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$Cu(OAc)_2 \cdot H_2O/NH_2NH_2 \cdot H_2O$: an efficient catalyst system that *in situ* generates Cu_2O nanoparticles and HOAc for Huisgen click reactions†

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A combination of $Cu(OAc)_2 \cdot H_2O$ and $NH_2NH_2 \cdot H_2O$, which *in situ* generates Cu_2O-NPs and HOAc in water at room temperature, has been developed as a highly efficient catalytic system for Huisgen click reactions. Our results indicate that the *in situ* generated Cu_2O-NPs and HOAc play important roles in the Huisgen click reaction.

Introduction

The azide–alkyne Huisgen cycloaddition, a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a 1,4- or 1,5-disubstituted 1,2,3-triazole, was developed by Rolf Huisgen.[1] The drawbacks of the classical Huisgen cycloaddition reaction are the requirement of high reaction temperatures and a lack of regioselectivity. Since Sharpless[2] and Meldal[3] independently discovered that copper(I) catalysts could facilitate the Huisgen azide–alkyne cycloaddition in a regiospecific manner to give only 1,4-disubstituted triazoles, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions have attracted significant attention due to their application in the synthesis of pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, biochemicals, polymers and functional materials.[4] The usual sources of the copper(I) catalyst for CuAAC reactions are Cu(I) salts or their complexes,[5] Cu(II) salts combined with a reducing agent (sodium ascorbate, metallic copper, hydrazine monohydrate, *etc.*)[2,6] and different sizes of metallic copper.[7]

Cu_2O is also a source of catalytic Cu(I) for CuAAC reactions. Using Cu_2O powder directly in a CuAAC reaction usually results in incomplete conversion, poor yields and long reaction times.[8] Recently, efforts have been made to enhance the catalytic efficiency of Cu_2O.[9–13] In 2010, Kong *et al.*[9] reported polyvinylpyrrolidone-coated Cu_2O nanoparticles as a catalyst for Huisgen click reactions in water at physiological temperatures (37 °C). The results in this paper indicated that Cu_2O-NPs were more efficient and less toxic than the commonly used $CuSO_4$/reductant catalyst systems. Hu *et al.*[10] have established a practical and effective catalytic method using $PhCO_2H$ as an additive. More recently, heterogeneous Cu_2O-NPs catalysts using charcoal,[11] and melamine–formaldehyde resin[12] as supports were prepared and applied in CuAAC reactions.

Hydrazine monohydrate[14] is an attractive reductant for reducing Cu(II) salts due to its strong reducibility and environmentally friendly by-products (nitrogen gas and water) and has been successfully used in CuAAC reactions.[15–17] Recently, Pathigoolla[16] and Kumar[17] prepared copper nanoparticles from a $CuSO_4 \cdot 5H_2O/NH_2NH_2 \cdot H_2O$ catalyst system, which efficiently catalyzed the CuAAC reaction under ambient, open-air conditions. Unfortunately, the amount of $NH_2NH_2 \cdot H_2O$ required was more than 10 times the stoichiometric amount, which is harmful to the environment because of the high toxicity of hydrazine itself. Thus, controlling the amount of the hydrazine is essential in order to be more environmentally conscious. In

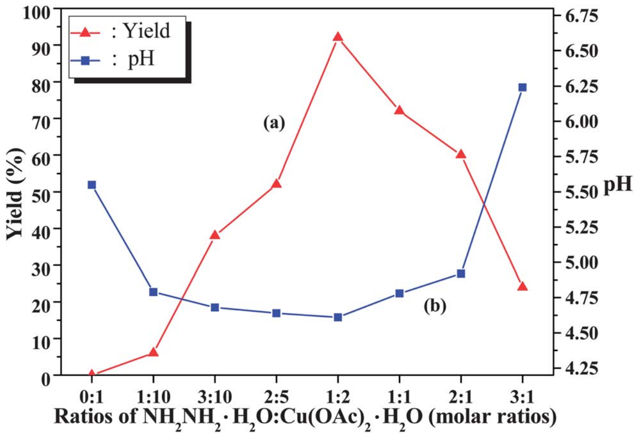

Fig. 1 Effect of the ratio of $NH_2NH_2 \cdot H_2O$ to $Cu(OAc)_2 \cdot H_2O$ on the yield and pH value.

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the work described in this paper, $Cu(OAc)_2 \cdot H_2O$ was selected as the Cu(II) salt and a stoichiometric amount [Cu(II) to Cu(I)] of hydrazine was used as the reducing agent. It is well known that $[(CuOAc)_2]_n$ is unstable in water and will immediately decompose to Cu_2O and HOAc,[18] which could act as the catalyst for the CuAAC reaction. To the best of our knowledge, there have been no CuAAC reactions in water catalyzed by *in situ* generated Cu_2O and HOAc, which should show better catalytic efficiency than that of isolated Cu_2O combined with HOAc.

Results and discussion

$NH_2NH_2 \cdot H_2O$ (0.1 mmol) was added to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol) in water (10 mL) with vigorous stirring. The solution turned into a dark yellow colored suspension instantaneously (see ESI†). The suspension did not subside for a long time. After filtration, the precipitate was dried for three days under high vacuum at room temperature. The reduced product was characterized by X-ray powder diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (see ESI†), which showed the product to be hollow spherical Cu_2O-NPs with sizes of 400–500 nm.

The reaction between propargyl phenyl ether and ethyl azidoacetate was selected as a model reaction. The reaction conditions were chosen as follows: propargyl phenyl ether (1 mmol), ethyl azidoacetate (1 mmol), $Cu(OAc)_2 \cdot H_2O$ (2 mol%) and water (1 mL). The influence of the ratio of $NH_2NH_2 \cdot H_2O$ to $Cu(OAc)_2 \cdot H_2O$ on the isolated yields of the model reaction (Scheme 1) were investigated.

As shown in Fig. 1 (line a), the yield increased significantly over the ratio range of 0 : 1 to 1 : 2, from 0 to 92%, and then decreased over the ratio range of 1 : 2 to 3 : 1, from 92% to 24%. Meanwhile, the pH value of the reaction mixture without adding the model substrates (as shown in Fig. 1, line b) decreased from 5.55 to 4.61, over the ratio range of 0 : 1 to 1 : 2, which can be attributed to the generation of HOAc in the solution. In addition, the pH value increased from 4.61 to 6.24, between the ratio range of 1 : 2 to 3 : 1, which can be attributed to neutralization of the generated HOAc and excess hydrazine. The relationship between the yield and the pH value indicates that the *in situ* generated HOAc is critical for the catalytic efficiency of Cu_2O-NPs. Thus, the optimum ratio of $NH_2NH_2 \cdot H_2O$ to $Cu(OAc)_2 \cdot H_2O$ is 1 : 2, at which ratio the generated amount of HOAc reaches its peak while hydrazine has been completely consumed.

In order to verify the relationship between the yield and the pH value again, the model reaction was carried out separately in varying amounts of water using $NH_2NH_2 \cdot H_2O$ (1 mol%)/$Cu(OAc)_2 \cdot H_2O$ (2 mol%) (molar ratio of 1 : 2) as the catalyst at room temperature. As shown in Fig. 2, the higher the amount of water, the higher the pH value and the lower the yield, which is consistent with the results mentioned above. Another experiment, using separate Cu_2O-NPs (1 mol%) and HOAc (4 mol%) as the catalyst for the model reaction, was carried out in water (1 mL) at room temperature. Unfortunately, the product yield was only 21% after 20 min, while the pH value was 3.84 and it took 110 min to finish the model reaction. The above result indicated that the catalytic activity of Cu_2O-NPs generated *in situ* was higher than that of separate Cu_2O-NPs. The reason for this is probably that the chemical equilibrium between the *in situ* generated Cu_2O-NPs and HOAc is shifted more to the side of CuOAc.[19–21] Therefore, the optimum amount of water is 1 mL.

Reactions involving a wide range of diversely substituted terminal alkynes and azides were carried out using the optimized conditions. As shown in Table 1, the reaction works well not only with alkyl azides, but also with aryl azides. All of the reactions were highly regioselective towards the 1,4-disubstituted triazoles within 30 min.

The proposed mechanism (Scheme 2) for the reaction is the same as the established mechanism shown in earlier reports.[22] The *in situ* generated HOAc plays many important roles in the reaction:[10,19–21] (a) HOAc breaks the crystal structure of Cu_2O to allow the formation of copper(I) carboxylates, which are highly efficient catalysts for the CuAAC reaction; (b) the acidity of HOAc is also necessary for the success of this conversion; (c) AcO^- acts as a bidentate ligand coordinated to the Cu(I) species of the monomer to promote the formation of dinuclear alkynyl–copper(I) intermediate (3) (see step 2); (d) it has an active effect on the cycloaddition (step 3) and protonation of the C–Cu bond (step 4).

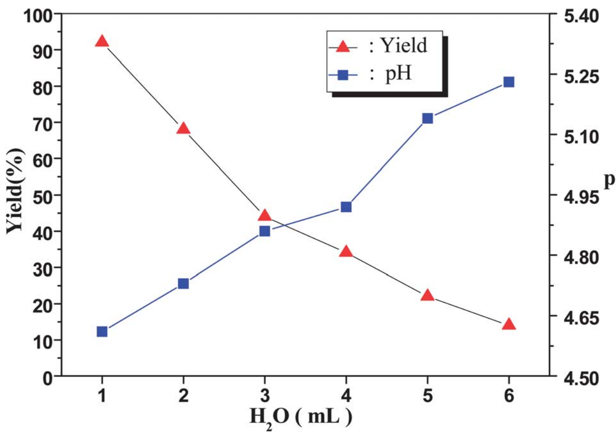
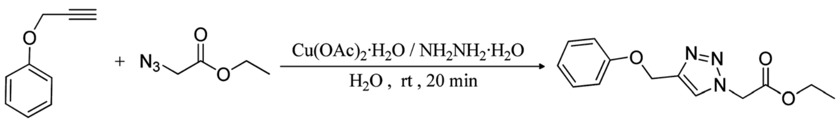
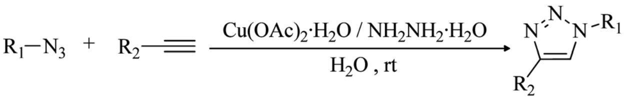


Fig. 2 Effect of the amount of H_2O on the model reaction.



Scheme 1 Model reaction for selecting the ratio of $NH_2NH_2 \cdot H_2O$ to $Cu(OAc)_2 \cdot H_2O$.

Table 1 Synthesis of triazoles using the $Cu(OAc)_2 \cdot H_2O/NH_2NH_2 \cdot H_2O$ system



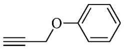
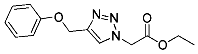
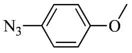
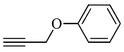
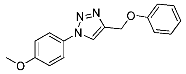
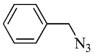
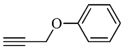
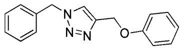
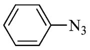
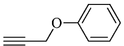
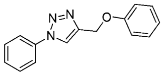
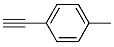
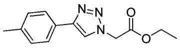
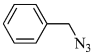
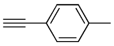
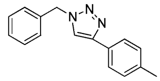
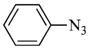
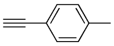
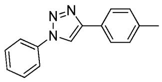
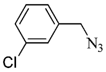
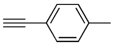
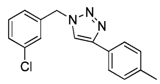
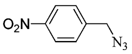
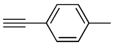
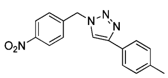
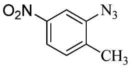
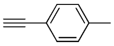
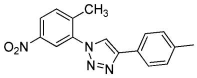
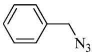
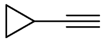
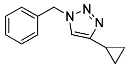
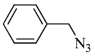
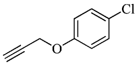
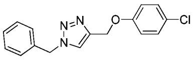
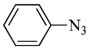
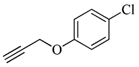
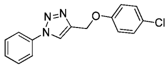
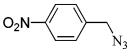
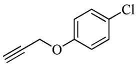
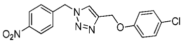
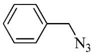
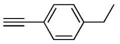
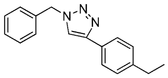
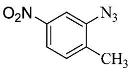
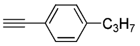
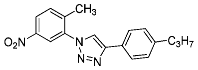
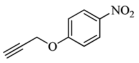
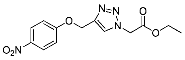
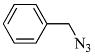
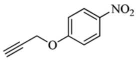
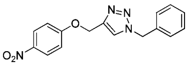
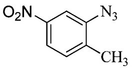
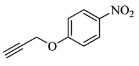
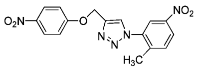
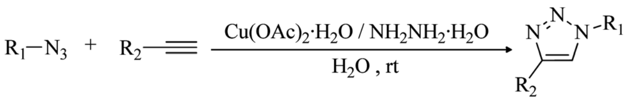
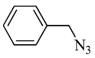
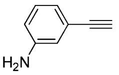
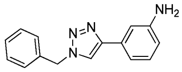
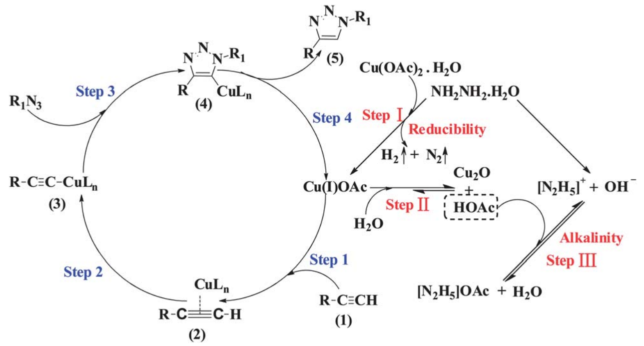
Entry	Azide	Alkyne	Product[a]	Time (min)	Yield[b] (%)
1	N_3CH_2COOEt			20	92
2				15	93
3				10	93
4				12	92
5	N_3CH_2COOEt			8	94
6				10	92
7				9	90
8				12	91
9				18	93
10				25	92
11				20	90
12				22	90
13				18	89
14				20	86
15				10	94
16				16	92
17	N_3CH_2COOEt			25	91
18				22	90
19				28	89

Table 1 (*Contd.*)



Entry	Azide	Alkyne	Product[a]	Time (min)	Yield[b] (%)
20				12	91

[a] Reaction conditions: terminal alkyne (1 mmol), azide (1 mmol), $NH_2NH_2 \cdot H_2O$ (1 mol%), $Cu(OAc)_2 \cdot H_2O$ (2 mol%), H_2O (1 mL), at room temperature. [b] Isolated yield.



Scheme 2 Proposed mechanism for the CuAAC reaction.

Conclusions

In summary, we have presented a novel and high yielding $Cu(OAc)_2 \cdot H_2O/NH_2NH_2 \cdot H_2O$ catalyst system, which could *in situ* generate Cu_2O-NPs and HOAc to catalyze Huisgen click cycloadditions in water at room temperature with relatively short reaction times. Such a method is interesting as it avoids not only the use of stabilizers, additional ligands and supports, but also the production of harmful substances.

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