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Synthesis of Bis-Thiazolidinones Using Chitosan-attached Nano-CuFe₂O₄ as an Efficient and Retrievable Heterogeneous Catalyst

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The preparation of bis-thiazolidinones has been achieved by a one-pot condensation reaction of araldehydes, ethylenediamine, and 2-mercaptoacetic acid in the presence of nano-CuFe₂O₄@chito-san under reflux conditions in toluene. The catalyst was characterized by powder X-ray diffraction (XRD), scanning electronic microscopy (SEM), vibrating sample magnetometer (VSM) measurements, thermal gravimetric analysis (TGA), and FT-IR spectroscopy. This method provides several advantages including excellent yields, wide range of products, reusability of the catalyst, and a low amount of the catalyst.

Keywords: Nano-CuFe₂O₄@chitosan; Bis-thiazolidinones; Ethylenediamine; 2-Mercaptoacetic acid; One-pot synthesis.

INTRODUCTION

Thiazolidinones show biological properties such as anticancer,¹ antiviral,² antibacterial,³ antituberculosis,⁴ and anti-AIDS⁵ activities. The preparation of bioactive compounds from readily accessible starting materials using one-pot multicomponent reactions (MCRs) has been attracting significant interest.^{6,7} Recently, reports have appeared on synthesis of bis-thiazolidinones in the presence of the catalysts such as HClO₄-SiO₂,⁸ zeolite,⁹ ChCl (choline chloride)/urea-based ionic liquid,¹⁰ and ZnCl₂.¹¹ Despite the availability of these methods, there remains adequate interest to find new routes for efficient, high-yielding, and mild approaches to achieve such systems. The eco-compatibility and employability of MCRs increase when theMCRs are used in association with a heterogeneous catalyst.¹²⁻¹⁴ Chitosan is a biopolymer that can be used as a green catalyst in many reactions.^{15–17} The presence of both hydroxyl and amino groups in chitosan makes it useful as an efficient catalyst. Ideally, utilizing environmental and green catalysts that can be simply recycled at the end of reactions has obtained significant attention in recent years. Magnetic materials have emerged as a suitable group of heterogeneous catalysts owing to their numerous applications in synthesis and catalysis. The surface of magnetic nanoparticles (MNPs) can be functionalized easily through appropriate surface modifications to enable the loading of a diverse required functionalities.^{18,19} Here we report the synthesis of bis-thiazolidinones by the one-pot pseudo-five-component condensation of araldehydes, ethylenediamine, and 2-mercaptoacetic acid with nano-CuFe₂O₄@chitosan as a reusable and robust heterogeneous catalyst under reflux conditions in toluene (Scheme 1).

RESULTS AND DISCUSSION

In the beginning, $CuFe_2O_4$ NPs were primed using coprecipitation, and oleic acid was used to prevent the agglomeration among the NPs. For preparing the chitosan-CuFe₂O₄ NPs, chitosan was first coated on the surface of the NPs through physical absorption; then glutaraldehyde was used to cross-link the chitosan, and the CuFe₂O₄-chitosan NPs were obtained. A schematic of the formation of the CuFe₂O₄-chitosan NPs is shown in Scheme 2.

The X-ray diffraction (XRD) patterns of nano-CuFe₂O₄@chitosan are shown in Figure 1. The crystallite size diameter (*D*) of the nano-CuFe₂O₄-chitosan was calculated using the Debye–Scherrer equation ($D = K\lambda/\beta \cos\theta$), where FWHM (full-width at half-maximum) is in radians and θ is the position of the maximum of

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Scheme 1. Synthesis of bis-thiazolidinones using nano-CuFe₂O₄@chitosan.

the diffraction peak. *K* is the so-called shape factor, which usually takes a value of ~0.9, and λ is the X-ray wavelength. The pattern agrees well with the reported pattern for nano-CuFe₂O₄-chitosan (JCPDS no. 34–0425). The average particle size was estimated by applying the Scherrer formula to the highest intensity peak. An average size of ~35–38 nm was obtained.

In order to investigate the morphology and particle size of the nanoparticles, the scanning electron microscopy (SEM) image of nanoparticles is presented in Figure 2. The SEM image shows particles with diameters in the range of nanometers. Figure 3 shows the Fourier transform infrared (FT-IR) spectrum of (a) chitosan, (b) $CuFe_2O_4$ NPs, and (c) nano- $CuFe_2O_4$ -chitosan. The FT-IR spectrum of chitosan (Figure 3(a)) displays a broad band at ~3400 cm⁻¹, which corresponds to the stretching vibrations of O–H and N–H groups. Peaks appearing at 2923 and 2855 cm⁻¹ are the characteristic of C–H stretching vibrations. The band at 1634 cm⁻¹ is assigned to the N–H bending vibration, and bands at 1375–1450 cm⁻¹ are assigned to the C–H bending vibration in chitosan. The band at 1084 cm⁻¹ displays the stretching vibrations of the C–O bond. The bands



Scheme 2. Schematic illustration of the formation of CuFe₂O₄-chitosan NPs.



Fig. 1. XRD patterns of nano-CuFe₂O₄@chitosan.

at 800–900 cm^{-1} display the bending vibration of the N–H bond.

From the FT-IR spectrum in Figure 3(b), two absorption bands at ~400–600 cm⁻¹ were observed, which correspond to the octahedral and tetrahedral sites of the positive ions of CuFe₂O₄, respectively. The higher absorption band at 606 cm⁻¹ corresponds to the intrinsic vibrations of tetrahedral complexes, and the lower absorption band at 436 cm⁻¹ is attributed to the vibrations of octahedral complexes.¹⁸ The broad absorption band at 3399 cm⁻¹ corresponds to hydroxyl groups stretching vibrations, while that at 1628 cm⁻¹ is due to the bending of H₂O adsorbed on the surface of CuFe₂O₄ NPs.

Figure 3(c) reveals the integration of $CuFe_2O_4$ NPs and chitosan in the nano- $CuFe_2O_4$ -chitosan. The amount of loading of nano- $CuFe_2O_4$ on chitosan was provided by inductively coupled plasma (ICP) spectroscopy, and the loading amount of nano- $CuFe_2O_4$ on chitosan was calculated to be 52.78 wt %.



Fig. 2. SEM image of nano-CuFe₂O₄-chitosan.

The magnetic properties of the nanoparticles were characterized using a vibrating sample magnetometer (VSM). Magnetic measurement shows that nano-CuFe₂O₄ and nano-CuFe₂O₄-chitosan have saturation magnetization values of 39.01 and 22.52 emu/g, respectively (Figure 4). These results indicate that the catalyst can be easily separated and recovered by an external magnetic field.

The thermal behavior of the magnetic nanocatalyst was investigated by thermogravimetry analysis (TGA). The TGA curve of the nano-CuFe₂O₄-chitosan shows the mass loss of the organic materials as it decomposes upon heating (Figure 5). The initial weight loss from the catalyst occurs in the range 25–200°C, which could be assigned to the loss of bound water or physically adsorbed solvent. The next TGA peak corresponds to a weight loss of 14% in the range 200–700°C, which is attributed to the decomposition of the organic species. Thus, the catalyst is stable up to 200°C.

To examine the effects of varying the catalyst and the reaction time for the synthesis of bis-thiazolidinones, the condensation reaction of 4-chlorobenzaldehyde (2 mmol), ethylenediamine (1 mmol), and 2-mercaptoacetic acid (2 mmol) was selected as a model. Yields were determined in the presence of MgO NPs, CuI NPs, Fe₃O₄ NPs, chitosan, and nano-CuFe₂O₄@chitosan, and the results are shown in Table 1. Nano-CuFe₂O₄@chitosan gave the best yields in the shortest time, and a very good yield of 86% was obtained with 5 mg of the catalyst, which did not improve further by increasing it to 7 mg. A reaction run in the absence of any catalyst gave a yield of only 9% (entry 1).

The results show that the present catalytic method is extendable to a wide variety of substrates to create a library of a variety of oriented bis-thiazolidinones (Table 2).

Owing to the presence of 2 and 2' equivalent stereogenic centers, bisthiazolidinones can be obtained as *rac*. 2R,2'R/2S,2'S and 2R,2'S-meso isomers. These bisthiazolidinones have been obtained, as previously reported, by the reaction of mercaptoacetic acid with N,N'-dibenzylidenethylendiamines.^{20,21} After work-up, the crude mixture of isomers was separated by silica gel column chromatography (diethyl ether/petroleum ether in variable ratio mixtures). In general, the meso isomers eluted more slowly than the corresponding racemates. The racemate isomer **4f** was obtained in higher yields than the meso isomer **4f** (81% for the *rac*. isomer **4f**, and 19% for

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Fig. 3. FT-IR spectrum of (a) chitosan, (b) $CuFe_2O_4$ NPs, and (c) nano-CuFe_2O_4-chitosan.

the *meso* isomer **4f**). The ¹H NMR spectra of the compounds **4a-4j** displayed a doublet of doublets at δ 3.917–3.870 ppm due to the methylene proton HA at C-5 (-CO-CHAHB-S) because of its interaction with the geminal proton HB at C-5 (-CO-CHAHB-S) and the proton at the chiral C-2 (S-CHAr-N); doublet of doublets at δ 3.574–3.527 ppm due to the methylene proton HB at C-5 (-CO-CHAHB-S) because of its interaction with the geminal proton HA (-CO-CHAHB-S) and a



Fig. 4. VSM curve of (a) CuFe₂O₄ NPs, and (b) nano-CuFe₂O₄-chitosan.



Fig. 5. TGA curve of nano-CuFe₂O₄-chitosan.

diastereotopic proton Ha (-N-CHaHb-CHaCHb-N-) of the ethylene fragment. This last proton Ha (-N-CHaHb-CHaCHb-N-) displayed a doublet of doublets or a multiplet at δ 2.675–2.634 ppm because of its interaction with the germinal proton Hb (-N-CHaHb-CHaCHb-N-) and the proton HB (-CO-CHAHB-S) at C-5. The Hb proton (-N-CHaHb-CHaCHb-N-) at the aliphatic chain suffered the anisotropic effect from the near amide group or aryl substituents and it shifted down field at δ 3.773– 3.732 ppm and overlapping with HB or HA (-CO-CHAHB-S) as a multiplet. These germinal protons of each methylene group reside in magnetically nonequivalent environments.^{20,21} H NMR of product **4f** is shown in Figure 6.

The reusability of the heterogeneous catalyst was explored using the model reaction system under the optimized conditions. After completion of the reaction, the magnetic nanocatalyst was easily and efficiently separated from the product by an external magnetic field. The nano-CuFe₂O₄-chitosan was washed 3–4 times with ethanol and dried at room temperature for 5 h. The separated catalyst could be used for five cycles. The reusability of the nano-CuFe₂O-chitosan catalyst was examined, and it was found that product yields decreased to a small extent on each reuse (run 1, 86%; run 2, 86%; run 3, 85%; run 4, 85%; run 5, 85%).

A probable mechanism for the synthesis of bisthiazolidine derivatives using nano-CuFe₂O₄-chitosan, is shown in Scheme 3. The mechanism involves a primary imine intermediate formation followed by the attack of the sulfur atoms of the 2-mercaptoacetic acid on the activated imine groups followed by intramolecular cyclization with the elimination of H₂O, giving rise to the

Entry	Solvent (reflux)	Catalyst (amount)	Time (min)	Yield% ^b
1	Toluene	No catalyst	300	9
2	DMF	MgO NPs (7 mol%)	250	42
3	Toluene	Cul NPs (4 mol%)	210	54
4	Toluene	Fe_3O_4 NPs (4 mol%)	240	30
5	Toluene	CuO NPs (6 mol%)	180	55
6	EtOH	Chitosan (15 mg)	200	38
7	DMF	Chitosan (15 mg)	200	50
8	Toluene	Chitosan (15 mg)	200	64
9	Toluene	Chitosan (20 mg)	200	65
10	EtOH	Nnano-CuFe ₂ O_4 (<i>a</i>)chitosan (5 mg)	100	56
11	CH ₃ CN	Nano-CuFe ₂ O_4 @chitosan (5 mg)	100	65
12	DMF	Nano-CuFe ₂ O_4 @chitosan (5 mg)	100	69
13	Toluene	Nano-CuFe ₂ O_4 @chitosan (3 mg)	90	82
14	Toluene	Nano-CuFe ₂ O_4 @chitosan (5 mg)	90	86
15	Toluene	Nano-CuFe ₂ O ₄ @chitosan (7 mg)	90	86

Table 1. Optimization of the reaction conditions^a

^a Reaction conditions: a mixture of 4-chlorobenzaldehyde (2 mmol), ethylenediamine (1 mmol), 2-mercaptoacetic acid (2 mmol) and the catalyst for various times.

^b Isolated yield.

cyclized product bis-thiazolidines. In this mechanism, the free hydroxyl and amino groups distributed on the surface of chitosan-supported nano-CuFe₂O₄ activate the C=O, C=N, and S-H groups through hydrogen bonding,²² for better reaction with the nucleophiles.

EXPERIMENTAL

Materials and methods

¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer in the presence of tetramethylsilane as internal standard. The IR spectra were recorded on an FT-IR Magna 550 apparatus using with KBr plates. Powder XRD was carried out on a Philips diffractometer (X'pert) with monochromatized Cu K α radiation ($\lambda = 1.5406$ Å). Microscopic morphology of products was visualized by SEM (QBSD). TGA curves are recorded using a V5.1A DUPONT 2000 instrument. The magnetic property of magnetite nanoparticles was measured with a VSM (Meghnatis Daghigh Kavir Co.; Kashan Kavir; Iran) at room temperature.

General procedure for the preparation of nano-CuFe₂O₄(a)chitosan

For preparation of nano-CuFe₂O₄@chitosan, chitosan (0.5 g) in 100 mL of 2.0 wt % acetic acid solution,

Table 2.	Yields of a	series of	bis-thiazolidinones	(racemate as ma	jor product) 4a–j ^a
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Entry	Aldehyde	Product	Time (min)	Yield% ^b	m.p. $(^{\circ}C)^{\text{Ref}}$	m.p. (°C)
1	4-Cl-C ₆ H ₄	4a	90	86	285-288 ²⁰	150-152
2	$2-Cl-C_6H_4$	4 b	93	84	210-211 ²⁰	143-145
3	C_6H_5	4 c	94	82	152–155 ⁸	155-157
4	$4-NO_2-C_6H_4$	4d	90	87	_	164–166
5	$3-NO_2-C_6H_4$	4 e	90	83	_	222-224
6	Pyridin-2-yl	4 f	93	83	$167 - 169^{21}$	170-172
7	Pyridin-3-yl	4g	95	78	$198 - 200^{21}$	191–193
8	Pyridin-4-yl	4h	93	80	224–225 ²¹	221-223
9	$4-CH_3-C_6H_4$	4i	98	77	_	158-160
10	4-Isopropyl-C ₆ H ₄	4j	100	75	_	163–165

^a Reaction conditions: a mixture of araldehyde (R = various) (2 mmol) and ethylenediamine (1 mmol), 2-mercaptoacetic acid (2 mmol) and nano-CuFe₂O₄@chitosan (5 mg) in toluene (5 mL) was refluxed for various times.

^b Isolated yield.

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Fig. 6. 1 H NMR of product **4f**.

1.5 g of oleic acid-modified $CuFe_2O_4$ NPs were added into a three-necked flask. The mixture was subjected with ultrasonic waves for 15 min and stirred for 10 min. Then, 2 mL of glutaraldehyde solution (25 wt %) was added into the mixture at 40°C, and the crosslinking reaction was carried out for 180 min. After the reaction, the composites were collected through magnetic separation and washed by deionized water and ethanol several times. The products were dried under vacuum.



Scheme 3. Schematic mechanism for the catalytic activity of nano-CuFe₂O₄@chitosan for the synthesis of the titled compound.

General procedure for the preparation of bis-thiazolidinones

A mixture of aldehydes (2 mmol), ethylenediamine (1 mmol), 2-mercaptoacetic acid (2 mmol), and 5 mg of nano-CuFe₂O₄@chitosan in toluene (5 mL) was refluxed. The reaction was monitored by TLC. After completion of the reaction, the nanocatalyst could be easily separated using an external magnet. The solvent was evaporated, and the crude mixture was separated by silica gel column chromatography (diethyl ether/ petroleum ether) to get the pure product.

Spectral data of new products

3,3'-(Ethane-1,2-diyl)bis(2-(4-nitrophenyl)thiazolidin-4-one) (4d). Yellow solid; m.p164–166°C, IR (KBr) cm⁻¹: 2932, 1672, 1523; ¹H NMR (400 MHz, DMSO d_6): 2.65–2.74 (m, 2H), 3.51–3.63 (m, 2H), 3.65–3.74 (m, 2H), 3.93 (dd, J = 1.9, 16 Hz, 2H), 6.04 (d, J = 1.9 Hz, 2H), 7.45 (d, J = 8 Hz, 4H), 8.09 (d, J = 8 Hz, 4H);¹³C NMR (100 MHz, DMSO- d_6): 32.6, 41.5, 63.7, 123.5, 130.1, 147.3, 150.5, 171.7; Anal. calcd for C₂₀H₁₈N₄O₆S₂: C, 50.62; H, 3.82; N, 11.81; S, 13.51; Found: C, 50.52; H, 3.75; N, 11.65; S, 13.44.

3,3'-(Ethane-1,2-diyl)bis(2-(3-nitrophenyl)thiazolidin-4-one) (4e). Cream-colored solid; m.p. 222–224°C, IR (KBr) cm⁻¹: 2922, 1665, 1514; ¹H NMR (400 MHz, DMSO-*d*₆): 2.62–2.67 (m, 2H), 3.54–3.57 (m, 2H), 3.63–3.66 (m, 2H), 3.87 (dd, J = 1.7, 15 Hz, 2H), 5.94 (d, J = 1.9 Hz, 2H), 7.55–7.76 (m, 4H), 8.02–8.08 (m, 4H);¹³C NMR (100 MHz, DMSO-*d*₆): 32.5, 41.6, 63.5, 126.4, 129.6, 130.7, 134.3, 143.8, 148.6, 171.6; Anal. calcd for C₂₀H₁₈N₄O₆S₂: C, 50.62; H, 3.82; N, 11.81; S, 13.51; Found: C, 50.74; H, 3.66; N, 11.78; S, 13.42.

3,3'-(Ethane-1,2-diyl)bis(2-(*p***-tolyl)thiazolidin-4one) (4i).** White solid; m.p.158–160°C, IR (KBr) cm⁻¹: 2928,1665; ¹H NMR (400 MHz, CDCl₃): 2.27 (s, 6H), 2.65–2.74 (m, 2H), 3.52–3.63 (m, 4H), 3.65 (dd, J = 1.8, 16 Hz, 2H), 5.47 (d, J = 1.5 Hz, 2H), 7.12 (s, 8H);¹³C NMR (100 MHz, CDCl₃): 20.5, 32.3, 39.4, 63.2, 126.8, 129.3, 135.2, 138.7, 171.2; Anal. calcd for C₂₂H₂₄N₂O₂S₂: C, 64.05; H, 5.86; N, 6.79; S, 15.54; Found: C, 63.91; H, 5.92; N, 6.88; S, 15.37.

3,3'-(Ethane-1,2-diyl)bis(2-(4-isopropylphenyl)thiazolidin-4-one) (**4j**). White solid; m.p.163–165°C, IR (KBr) cm⁻¹: 2954, 1665; ¹H NMR (400 MHz, CDCl₃): 1.14 (d, J = 7 Hz, 12H), 2.68–2.75 (m, 2H), 2.82–2.88 (m, 2H), 3.55–3.64 (m, 4H), 3.67 (dd, J = 1.8, 16 Hz, 2H), 5.47 (d, J = 1.4 Hz, 2H), 7.13 (d, J = 8 Hz, 4H), 7.15 (d, J = 8 Hz, 4H);¹³C NMR (100 MHz, CDCl₃): 23.4, 32.2, 33.4, 39.6, 63.1, 126.67, 126.75, 135.6, 149.8, 171.1; Anal. calcd for C₂₆H₃₂N₂O₂S₂:C, 66.63; H, 6.88; N, 5.98; S, 13.68; Found: C, 66.46; H, 6.79; N, 6.04; S, 13.58.

CONCLUSIONS

In conclusion, we have developed a simple and highly efficient protocol for the synthesis of bisthiazolidinones by one-pot pseudo-five-component condensation of araldehydes, ethylenediamine, and 2mercaptoacetic acid with nano-CuFe₂O₄-chitosan as a reusable and robust heterogeneous catalyst under reflux conditions in toluene. Atom economy, the wide range of products, excellent yields, reusability of the catalyst, and little catalyst loading are some of the important features of this protocol.

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Supporting information

Additional supporting information is available in the online version of this article.

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