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Article

Synthesis of Dihydroquinazolinone Derivatives Using Fe_3O_4@GO as an Efficient and Reusable Composite Nanocatalyst

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Abstract: Metal nanoparticles, due to their unusual properties especially the high surface-to-volume ratio than bulk metal has recently become the focus of intense work. Physical and chemical properties of the particles differ considerably differ from those of the compact solids. On the other hand quinazolinone derivatives are fused organic aza-heterocyclic compounds which have attracted considerable attention, because they exhibits a wide range of biological properties such as anti-cancer, anti-inflammatory, anti-convulsant and anti-hypertensive activities. In view of the biological importance of quinazoline and its derivatives, several synthetic strategies have been employed including the reactions of anthranilamide with aldehyde derivatives using acids catalyst. In this research, we have used composite metal-graphene-based nanocatalyst to produce different derivatives of dihydroquinazolines in mild reaction conditions and with easy, simple and economical work-up procedure in good-to-high yields. Also the catalysts could be recycled and reused several times without considerable reduction in its activity.

Keywords: Nanocatalyst, Fe_3O_4, Graphene oxide, Dihydroquinazoline.

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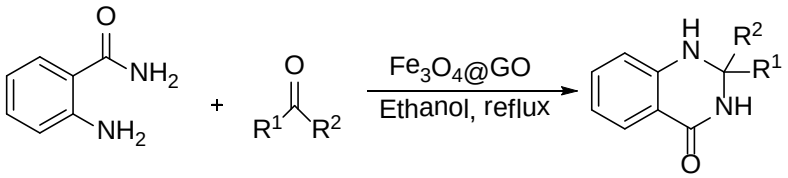
1. Introduction

In recent years, metal nanoparticles as heterogeneous catalysts have attracted a great deal attention in recent years because of their interesting structure and high catalytic activities. On the other hand, 2,3-dihydroquinazolinones are a class of heterocycles that attracted much attention because they have been reported to possess a wide range of pharmaceutical activities. These compounds can easily be oxidized to theirquinazolin-4(3H)-one analogue, which also include important pharmacologically and biological active; such as antifertility [1], antibacterial [2], antiviral, antitumor and antifungal. Many of the reported methods for synthesis of quinazolin-4(3H)-one analogues involves the condensation reaction of anthranilamide with aldehyde or ketone using acids as a catalyst such as $TiCl_4$–Zn [3] $Sc(OTf)_3$ [4], NH_4Cl [5], HCl [6], p-TSA [7], SmI_2 [8], DDQ [9], $CuCl_2$ [10], MnO_2 [11], I/KI [12], Yb(OTf) [13] and or solvent as oxidant [14].

Herein, we wish to report the application of composite metal-graphene-based nanocatalyst in direct synthesis of quinazolin-4(3H)-one derivatives from anthranilamide using aldehyde or ketone in ethanol under reflux conditions (Scheme 1).

Scheme 1. Synthesis of quinazolin-4(3H)-one derivatives.



2. Results and discussions

First, to optimize the reaction conditions, we carried out the reaction of 2-aminobenzamide (1 mmol) and aldehyde or ketone derivatives (1 mmol) as a model reaction in the presence of different organic solvents (Table 1). The results showed that ethanol was the solvent of choice. The effect of catalyst amount on reaction yield was determined, too (Table 2). A significant improvement was observed and the yield of the2-(3-nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone was enhanced to 60% after stirring the reaction mixture for 1/5 h. The best outcome, in terms of yield and the reaction time was obtained with 60 mg/mmol of graphene-supported metal nanocomposite.

Table 1. Optimization of the solvent for the Synthesis of 2-(3-nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone.[a]

Entry	Solvent	Time (h)	Isolated yield (%)
1	H_2O	4	50
2	CH_3CN	4	40
3	ETOH	1/5	80

4	ETOH/H_2O	1/5	60

[a] Conditions: 1 mmol 3-nitrobenzaldehyde, 1 mmol anthranilamide, 3 mL solvent.

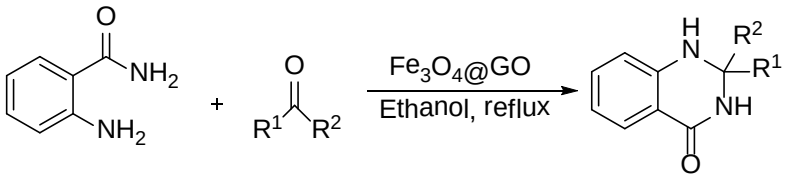
Table 2. Optimization of the catalyst amount for the Synthesis of 2-(3-nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone. [a]

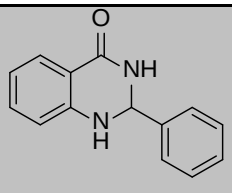
Entry	Catalyst amount (g)	Time (h)	Isolated yield (%)
1	0	5	20
2	0.02	1.5	40
3	0.04	1.5	60
4	0.06	1.5	80
5	0.08	1.5	75

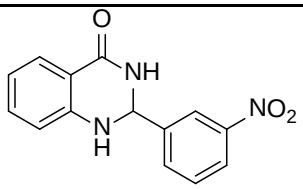
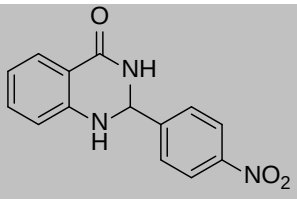
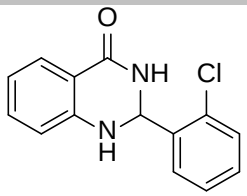
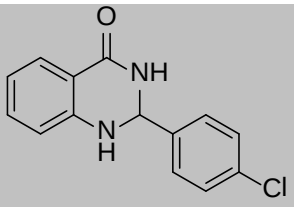
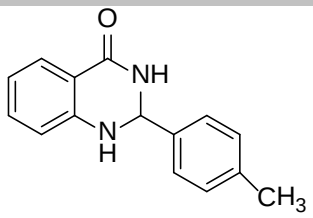
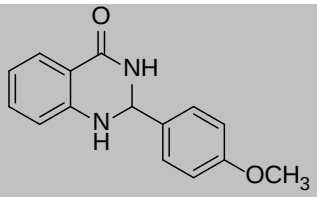
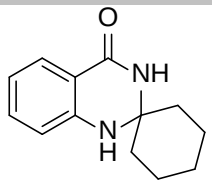
[a] Conditions: 1 mmol 3-nitrobenzaldehyde, 1 mmol anthranilamide, 3 mL ethanol, catalyst: graphene-supported Fe_3O_4 nanocomposite

The scope and generality of synthesis of dihydroquinazolinone derivatives are well showed with structurally diverse aldehydes or ketone. The results are summarized in Table 3.

Table 3. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones in the presence of Fe_3O_4@GO.



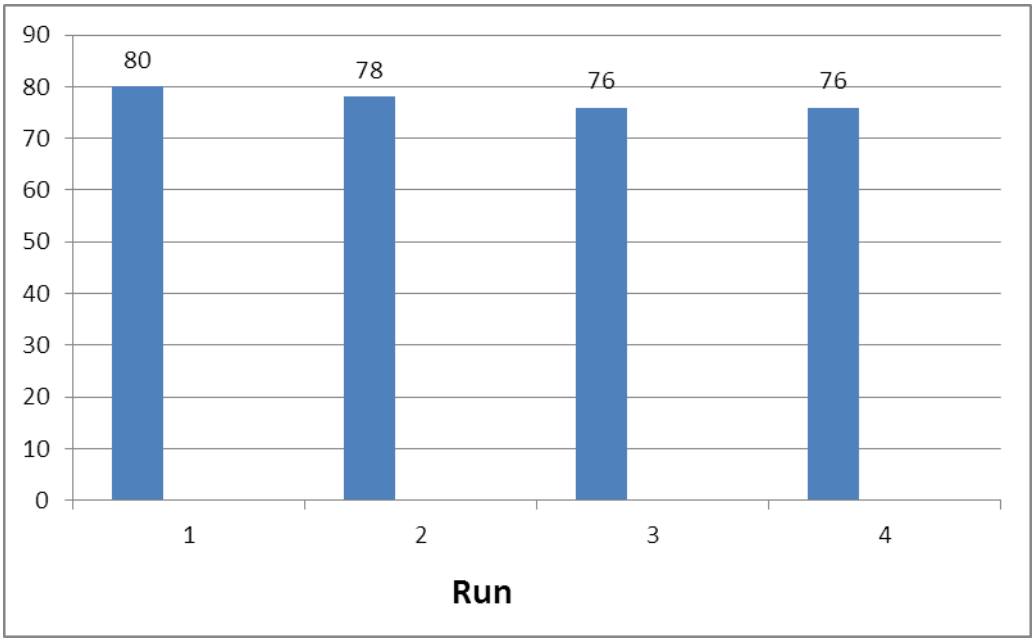
Entry	R^1/R^2	Product	Time (h)	Yield[b] (%)	MP (°C)	
					Found	Reported
1	Benzaldehyde		2/5	75	217-220	218–220[16]

2	3-Nitro benzaldehyde		1/5	80	199-200	190-192[17]
3	4-Nitro benzaldehyde		3	77	198-201	198-200[17]
4	2-Cl benzaldehyde		3/5	80	205-208	203-205[17]
5	4-Cl benzaldehyde		3	78	202-204	205–206[18]
6	4-Methyl benzaldehyde		4/5	72	228-231	233–234[16]
7	4-Methoxy benzaldehyde		5	70	192-193	192-193[16]
8	Cyclohexanone		3	72	218-220	217–219[19]

[b] Isolated yield.

Fig. 2 shows the reusability of the catalyst for the preparation of 2-(3-nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone. The model reaction was carried out under the optimized conditions. After completion of the reaction, the catalyst was extracted by magnetite and washed with acetone. Then used as such for subsequent runs (four times) under the same conditions without significant loss of its catalytic activity.

Figure 2. Recyclability of the nanocatalyst.



3. Experimental

3.1. Materials and methods

All chemicals were purchased from Merck, Fluka and Sigma-Aldrich companies and were used without further purification. All reactions and the purity of quinazoline derivatives were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate and *n*-hexane as eluents. Melting points were determined in open capillaries using an Electro thermal 9100 instrument. IR spectra were recorded on a Shimadzu FT-IR400s. ^{1}H NMR spectra were recorded on an Avance Bruker DRX-250MHz.

3.2. Synthesis of Fe_3O_4@GO

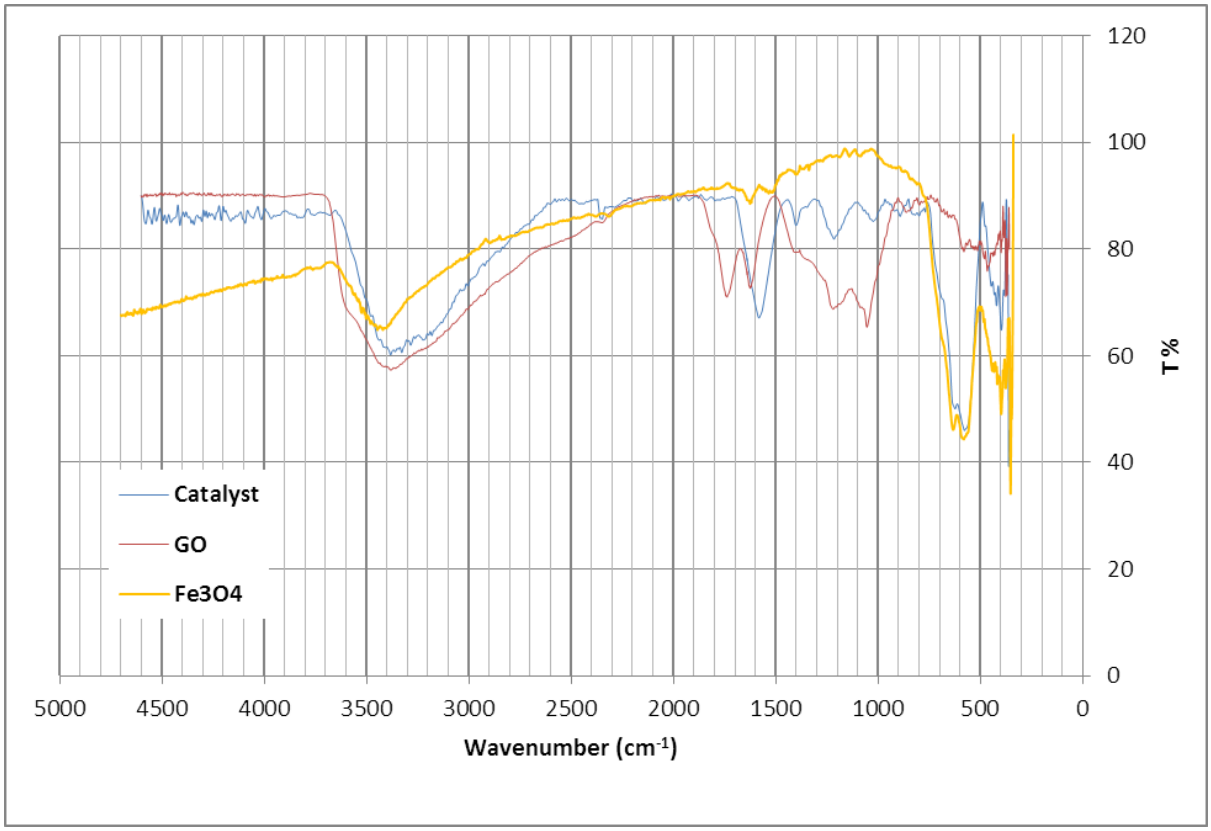
The sample of Fe_3O_4/GO was prepared as follows: 0.50 g GO was added in to a 100 mL flask H_2O of 1.56 g $FeCl_3.6H_2O$ and 0.58 g $FeCl_2.4H_2O$ under the protection of nitrogen condition for 0.05 h at 90 ^{0}C. Then the ammonia solution was added to adjust the pH to 10. The mixture was stirred at 90 ^{0}C for 2 h and then cooled to room temperature. Finally, Fe_3O_4@GO composite was separated

from the mixture using a permanent magnet, and rinsed with distilled water until the pH of solution reduced to 7.0, and then dried in vacuum oven at 70 ^{0}C for 12 h.

3.3. Characterization of the catalyst

The phase structure of the sample was obtained through X-ray diffraction (XRD) measurement. The diffraction peaks at 2θ = 30.39, 36.64, 43.66, 53.40, 57.40 specified [15]. The FT-IR spectra of GO and Fe_3O_4 and the Fe_3O_4@GO composite are shown in Fig. 1. The peak at 1090, 1380 and 1716 cm^{-1} corresponds to the C–O stretching vibration. The peak at 1618 cm^{-1} can be assigned to the aromatic skeletal C=C stretching vibration and the peak at 580 cm^{-1} correspond to the of Fe–O stretching.

Figure 1. The FT-IR spectra of GO, Fe_3O_4, Fe_3O_4@GO



3.4. General procedure for the synthesis of quinazolin-4(3H)-ones

Fe_3O_4@GO (0.06 g) was added to a solution of 2-aminobenzamide (0.136g, 1 mmol) and benzaldehyde (0.106g, 1 mmol) in 3mL of ethanol under reflux temperature for 2.5 h. After completion of reaction, as indicated by TLC (ethyl acetate/n-hexane 1/2), the catalyst was removed by magnet then washed with acetone and after drying could be ready to use for the next reaction without loss in activity. The crude product was filtered and recrystallized from ethanol to give products in good to high yields.

3.5. Spectral data

2-(4-Nitrophenyl)-2,3-dihydro-4(1H)-quinazolinone: Yellow solid; Mp: 198-200°C; IR (KBr): ν_{max} (cm^{-1}) = 3280, 3186, 2923,1647, 1612, 1521, 1487, 1348. ^{1}HNMR (250 MHz, DMSO): 8.351 (s, 1H, NH-CO), 8.158 (d, 2H, J = 7.7 Hz, ArH), 7.890 (s, 1H, NH), 7.719 (d, 2H, J = 7.7 Hz, ArH), 7.639 (d, 1H, J = 6.7 Hz, ArH) 7.179 (t, 1H, J = 7.5 Hz, ArH), 6.657 (t, 1H, J = 7.7 Hz, ArH), 6.643 (d, 1H, J = 6.5 Hz, ArH), 5.854 (s, 1H, CH).

4. Conclusion

In summary, we have delineated a highly efficient, and green method procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones of anthranilamide with aldehyde or ketone derivatives using Fe_3O_4@GOas catalyst. In other words, the most important feature of described method is use of organic solvent and reusability of the catalyst, increasing yields, reducing reaction time.

Acknowledgements

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Conflicts of Interest

The authors declare no conflict of interest.

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