

CuCr₂O₄ Nanoparticles: An Efficient Heterogeneous Catalyst for the Synthesis of Bis-thiazolidinones

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The preparation of bis-thiazolidinones has been achieved by a one-pot condensation reaction of araldehydes, ethylenediamine and thioglycolic acid in the presence of nano-CuCr₂O₄ nanoparticles under reflux conditions in toluene. This method provides several advantages including easy workup, excellent yields, short reaction times, reusability of the catalyst and low catalyst loading.

Keywords: CuCr₂O₄ nanoparticles, Bis-thiazolidinones, Ethylenediamine, One-pot, Thioglycolic acid

INTRODUCTION

The class of thiazolidinones includes compounds with important biological properties, such as antifungal [1], anti-inflammatory [2], anti-tumor [3], antitubercular [4], and anti-HIV [5] activities. The synthesis of bioactive heterocycles from readily accessible starting materials using one-pot multicomponent reactions (MCRs) has increased significant interest both from synthetic and medicinal chemists [6,7]. A few methods have been reported for the 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 purpose to propose a new route for an efficient, high yielding, and mild approach to achieve such systems. The eco-compatibility and employment of MCRs are enhanced when the multicomponent reaction is used in association with a heterogeneous catalyst [12]. Nanoscale heterogeneous catalysts should present higher surface areas, which are chiefly responsible for their catalytic activity [13,14]. CuCr₂O₄ nanoparticles, a typical example, have been used as a suitable catalyst in many reactions including

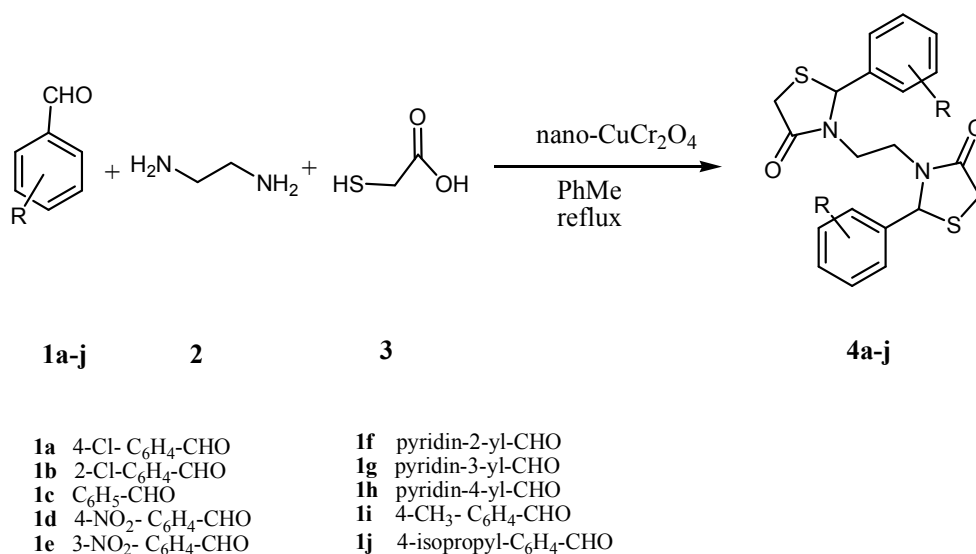
synthesis of pyrazolopyridines [15], synthesis of biscoumarins [16], synthesis of pyrazoles [17], oxidation of aniline to azoxybenzene [18] and hydroxylation of benzene [19]. Herein, we report the synthesis of bis-thiazolidinones by one-pot pseudo-five-component condensation of araldehydes, ethylenediamine and thioglycolic acid with nano-CuCr₂O₄ as a reusable and robust heterogeneous catalyst under reflux conditions in toluene (Scheme 1).

EXPERIMENTS

Chemicals and Apparatus

Reagent grade chemicals and solvents were purchased from Sigma-Aldrich or Merck and were used without further purification. NMR spectra were obtained on a Bruker Avance-400 MHz spectrometer (¹H NMR at 400 Hz, ¹³C NMR at 100 Hz) in DMSO-*d*₆ or CDCl₃ using TMS as an internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. The IR spectra were recorded on FT-IR Magna 550 apparatus using with KBr plates. Melting points were determined on Electro thermal 9200, and are not corrected. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu Kα radiation (λ = 1.5406 Å).

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Scheme 1. Synthesis of thiazolidinones

Microscopic morphology of products was visualized by SEM ((MIRA 3 TESCAN).

Preparation of CuCr₂O₄ Nanoparticles

CuCr₂O₄ nanoparticles were prepared according to the co-precipitation method reported by Edrissi *et al.* [22]. Cu(NO₃)₂·6H₂O (1.4 g, 0.005 mol) and Cr(NO₃)₃·9H₂O (4.0 g 0.010 mol) were dissolved in distilled water (50 ml). The mixed solution was subsequently added to 100 ml of distilled water, containing 5% glycerol as capping agent, under stirring. 1.5 M aqueous solution of precipitating agent (NaOAc) was added dropwise until the pH value of solution was adjusted to 10. During the mixing procedure, the temperature of solution was maintained about 60 °C. Then, the temperature was further increased to 80 °C at which the precipitation occurred. The fine precipitates were centrifuged and subsequently washed with distilled water and ethanol several times, and then dried in an oven at 60 °C for 2 h. Finally, after calcination at 600 °C for 5 h, CuCr₂O₄ nanoparticles were obtained.

General Procedure for the Preparation of Bis-thiazolidinones

A mixture of aldehydes (2 mmol), ethylenediamine(1 mmol), thioglycolic acid (2 mmol) and 3 mol% of CuCr₂O₄ nanoparticles in PhMe (5 ml) was refluxed. The reaction was monitored by TLC. After completion of the reaction,

CHCl₃ was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by centrifuging. The CHCl₃ was evaporated and the crude mixture was separated by silica gel column chromatography (diethyl ether/petroleum ether) to get pure product.

Spectral Data of Products

3,3'-(Ethane-1,2-diyl)bis(2-(4-nitrophenyl)thiazolidin-4-one) (4d). yield: 85%, Yellow Solid; m.p.: 164-166 °C, IR (KBr) cm⁻¹: 2935, 1670, 1521; ¹H NMR (400 MHz, DMSO-*d*₆): 2.64-2.73 (m, 2H), 3.53-3.6 (m, 2H), 3.67-3.73 (m, 2H), 3.92 (dd, *J* = 1.9, 16Hz, 2H), 6.03 (d, *J* = 1.9Hz, 2H), 7.46 (d, *J* = 8Hz, 4H), 8.07 (d, *J* = 8Hz, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆): 32.7, 41.6, 63.4, 123.9, 130.1, 147.2, 150.2, 171.6; Anal. Calcd. for C₂₀H₁₈N₄O₆S₂: C, 50.62; H, 3.82; N, 11.81; S, 13.51; Found: C, 50.53; H, 3.77; N, 11.68; S, 13.45.

3,3'-(Ethane-1,2-diyl)bis(2-(3-nitrophenyl)thiazolidin-4-one) (4e). yield: 82%, Cream solid; m.p.: 222-224 °C, IR (KBr) cm⁻¹: 2932, 1663, 1516; ¹H NMR (400 MHz, DMSO-*d*₆): 2.63-2.69 (m, 2H), 3.53-3.59 (m, 2H), 3.62-3.68 (m, 2H), 3.88 (dd, *J* = 1.7, 15 Hz, 2H), 5.95 (d, *J* = 1.9 Hz, 2H), 7.53-7.72 (m, 4H), 8.01-8.09 (m, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆): 32.4, 41.4, 63.1, 126.2, 129.4, 130.8, 134.1, 143.9, 148.4, 171.5; Anal. Calcd. for C₂₀H₁₈N₄O₆S₂: C, 50.62; H, 3.82; N, 11.81; S, 13.51;

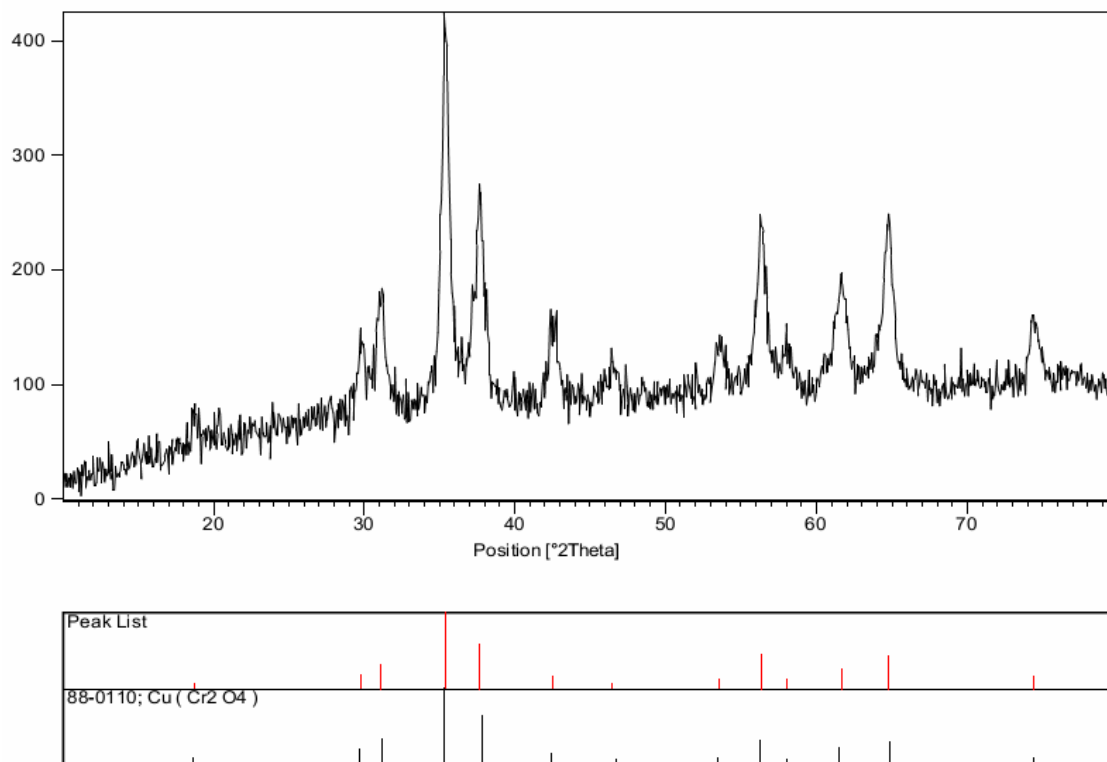


Fig. 1. The XRD pattern of CuCr₂O₄ nanoparticles.

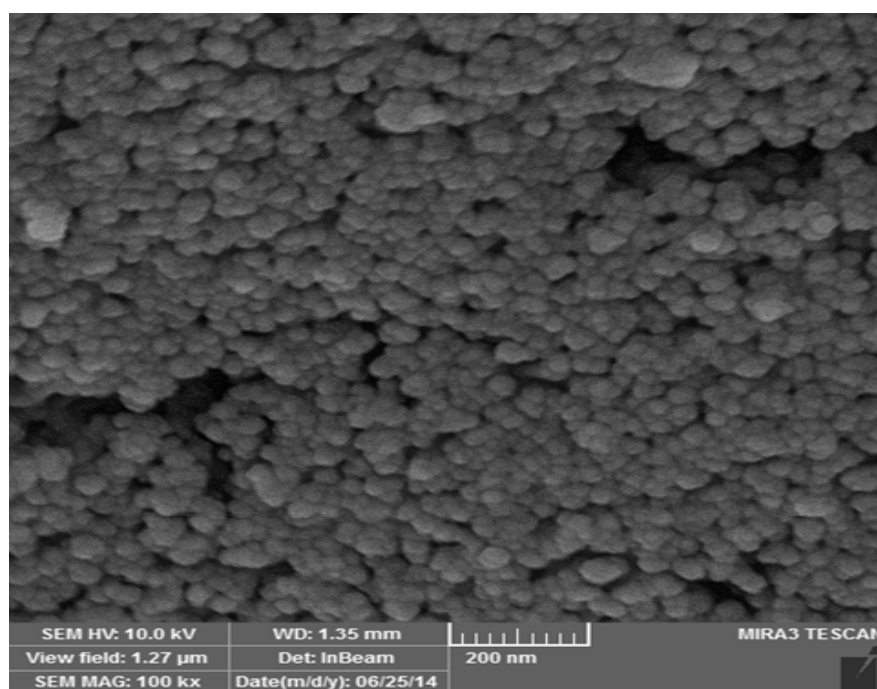


Fig. 2. SEM image of CuCr₂O₄ nanoparticles.

Found: C, 50.73; H, 3.64; N, 11.74; S, 13.46.

3,3'-(Ethane-1,2-diyl)bis(2-(p-tolyl)thiazolidin-4-one) (4i). yield: 75%, White solid; m.p.: 158-160 °C, IR (KBr) cm^{-1} : 2929,1669; ^1H NMR (400 MHz, CDCl_3): 2.28 (s, 6H), 2.68-2.75 (m, 2H), 3.53-3.61 (m, 4H), 3.67 (dd, $J = 1.8$, 16 Hz, 2H), 5.46 (d, $J = 1.5$ Hz, 2H), 7.11 (s, 8H); ^{13}C NMR (100 MHz, CDCl_3): 20.8, 32.1, 39.5, 63.2, 126.7, 129.3, 135.3, 138.9, 171.1; Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2$: C, 64.05; H, 5.86; N, 6.79; S, 15.54; Found: C, 63.92; H, 5.95; N, 6.87; S, 15.36.

3,3'-(ethane-1,2-diyl)bis(2-(4-isopropylphenyl)thiazolidin-4-one) (4j). yield: 73%, White solid; m.p.: 163-165 °C, IR (KBr) cm^{-1} : 2955, 1661; ^1H NMR (400 MHz, CDCl_3): 1.17 (d, $J = 7$ Hz, 12H), 2.69-2.78 (m, 2H), 2.8-2.89 (m, 2H), 3.55-3.64 (m, 4H), 3.68 (dd, $J = 1.8$, 16 Hz, 2H), 5.48 (d, $J = 1.4$ Hz, 2H), 7.13 (d, $J = 8$ Hz, 4H), 7.16 (d, $J = 8$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3): 23.4, 32.2, 33.4, 39.6, 63.1, 126.67, 126.75, 135.6, 149.8, 171.1; Anal. Calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_2\text{S}_2$: 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.

RESULTS AND DISCUSSION

Characterization of Copper Chromite Nanoparticles

The catalyst was prepared by the co-precipitation method using NaOAc solution as the precipitating agent. $\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ were used as the starting materials for the synthesis of copper chromite nanoparticles. This method is simple and inexpensive. The XRD patterns for CuCr_2O_4 are shown in Fig. 1. The particle size of CuCr_2O_4 nanoparticles was investigated by XRD pattern. The crystallite size diameter (D) of the CuCr_2O_4 nanoparticles 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 diffraction peak, K is the so-called shape factor, which usually takes a value of about 0.9, and λ is the X-ray wavelength. The pattern agrees well with the reported pattern for CuCr_2O_4 nanoparticles (JCPDS No. 88-0110). The average particle size was estimated by applying the Scherrer formula on the highest intensity peak. An average size of around 22-28 nm was obtained.

The SEM micrograph provides more accurate

information on the particle size and morphology of the CuCr_2O_4 nanoparticles (Fig. 2). The SEM image shows that the nanoparticles have a uniform size and spherical shape.

In the FT-IR (Fourier-transform infrared spectroscopy) spectra (Fig. 3), the absorption bands at 615, 514 cm^{-1} were assigned to $\text{Cr}_2\text{O}_4^{2-}$ group. The bands at 911 and 999 cm^{-1} refer to the Cr-O bond of the chromate group [22].

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), thioglycolic acid (2 mmol) was selected as a model. Yields were determined in the presence of MgO NPs, CuI NPs, Fe_3O_4 NPs and CuCr_2O_4 NPs and the results are shown in Table 1 (entries 2-11). Nano- CuCr_2O_4 gave the best yields in the shortest time and a very good yield of 84 % was obtained with 3 mol%, which was not improved by increasing to 4 mol%. A reaction run in the absence of any catalyst gave a yield of only 9 % (entry 1).

The above results obviously show that the proposed catalytic procedure is extendable to a wide variety of substrates to construct a diversity-oriented library of bis-thiazolidinones (Table 2). Owing to the presence of 2 and 2' equivalent stereogenic centers, bithiazolidinones can be obtained as *rac.* 2R,2'R/2S,2'S and 2R,2'S-*meso* isomers. These bithiazolidinones have been obtained, as previously reported, by the reaction of mercaptoacetic acid with N,N'-dibenzylidenethylenediamines [20,21]. After workup, the crude mixture of isomers was separated by silica gel column chromatography (diethyl ether/petroleum ether in variable ratio mixtures). In general, *meso* isomers eluted more slowly than corresponding racemates. The *racemate* isomer 4f was obtained in higher yields than *meso* isomer 4f (80% for the *rac.* isomer 4f and 20% for the *meso* isomer 4f). The ^1H NMR spectra of the compounds 4a-4j displayed a doublet of doublets at δ 3.80-3.95 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 3.50-3.75 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 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

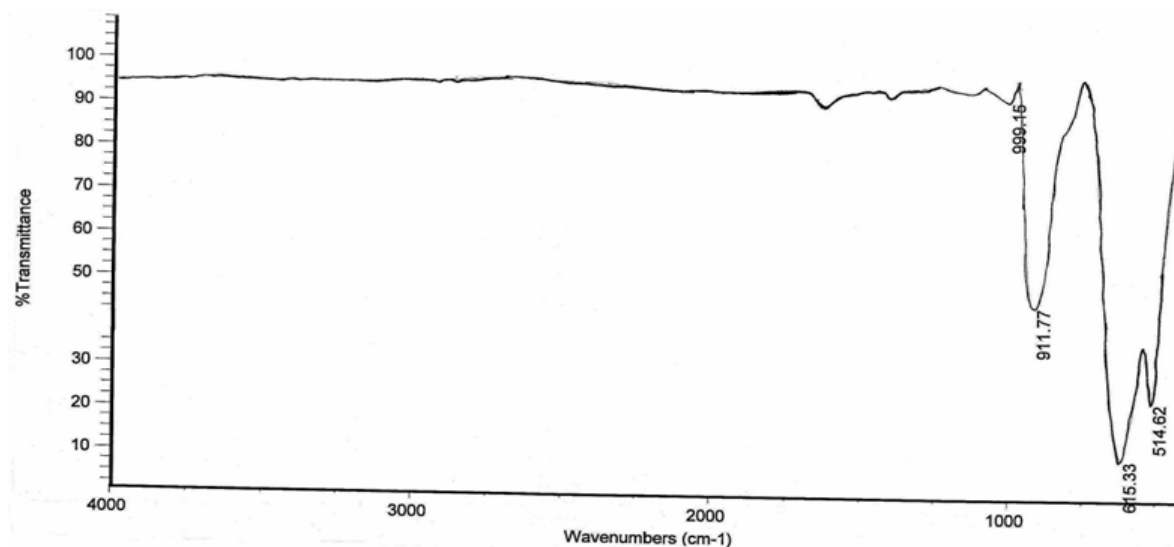


Fig. 3. FT-IR spectrum of CuCr₂O₄ nanoparticles.

Table 1. Optimization of the Reaction Conditions (Catalyst, Duration of Reaction) for the Preparation of Bis-thiazolidinones from 4-Chlorobenzaldehyde (2 mmol), Ethylenediamine (1 mmol), Thioglycolic Acid (2 mmol) (Scheme 1)^a

Entry	Solvent (Reflux)	Catalyst (mol%)	Time (min)	Yield (%)
1	Toluene	No catalyst	300	9
2	DMF	MgO NPs (6)	240	40
3	Toluene	CuI NPs (5)	200	52
4	Toluene	Fe ₃ O ₄ NPs (4)	240	30
5	Toluene	CuO NPs (6)	180	55
6	EtOH	CuCr ₂ O ₄ NPs (3)	120	59
7	CH ₃ CN	CuCr ₂ O ₄ NPs (3)	120	62
8	DMF	CuCr ₂ O ₄ NPs (3)	100	67
9	Toluene	CuCr ₂ O ₄ NPs (2)	90	81
10	Toluene	CuCr ₂ O ₄ NPs (3)	90	84
11	Toluene	CuCr ₂ O ₄ NPs (4)	90	84

^aReaction conditions: a mixture of 4-chlorobenzaldehyde (2 mmol), ethylenediamine (1 mmol), thioglycolic acid (2 mmol) and catalyst for various times. ^bIsolated yield.

Table 2. Yields of a Series of Bis-thiazolidinones 4a-j (R = Various) Prepared from a Mixture of an Araldehyde 1 (R = Various) (2 mmol), Ethylenediamine (1 mmol), Thioglycolic Acid (2 mmol) and CuCr₂O₄ Nanoparticles (3 mol%) in Refluxing Toluene (5 ml) for Various Times (Scheme 1)^a

Aldehyde	Product (racemate)	Time (min)	Yield (%) ^a	m. p. (°C) ^{ref}	m. p. (°C)
4-Cl-C ₆ H ₄	4a	90	84	285-288 [20]	150-152
2-Cl-C ₆ H ₄	4b	93	82	210-211 [20]	143-145
C ₆ H ₅	4c	94	80	152-155 [8]	155-157
4-NO ₂ -C ₆ H ₄	4d	90	85	-	164-166
3-NO ₂ -C ₆ H ₄	4e	90	82	-	222-224
Pyridin-2-yl	4f	93	81	167-169 [21]	170-172
Pyridin-3-yl	4g	95	76	198-200 [21]	191-193
Pyridin-4-yl	4h	93	79	224-225 [21]	221-223
4-CH ₃ -C ₆ H ₄	4i	98	75	-	158-160
4-Isopropyl-C ₆ H ₄	4j	100	73	-	163-165

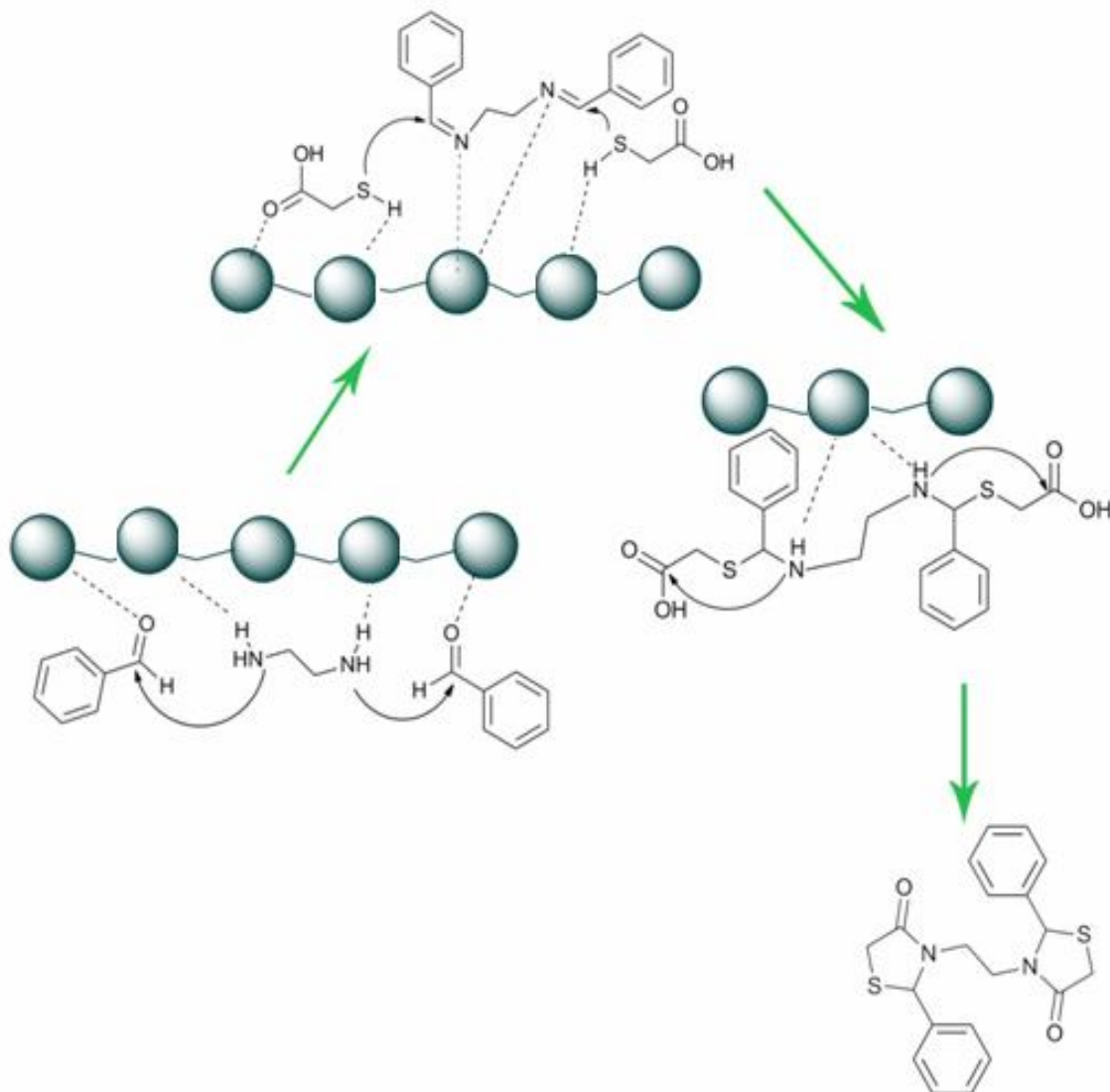
^aReaction conditions: a mixture of araldehyde 1 (R = various) (2 mmol), ethylenediamine (1 mmol), thioglycolic acid (2 mmol) and CuCr₂O₄ nanoparticles (3 mol%) in toluene (5 ml) was refluxed for various times. ^bIsolated yield.

at δ 2.50-2.85 ppm because of its interaction with the germinal proton H_b (-N-CHaHb-CHaCHb-N-) and the proton HB (-CO-CHAHB-S) at the C-5. The H_b proton (-N-CHaHb-CHaCHb-N-) at the aliphatic chain suffered the anisotropic effect from the near amide group or aryl substituents and it went to down field at δ 3.35-4.0 ppm appearing overlapped with HB or HA (-CO-CHAHB-S) as a multiplet. These germinal protons of each methylene group reside in magnetic non-equivalent environments [20,21].

The recoverability of the nano-CuCr₂O₄ NPs catalyst was examined for the synthesis of product 4a and it was found that product yields decreased to a small extent on each reuse (run 1, 84%; run 2, 84%; run 3, 83%; run 4, 83%; run 5, 82%). In the recycling procedure of CuCr₂O₄ NPs, CHCl₃ was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the

solvent and was separated by centrifuging. The deposited catalyst was washed with ethanol 4-5 times to confirm the complete removal of any organic residuals; the catalyst was reused for further catalytic reaction cycles.

A probable mechanism for the synthesis of bis-thiazolidine derivatives using nano-CuCr₂O₄, is shown in Scheme 2. A proposed mechanism is outlined *via* primary imine intermediate formation followed by attack of the sulfur atoms of the thioglycolic acids on the activated imine groups followed by intramolecular cyclization with the elimination of H₂O giving rise to the cyclized product bis-thiazolidines. In this mechanism, the surface atoms of nano-CuCr₂O₄ activate the C=O, C=N, and S-H groups for better reaction with nucleophiles. These surface atoms behave as the centers where chemical reactions could be catalytically stimulated.



Scheme 2. A probable mechanism for the synthesis of bis-thiazolidine derivatives

CONCLUSIONS

In conclusion, we have developed a simple and highly efficient protocol for the synthesis of bis-thiazolidinones by one-pot pseudo-five-component condensation of araldehydes, ethylenediamine and thioglycolic acid with nano-CuCr₂O₄ as a reusable and robust heterogeneous catalyst under reflux conditions in toluene. The remarkable advantages of this methodology are high yields, short reaction times, recycling of the catalyst and little catalyst loading.

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