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$CuCr_2O_4$ 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-$CuCr_2O_4$ 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: $CuCr_2O_4$ 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 $HClO_4$-SiO_2 [8], Zeolite [9], ChCl (Choline Chloride)/urea based ionic liquid [10] and $ZnCl_2$ [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]. $CuCr_2O_4$ 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-$CuCr_2O_4$ as a reusable and robust heterogeneous catalyst under reflux conditions in toluene (Scheme 1).

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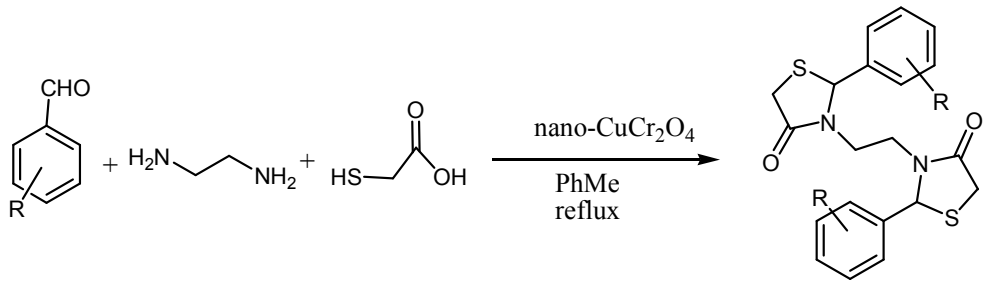
EXPERIMENTS

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 (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 or $CDCl_3$ 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).



1a-j **2** **3** **4a-j**

1a 4-Cl- C_6H_4-CHO
1b 2-Cl-C_6H_4-CHO
1c C_6H_5-CHO
1d 4-NO_2- C_6H_4-CHO
1e 3-NO_2- C_6H_4-CHO
1f pyridin-2-yl-CHO
1g pyridin-3-yl-CHO
1h pyridin-4-yl-CHO
1i 4-CH_3- C_6H_4-CHO
1j 4-isopropyl-C_6H_4-CHO

Scheme 1. Synthesis of thiazolidinones

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

Preparation of $CuCr_2O_4$ Nanoparticles

$CuCr_2O_4$ nanoparticles were prepared according to the co-precipitation method reported by Edrissi *et al*. [22]. $Cu(NO_3)_2{\cdot}6H_2O$ (1.4 g, 0.005 mol,) and $Cr(NO_3)_3{\cdot}9H_2O$ (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, $CuCr_2O_4$ 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 $CuCr_2O_4$ nanoparticles in PhMe (5 ml) was refluxed. The reaction was monitored by TLC. After completion of the reaction, $CHCl_3$ was added to dilute the reaction mixture after terminating the reaction. The catalyst was insoluble in the solvent and was separated by centrifuging. The $CHCl_3$ 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 ºC, IR (KBr) cm^{-1}: 2935, 1670, 1521; ^{1}H 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); ^{13}C 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 $C_{20}H_{18}N_4O_6S_2$: 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 ºC, IR (KBr) cm^{-1}: 2932, 1663, 1516; ^{1}H 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); ^{13}C 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 $C_{20}H_{18}N_4O_6S_2$: C, 50.62; H, 3.82; N, 11.81; S, 13.51;

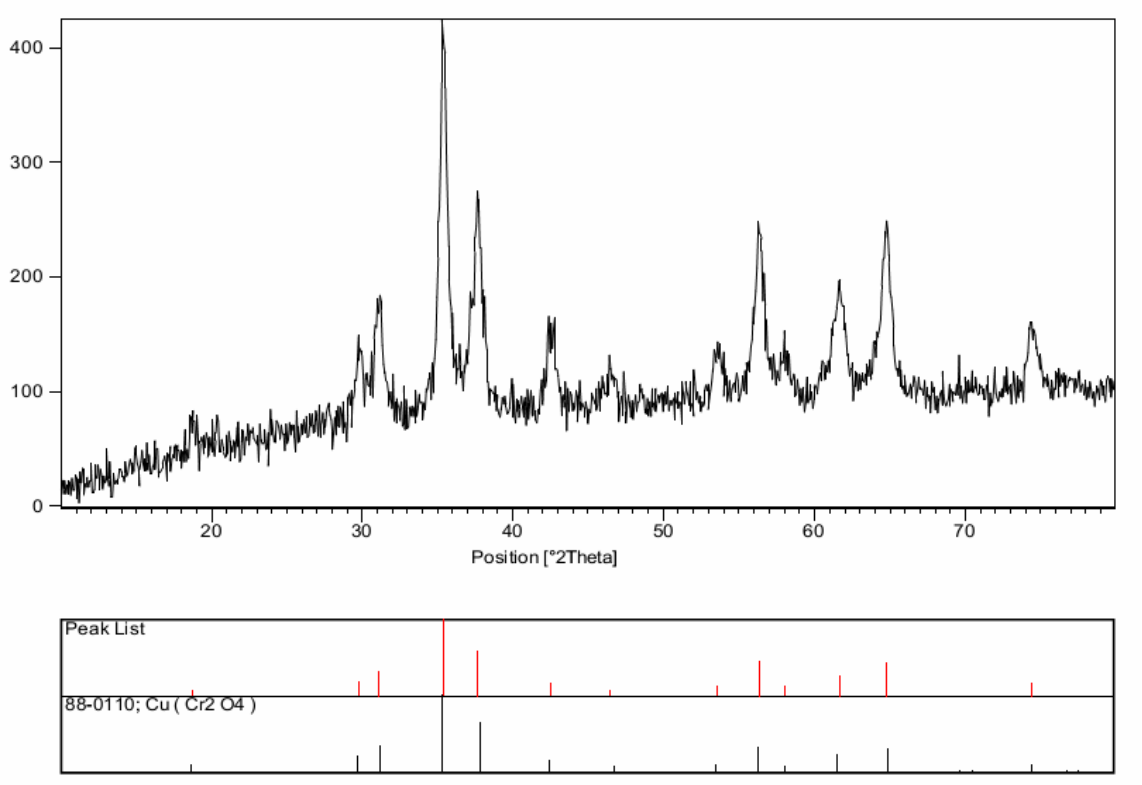


Fig. 1. The XRD pattern of $CuCr_2O_4$ nanoparticles.

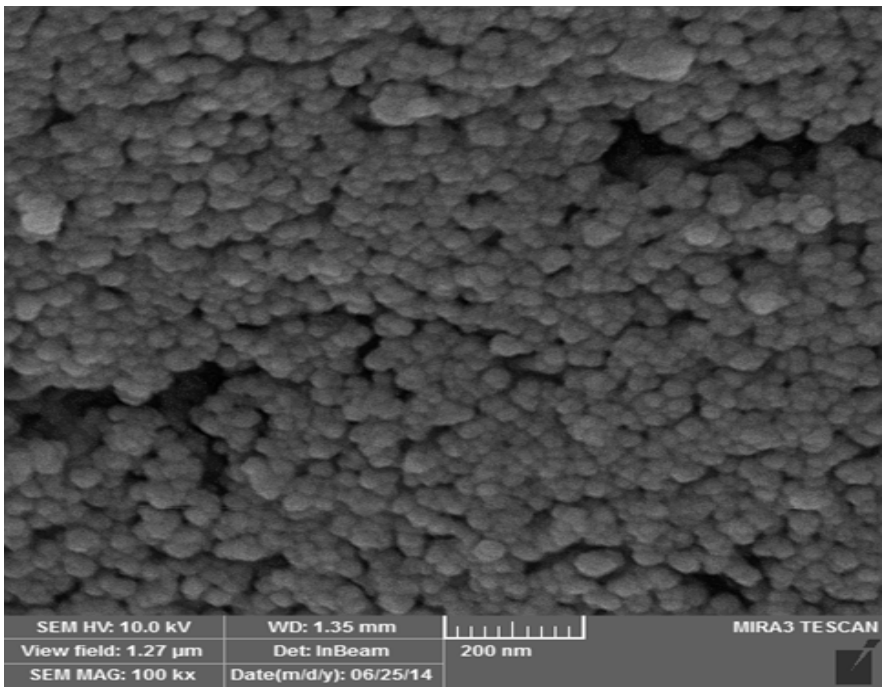


Fig. 2. SEM image of $CuCr_2O_4$ nanoparticles.

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 ºC, IR (KBr) cm^{-1}: 2929,1669; ^{1}H 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 $C_{22}H_{24}N_2O_2S_2$: 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 ºC, IR (KBr) cm^{-1}: 2955, 1661; ^{1}H 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 $C_{26}H_{32}N_2O_2S_2$: 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. $Cu(NO_3)_2{\cdot}6H_2O$ and $Cr(NO_3)_3{\cdot}9H_2O$ 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 $Cr_2O_4^{2-}$ 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, 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 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 ^{1}H 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

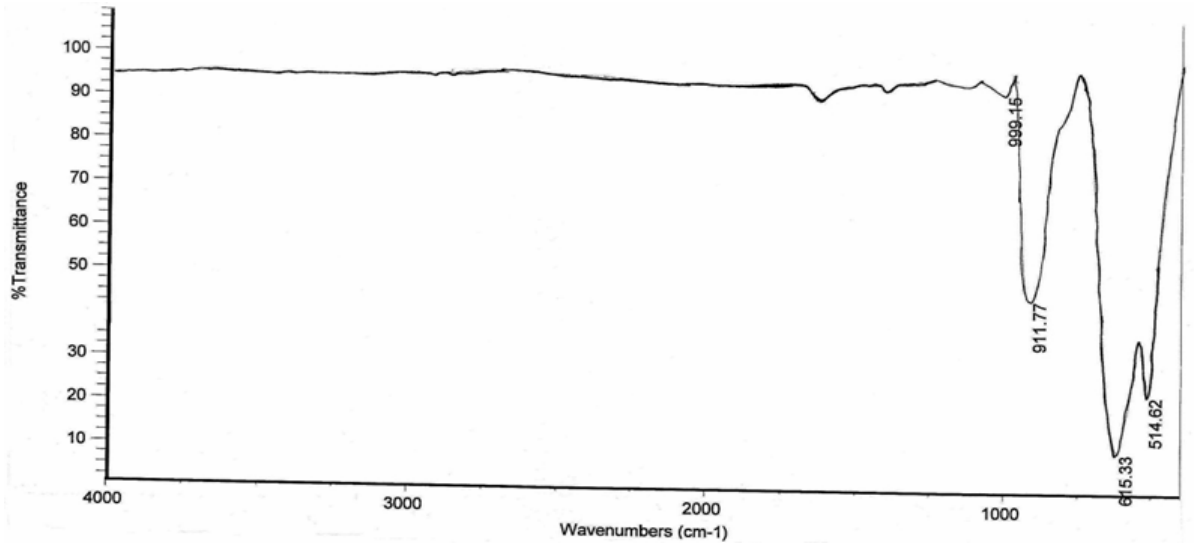


Fig. 3. FT-IR spectrum of $CuCr_2O_4$ nanoparticles.

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_3O_4 NPs (4)	240	30
5	Toluene	CuO NPs (6)	180	55
6	EtOH	$CuCr_2O_4$ NPs (3)	120	59
7	CH_3CN	$CuCr_2O_4$ NPs (3)	120	62
8	DMF	$CuCr_2O_4$ NPs (3)	100	67
9	Toluene	$CuCr_2O_4$ NPs (2)	90	81
10	Toluene	$CuCr_2O_4$ NPs (3)	90	84
11	Toluene	$CuCr_2O_4$ NPs (4)	90	84

[a]Reaction conditions: a mixture of 4-chlorobenzaldehyde (2 mmol), ethylenediamine (1 mmol), thioglycolic acid (2 mmol) and catalyst for various times. [b]Isolated 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 $CuCr_2O_4$ Nanoparticles (3 mol%) in Refluxing Toluene (5 ml) for Various Times (Scheme 1)[a]

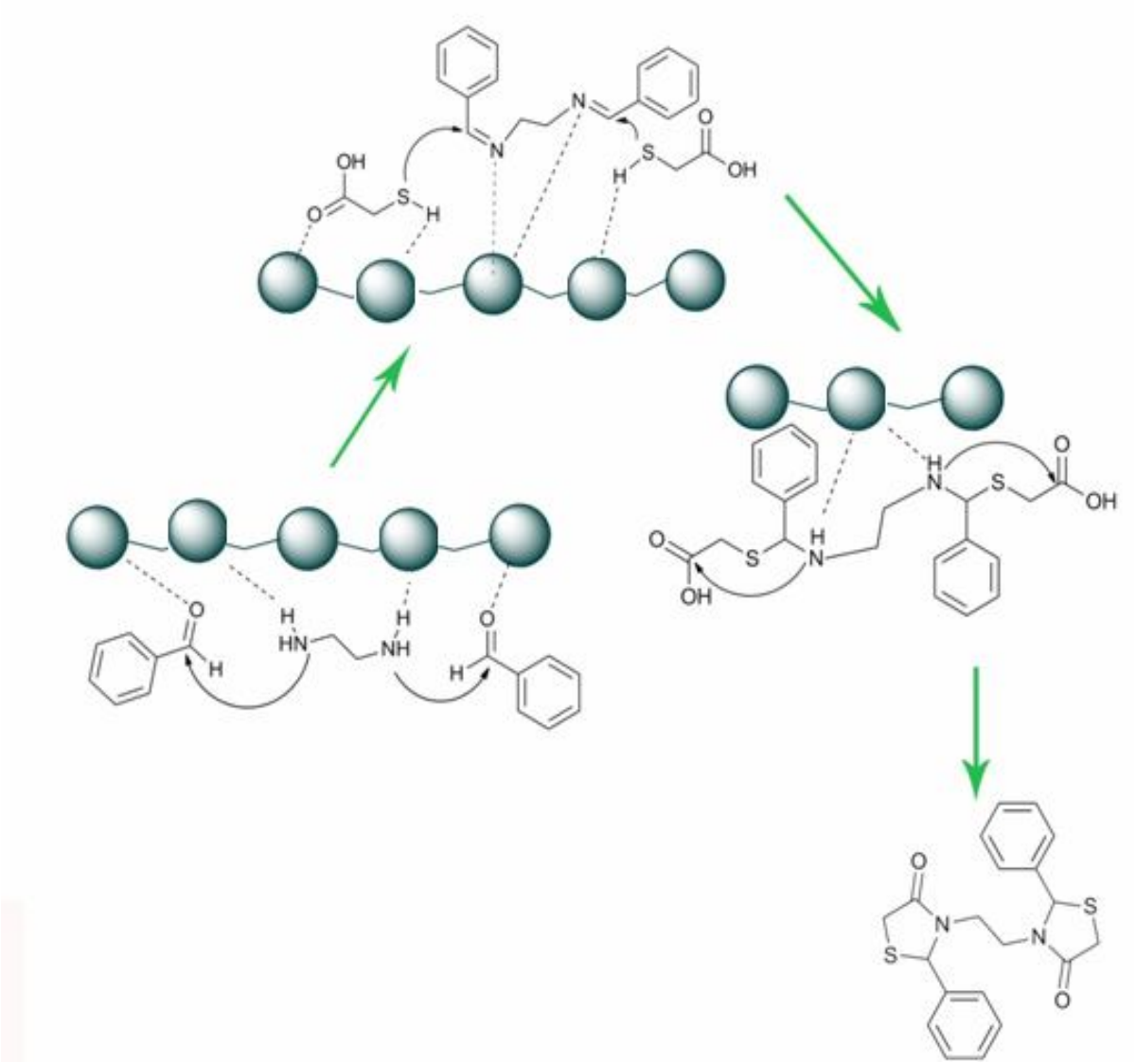
Aldehyde	Product (racemate)	Time (min)	Yield (%) [a]	m. p. (°C) [ref]	m. p. (°C)
4-Cl- C_6H_4	4a	90	84	285-288 [20]	150-152
2-Cl-C_6H_4	4b	93	82	210-211 [20]	143-145
C_6H_5	4c	94	80	152-155 [8]	155-157
4-NO_2-C_6H_4	4d	90	85	-	164-166
3-NO_2-C_6H_4	4e	90	82	-	222-224
Pyridin-2-yl	4f	93	81	167-169 [21]	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_6H_4	4i	98	75	-	158-160
4-Isopropyl-C_6H_4	4j	100	73	-	163-165

[a]Reaction conditions: a mixture of araldehyde 1 (R = various) (2 mmol), ethylenediamine (1 mmol), thioglycolic acid (2 mmol) and $CuCr_2O_4$ nanoparticles (3 mol%) in toluene (5 ml) was refluxed for various times. [b]Isolated yield.

at δ 2.50-2.85 ppm because of its interaction with the germinal proton Hb (-N-CHaHb-CHaCHb-N-) and the proton HB (-CO-CHAHB-S) at the 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 went to down field at d 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-$CuCr_2O_4$ 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 $CuCr_2O_4$ NPs, $CHCl_3$ 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-$CuCr_2O_4$, 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 H_2O giving rise to the cyclized product bis-thiazolidines. In this mechanism, the surface atoms of nano-$CuCr_2O_4$ 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-$CuCr_2O_4$ 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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