 °C for 20 h, a yield of 83% resulted (Table 1, entries 1–3). Next, it was tried with 1 mol % $CuSO_4·5H_2O$ at 40 °C, 60 °C, 80 °C, and 100 °C respectively (Table 1, entries 4–7). The results in Table 1 showed that the higher the reaction temperature the shorter the reaction time needed for a complete transformation. For example, the reaction could complete within 30 min at 100 °C to give the corresponding product in a yield of 85%. In contrast, the reaction needed 10 h to complete at 40 °C. Based on the results obtained so far, it is concluded that either heating or addition of $CuSO_4·5H_2O$ could accelerate this reaction remarkably and a combination of $CuSO_4·5H_2O$ and thermal condition could afford the desired product in high efficiency within short reaction period (Table 1, entry 7).

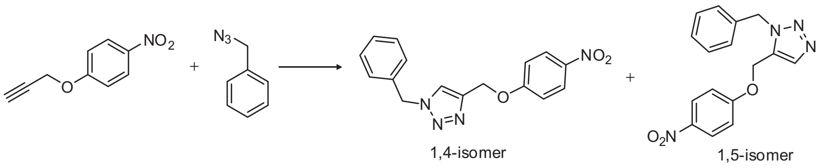
To investigate the effect of $CuSO_4·5H_2O$ on the regio-selectivity of Huisgen-click cyclization, the reaction between benzyl azide and *p*-nitrophenyl propargyl ether was selected as another model reaction as this reaction usually produces a mixture of 1,4- and the 1,5-substituted regioisomers. The reaction was carried out at 100 °C in the presence or absence of Cu(II) catalysts respectively. It turned out that without $CuSO_4·5H_2O$, the reaction gave 1,4-isomer and 1,5-isomer in a ratio of 75 to 25 (Table 2, entry 1). When it was carried out in the presence of $CuBr_2$, $Cu(OAc)_2·H_2O$, and $CuSO_4·5H_2O$ with a 10^{-7} mol % loading at 100 °C, it gave the 1,4-isomers and 1,5-isomers in a ratio of 78 to 22, 89 to 11, and 95 to 5, respectively (Table 2, entries 2, 4 and 7). These results indicated $CuSO_4·5H_2O$ showed the best regioselectivity among the tested Cu(II) catalysts. Further studies showed that increasing the loading of Cu(II) could improve the regioselectivity accordingly. In fact, the ratio of 1,4- to 1,5-isomers could reach to near 100:0 when the loading of $CuBr_2$, $Cu(OAc)_2·H_2O$, and $CuSO_4·5H_2O$ increased to 1 mol %, 1 mol %, and 10^{-2} mol %, respectively (Table 2, entries 3, 5, and 8). It was also found that a further increase of the loading of $CuSO_4·5H_2O$ to 1 mol % or 10 mol % did not improve the reaction obviously. Then, VcNa/$CuSO_4·5H_2O$ and CuCl were also tested as possible catalysts for this reaction. We observed that under similar conditions the regioselectivity is almost the same as that of $CuSO_4·5H_2O$ (seeing Supporting information). Therefore, the optimized conditions are as follows: $CuSO_4·5H_2O$ (1 mol %) as the catalyst, water as the solvent, and 100 °C as the reaction temperature. By the way, the plausible mechanism of $CuSO_4$-catalyzed Huisgen-click reactions between organic azides and alkynes might be similar with literature report.[13f]

To study the scope the above reaction, a wide range of diversely substituted terminal alkynes and azides were tried. As shown in Table 3, the reactions work well not only with alkyl azides, but also with aryl azides. It is worth to mention that the reaction could proceed smoothly even when both the alkynes and the azides are in solid states. (Table 3, entry 11).

In a further aspect, as organic azides are generally unstable and potentially explosive, we then tried a one-pot synthesis of 1,4-disubstituted triazoles directly from alkyl halides, NaN_3, and

Table 2

Synthesis of 1,2,3-triazole from *p*-nitrophenyl propargyl ether and benzyl azide



Entry	Copper source[a]	Catalyst loading (mol %)	*T* (°C)	1,4-Isomer:1,5-isomer[b]	Yield[c] (%)
1	None		100	75:25	54
2	$CuBr_2$	10^{-7}	100	78:22	82
3	$CuBr_2$	1	100	96:4	82
4	$Cu(OAc)_2·H_2O$	10^{-7}	100	89:11	85
5	$Cu(OAc)_2·H_2O$	1	100	100:0[d]	83
6	$CuSO_4·5H_2O$	20	25	100:0[d]	84
7	$CuSO_4·5H_2O$	10^{-7}	100	95:5	86
8	$CuSO_4·5H_2O$	10^{-2}	100	100:0[d,e]	87
9	$CuSO_4·5H_2O$	1	100	100:0[d,f]	88
10	$CuSO_4·5H_2O$	10	100	100:0[d]	87
11	$CuSO_4·5H_2O$/VcNa	1	100	100:0[d]	90
12	CuCl	1	100	100:0[d]	89

[a] Reaction conditions: terminal alkyne (1 mmol), azide (1.2 mmol), H_2O (2 mL).

[b] NMR ratio of the crude product (seeing Supporting information).

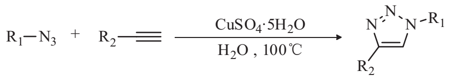
[c] Isolated yields.

[d] Approximate 100:0.

[e] The reaction time is 5 h.

[f] The reaction time is 50 min.

Table 3
Synthesis of triazoles using $CuSO_4{\cdot}5H_2O$ as the catalyst



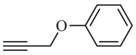
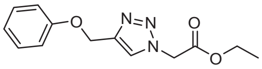
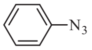
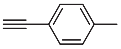
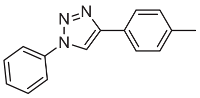
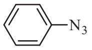
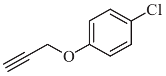
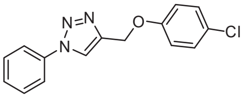
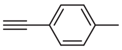
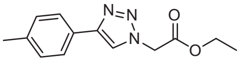
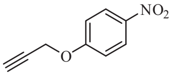
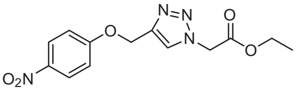
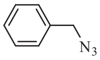
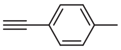
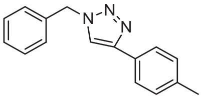
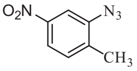
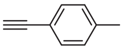
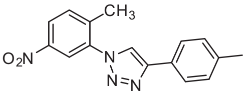
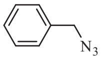
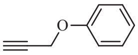
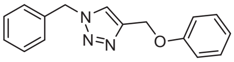
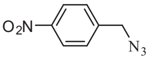
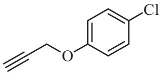
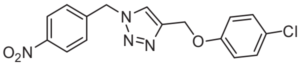
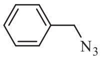
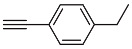
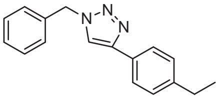
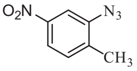
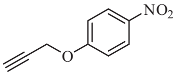
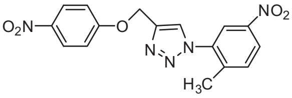
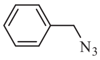
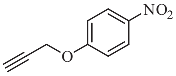
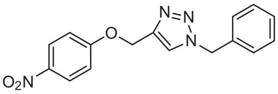
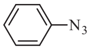
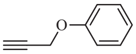
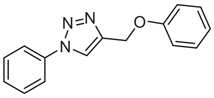
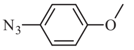
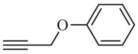
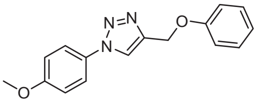
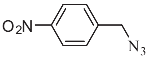
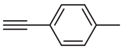
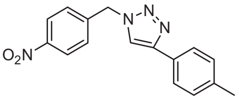
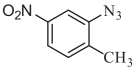
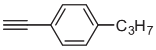
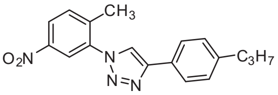
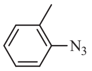
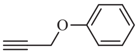
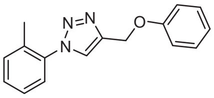
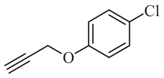
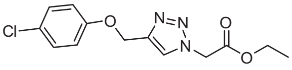
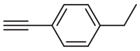
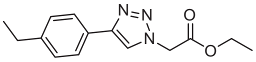
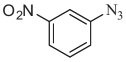
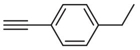
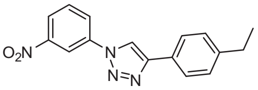
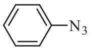
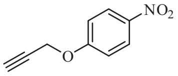
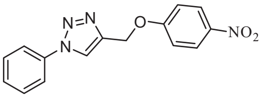
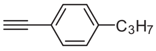
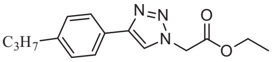
Entry	Azide	Alkyne	Product[a]	Times (min)	Yield[b] (%)
1	N_3CH_2COOEt			30	85
2				30	83
3				40	79
4	N_3CH_2COOEt			30	85
5	N_3CH_2COOEt			50	86
6				30	85
7				60	86
8				40	88
9				40	78
10				30	89
11				80	85
12				50	88
13				30	82
14				40	81
15				50	86
16				60	90
17				30	88

Table 3 (*continued*)

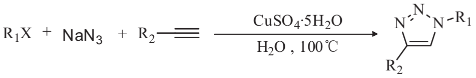
Entry	Azide	Alkyne	Product[a]	Times (min)	Yield[b] (%)
18	N_3CH_2COOEt			30	82
19	N_3CH_2COOEt			30	84
20				50	88
21				40	83
22	N_3CH_2COOEt			30	79

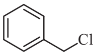
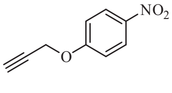
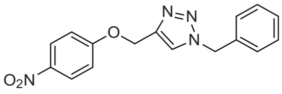
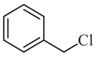
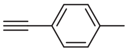
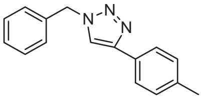
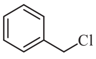
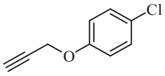
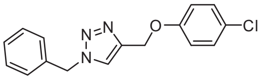
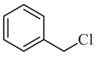
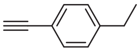
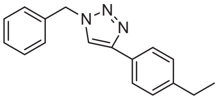
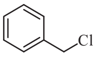
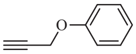
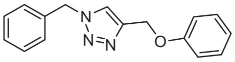
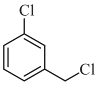
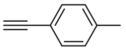
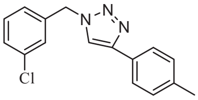
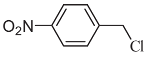
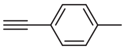
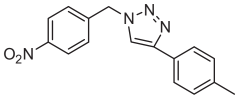
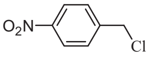
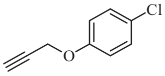
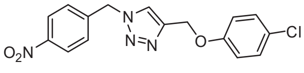
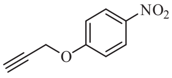
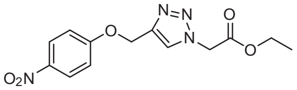
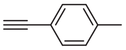
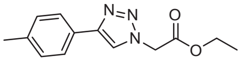
[a] Reaction conditions: terminal alkyne (1 mmol), azide (1.2 mmol), $CuSO_4 \cdot 5H_2O$ (1 mol %), H_2O (2 mL), 100 °C.

[b] Isolated yields.

Table 4

One-pot synthesis of triazoles from alkyl halides, NaN_3, and alkynes



Entry	R_1X	R_2—≡	Product[a]	Times (min)	Yield[b] (%)
1				60	89
2				50	90
3				60	84
4				50	85
5				50	93
6				60	86
7				60	90
8				70	86
9	$ClCH_2COOEt$			60	90
10	$ClCH_2COOEt$			60	85

[a] Reaction conditions: terminal alkyne (1 mmol), sodium azide (1.2 mmol), alkyl halide (1.2 mmol), $CuSO_4 \cdot 5H_2O$(1 mol %), H_2O (2 mL), 100 °C.

[b] Isolated yields.

alkynes. To our delight, under the conditions mentioned above, alkynes could react smoothly with the in situ generated organic azides from alkyl halides and NaN_3 to give the corresponding products in excellent yields (Table 4).

To elucidate the mechanism of the Cu(II) catalyzed one-pot three-component reaction of alkyl halides, NaN_3, and alkynes, the following control experiment was carried out. It was observed that upon addition of an aqueous solution of NaN_3 into the solution of $Cu(OAc)_2 \cdot H_2O$ in water, it turned into pale yellow colored suspension quickly. After a few minutes, red solids precipitated. The structure of this solid compound was determined by XRD as Cu_2O particles (seeing Supporting information). According to our previous study,[5c] Cu_2O should have been generated from the hydrolysis of CuOAc, indicating that during that process Cu(I) must have been in situ generated through reaction of $Cu(OAc)_2$ with sodium azide. In other words, in the one-pot tandem process, Cu(II) was reduced to Cu(I) by sodium azide. While our observation that sodium azide could act as both an azidonation reagent and a reducing agent in the three-component Huisgen-click reaction is actually consistent with what was proposed by Bharate[13a] for a one-pot three-component reaction among boronic acid, sodium azide, and terminal alkyne, it is the first time that sodium azide has been directly proved as a reducing agent for Cu(II) in water by a visible chemical reaction.

In conclusion, we presented a simple protocol for the Huisgen-click reaction using 1 mol % $CuSO_4 \cdot 5H_2O$ as the catalyst at 100 °C in water. The simple direct heat method could not only greatly accelerate the Huisgen-click reaction rate, but also retain its good regioselectivity. Furthermore, the protocol was proved to be suitable for one-pot three-component reactions of alkyl halides, NaN_3, and alkynes. In exploring the reaction mechanism, it was clearly proved for the first time by a visible chemical reaction that sodium azide acted as a reducing agent for the Cu(II)-catalyzed three-component Huisgen-click reaction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.108.

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