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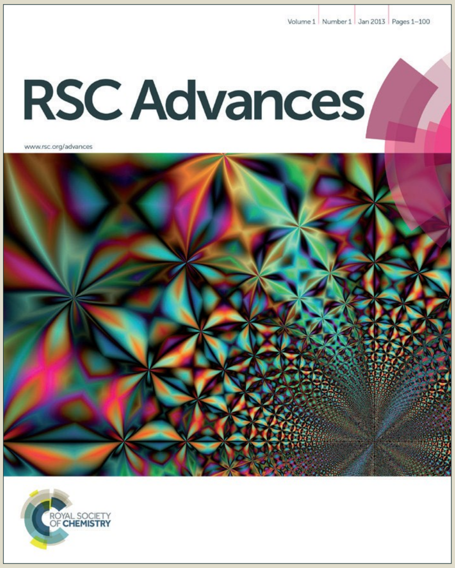

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Journal Name

COMMUNICATION

Ligand-free reusable nano copper oxide-catalyzed synthesis of 3-amino-1,4-diynes†

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Synthesis of 3-amino-1,4-diynes have been developed by the two-component coupling of *N,N*-dimethyl formamide dimethyl acetal with terminal alkynes using CuO nano particle as an efficient catalyst under mild reaction conditions in ambient air. The procedure is applicable to aryl, alkyl, alkenyl, heteroaryl alkynes. The CuO nanoparticles are easily recyclable without the loss of significant catalytic activity.

Propargylamines are synthetically versatile intermediates for the preparation of various biologically active molecules.[1] They also act as the key intermediate for the construction of isosteres, β-lactams, oxotremorine substrates, conformationally restricted peptides, and therapeutic drug molecules.[2] This important structural unit is generally used in organic synthesis as the versatile building blocks for the synthesis of nitrogen-containing heterocyclic compounds such as pyrrolidines, pyrroles, aminoindolizines etc.[3]

Due to the immense biological activities, as well as remarkable utility in organic synthesis, synthesis of these scaffolds is a demanding task. Over the past few decades they have been synthesized mainly by nucleophilic attack of metal acetylides to imines[4] or by using transition metal catalysts.[5] However, the efficient methods for the synthesis of 3-amino-1,4-diynes are very limited.[4] Regardless of their efficiency and reliability, those methods have a major limitation of using stoichiometric amount of metal in their reactions. The direct catalytic coupling using terminal alkynes for alkynylation would be more preferable because it eliminates the need for the stoichiometric preparation of alkyne anions. But the direct couplings of terminal alkynes with acetals have been rarely studied.[6] In 2010, Zhang *et al.* developed a copper-catalyzed efficient method for the cross-coupling of the C-OMe bond adjacent to a nitrogen atom with terminal alkynes to synthesize 3-amino-1,4-diynes.[7] But, the reaction is promoted by expensive phosphine ligand and molecular sieves in nitrogen atmosphere. Despite the advantages of homogeneous metal catalyst, difficulties in recovering and recycling severely obstruct its wide use in industry. So finding an alternative general and efficient method is always in demand.

A tremendous growth in the field of nanoscience and nanotechnology has been observed in the last decade. Metal nanoparticles have attracted considerable interest in synthetic organic chemistry due to their high catalytic activity, reusability and also the benign character in the context of green chemistry.[8] In general, nanoparticles are more effective compared to the bulk material due to having their high surface-to-volume ratios which can provide better dispersion of the active sites and therefore increasing their catalytic activity.[8j] In addition, nanoparticles have high zeta potential which suppress the aggregation of nanoclusters[8k] and also show greater activities which avoid the use of ligands.[8l] These features of the nano-materials, specially the salts of copper have been successfully utilized for various organic transformations.[9]

Very recently, we have developed an environmentally benign nano-CuO catalyzed “on-water” strategy for the one-pot synthesis of isoindolo[2,1-*a*]quinazolines.[10a] Moreover, we found that nano In_2O_3 is an effective catalyst for the synthesis of propargylamines by the three component coupling of alkyne, dichloromethane, and amines.[10b] These results motivated us to use of nanoparticles as catalyst in organic transformations. In continuation of our efforts in the field of nanocatalysis in organic synthesis,[10] herein, we are pleased to report a simple and convenient approach to synthesize 3-amino-1,4-diynes *via* a two-component coupling of *N,N*-dimethyl formamide dimethyl acetal with various terminal alkynes using copper oxide nanoparticles as catalyst in 1,2-DCE under reflux without using any ligand (Scheme 1).‡

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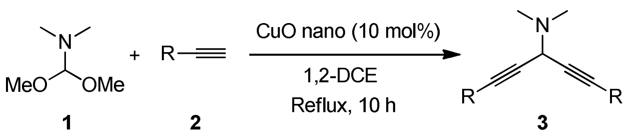
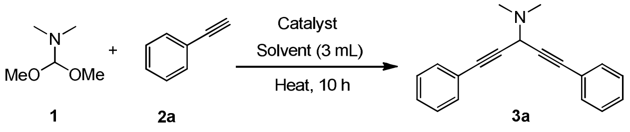


Scheme 1 CuO nanoparticles-catalyzed synthesis of 3-amino-1,4-diynes.

We started our study by choosing *N*,*N*-dimethyl formamide dimethyl acetal (**1**) and phenylacetylene (**2a**) as the model substrates for this two component reaction using 5 mol% CuO nano as the catalyst in 1,2-dichloroethane (1,2-DCE) under reflux for 10 h. To our delight, the desired product **3a** was obtained in 68% yield (entry 1, Table 1). Inspired by this result, we carried out the reaction employing CuO nano as a catalyst in different solvent media and the results are summarized in Table 1. 1,2-DCE appeared to be the best choice among the common solvents like MeCN, THF, EtOH, PEG-400, DMF, DMSO, toluene (entries 4-10, Table 1). Increasing the amount of catalyst (10 mol%) improved the yield to 87%, (entry 2, Table 1) whereas decreasing the amount of catalyst (2 mol%) decreased the yield (entry 3, Table 1). Then various metal nano catalysts such as In_2O_3, NiO, ZnO were also screened (entry 11-13, Table 1); nano CuO was found to be the most effective one among these nano catalysts. Moreover, CuBr, CuO powder and Cu_2O powder were also tested but they were not so effective like CuO nano (entry 14-16, Table 1). In absence of the catalyst, no formation of the desired product was observed (entry 17, Table 1). Finally, optimized reaction conditions were achieved using *N*,*N*-dimethyl formamide dimethyl acetal (**1**, 0.5 mmol) and phenylacetylene (**2a**, 1.5 mmol) in presence of 10 mol% of CuO nano in 3 mL of 1,2-DCE solvent under reflux for 10 h (entry 2, Table 1) in ambient air.

Table 1 Optimization of the reaction conditions[a]

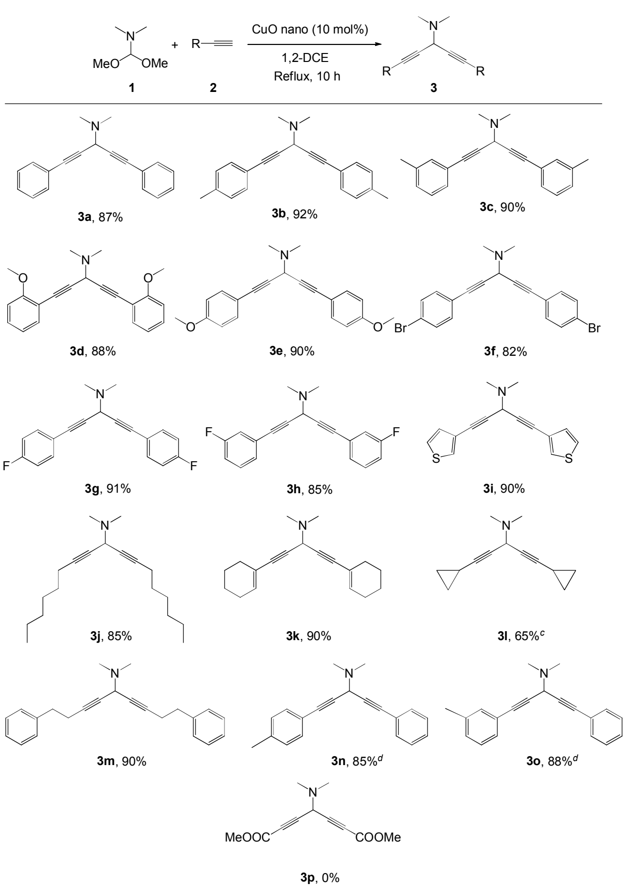


Entry	Catalyst (mol%)	Solvent (3 mL)	Temp. (°C)	Yield[b] (%)
1	CuO nano (5)	1,2-DCE	reflux	68
2	CuO nano (10)	1,2-DCE	reflux	87
3	CuO nano (2)	1,2-DCE	reflux	52
4	CuO nano (10)	MeCN	reflux	-
5	CuO nano (10)	THF	reflux	25
6	CuO nano (10)	EtOH	reflux	-
7	CuO nano (10)	PEG-400	90	-
8	CuO nano (10)	DMF	90	-
9	CuO nano (10)	DMSO	90	-
10	CuO nano (10)	Toluene	90	20
11	In_2O_3 nano (10)	1,2-DCE	reflux	20
12	ZnO nano (10)	1,2-DCE	reflux	15
13	NiO nano (10)	1,2-DCE	reflux	12
14	CuBr (10)	1,2-DCE	reflux	38
15	CuO powder (10)	1,2-DCE	reflux	<10
16	Cu_2O powder (10)	1,2-DCE	reflux	<10
17	-	1,2-DCE	reflux	-

[a] Reaction conditions: 0.5 mmol of **1** and 1.5 mmol of **2a** in presence of catalyst in solvent (3 mL) under heating in air for 10 h; [b] Isolated yields.

Under the optimized reaction conditions, the scope and limitations of the present protocol were investigated with a variety of terminal alkynes, which are summarized in Table 2. Various phenylacetylenes containing different substituents on phenyl moiety such as –Me (**3b**, **3c**), –OMe (**3d**, **3e**), -Br (**3f**) –F (**3g**), led to the corresponding products in good to excellent yields. *Ortho* substituted phenylacetylene (**3d**) furnished the desired product in good yield. Heteroaryl alkyne like 3-ethynyl thiophene was well tolerated under the present reaction conditions without forming any polymerization (**3i**). Moreover, aliphatic alkyne such as 1-octyne gave the corresponding *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine (**3j**) with excellent yield which also proves the general applicability of this present protocol. Alkenyl phenylacetylene such as 1-ethynylcyclohex-1-ene also reacted effectively under the present optimized conditions (**3k**). Interestingly, It is notable that ethynylcyclopropane also reacted successfully under the present reaction conditions (**3l**). 1-Phenyl-1-propyne smoothly participated in this reaction with 90% yield (**3m**). We are pleased to find that the present protocol is also effective for the synthesis of unsymmetrical 3-amino-1,4-diynes (**3n** and **3o**). However, methyl propiolate did not give the desired 3-amino-1,4-diyne under the present reaction conditions (3p). The presence of electron-withdrawing groups such as 3-nitro and 3-cyano phenylacetylene were also failed to proceed the reaction.

Table 2 Substrate scopes of the reaction^{a,b}



^{a}Reaction conditions: 0.5 mmol of **1** and 1.5 mmol of **2** in presence of 10 mol% CuO nano in 1,2-DCE (3 mL) under reflux in air for 10 h; ^{b}Isolated yields; ^{c}Reaction performed in a sealed vessel under refluxing temperature; ^{d}Reaction conditions: 0.5 mmol of **1**, 0.75 mmol of two different alkynes (**2**) each, 10 mol% CuO nano, 1,2-DCE (3 mL) under reflux in air for 10 h.

Reusability of the catalyst was also studied to make this protocol more effective. After completion of the reaction, DCM (10 mL) was added to the reaction mixture. Then the insoluble CuO nanoparticles were filtered by Teflon membrane (PTFE, 0.2 mm pore size). The CuO nanoparticles were thoroughly washed with the DCM, dried and reused for the next cycle. The catalyst was found to be effective up to fifth cycle giving a conversion of 82% in the case of **3a** (Table 3).

Table 3 Recycling of the CuO nano for synthesizing **3a**^{a}

No of cycles	Yields^b (%)	Time (h)
1	87	10
2	87	10
3	85	10
4	84	12
5	82	12

^{a}Carried out with 0.5 mmol of **1** and 1.5 mmol of **2a** in the presence of 10 mol% CuO nano in 1,2-DCE (3 mL) under reflux. ^{b}Isolated yields.

The morphology of the CuO nano was determined by HRTEM. A comparative study of HRTEM of the fresh catalyst and the recovered catalyst after fourth cycles (Fig. 1) shows that the catalyst does not undergo substantial leaching or agglomeration during the recycling process.

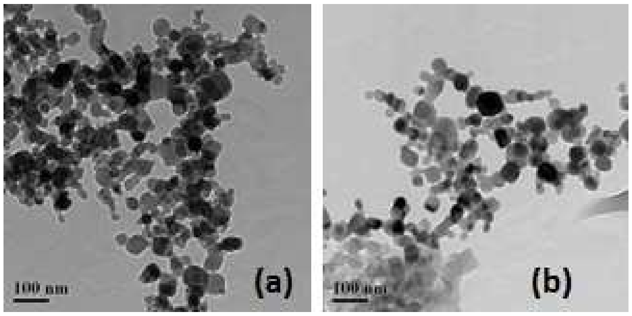
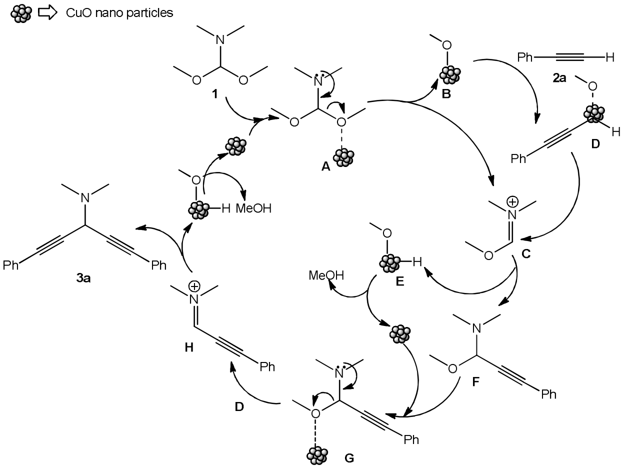


Fig. 1 HRTEM images of (a) fresh CuO nanoparticles and (b) CuO nanoparticles after the fourth cycle.

A plausible mechanism for the formation **3a** is exposed in Scheme 2. Initially, CuO nanoparticles facilitate the elimination of the methoxy group of *N*,*N*-dimethylformamide dimethyl acetal (**1**) through the coordination with oxygen atom to give the iminium type intermediate **C** along with the formation of **B**. Then the **B** reacts with phenyl acetylene (**2a**) to produce the [alkenyl–CuO] cluster **D**. Next the [alkenyl–CuO] cluster **D** attacks the iminium intermediate **C** to afford the intermediates **G** and **E**. The intermediate **G** afforded the final product **3a** through the intermediate **H**. The CuO nanoparticles regenerated from the intermediate **E** by the elimination of MeOH. Due to the greater surface to volume ratio of the CuO nanoparticles in compare to the CuO powder (bulk counterpart), it facilitates the elimination of the acetal part from **1** as well as activates the alkyne with greater effectiveness to form the alkenyl-CuO cluster which consecutively aid the reaction towards product formation.



Scheme 2 Plausible reaction pathway.

Conclusions

In conclusion, copper oxide nanoparticles have been found to be an efficient catalyst for the synthesis of 3-amino-1,4-diynes by the two-component coupling of *N*,*N*-dimethyl formamide dimethyl acetal with various terminal alkynes. The reactions proceed smoothly with high yields without additional external ligand or additive. The catalyst can be reused up to fifth cycle without the loss of significant catalytic activity. The notable advantages of the present method are general applicability to various alkynes including heteroaryl and aliphatic, ligand-free synthesis, operational simplicity, clean reaction, production of no hazardous waste, open air reaction conditions and high yields. We believe that our new protocol using CuO nanoparticles will find widespread applications in academic laboratories as well as in industry.

Acknowledgements

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Notes and references

‡General procedure for the synthesis of 3-amino-1,4-diynes **3**: A mixture of *N*,*N*-dimethyl formamide dimethyl acetal (**1**, 70 μL, 0.5 mmol) and terminal alkyne (**2**, 1.5 mmol) was stirred in presence of commercially available nano CuO (Sigma-Aldrich, nanopowder, <50 nm particle size, 10 mol%) in 3 mL of 1,2-DCE under refluxed conditions for 10 h. After completion of the reaction (TLC), 10 mL of DCM was added to the reaction mixture. Then the insoluble CuO nanoparticles were filtered by Teflon membrane (PTFE, 0.2 mm pore size). The CuO nanoparticles was thoroughly washed with the DCM, dried and reused for the next cycle. Water was added to the filtrate and extracted with DCM (10 mL) followed by washing with brine (5 mL) and dried over Na_2SO_4. The crude residue was obtained after evaporation of the solvent in vacuum and purified by column chromatography on silica gel (60−120 mesh) using petroleum ether/ethyl acetate (9:1) as the eluent to afford the pure product (**3**).

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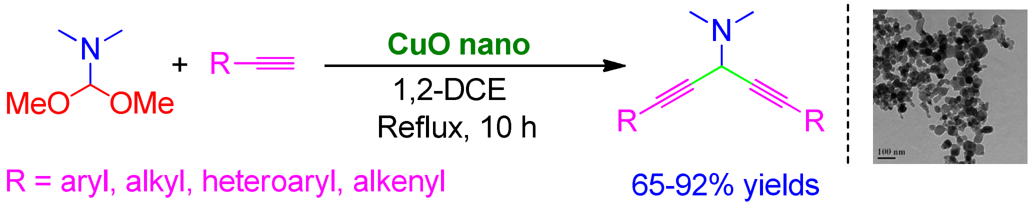
Graphical Abstract

Ligand-free reusable nano copper oxide-catalyzed synthesis of 3-amino-1,4-diynes

Subhajit Mishra, Sougata Santra and Alakananda Hajra*



Broad substrates scope • High yields

Ligand-free synthesis • Reusability of catalyst

Synthesis of 3-amino-1,4-diynes have been developed by the two-component coupling of *N*,*N*-dimethyl formamide dimethyl acetal with terminal alkynes using CuO nano particle as an efficient catalyst under mild reaction conditions.