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Synthesis of propargylamines catalyzed by *in situ* generated copper nanoparticles in water

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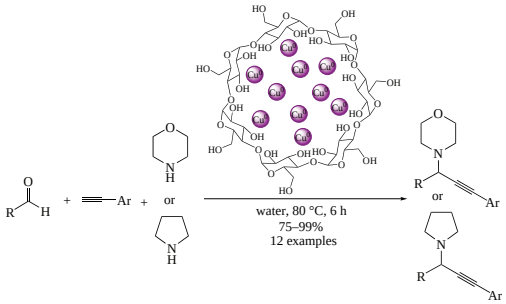
An efficient and green protocol for the A^3 coupling reaction of aldehyde, amine and alkyne involves the use of copper nanoparticles and β-cyclodextrin in water. The copper nanoparticles are generated *in situ* by reduction with green and cheap sodium hydroxymethanesulfinate (rongalite) while β-cyclodextrin serves as a stabilizing agent and a phase-transfer catalyst.



Keywords: A^3 coupling reaction, copper nanoparticles, propargylamines, rongalite, β-cyclodextrin, Mannich reaction.

Propargylamines are found in a variety of pharmaceutical molecules and natural products.[1–3] They are also major skeletons or synthetically key intermediates in the preparation of many biologically active nitrogen-containing compounds.[4,5] The most effective and straightforward way to synthesize propargylamines is the three-component coupling of aldehyde, amine and alkyne (A^3 coupling) being a version of the Mannich-type reaction. Various catalysts based on Cu, Ag, Au, Pd, Ni, Fe, In as well as Et_3Al/ZnI_2 under different conditions have been reported so far.[6–13] However, some of these methods suffered from harsh reaction conditions, the use of harmful solvents and the requirement of expensive metal catalysts. Hence, the development of green approach to access propargylamines is still of great significance.

The application of copper nanoparticles (CuNPs) in synthetic chemistry has attracted much attention in recent years due to excellent catalytic activity, low toxicity and low cost. Copper nanoparticles have already shown better catalytic activity in the A^3 coupling reaction compared to other metal catalysts.[14–21] Generally, the generation of CuNPs involved reduction of copper salts with the suitable reducing agents such as $NaBH_4$,[22] $N_2H_4{\cdot}H_2O$[23] and amines.[24] However, most of these reducing agents are hazardous. Moreover, CuNPs were usually synthesized separately prior to their use in reactions. Therefore, the search for environmentally benign, cost effective and operationally simple method for CuNPs catalyzed reactions is highly desirable. Recently,[25] Poshala reported a click reaction to access 1,4-disubstituted 1,2,3-triazoles using *in situ* generated CuNPs in water with the employment of sodium hydroxymethanesulfinate (rongalite) as a cheaper and green reducing agent. Inspired by this contribution, we herein report the synthesis of propargylamines catalyzed by *in situ* generated CuNPs in water.

Initially, benzaldehyde **1a**, morpholine **2a** and phenylacetylene **3a** were selected as the model substrates to optimize the reaction conditions. Rongalite was selected as the reducing agent while β-cyclodextrin (β-CD) was added to stabilize the copper nanoparticles. After systematic exploration, it was observed that when the reaction was catalyzed by CuNPs *in situ* generated from $CuSO_4{\cdot}5H_2O$ (0.1 equiv.), rongalite (0.5 equiv.) and β-CD (0.02 equiv.) in water (2 ml) at room temperature for 24 h, the desired product **4a** was obtained in nearly quantitative yield (Table 1, entry 1). Switching from $CuSO_4{\cdot}5H_2O$ to $CuCl_2$ or $Cu(OAc)_2{\cdot}H_2O$ led to a sharp drop in the yield (entries 2 and 3). Other sulfur-containing reducing agents such as sodium dithionite and thiourea dioxide were also tried, however, only moderate yields were obtained (entries 4 and 5). Poor yield was

Table 1 Optimization of reaction conditions.[a]

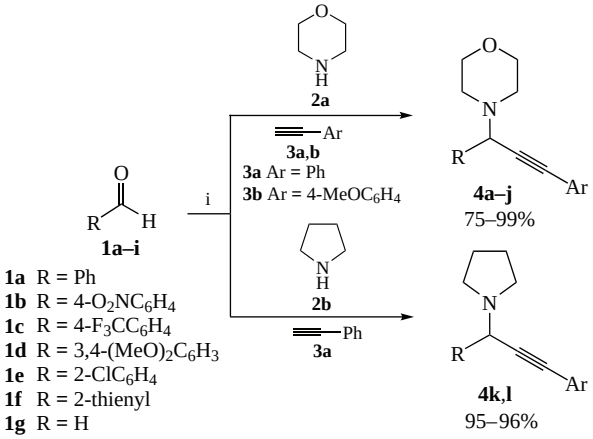
Entry	Cu salt	Reducing agent	β-CD equiv.	Temperature/°C	Time/h	Yield of **4a** (%)[b]
1	$CuSO_4{\cdot}5H_2O$	rongalite	0.02	25	24	99
2	$CuCl_2$	rongalite	0.02	25	24	41
3	$Cu(OAc)_2{\cdot}H_2O$	rongalite	0.02	25	24	72
4	$CuSO_4{\cdot}5H_2O$	sodium dithionite	0.02	25	24	46
5	$CuSO_4{\cdot}5H_2O$	thiourea dioxide	0.02	25	24	68
6	$CuSO_4{\cdot}5H_2O$	–	0.02	25	24	14
7	$CuSO_4{\cdot}5H_2O$	rongalite	0.01	25	24	84
8	$CuSO_4{\cdot}5H_2O$	rongalite	–	25	24	28
9	$CuSO_4{\cdot}5H_2O$	rongalite	0.02	60	12	99
10	$CuSO_4{\cdot}5H_2O$	rongalite	0.02	80	6	99
11	$CuSO_4{\cdot}5H_2O$	rongalite	0.02	100	6	90
12	–	rongalite	0.02	80	6	0
13	$CuSO_4{\cdot}5H_2O$[c]	rongalite	0.02	80	6	73

[a] Benzaldehyde **1a** (1 mmol), morpholine **2a** (1.2 mmol), phenylacetylene **3a** (1.5 mmol), copper salt (0.1 equiv.), reducing agent (0.5 equiv.), β-CD, water (2 ml). [b] Isolated yield. [c] 5 mol% of $CuSO_4{\cdot}5H_2O$ was used.

obtained in the absence of rongalite (entry 6). Lowering the β-CD loading also decreased the product yield, and no reaction was observed in the absence of β-CD (entries 7 and 8). It was assumed that β-CD not only served as the phase-transfer catalyst but also efficiently stabilized the CuNPs by a large number of primary and secondary hydroxy groups.[26] Varying the temperature from 60 to 100 °C delivered **4a** in excellent yields in short reaction times. Reaction at 80 °C was sufficient to give **4a** in nearly quantitative yield within 6 h (entries 9–11). No reaction occurred in the absence of copper salt, and lowering the catalyst loading decreased the product yield to 73% (entries 12 and 13).

The substrate scope was then explored (Scheme 1).† Amines such as morpholine **2a** and pyrrolidine **2b** showed good reactivities, affording the corresponding products **4a** and **4k** in 99 and 95% yields, respectively. Both aromatic **1a**–**f** and aliphatic **1g**–**i** aldehydes reacted well with the amines and alkynes, giving the desired products **1a**–**l** in good to excellent yields (75–99%). For benzaldehydes **1a**–**e**, there was no significant influence of electronic effect on the reaction. In sharp contrast, 4-hydroxybenzaldehyde (R = 2-HOC_6H_4) did not survive, and no corresponding product was observed. 2-Thiophenecarboxaldehyde **1f** also coupled with morpholine and phenylacetylene to provide product **4f** in 82% yield.

Extra experiments were performed in order to gain some insight into this reaction. When the mixture of $CuSO_4{\cdot}5H_2O$, rongalite and β-CD was stirred at room temperature or under heating for 30 min, blackish brown color precipitate was formed (see Online Supplementary Materials, Figure S1). The X-ray diffraction (XRD) patterns of such precipitate showed three sharp peaks at 43.3, 50.4 and 74.3° [Figure 1(*a*)], which should be assigned to (111), (200) and (220) planes of Cu nanoparticles (JCPDS, card no. 04-0836). The average crystallite size of



Scheme 1 *Reagents and optimized conditions*: i, aldehyde **1** (1 mmol), amine **2** (1.2 mmol), alkyne **3** (1.5 mmol), $CuSO_4{\cdot}5H_2O$ (0.1 equiv.), rongalite (0.5 equiv.), β-CD (0.02 equiv.), water (2 ml), 80 °C, 6 h.

† *General procedure for the synthesis of* **4a**–**l**. In an oven dried round bottom flask, aldehyde **1** (1.0 mmol), amine **2** (1.2 mmol) and alkyne **3** (1.5 mmol) were added to a mixture of $CuSO_4{\cdot}5H_2O$ (25.0 mg, 0.1 mmol), rongalite (77 mg, 0.5 mmol), and β-CD (23 mg, 0.02 mmol) in H_2O (2 ml). The mixture was stirred at 80 °C for 6 h. Afterwards, the mixture was extracted with ethyl acetate (3 × 10 ml), the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using petroleum ether/ethyl acetate (10 : 1, v/v) as eluent.

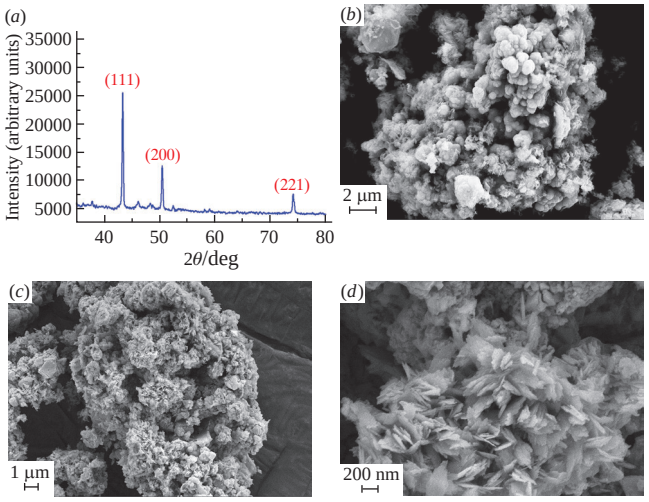
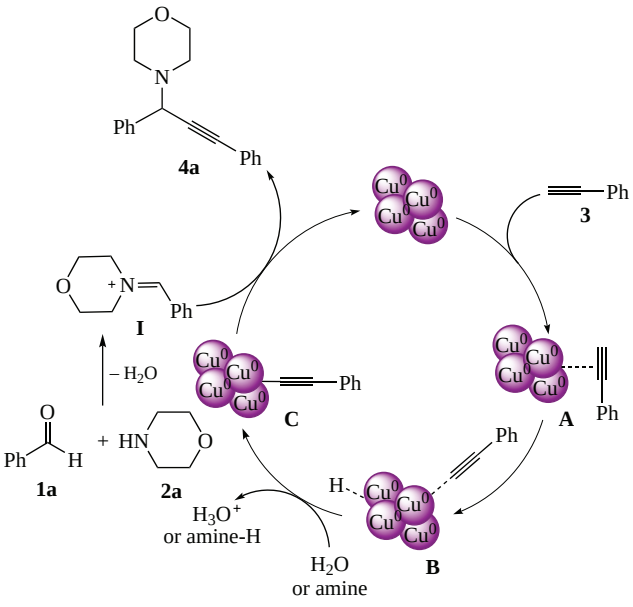


Figure 1 (*a*) XRD pattern of synthesized CuNPs; (*b*) SEM image 2 μm scale; (*c*) SEM image 1 μm scale; and (*d*) SEM image 200 nm scale.

CuNPs is about 40 nm according to the Scherrer's equation.[24] Scanning electron microscopy (SEM) images showed that the CuNPs were slightly agglomerated [Figure 1(*b*),(*c*)]. When the image was enlarged to 30 000 times, a flower-like structure was observed [Figure 1(*d*)]. The results of the elemental analysis through energy dispersive X-ray spectroscopy (EDX) showed that precipitate contained carbon (31.75%), oxygen (17.04%), and Cu (51.21%). This result might confirm that CuNPs were stabilized by β-CD (see Online Supplementary Materials, Figure S6).

According to the supposed mechanism (Scheme 2), benzaldehyde **1a** initially reacts with morpholine **2a** to generate iminium ion **I**. Meanwhile, the activation of the C–H bond of phenylacetylene **3a** by CuNPs delivers alkenyl–Cu intermediate **A**. Then, intermediate **A** attacks iminium ion **I** to provide the corresponding product **4a**. In principle, this mechanism is in a good agreement with the classical Mannich pathway involving the addition of C-nucleophile at the intermediate iminium salt.

In summary, we have developed an efficient and green protocol for the A^3 coupling reaction of aldehyde, amine and alkyne using CuNPs in water. The green and cheap rongalite was used as the reducing agent to generate the CuNPs *in situ*. β-Cyclodextrin served not only as a stabilizing agent but also as



Scheme 2

a phase-transfer catalyst. The reaction proceeded smoothly to afford the corresponding propargylamines in good to excellent yields.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.030.

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