Received: 22 February 2015

Revised: 22 May 2015

(wileyonlinelibrary.com) DOI 10.1002/aoc.3354

Applied Organometallic

Chemistry

Synthesis and characterization of copper(II) Schiff base complex supported on Fe₃O₄ magnetic nanoparticles: a recyclable catalyst for the one-pot synthesis of 2,3-dihydroquinazolin-4(1H)-ones

Accepted: 16 June 2015

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Fe₃O₄–Schiff base of Cu(II) is found to be a recyclable and heterogeneous catalyst for the rapid and efficient synthesis of various 2,3-dihydroquinazolin-4(1H)-one derivatives from the two-component condensation of 2-aminobenzamide and an aldehyde. This reaction is simple, green and cost-effective. Separation and recycling can also be easily done by magnetic decantation of the Fe₃O₄ nanoparticles with an external magnet. The prepared catalyst was characterized using thermogravimetry, Fourier transform infrared spectroscopy, vibrating sample magnetometry, inductively coupled plasma analysis, X-ray diffraction and scanning electron microscopy. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: magnetic nanoparticle; 2,3-dihydroquinazolin-4(1H)-one; 2-aminobenzamide, Schiff base; copper(II)

Introduction

Nitrogen heterocyclic compounds are produced by the chemical industry and academia for a variety of applications, including those related to biological activities, such as antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant and vasodilating behaviour.^[1] In particular, 2,3-dihydroquinazolin-4(1H)-one derivatives are used as reagents in manufacturing and industry.^[2] Furthermore, the quinazolinone skeleton is frequently found in various natural products. Some examples include the anticancer compound trimetrexate, the sedative methaqualone, the α -adrenergic receptor antagonist doxazosin and the antihypertensive agent ketanserin.^[3] Several strategies for their synthesis have been developed: condensation of anthranilamide with an aldehyde or ketone using p-toluenesulfonic acid as a catalyst;^[4] desulfurization of 2-thioxo-4(3H)-quinazolinones;^[5] reaction of isatoic anhydride with Schiff bases;^[6] and one-step conversion of 2-nitrobenzamides to 2,3dihydro-4(1H)-quinazolinones.^[7]

Recently, magnetic nanoparticles have attracted much attention among the academic and industrial scientific community.^[8–13] Because of the advantages of a larger surface area to volume ratio as well as homogeneity in aqueous solution, biomolecule-coated nanoparticles have shown promising applications in complicated biosystems.^[14,15] Through a combination of the unique optical, electronic or magnetic properties of nanoparticles with various probes, functionalized nanoparticles have become an exploitable field for biosensing and diagnostic applications.^[16] Nanoparticles have attracted significant interest as efficient supports for homogeneous catalyst immobilization.^[17,18] The immobilization of homogeneous catalysts facilitates easy catalyst recovery and recycling, as well as product separation, and is a longstanding pursuit of catalysis science.^[19] When the size of the support material is decreased to the nanometre scale, the activity of nanoparticle-supported catalysts can be significantly improved, compared to homogeneous catalysts immobilized on conventional support matrices.^[20]

Experimental

Materials

Chemicals and solvents used in this work were obtained from Sigma-Aldrich, Fluka or Merck and were used without further purification.

Instrumentation

The particle size and morphology were investigated using a JEOL JEM-2010 scanning electron microscopy (SEM) instrument at an accelerating voltage of 200 kV. Fourier transform infrared (FT-IR) spectra were recorded as KBr pellets with a Bruker VRTEX 70 FT-IR spectrophotometer. Thermogravimetric analysis (TGA) curves were recorded using a PL-STA 1500 device (Thermal Sciences). ¹H NMR and ¹³C NMR spectra were recorded with a Bruker FX 400Q NMR

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spectrometer. The amount of Cu in the catalyst was measured using an inductively coupled plasma (ICP) atomic emission spectrometer (Sare Kelasam, PerkinElmer, Optima 8000). Vibrating sample magnetometry (VSM) measurements were performed using an MDKFD VSM instrument. Magnetization measurements were carried out in an external field of up to 15 kOe at several temperatures. X-ray diffraction (XRD) was conducted using a PW3050/60 goniometer. The generator settings were 40 mA/40 kV with Cu K α radiation of $\lambda = 1.5406$ Å. Continuous scanning was carried out from 10.01° as 2θ start position to 79.95° as 2θ end position, with a step size of 0.02° and step time of 48.19 s.

Preparation of magnetic Fe₃O₄ nanoparticles

A mixture of FeCl₃·6H₂O (5.838 g, 0.022 mol) and FeCl₂·4H₂O (2.147 g, 0.011 mol) was dissolved in 100 ml of deionized water in a threenecked flask (250 ml) at 80°C under nitrogen atmosphere. Subsequently, 10 ml of aqueous NH₃ solution (32%) was added into the mixture within 30 min with vigorous mechanical stirring. The resulting black precipitate was isolated by magnetic decantation, washed with double-distilled water until neutral, further washed twice with ethanol and dried at 80°C in vacuum to afford Fe₃O₄ (2.90 g).

Preparation of Schiff base complex of Cu(II)

The Schiff base was prepared as follows. 3-Aminopropyl(triethoxy)silane (1 mmol, 0.176 g) in ethanol (25 ml) was added to a solution of salicylaldehyde (1 mmol, 0.122 g) in ethanol (5 ml) at room temperature. The colour of the reaction solution changed to yellowish, due to imine formation (conversion was up to 95%, measured using TLC). The resulting Schiff base ligand, as a bright yellow precipitate, was separated by filtration. This yellow-coloured precipitate was collected and washed with ethanol. The precipitate was dried under vacuum at room temperature. The crude product was recrystal-lized from ethanol to afford the pure product.

The Schiff base complex with metal ions was prepared as follows. A solution of the corresponding Schiff base (2 mmol) in ethanol and anhydrous $Cu(NO_3)_2$ (0.178 g, 1 mmol) were mixed at room temperature and left to stand for 4 h under stirring. A colour change from yellow to light green was observed. Then the complex was filtered and was washed with a large excess of ethanol. The greenish blue-coloured precipitate was collected and dried under vacuum at room temperature. Then the product was purified by recrystallization from ethanol, affording the resulting pure Schiff base complex.

Preparation of Fe₃O₄-schiff base of Cu(II)

The supported copper(II) complexes were prepared by adding a suspension of magnetic nanoparticles (2 g) in ethanol (5 ml) to a vigorously stirred Schiff complex of metal ions (1 mmol). The resulting mixture was refluxed for 4 h. The solvent was removed and the resulting solid was dried at 80°C overnight to afford Fe₃O₄–Schiff base complex of Cu(II) (21% was loaded on magnetic nanoparticles, as was determined using TGA). The FT-IR spectrum of the catalyst showed the expected bands, including a distinctive band due to C=N stretching.

General procedure for preparation of 2,3-dihydroquinazolin-4 (1H)-ones

A mixture of 2-aminobenzamide (1 mmol), aldehydes (1 mmol) and Fe_3O_4 -Schiff base complex of Cu(II) (1.5 mol%) was stirred in

ethanol (5 ml) under reflux conditions for the appropriate time, as given in Table 1. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to room temperature. After reaction completion, catalyst was separated using an external magnet and the reaction mixture washed with ethanol. The filtrate was concentrated to dryness, and the crude solid product washed with diethyl ether to afford pure 2,3-dihydroquinazolin-4(1H)-ones in 95–98% yields (Table 1).

Results and discussion

Characterization of Cu(II)–Schiff base complex-functionalized magnetic Fe_3O_4 nanoparticles

The process for the preparation of the Fe_3O_4 -Schiff base of Cu(II) catalyst is depicted in Scheme 1, showing the most probable modes for coordination of Cu to imine-modified magnetic nanoparticles. First, imine is typically prepared by the condensation of primary amine and aldehyde. Then, copper(II) nitrate is added to the resulting imine. Subsequently, the Schiff base complex is reacted with magnetic nanoparticles to obtain Cu(II)–Schiff base complex-functionalized magnetic Fe_3O_4 nanoparticles. The prepared catalyst was characterized using FT-IR spectroscopy, TGA, SEM, VSM, ICP analysis and XRD.

Figure 1(a)-(d) shows the FT-IR spectra obtained for Schiff base ligand, Schiff base complex of Cu(II), Fe₃O₄ nanoparticles and Fe₃O₄-Schiff base of Cu(II), respectively. Figure 1(a), showing the spectrum of the free ligand, exhibits a C=N stretch band at 1633 cm⁻¹, while in the spectrum of the complex, this band shifts to lower frequency and appears at 1624 cm^{-1} due to coordination of the nitrogen with the metal (Fig. 1(b)). A strong absorption at 580 cm⁻¹ is characteristic of the Fe–O stretching vibration, but, for Fe₃O₄ nanoparticles, this appears blue-shifted at 572 cm⁻¹ due to the size reduction. The broad feature at 3000–3500 cm⁻¹ for magnetic nanoparticles corresponds to the -OH stretching of hydroxyl groups. In the spectrum of Fe_3O_4 -Schiff base of Cu(II) (Fig. 1(d)), a band appears at 1620 cm⁻¹ due to imine bond (mainly ascribed to C=N stretching). The absorptions around 1111 and 1001 cm⁻¹ correspond to Si–O stretching vibration. The band observed at about 2854–2922 cm^{-1} can be assigned to the aliphatic C–H group.

Table 1. Synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives ^a							
RCHO + $2NH_2C_6H_4CONH_2$ <u>Reaction Conditions</u> DHQ							
Entry	Aldehyde	Time (min)	Yield (%) ^b	M.p. (°C)			
1	4-CIC ₆ H ₄ CHO	210	95	199–200 ^[3]			
2	4-CH ₃ C ₆ H ₄ CHO	105	99	225–230 ^[21]			
3	4-BrC ₆ H ₄ CHO	165	97	197–200 ^[22]			
4	4-CH ₃ OC ₆ H ₄ CHO	135	99	186–189 ^[21]			
5	3,4-(CH ₃ O) ₂ C ₆ H ₄ CHO	60	99	211–216 ^[3]			
6	C₀H₅CHO	60	99	219–223 ^[3]			
7	4-C ₂ H ₃ OC ₆ H ₄ CHO	180	95	161–165 ^[24]			
8	4-FC ₆ H ₄ CHO	165	98	189–192 ^[22]			
9	3-BrC ₆ H ₄ CHO	150	99	184–185 ^[23]			
10	C ₃ H ₇ CHO	30	94	160-164 ^[24]			

^aReaction conditions: aldehyde (1 mmol), 2-aminobenzamide (1 mmol), catalyst (1.5 mol%) and ethanol solvent (10 ml) at reflux temperature. DHQ, 2,3-dihydroquinazolin-4(1H)-one derivative.
^bIsolated yield.



Scheme 1. Synthesis of Fe₃O₄-Schiff base of Cu(II).



Figure 1. FT-IR spectra of (a) Schiff base ligands [(OH)-salen], (b) Schiff base complex of Cu(II), (c) Fe₃O₄ nanoparticles and (d) Fe₃O₄–Schiff base of Cu(II).

TGA was also performed. The profiles obtained are presented in the supporting information.

SEM images of Fe₃O₄–Cu)II) Schiff base complex at different magnifications are shown in Fig. 2. The Fe₃O₄–Schiff base of Cu)II) exhibits a cluster of aggregated spherical particles with an average size of between 70 and 80 nm in diameter. The surface morphology of the supported Schiff base of Cu)II) is practically identical to that of molecular sieve supports and is composed of relatively wellformed, spherical particles having rather uniform coating of organic layers.^[25]

The magnetic properties of Fe₃O₄–Cu)II) Schiff base complex were characterized using VSM (Fig. 3). The saturation magnetization is 47.0 emu g⁻¹. A slight decrease of the saturation magnetization of Fe₃O₄–Schiff base of Cu(II) is due to the successful grafting of the Schiff base of Cu on the surface of the Fe₃O₄ nanoparticles. It is reported that the saturation magnetization of bare Fe₃O₄ nanoparticles is 69.23 emu g⁻¹.^[26]





Figure 2. SEM images of ${\rm Fe_3O_4-Schiff}$ base of Cu(II) at different magnifications.

Furthermore, ICP optical emission spectral analyses show that Cu(II) is supported on the Fe_3O_4 nanoparticles. The Cu concentration is found to be 5.075% in Fe_3O_4 -Schiff base of Cu(II).

The XRD pattern of Fe₃O₄–Schiff base of Cu(II) is consistent with the patterns of spinel ferrites described in the literature (Fig. 4). The XRD pattern of the synthesized nanoparticles shows six characteristic peaks at $2\theta = 30.4^{\circ}$, 35.7°, 43.3°, 53.7°, 57.3° and 62.9° related to the corresponding indices (220), (311), (400), (422), (511) and (440), respectively.^[27]



Figure 3. Magnetization curve for Fe₃O₄-Schiff base of Cu(II).



Figure 4. XRD pattern Fe₃O₄-Schiff base of Cu(II).

Catalytic studies

In connection with our ongoing work on multi-component condensations,^[21–23,25,28,29,31] we now report a facile, rapid and one-pot two-component combination for the preparation of 2,3-dihydroquinazolin-4(1H)-one derivatives in the presence of Schiff base complex of Cu(II) immobilized on Fe₃O₄ as a heterogeneous, non-toxic,^[30] reusable, inexpensive and easily available catalyst (Scheme 2).

In an initial endeavour, 4-bromobenzaldehyde (1 mmol) and 2-aminobenzamide (1 mmol) were stirred at room temperature in the absence of catalyst under reflux conditions in ethanol. After 24 h, the resulting yield is very poor (Table 2, entry 1). In order to find an appropriate amount of catalyst and optimal temperature, various amounts of catalyst were screened at different temperatures.

In this connection, we investigated the outcome of the reaction with various amounts of $\rm Fe_3O_4-Schiff$ base complex of Cu(II). An



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Table 2. Optimization of amount of Fe_3O_4 -Schiff base of $Cu(II)^a$ nitriles.						
Entry	Catalyst	Time (min)	Yield (%) ^b			
1	No catalyst	600	Trace ^c			
2	Fe ₃ O ₄ –Schiff base of Cu(II) (0.39 mol%)	165	46			
3	Fe ₃ O ₄ -Schiff base of Cu(II) (0.79 mol%)	165	57			
4	Fe ₃ O ₄ –Schiff base of Cu(II) (1.18 mol%)	165	74			
5	Fe ₃ O ₄ –Schiff base of Cu(II) (1.5 mol%)	165	97			
6	Fe ₃ O ₄ –Schiff base of Cu(II) (2.37 mol%)	165	97			
7	Fe ₃ O ₄ nanoparticles (20 mg)	360	Trace			
8	Homogeneous Schiff base of Cu(II) (20 mg)	300	97			
^a Reaction conditions: 4-boromobenzaldehyde (1 mmol), 2- aminobenzamide (1 mmol) and ethanol solvent (10 ml) under reflux conditions. ^b lsolated yield.						
^c Reaction proceeds in the absence of catalyst.						

increase in the quantity of Fe₃O₄–Schiff base complex of Cu(II) from 0.39 to 1.5 mol% enhances the product yield from 46 to 97% (Table 2, entries 2–5). It is evident that the best result is obtained when using of 1.5 mol% of Fe₃O₄–Schiff base complex of Cu(II) (Table 2, entry 5). A greater amount of catalyst has substantially less effect on the yield and time of the reaction (Table 2, entry 6). Most significantly, reactions with unfunctionalized magnetic nanoparticles afford trace amounts of the expected product (Table 2, entry 7), which confirms the role of the Schiff base complex of Cu(II) in the catalysis (Table 2, entry 8).

With this optimized result in hand, we further investigated the best reaction conditions. The reaction conditions were optimized by conducting the reaction at various temperatures, namely room temperature (25°C), 45, 60 and 80°C. It is observed that the yield increases as the reaction temperature increases (Table 3).

The optimized reaction conditions were subsequently applied to the reaction between various aldehydes and 2-aminobenzamide (Table 1). In most cases, the desired 2,3-dihydroquinazolin-4(1H)ones are obtained in high yields. Aromatic aldehydes with electronrich and electron-deficient substituents work well. In a typical procedure, 1 mmol of aldehyde and 1 mmol of 2-aminobenzamide were mixed in ethanol in the presence of 1.5 mol% of Fe₃O₄–Schiff base complex of Cu(II) and the reaction mixture was stirred for 60–210 min. After work-up, the corresponding 2,3-dihydroquinazolin-4(1H)-one is obtained in good yield.

Table 3. Optimization of reaction temperature ^a					
Entry	Temperature (°C)	Yield (%) ^b			
1	25	Trace ^c			
2	45	Trace ^c			
3	60	20			
4	80	96			
^a Reaction conditions: 4-boromobenzaldehyde (1 mmol), 2- aminobenzamide (1 mmol) and ethanol solvent (10 ml) at reflux temperature.					

^blsolated yield.

^cReaction proceeds in the absence of catalyst.



Figure 5. Reuse of the nanocatalyst for the preparation of 2-(3,4-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one.

Reusability of Fe₃O₄-schiff base of Cu(II)

Reusability of Fe_3O_4 -Schiff base complex of Cu(II) was confirmed by performing a series of consecutive experiments. After completion of the reaction, nanoparticles were magnetically separated. The deposited catalyst was washed three to four times with ethanol to ensure the complete removal of any organic residuals. The catalytic system could be reused directly for the next cycle after full extraction. The results shown in Fig. 5 clearly indicate that no loss of activity occurs in five runs. Yields of the product decrease after the seventh reuse of the catalyst.

Conclusions

We have described a successful strategy, an efficient and convenient green synthesis, for the preparation of 2,3-dihydroquinazolin-4(1H)ones, which involves a valuable two-component cyclo condensation reaction of aldehydes and 2-aminobenzamide using an inexpensive, non-toxic and easily available Fe₃O₄–Schiff base of Cu(II) catalyst. The method offers several advantages including high yield of products, a recyclable catalyst and easy experimental work-up. The catalyst can be recovered from the reaction by decantation of the reaction mixture in the presence of an external magnet and can be used in up to seven runs with little loss of activity.

Acknowledgements

The authors thank the research facilities of llam University, llam, lran, for financial support of this research project.

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Supporting information

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