



Mannich Reaction Catalyzed by L-Cysteine-Decorated ZnS Nanoparticles for P-amino Carbonyl Compound Synthesis

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One-pot three-component Mannich reactions of ketone, aromatic aldehyde and aromatic amines were efficiently catalyzed by recyclable heterogeneous L-Cysteine supported on ZnS nanoparticles at the ambient temperature to give various p—amino carbonyl compounds with high yields. This simple method has some advantages such as mild condition and no environmental pollution. Structures of the compounds were confirmed by ¹H NMR and IR spectral analyses. ZnS nanoparticles were prepared in hydrothermal procedure from an aqueous solution of Zinc acetate and NaS in the presence of L-Cysteine. L-Cysteine supported on ZnS nanoparticles was characterized by FT-IR, TEM, TGA/DTA and XRD analysis.

Keywords: Mannich, L-Cysteine, Functionalized ZnS, p-amino carbonyl

INTRODUCTION

Nowadays, multi-component reactions (MCRs) have been developed as an efficient and environmentally benign procedure. Mannich reaction as one of the MCRs subsets has an extensive application in synthesis of materials such as organic synthesis of p-amino carbonyl compounds.

Notably, this reaction can be promoted by a wide array of catalysts such as CeCl₃·7H₂O [1], Cs_{2.5}H_{0.5}PW₁₂O₄₀ [2], Salen Zn complex [2], silica sulfuric acid [3], and NbCl₅ [4]. Unfortunately, several severe drawbacks including high cost, harsh reaction conditions, long reaction time, the requirement for a large excess of reagents or catalysts, the difficulty of



products separation, low yield and the use of toxic solvents are associated with some catalysts. Although, recent protocols have made this route more practical, development of simple, recyclable, and environmentally friendly approaches that can be performed at ambient temperature for Mannich reactions are still required.

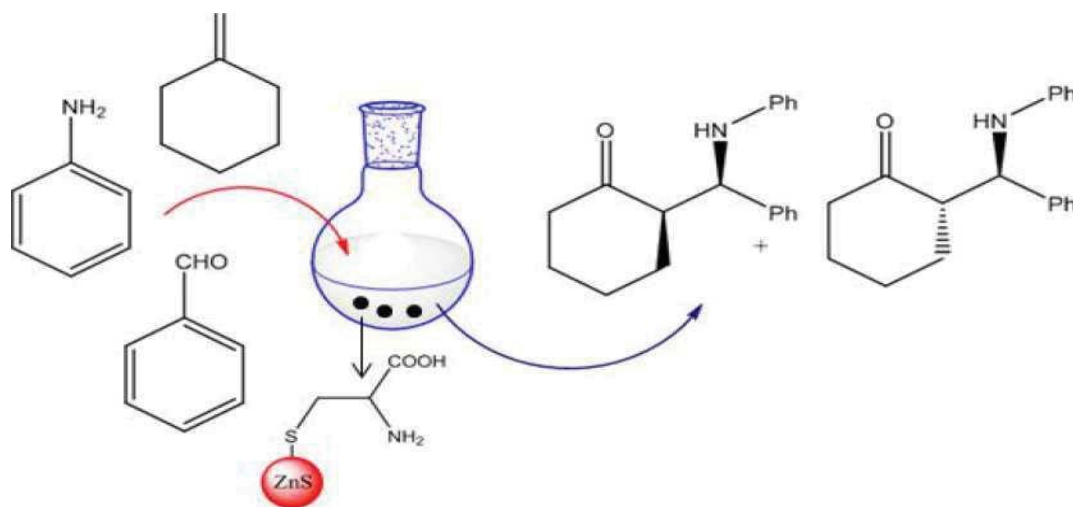
Over the past decades, nanoparticles have attracted scientist's attention because of their extraordinary properties such as high surface/weight ratio, greatly enhanced reactivity, selectivity compared to their bulk counterparts, and superhydrophobic/hydrophilic surface [5]. Although there are many nanoparticles such as CdS: Mn/ZnS [6], ZnO [7], there is still scope for novel nanoparticles with less toxicity, reaction time and filler concentration.

In this study, the synthesis of p-amino carbonyls was investigated by using one-pot Mannich-type reaction between cyclohexanone, aryl aldehydes and amines at room temperature by using L-Cysteine supported on ZnS nanoparticles as a novel heterogeneous Organo/Nano catalyst (Scheme 1).

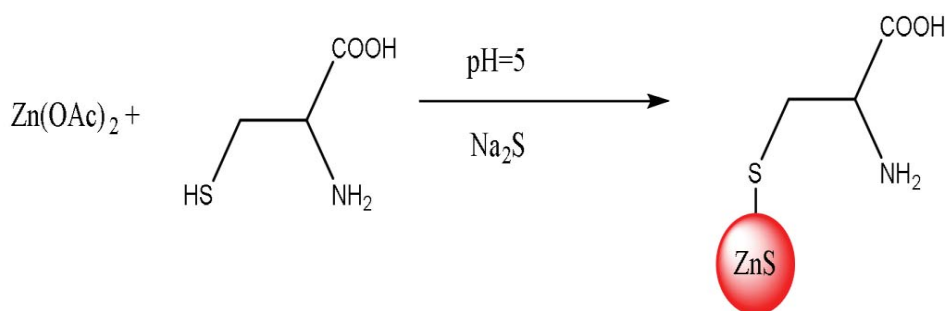
EXPERIMENTAL

General

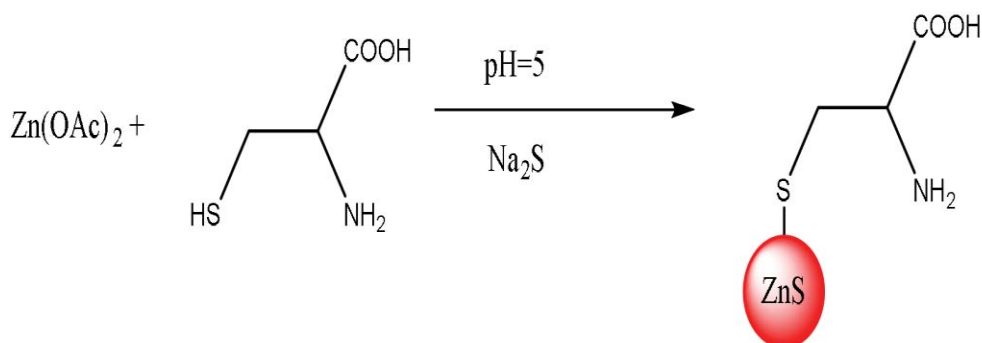
All materials were purchased from Merck (Darmstadt, Germany) with analytical grade and used as received. All experiments were carried out by deionized water. Transmission electron microscopy (TEM) was taken using a transmission electron microscope (Philips cm30) equipped with CCD Camera at an acceleration voltage of 80 kV. Samples for TEM were prepared by putting a drop of solution on a carbon-coated copper grid. X-ray diffraction (XRD) studies were done with Unisantis XMD-300. Differential thermal analysis (DTA/TGA) was done by Bahr STA-503. Fourier transform infrared (FTIR) spectra of samples in the form of KBr pellets were recorded using a Nicolet Avatar 370-FTIR spectroscopy.



Scheme 1. Synthesis of p-amino carbonyl with L-Cysteine supported on ZnS nanoparticles



Scheme 2. Synthesis of L-Cysteine supported on ZnS nanoparticles



Scheme 2. Synthesis of L-Cysteine supported on ZnS nanoparticles



The Mannich reaction was monitored by TLC using silica gel plates and the products were identified by comparison of their spectra and physical data with those of the authentic samples. Melting points were measured on an Electrothermal 9100 apparatus. Also, the products were characterized with ^1H NMR using BRUKER AVANCE III

FT-NMR spectrometer at 300 MHz.

Synthesis of L-Cysteine Supported on ZnS Nanoparticles

$\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (1.32 g, 6 mmol) was dissolved in deionized water (50 ml), after which L-cysteine (4.5 mg, 1 mmol) was slowly added to the solution along with the stirring for 10 min at room temperature using a magnetic stirrer. $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (2.16 g, 9 mmol) dissolved in 5 ml of deionized water was added to the mixture and the stirring continued until a clear solution was obtained. Finally, urea solution (0.9 M) was added dropwise until the pH was adjusted to 9-10.

Table 1. Effect of Solvent and Catalyst on Mannich Reaction

No.	Solvent	Cat. (g)	Temp. ($^{\circ}\text{C}$)	Yield (%)
1 ^a	Ethanol	0.01	RT	79
2	Dichloromethane	0.01	RT	44
3	Water	0.01	RT	35
4	Methanol	0.01	RT	83
5	None	0.01	RT	-
6 ^b	Ethanol	0.01	RT	78
7 ^c	Ethanol	0.01	RT	75
8 ^d	Ethanol	0.01	RT	71
9 ^e	Ethanol	0.01	RT	70



10	Ethanol	0.00	RT	-
11	Ethanol	0.02	RT	75
12	Ethanol	0.01	40	79
13	Ethanol	0.01	50	80
14	Ethanol	0.01	60	81
15	Ethanol	0.01	70	81

All reaction duration were 48 h in 3 ml of solvent. Condition of reaction: benzaldehyde (1.0 mmol), aniline (1.0 mmol), cyclohexanone (1.0 mmol). ^aThe optimized condition for catalyst. ^{b-e}Using the recycling catalyst. The resulting liquid was transferred into a 100 ML Teflon-lined stainless-steel autoclave and tightly sealed. Hydrothermal treatment was carried out at 150 °C for 10 h. The resulting precipitates were centrifuged at 4,000 rpm for 5 min. The particles were washed several times using double distilled water, absolute ethyl alcohol and HCl (5%) solution to remove the last traces of adhered impurities. The washed particles were dried at 60 °C in the vacuum oven for 24 h. The products were denoted as L-Cysteine supported on ZnS nanoparticles (Scheme 2).

General Procedure of Mannich Product

A heterogeneous solution of benzaldehyde (1.0 mmol), aniline (1.0 mmol), cyclohexanone (1.0 mmol) and L- cysteine supported on ZnS nanoparticles (10 mg) in EtOH (3 ml) was produced and stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration and the solvent evaporated. Then, the crude product was purified by plating. P-Amino ketones (1-14), characterized using ¹H NMR and IR spectra, and melting points were compared with those previously reported in the literature (Table 2).



RESULTS AND DISCUSSION

Characterization of the Catalyst

L-Cysteine supported on ZnS nanoparticles was prepared hydrothermally according to scheme 2 from an aqueous solution of Zinc Acetate, L-Cysteine and Na₂S in an autoclave. It was characterized by FT-IR, TEM, TGA/DTA, and XRD analysis.

Table 2. Synthesis of P-Amino Carbonyl with Various Substitutions

Entry	R	R	Yield		M.p. (°C)
			(%)	Anti/syn ^a	
1	H	H	79	45/55	117 [9]
2	4-CH ₃	H	79	73/27	116 [10]
3	4-Cl	H	65	61/39	134 [10]
4	3-CH ₃	4-CH ₃	70	99/1	122 [11]
5	H	4-CH ₃	69	71/29	126 [12]
6	3-CH ₃	4-Cl	77	99/1	129 [11]
7	3-CH ₃	H	74	73/27	136 [12]
8	4-CH ₃	4-NO ₂	73	74/26	122 [10]
9	3-CH ₃	4-NO ₂	78	56/44	161 [11]
10	3-Cl	4-CH ₃	73	99/1	123 [10]
11	3-Cl	4-Cl	78	88/12	124 [13]
12	3-Br	4-OCH ₃	69	35/65	121
13	3-Cl	4-OCH ₃	68	19/81	127 [14]
14	3-I	4-OCH ₃	75	49/51	112

^aAnti/syn ratio was determined by ¹H NMR. Condition of reaction: benzaldehyde (1.0

mmol), aniline (1.0 mmol), cyclohexanone (1.0 mmol) and catalyst (10 mg) in EtOH (3 ml) at room temperature.

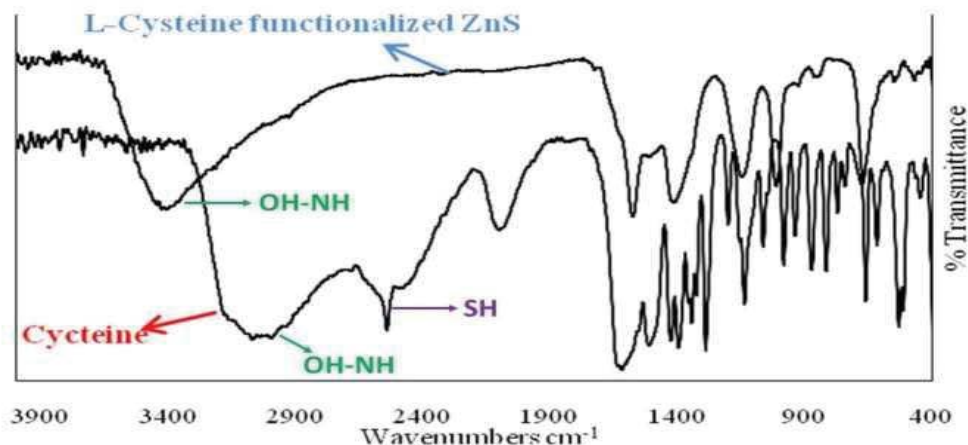


Fig. 1. FT-IR spectra of L-cysteine supported on ZnS.

Functionalization validation. Figure 1 shows the FT-IR spectra of L-Cysteine supported on ZnS nanoparticles in comparison with L-cysteine. The absorption band of L-Cysteine supported on ZnS nanoparticles around 1600 cm^{-1} (COO^-), 1350 cm^{-1} (COO^-) and $3500\text{-}3000\text{ cm}^{-1}$ (OH, COOH) might be due to the existence of $-\text{COO}^-$ group. Furthermore, the peak at $2900\text{-}3420\text{ cm}^{-1}$ and $600\text{-}800\text{ cm}^{-1}$ indicate $-\text{NH}_2$ and C-S group, respectively. There are coexisting IR absorption bands of $-\text{COO}^-$ and $-\text{NH}_2$ observed on both L-cysteine and L-Cysteine supported on ZnS nanoparticles, which can imply that carboxylic acid and the amino group were on the surface of the ZnS nanoparticles. Moreover, the S-H group vibration for L-Cysteine in 2560 cm^{-1} disappeared in L-Cysteine supported on ZnS nanoparticles; therefore, FTIR studies strongly validate the functionalization of ZnS nanoparticles with L-Cysteine.

Morphological characterization. The morphological properties of L-Cysteine supported on ZnS nanoparticles were determined by TEM analysis. TEM image showed fine spherical ZnS nanoparticles. The average particle size of L-cysteine supported on ZnS nanoparticles was 30 nm, which is in agreement with the crystal size calculated from the XRD patterns.

Thermal degradation. Figure 3 presents the TGA/DTA curve for L-Cysteine supported on ZnS nanoparticles. A small weight loss ($\sim 4\%$) was observed below $100\text{ }^\circ\text{C}$, which may be



due to the presence of moisture or the last traces of solvent. The second weight loss happened in 100-370 °C was attributed to the thermal decomposition of cysteine function (4%). The other weight loss (3%) occurred in the temperature range from 370-700 °C, attributed to the thermal decomposition and oxidation of ZnS to ZnO compounds [8]. As TG shows, about 4% of L-Cysteine is set on ZnS. Each 5 mg catalyst contains 92% (4.6 mg) ZnS and 4% (0.2 mg) of L-Cysteine.

XRD analysis. The XRD patterns of L-Cysteine supported on ZnS nanoparticles is shown in Fig. 4. L- Cysteine supported on ZnS nanoparticles revealed three broad peaks at around $2\theta = 28.8, 47.5$ and 56.6° (d-spacing: 3.09, 1.91 and 1.62 Å) corresponding to the (1 1 1), (2 2 0) and (3 1 1) crystal planes of ZnS nanoparticles, respectively. Furthermore, the average crystallite size was approximately 33 nm, as estimated from the half-width of diffraction peaks using the Debye- Scherrer equation.

Optimization of Mannich Reaction

The stepwise optimization was performed to achieve the lowest reaction time and the maximum reaction yield for the benzaldehyde, aniline, and cyclohexanone. To optimize conditions, cyclohexanone, benzaldehyde, and aniline reactions were examined under various conditions catalyzed by L-Cysteine supported on ZnS nanoparticles. At the first step, the effect of different solvents was investigated on Mannich reaction (Table 1). It was observed that Methanol has a higher yield (83%); however, considering environmental issues, EtOH was chosen as a green solvent (Table 1) with 79% yield.

In the next optimization step, the effect of reaction temperature was examined. The catalyst did not show a better yield above the room temperature. Furthermore, the effect of catalyst amount on the Mannich reaction yield was studied (Table 1). The Mannich reaction by 0.01 g of L-Cysteine supported on ZnS nanoparticles in ethanol at RT was concluded as the optimum condition.

Scope and Selectivity of Mannich Reaction

In order to investigate the scope and selectivity of Mannich reaction, a variety of substitutions on the aniline and benzaldehyde were used (Scheme 3). The existence of electron donating groups on the aniline leads to anti isomer more than syn-isomer selectivity, especially in the

entries 4,6,10 (Table 2). On the other hand, the existence of the methoxy group on benzaldehyde changed the equation in favor of syn-isomer (entry 12, 13). Generally, the electron donating groups may cause increasing the catalyst selectivity while electron withdrawing may affect in a reducing way.

To study the reusability of the catalyst, the catalyst was recovered from the reaction mixture by filtration and washed with water followed by drying at 110 °C for 15 min. Then, the catalyst was used for the model reaction under the similar reaction conditions for 5 cycles. After every reaction cycle, this process was repeated. The results are reported in Table 1 which confirm the good recyclability of our catalyst

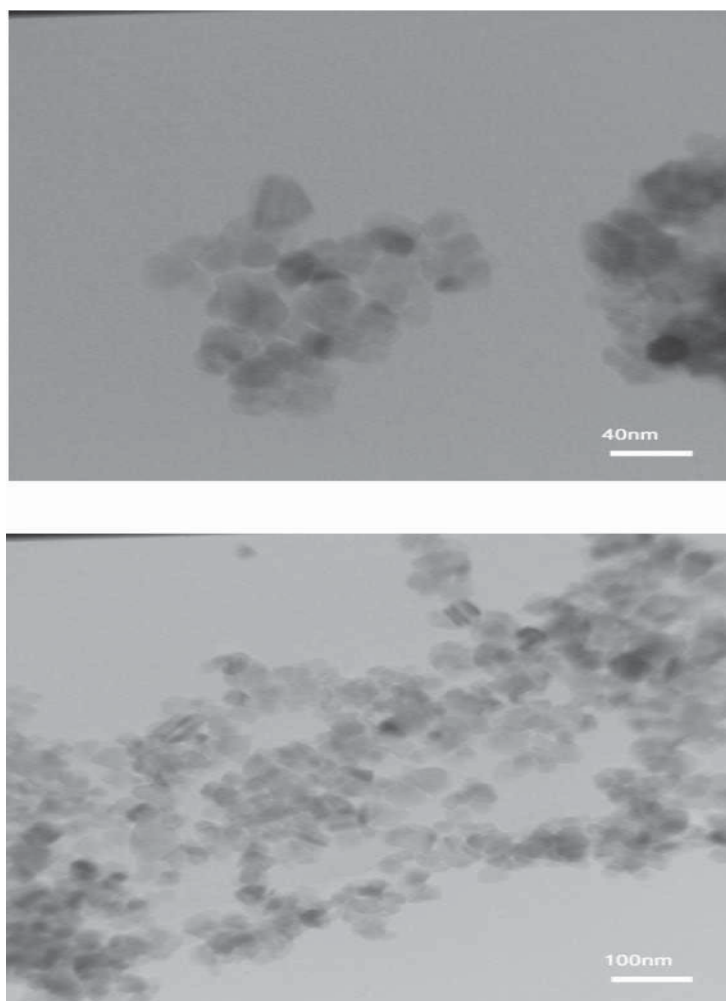


Fig. 2. TEM of L-Cysteine supported on ZnS nanoparticles.

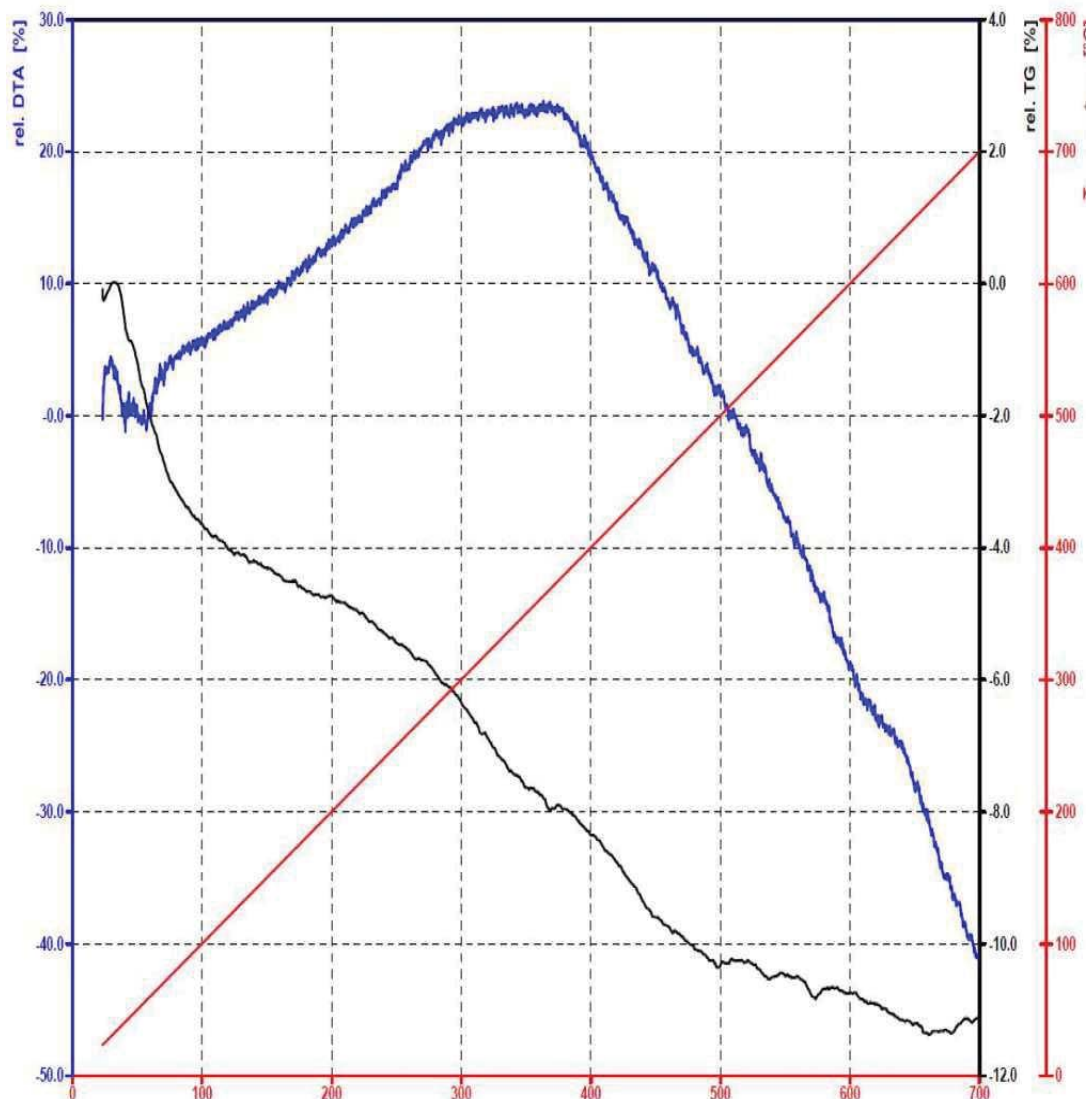


Fig. 3. TGA/DTA diagram of L-Cysteine supported on ZnS nanoparticles.

To show the efficiency of our catalyst in comparison with other reported catalysts, we summarized some results for the Mannich reaction of aniline and benzaldehyde with cyclohexanone (Table 3).

CONCLUSIONS

The environmentally friendly L-Cysteine supported on ZnS nanoparticles was synthesized, characterized, and used as a heterogeneous organo/nanocatalyst. Furthermore, the effects of the amount of catalyst, different solvents, and temperature on the reaction yield were studied to find optimum condition. The efficiency of the catalyst was examined by Mannich reaction

in the synthesis of p—amino carbonyl compounds. The catalyst showed good to excellent catalytic efficiency for the direct Mannich reaction in EtOH under mild conditions. Moreover, the catalyst showed good stability and could be recycled and used for five times.

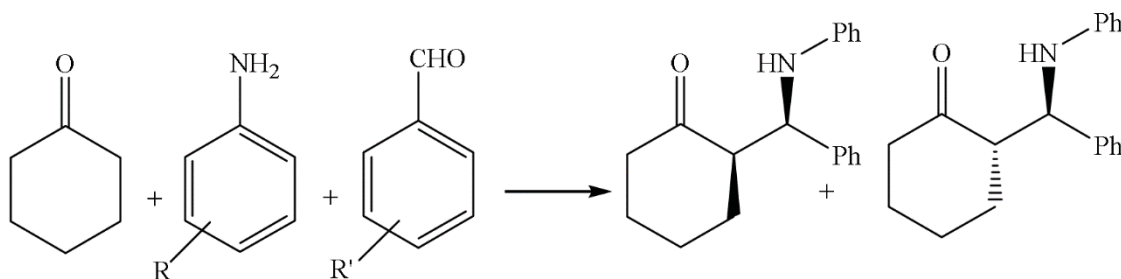
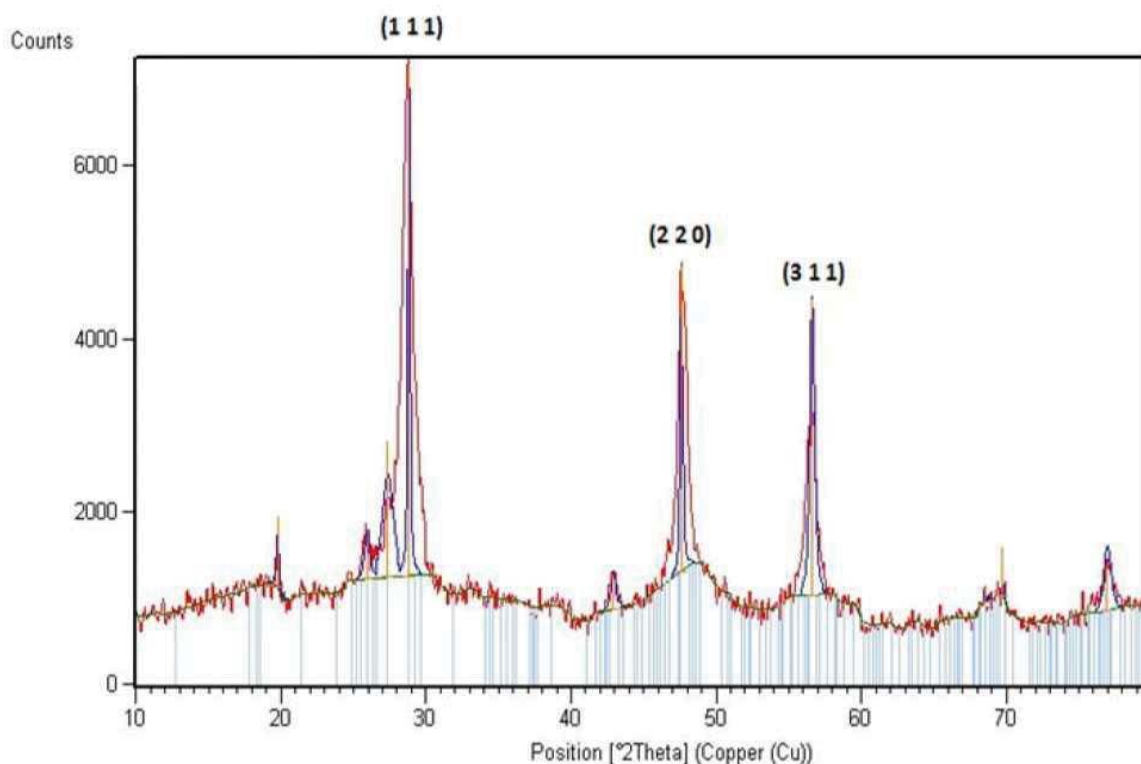


Fig. 4. XRD analysis of L-Cysteine supported on ZnS nanoparticles.



Scheme 3. Synthesis of p-amino carbonyl by L-Cysteine supported on ZnS nanoparticles



Table 3. Comparison of Efficiency of the Catalyst with some other Literatures

Entry	Catalyst	Temp.			Yield (%)
		Solvent	(°C)	Time	
1	Polymeric laponite nanoclay	Solvent-free	RT	24 h	64 [15]
2	IL	EtOH	60	30 min	75 [16]
3	Bi (OTf) ₃ .4H ₂ O	Water	RT	7 h	83 [17]
4	L-Cysteine-functionalized ZnS nanoparticles	EtOH	RT	48 h	81 (This work)



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