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Original article

Magnetically recyclable copper modified GO/Fe_3O_4 catalyst for efficient synthesis of quinazolinones

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A R T I C L E I N F O

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A B S T R A C T

A series of bioactive quinazolinones were effectively synthesized by the condensation of halide benzamide with amino acid using magnetically recyclable GO/Fe_3O_4–CuI as catalyst. Magnetic GO/Fe_3O_4–CuI was prepared via a simple chemical method and characterized by FTIR, powder XRD, and SEM. This heterogeneous copper catalyst can be easily separated from reaction mixtures by an external permanent magnet and reused without any obvious loss in activity which shows its applicability as a reusable and promising catalyst for quinazolinones synthesis.

1. Introduction

Recently, there has been growing interest in transition metal-catalyzed C–N and C–C bond forming processes [1]. In particular, the copper-catalyzed Ullmann-type *N*-arylations have received enormous attention and have been widely used to prepare quinazolinones derivatives [2], whose subunits are extensively used in medicinal chemistry as a pharmacophore [3], with applications such as hypnotic, sedative, analgesic, antibacterial, and antitumor agents [4], or to modify known bioactive molecules and to potentiate their biological activities [5].

Generally, copper salts have been used as homogeneous catalyst systems to catalyze synthesis of quinazolinone~~s~~ derivatives from ortho-amino- or-nitrobenzoic acid derivatives, aryl halides [6]. Although homogeneous copper catalysts have many advantages, such as high turnover number, good activity, and good selectivity [7], they are difficult to separate from reaction mixtures and reuse. Furthermore, the residual copper metal along with the final products may cause serious problems in the synthesis of pharmaceuticals [8]. In light of these problems, various catalysts supports have been explored, such as polymers [9], zeolite [10] and mesoporous particles [11] that can be efficiently reused while keeping the inherent activity of the catalytic center. In recent years, magnetic nanoparticles supported on various materials for recovery have provided new ways to develop recyclable catalyst [12].

It is well known that graphene oxide (GO), one of the most important derivatives of graphene, has a unique planar structure[13], huge surface area (2630 $m^2 g^{-1}$) [14], and a variety of oxygen-containing functional groups [15], which renders it a good candidate for supporting other functional materials. What's more, the acidic and oxidative nature of these oxygen functionalities allow it to function as a solid acid catalyst or green oxidant [16].

In this study, we prepared a magnetically recyclable heterogeneous catalyst GO/Fe_3O_4–CuI for the synthesis of quinazolinones by the condensation of halide benzamide with amino acid, which is rarely reported [17]. The catalyst gave the desired products in good yields and could be reused several times without any loss of its catalytic activity, which showed its applicability as a reusable and promising catalyst for quinazolinones synthesis.

2. Experimental

2.1. Sample preparation procedures

GO was synthesized by natural graphite powder oxidation according to the Hummers method [18]. GO (200 mg) was dispersed in 60 mL of 1-methyl-2-pyrrolidone with ultrasonication for 1 h [19], and the mixture was heated to 190 °C under nitrogen atmosphere (Scheme 1). Fe(acac)$_3$ (1.413 g) was dissolved

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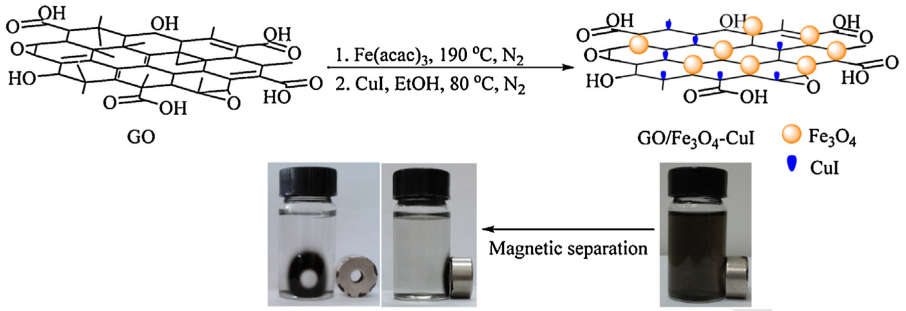

Scheme 1. Preparation of GO/Fe_3O_4–CuI catalyst and magnetic separation of GO/Fe_3O_4–CuI catalyst from water.

in 40 mL of 1-methyl-2-pyrrolidone and then dropped into the GO solution under stirring for 2 h. After the reaction finished and cooled to room temperature, the precipitate was separated by magnet and dispersed in ethanol. Finally, the resulting black powder was washed several times with acetone and vacuum dried at 45 °C overnight.

The obtained GO/Fe_3O_4 (0.50 g) and CuI (0.25 g) were dispersed in 50 mL ethanol under nitrogen atmosphere (Scheme 1). Then the mixture was stirred at 80 °C overnight. The GO/Fe_3O_4–CuI powder was retrieved by an external permanent magnet, and washed with deionized water and ethanol. Finally, the GO/Fe_3O_4–CuI powder was dried under vacuum at 45 °C overnight for further use. The prepared GO/Fe_3O_4–CuI was characterized by FTIR, powder XRD, and SEM. The doped concentration of CuI was detected by ICP–AES.

2.2. Typical procedure for the condensation synthesis of quinazolinones

2-Iodobenzamide **1a** (1.0 equiv.), 2-aminoisovaleric acid **2a** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.) and GO/Fe_3O_4–CuI (Cu^+ 0.03 equiv.) were added to DMSO/ethylene glycol (60:1, v/v) in a round bottom flask. The reaction was monitored by TLC. The product was purified by column chromatography with petroleum ether/ethyl acetate (3:1, v/v) to give pure white solid **3a**. Other products were synthesized through the same procedure and characterized by ^1H NMR and ^{13}C NMR. Their molecular masses were determined by HRMS.

3. Results and discussion

Fourier-transform infrared spectroscopy (FTIR) spectra of GO, GO/Fe_3O_4, and GO/Fe_3O_4–CuI are presented in Fig. 1. Characteristic peaks of GO/Fe_3O_4–CuI are basically the same with GO and GO/Fe_3O_4. The FTIR pattern of GO shows the presence of the oxygen-containing functional groups. The peaks at 3370 cm^{-1}, 1730 cm^{-1} are the results of the stretching of O–H, C=O in COOH. The band at 1622 cm^{-1}, 1230 cm^{-1}, and 1056 cm^{-1} can be assigned to aromatic C=C, carboxy C–O, and alkoxy C–O stretches [20], respectively. The FTIR spectra of GO/Fe_3O_4–CuI and GO/Fe_3O_4 differ from that of GO as evidenced by the new band at 580 cm^{-1} [21]. The peak at 1730 cm^{-1} disappeared in the FTIR pattern of GO/Fe_3O_4–CuI and the new peaks that emerged from 800 cm^{-1} to 1000 cm^{-1} are attributed to the formation of –COO$^-$ after the complex reaction with CuI.

Fig. 2 shows the XRD pattern of GO/Fe_3O_4–CuI. The main peaks at 25.4°, 41.6°, and 49.2°, marked by their indices (1 1 1), (2 2 0), and (3 1 1) [22], show the characteristics of CuI on GO/Fe_3O_4. Besides these, no significantly different peaks are observed among the diffraction patterns of GO, GO/Fe_3O_4 and GO/Fe_3O_4–CuI, which indicates that the CuI was finely attached on GO/Fe_3O_4.

SEM observation was also undertaken to characterize the morphologies of the GO/Fe_3O_4 and GO/Fe_3O_4–CuI composites. As is shown in Fig. 3a, GO/Fe_3O_4 sheets show the sheet-like structure with smooth surfaces and wrinkled edges. GO/Fe_3O_4–CuI sheets present similar morphology with the parent GO/Fe_3O_4. CuI composites are uniformly distributed on the surface of GO/Fe_3O_4–CuI sheets. ICP–AES detected the CuI doped concentration is up to 10.1 wt% which implies CuI successfully doped on the GO/Fe_3O_4 sheets.

To demonstrate its activity for the synthesis of quinazolinones derivatives, the reaction of 2-iodobenzamide **1a** and 2-aminoisovaleric acid **1b** was used as a model reaction catalyzed by magnetic GO/Fe_3O_4–CuI. Clearly, the results in Table 1 show that the reaction could be catalyzed by several copper salts. While with the amount of copper was 0.03 equivalent immobilized on GO/Fe_3O_4, the reaction went smoothly with a respective high productivity (compare entries 2–8, Table 1). To further obtain the optimal

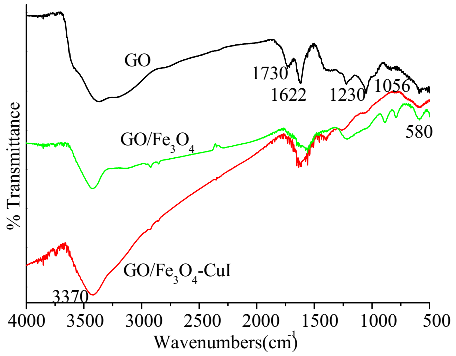

Fig. 1. IR spectra of GO, GO/Fe_3O_4 and GO/Fe_3O_4–CuI.

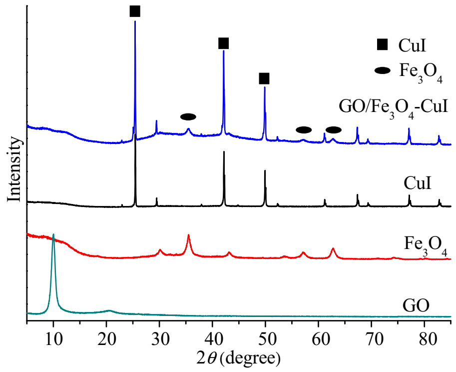

Fig. 2. XRD patterns of GO, Fe_3O_4, CuI and GO/Fe_3O_4–CuI.

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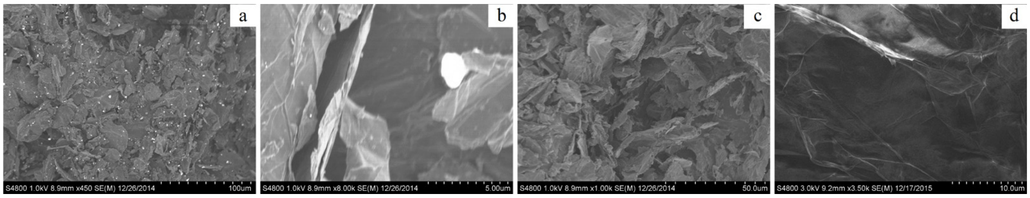
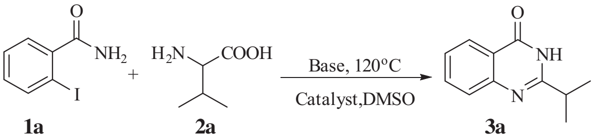


Fig. 3. SEM images of GO/Fe_3O_4–CuI ((a) and (b)), GO/Fe_3O_4 (c) and GO (d).

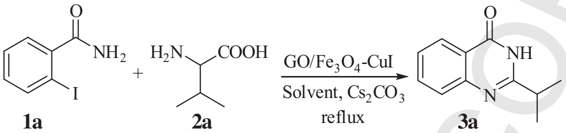
Table 1
Effect of different catalyst and base on the synthesis of 2-isopropylquinazolin-4(3*H*)-one (**3a**)[a].



Entry	Catalyst	Base	Yield (%)[d]	Cu (mol%)
1	/	K_2CO_3	0	/
2	CuBr	K_2CO_3	15	3.0
3	CuI	K_2CO_3	20	3.0
4	CuCl	K_2CO_3	trace	3.0
5	$CuCl_2$	K_2CO_3	trace	3.0
6	GO	K_2CO_3	5	/
7	GO/Fe_3O_4	K_2CO_3	7	/
8	GO/CuI	K_2CO_3	25	3.0
9	GO/Fe_3O_4–CuI	K_2CO_3	27	3.0
10	GO/Fe_3O_4–CuI	Cs_2CO_3	30	3.0
11	GO/Fe_3O_4–CuI	Na_2CO_3	15	3.0
12	GO/Fe_3O_4–CuI	*t*-BuOK	0	3.0
13	GO/Fe_3O_4–CuI	Cs_2CO_3	42[b]	3.0
14	GO/Fe_3O_4–CuI	Cs_2CO_3	48[b,c]	3.0

[a] 2-Iodobenzamide **1a** (1.0 equiv.), 2-aminoisovaleric acid **2a** (2.0 equiv.), K_2CO_3 (2.0 equiv.), catalyst (Cu^+ 0.03 equiv.), DMSO (3.0 mL), 120 °C.
[b] Cs_2CO_3 (3.0 equiv.).
[c] 2-Aminoisovaleric acid **2a** (3.0 equiv.).
[d] Isolate yield.

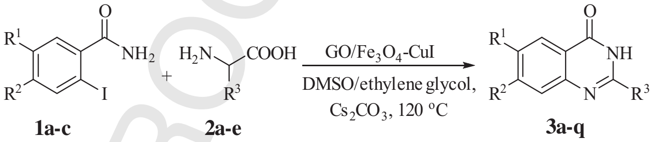
Table 2
Optimization of solvent on the synthesis of 2-isopropylquinazolin-4(3*H*)-one (**3a**) in the presence of GO/Fe_3O_4–CuI as catalyst[a].



Entry	Solvent (v/v)	Yield (%)[d]
1	DMSO	48
2	DMF	37
3	NMP	20
4	ethylene glycol	0
5	DMSO/ethanol (60:1)	56
6	DMSO/isopropanol (60:1)	49
7	DMSO/*t*-butanol (60:1)	52
8	DMSO/*t*-pentyl alcohol (60:1)	57
9	DMSO/ethylene glycol (60:1)	72
10	DMSO/ethylene glycol (50:1)	52
11	DMSO/ethylene glycol (70:1)	56
12	DMSO/ethylene glycol (60:1)	60[b]
13	DMSO/ethylene glycol (60:1)	62[c]

[a] 2-Iodobenzamide **1a** (1.0 equiv.), 2-aminoisovaleric acid **2a** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.), catalyst (Cu^+ 0.03 equiv.), solvent (3.0 mL).
[b] Catalyst (Cu^+ 0.024 equiv.).
[c] Catalyst (Cu^+ 0.039 equiv.).
[d] Isolate yield.

Table 3
Scope of 2-iodobenzamide and amino acid in synthesis of quinazolinone derivatives[a].



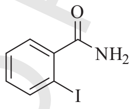
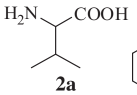
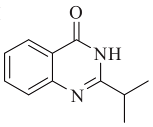
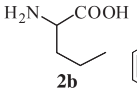
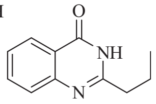
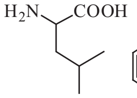
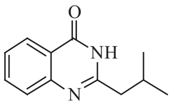
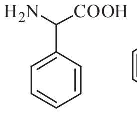
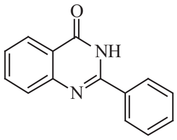
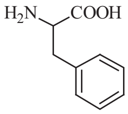
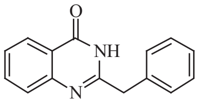
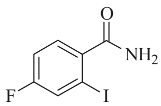
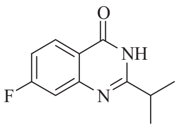
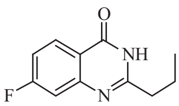
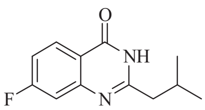
Entry	1	2	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	72
2	**1a**	 **2b**	 **3b**	74
3	**1a**	 **2c**	 **3c**	90
4	**1a**	 **2d**	 **3d**	61
5	**1a**	 **2e**	 **3e**	66
6	 **1b**	**2a**	 **3f**	79
7	**1b**	**2b**	 **3g**	58
8	**1b**	**2c**	 **3h**	86

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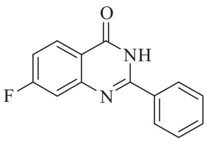
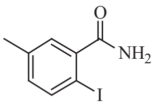
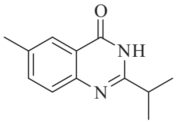
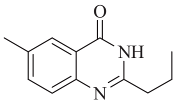
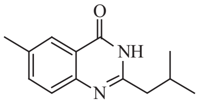
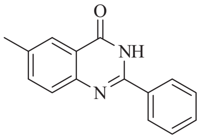
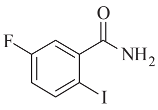
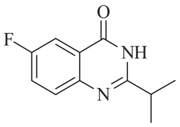
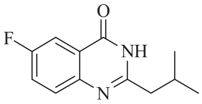
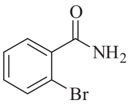
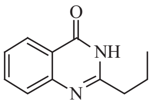
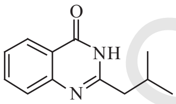
Table 3 (*Continued*)

Entry	1	2	Product	Yield (%)[b]
9	**1b**	**2d**	 **3i**	84
10	 **1c**	**2a**	 **3j**	40
11	**1c**	**2b**	 **3k**	53
12	**1c**	**2c**	 **3l**	49
13	**1c**	**2d**	 **3m**	49
14	 **1d**	**2a**	 **3n**	41
15	**1d**	**2c**	 **3o**	43
16	 **1e**	**2b**	 **3b**	58
17	**1e**	**2c**	 **3c**	69

[a] 2-Iodobenzamide **1a** (1.0 equiv.), 2-aminoisovaleric acid **2a** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.), catalyst (Cu^+ 0.03 equiv.), 3.0 mL DMSO/ethylene glycol (60:1, v/v), 120 °C.
[b] Isolate yield.

conditions, different copper content, various bases and solvent were screened. The results revealed that the yield was up to 72% with the moderate addition of DMSO/ethylene glycol (60:1, v/v) and Cs_2CO_3 (3.0 equiv.) as base at 120 °C (Table 2, entry 9).

The scope of GO/Fe_3O_4–CuI-catalyzed cascade reactions of halide benzamideand with amino acids was investigated under the optimized conditions: GO/Fe_3O_4–CuI (Cu^+ 0.03 equiv.) as the catalyst, 3 equiv. of Cs_2CO_3 as the base, DMSO/ethylene glycol (60:1, v/v) as the solvent at 120 °C. All the examined substrates provided moderate to excellent yields (Table 3). Importantly, the catalyst recycled by permanent magnet retained their catalytic activity for the synthesis of 2-isopropylquinazolin-4(3*H*)-one (**3a**) under the same reaction conditions, with the corresponding yields not significantly reduced (Table 4).

Table 4
Reuse the catalyst for the synthesis of **3a**[a].

Entry	2-aminoisovalericacid (mmol)	Catalyst (mg)	Yield (%)[b]
Fresh	0.60	40	72
1st turn	0.52	35	73
2nd turn	0.45	30	70
3rd turn	0.42	28	75
4th turn	0.30	20	73

[a] 2-Iodobenzamide **1a** (1.0 equiv.), 2-aminoisovaleric acid **2a** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.), catalyst (Cu^+ 0.03 equiv.), 3.0 mL DMSO/ethylene glycol (60:1, v/v), 120 °C.
[b] Isolate yield.

4. Conclusion

In summary, we have successfully prepared the magnetically recyclable heterogeneous catalyst GO/Fe_3O_4–CuI, which exhibited high catalytic activity for the synthesis of quinazolinones derivatives by the condensation of halide benzamide with amino acid. Due to its unique planar structure, huge surface area, magnetism, and chemicals features, the catalyst shows high catalytic efficiency, magnetically recoverability, and reusability, such that it can be used several times to give desired products without any obvious loss of ~~its~~ catalytic activity. The magnetically recyclable catalyst GO/Fe_3O_4–CuI shows its applicability as a reusable and promising catalyst for quinazolinones synthesis.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.01.055.

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