Green Catalytic Process for Click Synthesis Promoted by Copper Oxide Nanocomposite Supported on Graphene Oxide

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Abstract: The catalytic activity of graphene oxide supported copper oxide (CuO–GO) has been investigated in Click synthesis of 1,2,3-triazole derivatives under green reaction conditions. In the context of green approach, water is used as solvent under ligand free and aerobic conditions at room temperature, with low catalyst loading (0.2 mol%) while ensuring the recovery and reusability of the catalyst. The catalyst affords excellent selectivity in formation of the desired products in good to excellent yields. Further, the work-up procedure adopted here is clean and simple, while recycling the organic solvents that one used for work-up procedure. It is proposed

Introduction

Huisgen 1,3-dipolar cycloaddition of azides and alkynes is the one of the most popular Click reactions.^[1] This non-catalyzed cycloaddition generally requires high temperature or pressure, and involves the formation of a mixture of 1,4- and 1,5-triazoles, which makes it unsuitable for highly functionalized molecules due to harsh conditions and limited selectivity. In 2002, Meldal et al.^[2] and Sharpless et al.^[3] reported the copper(I)-catalyzed azide-alkyne click chemistry (CuAAC) under mild conditions.^[4] Subsequently, it has become a popular strategy for the synthesis of triazoles using commercially available Cu^I salts and Cu^I species, generated in situ from Cu^{II} salts in the presence of sodium ascorbate under homogeneous reactions.^[5] Apart from Cu₂O, Cu and CuO catalysts, Cu^{II} salt, viz. $Cu(OAc)_2$, was used as a catalyst for the cycloaddition of azides and alkynes in the absence of sodium ascorbate.^[6] Nano-sized CuO materials were efficiently used as excellent in the absence of a reducing agent in water.^[7] The main disadvantage of the copper-catalyzed 1,3-dipolar cycloaddition under hothat the functional groups present on the GO surface are effective for preventing the aggregation of the catalytically active copper oxide species during the reaction. Moreover, the excellent performance of CuO–GO nanocomposite is ascribed to the excellent dispersity of the catalyst in water, hydrophilic nature of the GO for the accumulation of organic substrates in water and the "Breslow effect."

Keywords: alkynes; azides; click chemistry; copper oxide nanoparticles; graphene oxide; nano composite

mogeneous conditions is the presence of a significant amount of copper complexes in the end products. To circumvent the problems associated with copper contamination, heterogeneous copper catalysts have been developed for metal-free end products^[8] However, the study of Click chemistry in water medium is of prime importance^[9-14] due to lack of stability and reactivity of the catalyst in water.^[15] Consequently, the development of solid supported copper nanocatalysts is one of the most promising areas of research in recent years.^[16] Indeed, copper nanoparticles are treated as clean and economical catalysts due to their non-toxicity, low-cost, high stability, and environmental friendly nature for Click reaction with the advantage of recyclability and reusability.^[17]

On the other hand, in a way of utilizing the advantages of graphite/graphene based materials as supports for Cu catalysts,^[18] a facile and robust approach has been reported for the Click synthesis promoted by graphene nano sheets supported Cu₂O NPs as recyclable and reusable heterogeneous catalyst.^[19] However, this method requires 2 mol% of the catalyst and extended reaction times (24–48 h) in water–ethanol

solvent system. Subsequently, a reduced graphene oxide/cuprous oxide (RGO/Cu₂O) nanocomposite has been used for the Click reaction in water at elevated temperatures.^[20] Especially, graphene oxide (GO) has extensively been used as a support for catalytically active species for a wide range of organic transformations.^[21-24] GO is a highly oxygenated with hydroxyl and epoxide functional groups on its basal plane, in addition to carbonyl and carboxyl groups located at the sheet edges.^[25] These oxygen functionalities make GO surface highly hydrophilic and can stabilize the dispersion of the GO sheets in water and facilitate the deposition of metal or metal oxide NPs onto the GO surface. Therefore, the development of an improved catalytic process especially for Click synthesis using supported, recoverable heterogeneous catalysts would make it simpler, economically viable and ecofriendly.

Results and Discussion

Herein, we made an attempt to combine the advantages of GO and CuO for Click synthesis of various triazole derivatives under clean, economic and environmentally friendly reaction conditions. CuO–GO nanocomposites are used as recoverable and reusable heterogeneous catalysts with low catalyst loading in water at room temperature. The catalytic potential of CuO–GO nanocomposite was investigated in the model reaction between phenyl azide (1a) and phenylacetylene (2a) to obtain the 1,2,3-trizole product (3a) via Click reaction. To optimize the reaction conditions, various copper salts were screened and the results are presented in Table 1.

The catalytic activity of CuO-GO nanocomposite was investigated in the Click reaction of various

Table 1. Catalyst screening in the formation of **3a**.

Entry	Catalyst ^[a]	Solvent	T (°C)	Yield (%) ^[b]
1	CuNPs (10% w/w)	Et ₃ N	65	70
2	Cu (10 mol%)	Et ₃ N	35	0
3	CuO (10 mol%	Et ₃ N	35	0
4	Cu ₂ O (10 mol%)	Et ₃ N	70	0
5	Graphene Oxide (10% w/w)	H ₂ O	25	0
6	CuSO ₄ ·5H ₂ O (1 equiv)/ N ₂ H ₄ ·H ₂ O (1.2 equiv)	H ₂ O/CH ₃ CN	25	75
7	CuO–GO (0.2% w/w)	H ₂ O	25	83

^[a] Reactions were performed 1 mmol scale using an equimolar ratio of azide–alkyne for 1h.

^[b] Isolated yield.

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azides (1a-s) and alkynes (2a-s) in water at room temperature. To demonstrate the substrate scope, a series of experiments were performed with different substrates such as aryl azides and alkynes. The effect of both electron-withdrawing and electron donating groups were studied and the results are shown in Table 2. As seen in Table 2, the reaction proceeded smoothly with unsubstituted aryl and benzyl azides (Table 2, entries a, e-h) and phenylacetylene (Table 2, entries a, b, e, j, o, q), electron-withdrawing paranitro- and para-bromobenzyl azides (Table 2, entries j-p) and *para*-methoxyphenylacetylene (Table 2, entries c, f, k) and with electron-releasing para-substituted aryl azide (Table 2, entries q-s) and with different alkynes (Table 2, entries d, h, i, s) in an almost similar way. The isolated yields were comparable in the synthesis of 1,2,3-triazoles for various substrates which ranges from 91% to 95% within 10-20 min. The substrates with hydrophilic functional groups gave the product in excellent yields relatively in short reaction time (Table 2) due to their easy solubility in water. The structure of 3g was confirmed by a single crystal X-ray crystallography (Figure 1, supporting information).^[26] The XRD pattern of CuO–GO nanocomposite catalyst is shown in Figure 1. The diffraction peak at $\sim 25^{\circ}$ is attributed to the (002) reflection of the GO structure, the reflection is consistent with the graphene-based composite.^[27] The Bragg reflections in the XRD pattern were observed at 35.9°, 38.2°, 48.3°, 58.2° , 61.4° , and 67.5° correspond to the (-111), (111), (-202), (202), (-113) and (220) planes of a single-phase with a monoclinic structure (JCPDS No. 80-1917), respectively, indicating the successful formation of CuO NPs on GO surface (Figure 1).^[28]

The morphology of CuO–GO nanocomposite catalysts and the deposition of CuO NPs on the surface of GO were characterized using TEM as shown in Figure 2. TEM image of CuO–GO nanocomposite shows well deposition and uniform distribution of CuO NPs on the surface of GO as depicted in Figure 2(a). The particle size of CuO NPs was calculated from TEM and found to be in the range of 15–50 nm.

The high catalytic activity of CuO–GO nanocomposite was explained based on high dispersity of CuO– GO nanocomposite in water followed by interaction of organic substrates with CuO NPs attached to GO



Figure 1. XRD pattern of CuO-GO nanocomposite

$R^{1}-N_{3}$ + = R^{2} $\xrightarrow{CuO-GO}_{H_{2}O, 25 \ ^{\circ}C}$ $\stackrel{R^{1}}{\stackrel{N}{\underset{N}{\longrightarrow}}}_{N}$ R^{2}									
	1	2	3(a–s)						
Entry	R ¹ (1)	R ² (2)	Product (3) ^[a]	Time (min)	Yield (%) ^[b]				
а	C ₆ H ₅	C ₆ H ₅	3a	10	96				
b	1-Cl-2-F-C ₆ H ₃	C_6H_5	3b	20	95				
с	1-Cl-2-F-C ₆ H ₃	p-CH ₃ OC ₆ H ₄	3c	15	92				
d	1-Cl-2-F-C ₆ H ₃	p-C ₂ H ₅ C ₆ H ₄	3d	20	90				
е	$C_6H_5CH_2$	C_6H_5	3e	10	95				
f	$C_6H_5CH_2$	p-CH ₃ OC ₆ H ₄	3f	10	93				
g	$C_6H_5CH_2$	p-C ₂ H ₅ C ₆ H ₄	3g	15	92				
h	$C_6H_5CH_2$	C ₂ H ₄ OH	3h	20	89				
i	$C_6H_5CH_2$	THPO	3 i	15	87				
j	$4-NO_2C_6H_4CH_2$	C ₆ H ₅	Зј	10	94				
k	$4-NO_2C_6H_4CH_2$	p-CH ₃ OC ₆ H ₄	3k	10	92				
T	4-NO ₂ C ₆ H ₄ CH ₂	<i>p</i> -C ₂ H ₅ C ₆ H ₄	31	12	90				
m	4-NO ₂ C ₆ H ₄ CH ₂	C ₂ H ₄ OH	3m	10	87				
n	4-NO ₂ C ₆ H ₄ CH ₂	THPO	3n	15	85				
0	$4-BrC_6H_4$	C_6H_5	30	10	95				
р	4-BrC ₆ H ₄	p-C ₂ H ₅ C ₆ H ₄	3р	12	90				
q	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	3q	15	95				
r	4-CH ₃ OC ₆ H ₄	C ₂ H ₄ OH	3r	10	92				
s	4-CH ₃ OC ₆ H ₄	C ₃ H ₆ OH	3s	12	90				

Table 2. Click synthesis of 1,2,3-triazoles in water using CuO-	-GO.
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^[a] Reactions were performed with phenyl acetylene (0.837 mmol) and aryl azide (0.837 mmol), CuO–GO catalyst (3 mg, 0.227 mol%) and 5 mL of water under air at 25 °C.

^[b] Isolated yield.



Figure 2. TEM images of CuO–GO nanocomposite: Catalyst before use (a) and after three catalytic cycles (b)

hydrophilic support. The high yields of required product are not only attributed to the hydrophilic GO surface but also to the "Breslow effect" that is, influence of water solvent.^[29,30] During the reaction in water, the hydrophilic nature of GO surface will allow the phenyl acetylene and aryl azide to interact each other on the surface of GO thereby increasing the yields of 1,2,3-triazoles. GO support enhance the mass transfer of organic precursors during the reaction resulting in high catalytic activity of CuO–GO nanocomposite catalyst.

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Figure 3. Reusability of CuO–GO nanocomposite in the formation of 3a

It is verified that the CuO–GO nanocomposite is recyclable for Click reaction between phenylacetylene and phenyl azide. Reusability of the catalyst can be explained by the stabilization of the catalytically active CuO NPs species on the GO surface upon completion of the reaction. Significantly, this catalyst system can be reused at least five times with retention of its catalytic performance as showed in Figure 3. A slight decrease in activity was observed over five successive runs is due to partial leaching of CuO active species into water during the reaction. AAS analysis of the reused catalyst showed that there was 1.9 wt % loss of CuO in the used catalyst after three cycles compared to the fresh catalyst. The reaction requires long reaction time when recycled catalyst was used.

In order to investigate the stability of CuO NPs on GO surface after catalytic tests in the Click reaction between phenyl acetylene and phenyl azide, CuO-GO nanocomposite was characterized using TEM after three cycles. TEM image of used CuO-GO catalyst is shown in Figure 2(b). As shown in Figure 2(b), the CuO NPs in the used catalyst still possess a smaller size, uniform shape with better dispersion of CuO NPs, and keep the well sheet like structure of GO after catalytic tests. From TEM analysis, it was observed that the CuO NPs of used CuO-GO catalyst is almost unchanged size and well dispersed on GO surface even after extended recycling experiments.

Conclusions

In summary CuO–GO nanocomposite catalyst has proved to be highly efficient for the Click reaction of variety of phenyl acetylenes and aryl azides. The reactions are faster and 1,2,3-triazoles are isolated directly from the reaction flask without any further purification by column chromatography. Sustainable reaction conditions are developed for the Click synthesis of 1,2,3-triazole derivatives using water as a solvent. Further, the reactions are carried out under ligand free and aerobic conditions at room temperature using low catalyst loading. Further, the catalysts are recycled and its catalytic activity is retained for up to five cycles.

Experimental Section

Preparation CuO-GO nanocomposite

CuO–GO nanocomposite was prepared according to the previously reported method.^[31] In brief, 50 mg of GO was dispersed in 50 mL of isopropyl alcohol to afford a black dispersion by sonicating for 30 min. Then, 0.14 g of Cu(OA-c)₂·H₂O was mixed to homogeneous GO. The brown dispersion was heated to ~83 °C under vigorous stirring for 30 min. Then, 5 mL of deionized (DI) water was rapidly added into the above boiling solution and the reaction mixture was further heated at 83 °C for 30 min. During this process, the initial brown color of the dispersion gradually turned to black. Then the reaction mixture was cooled to room temperature. Thus synthesized composite was centrifuged and then washed with ethanol several times and dried at 70 °C in air overnight. 5 wt % of Cu catalyst was found in the CuO–GO nanocomposite by AAS analysis.

Click reaction

CuO–GO catalyst (3 mg, 0.227 mol% vs. phenyl acetylene) was added to the reaction vessel with 5 mL of water, sonicated for 5 min to afford the black suspension. Then phenyl acetylene (0.837 mmol) and aryl azide (0.837 mmol) were mixed with catalyst suspension. The resulting mixture was stirred at 25 °C for required time and the reaction was monitored by thin layer chromatography (TLC). The mixture was filtered by rinsing with ethyl acetate (5 mL × 2). The combined organic layers were separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the desired product as confirmed by ¹H, ¹³C NMR and HR-MS. Purity of the product was confirmed by ¹H NMR.

Reusability study of the CuO-GO composite catalysts

After completion of the first cycle as described above, the CuO–GO nanocomposite catalysts was recovered by filtration over a Teflon membrane (PTFE, 0.2 mm pore size) and used again in the next cycle, after thorough washing with ethyl acetate followed by water and acetone and subsequently dried at 60 °C.

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